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EDITORIAL

Does size matter? Addressing pack size and antibiotic duration

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In Australia, most antibiotics are prescription-only so prescribers are the custodians of judicious use. They need to balance their concerns about antibiotic resistance with their responsibility for individual patient management. Prescribing with no clinical indication, inappropriate drug choice, and suboptimal dosing and duration can all contribute to antimicrobial resistance.[1,2] Clinical practice guidelines are therefore important for improving the quality and cost-effectiveness of infectious disease management. However, subtle factors such as the size of antibiotic packs could impact on judicious antibiotic use.

Antibiotic prescribing in primary care is largely empiric and symptom based. Antibiotics are usually started without microbiological testing. Clinical practice guidelines usually focus on antibiotic choice, with a recommended dose, frequency and duration, but have limited advice on resistance patterns.[3] Optimising the dose and duration of antibiotic treatment could simultaneously minimise both the symptomatic period and the selection pressure for resistance.[4]

Clinical practice guideline recommendations differ globally, particularly for the duration of antibiotic therapy.[5,6] When two UK guidelines for community-acquired pneumonia were critically assessed, there was a key difference of 2–3 days in the recommended course of antibiotics for infections of low–moderate severity.[5] Similarly, there were major differences in the recommended treatment duration for paediatric infections across seven reputable clinical practice guidelines.[6] The fact that recommendations about the duration of therapy are based more on expert opinion than strong scientific evidence is not widely appreciated by clinicians.

It is clear that no 'one-size-fits-all' for the length of an antibiotic course.[4] Infection resolution requires the antimicrobial to reach and remain at the site of infection in a sufficient concentration for a sufficient time. Concentration-dependent antibiotics such as aminoglycosides display maximal bactericidal activity at high concentrations, even if these concentrations are maintained for a relatively short time. In contrast, antibiotics displaying time-dependent activity, for example beta-lactams, require free drug at the infection site to be above the minimum inhibitory concentration or breakpoint concentration for a longer time. Duration can therefore be influenced by not only the dose prescribed but also the inherent characteristics of the antibiotic.[7]

Judicious antibiotic use needs to balance prescribing for too short a period (causing treatment failure, delayed return to health or the development of complications) with overprescribing which increases the risk of resistance, non-adherence, adverse effects and cost. Sub-therapeutic antibiotic concentrations can encourage antibiotic-resistant bacteria.[8] Other considerations when prescribing include the characteristics of the infecting organism, the patient's immune status and the bacterial gene pool.

While clinical evidence favours prolonged treatment to prevent the relapse of conditions such as enterococcal endocarditis, only short courses are needed for uncomplicated urinary tract infections in women. Evaluation of 13 meta-analyses to optimise antimicrobial duration in common bacterial infections determined that the duration of therapy could be shortened in most of these infections by at least three days without compromising patient outcomes.[9] However, for many infections managed in the community, the optimum treatment duration is unknown.

To improve the likelihood of success in clinical trials, a longer duration of antibiotics than the theoretical minimum may be used. Only after establishing efficacy are equivalence trials of shorter durations conducted. As non-inferiority trials require large numbers of patients, cost drives trial design towards single rather than multiple duration arms. Several pharmacokinetic and pharmacodynamic models have been proposed for duration-randomised trials to overcome cost as a barrier.[10] To extend the lifespan of antibiotics there needs to be collaboration between researchers, clinicians and the pharmaceutical industry to conduct equivalence trials. These are needed to determine the optimal minimum antibiotic regimen for common infections in Australia.

Ambiguity about the optimal duration of treatment for a particular indication contributes to uncertainty about how many doses to put in a pack. However, pack size heavily influences the duration of use. It will continue to do so while consumers are given advice to 'complete the antibiotic course'.

A 2015 analysis of published data on the most commonly prescribed antibiotics in Australian primary

care and their most common indications found a clear mismatch between the recommended treatment duration in clinical practice guidelines and the pharmaceutical industry packaging.[11] Of 32 common prescribing scenarios, 10 had doses in surplus and 18 had a shortfall, leaving only four where the pack size matched the recommended duration. In only two cases was a shortfall addressed by a repeat prescription.

Any mismatch between pack size and doses consumed might contribute to leftover antibiotics in the community. If these antibiotics are subsequently taken by the patient or someone else, it would contribute to potentially inappropriate use and, thereby, resistance. Alternatively, unused antibiotics could be discarded into the environment (landfill or waste water) which may facilitate the development or proliferation of resistant strains of bacteria.[12]

While solutions are not obvious, we must be willing to try strategies to reduce the mismatch between guidelines and antibiotic packaging. Regulations could require the industry to package antibiotics in accordance with clinical practice guidelines. While multiple pack sizes would increase costs, government incentives for the production of small packs could increase dispensing flexibility and minimise waste.

Prescribing software could improve adherence to clinical practice guidelines by commencing with the intended indication instead of the antibiotic. The indication would activate consensus regimens supported by evidence (or lack thereof). Prescriptions would not be printed until dose, frequency and importantly duration were entered, overriding the default pack and calculating the required quantity. Pharmacists would require corresponding dispensing software. They would also need to spend more time to implement safety strategies to prevent the reuse of broken packs with varying expiry dates.

Clinicians and the public should be informed that completing the pack is no longer supported by evidence and that resistance is primarily due to overuse. Patients should be empowered to stop their antibiotic after a specified minimum number of days or when they feel better (whichever comes first) and to return any unused doses for safe disposal to the pharmacy where the medicine was dispensed.[13] These and similar strategies warrant discussion to potentially extend the lifespan of antibiotics without compromising patient care. <

Conflict of interest: none declared

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LETTERS

Letters to the Editor

Dry eye: serum eye drops

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The recent article on dry eye suggested that autologous serum eye drops, for the treatment of refractory cases, are only available in hospitals.[1] However, autologous serum eye drops are manufactured by the Australian Red Cross Blood Service for compassionate supply in the eastern Australian states. Production also occurs via Cell and Tissues Therapies WA and other services.

After referral from an ophthalmologist, suitable patients can have their blood collected at a blood donor centre. In-hospital collection by the Blood Service, usually in the outpatient setting, is reserved for patients with significant co-morbidity.

Limited data were available on Australian patients with dry eye treated with serum eye drops so the Blood Service performed a prospective questionnaire study.[2] Significant improvements in symptom frequency and severity were reported for dryness, ocular pain and grittiness at two and 12 months. These findings support other evidence of autologous serum eye drops as a well-tolerated treatment for dry eye and corneal epithelial defects in patients failing other therapies.[3]

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Acknowledgment: This letter was written with the approval and on behalf of Phillip Mondy's co-authors.[2]

The author and co-authors have been employed by the Australian Red Cross Blood Service, which provides autologous serum eye drops on a compassionate basis.

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ARTICLE

Optimal antimicrobial duration for common bacterial infections

SUMMARY

Most antibiotic use in Australia arises from prescriptions in the community.

The risk of antibiotic-related adverse events, including resistance, increases with longer treatment courses.

When antibiotics are indicated for treatment, short courses are as effective as standard ones for most common infections.

Therapeutic Guidelines: Antibiotic is a key reference for antimicrobial prescribing in Australia.

General practitioners play a key role in reducing antibiotic use.

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Introduction

Optimising prescribing of antibiotics in the community is important because it is where most antibiotics are prescribed. In 2015, 30% of all patients attending a general practice received an antibiotic prescription.[1] Most are for acute respiratory infections, and in quantities several-fold more than recommended by Australian guidelines.[2] Repeat prescriptions have been highlighted as a cause for over-use in this setting.[1]

Yet antibiotics are not entirely benign. Their use can be associated with adverse events such as toxicity, allergy (including anaphylaxis), candidiasis, *Clostridium difficile* infection, and antimicrobial resistance – both at community and individual levels.[3-6] The more they are used, the greater the likelihood of adverse events, including resistance.[4-7]

It is important for prescribers to be up to date with best-practice antibiotic prescribing for common infections (Box), particularly the duration of treatment. In Australia, antibiotic prescribing is ideally concordant with the Therapeutic Guidelines: Antibiotic.[8] While other resources are commonly used, such as the Australian Medicines Handbook and MIMS, it is Therapeutic Guidelines that offers comprehensive information on the clinical indications for antibiotic prescription and advice on antibiotic choice, dose and duration. It is also the guideline currently endorsed by the Australian Commission on Safety and Quality in Health Care as the preferred reference for prescribing in the absence of local guidelines.

Antimicrobials are not always needed

Antibiotics are not necessary for most acute respiratory infections including acute rhinosinusitis, acute sore throat and acute otitis media. This is not just because so many of these infections are viral, but because even when the infection is bacterial, the benefits of antibiotic therapy for most patients are modest and outweighed by the harm from adverse effects.[9-12] Australian and local guidelines provide recommendations on when antimicrobial therapy should be used for these conditions.[8,13]

Box Best-practice antimicrobial prescribing in general practice

Do:

- consider microbiological testing to direct therapy (e.g. urinary tract infection, abscess), especially when the causative organism is difficult to predict (e.g. recurrent or unresponsive infection, or overseas travel)
- use the current version of Therapeutic Guidelines: Antibiotic, or available local guidelines
- know *why* you are prescribing the antibiotic (document indication and duration in the medical record)
- prescribe the shortest duration of therapy (or total number of tablets), even if this means the pharmacist breaking the pack.

Don't:

- culture every infection, or potential infection (especially urine in residential aged-care facilities)
- prescribe an antimicrobial without an appropriate indication
- routinely provide a repeat prescription.

Practice points on optimising antibiotic prescribing

It can be difficult to clinically differentiate a patient with a trivial acute respiratory infection from one at an early stage of serious bacterial infection, particularly in children.[14] One option is to 'watch and wait' and ask patients to return if there is clinical deterioration. An alternative is to prescribe an antibiotic but advise the patient to not have it dispensed unless specific symptoms occur. In the setting of acute respiratory infection, this has been shown to reduce antibiotic use by 50% with no significant decrease in patient satisfaction, and importantly no increase in complication rates.[15]

When antibiotics are prescribed, the duration (or number of tablets) should be written on the prescription. This should enable the pharmacist to supply only the number of tablets or capsules required (even if it means breaking the antibiotic pack) which avoids excessive antibiotic use. Repeat scripts are almost never required and we recommend changing the default setting to 'no repeats' in electronic prescribing software when technically feasible.

Antibiotic duration for common infections

Historically, the recommendations for duration of antibiotic treatment have been largely arbitrary. The theoretical principles have been to use enough antibiotic to eliminate the infecting organism and prevent the development of resistance. However, empirical evidence does not support this – shorter courses are nearly always as effective as standard ones.[16] Also, the longer the antibiotic exposure, the greater the pressure to select for antibiotic resistance in commensal bacteria that may cause serious infection in the future.[6,17]

Currently recommended antibiotic durations for the most common bacterial infections managed in general practice are shown in the Table. The total tablet quantity for the suggested duration in adults is included.

Evidence for short-course antimicrobial therapy

There is evidence to support recommendations for shorter antibiotic courses.

Acute rhinosinusitis

A systematic review of 12 studies found no significant difference in clinical cure rate, microbiological efficacy and relapse when 3–7 days versus 6–10 days of antibiotics were given for acute bacterial sinusitis.[16]

Acute tonsillopharyngitis

Short-course antibiotic treatment (5–7 days vs standard 10 days) is associated with equivalent rates of clinical cure in acute tonsillopharyngitis.[18] There is inferior bacteriological eradication, but this is of unknown clinical significance. It also is not known whether short-course therapy reduces the risk of non-suppurative complications (acute rheumatic fever and glomerulonephritis). A full 10-day course is still currently recommended to prevent these complications, especially in high-risk populations (previous history, remote indigenous populations).

Acute otitis media

A systematic review of short-course (<7 days) versus longer duration therapy in children with acute otitis media found that short-course therapy is non-inferior for clinical cure measured at one month and is associated with a significant reduction in gastrointestinal adverse events.[19]

Mild community-acquired pneumonia

Australian studies show that a penicillin and doxycycline (or a macrolide) is effective and safe for most patients with community-acquired pneumonia.[20] Monotherapy is recommended for mild infections providing the patient's progress can be reviewed after 48 hours.[8] A duration of 5–7 days of antibiotics is recommended in adults. This is supported by a systematic review showing no significant difference in outcomes between 3–7 days of antibiotics compared to 7 days or longer.[16] For children with non-severe pneumonia there is no difference between 3 versus 5 days of antibiotics.[21] Therapeutic Guidelines: Antibiotic currently recommends 5 days of oral antibiotics.[8] However, 3 days is endorsed by other Australian expert groups such as the Australian and New Zealand Paediatric Infectious Diseases group.[22]

Acute uncomplicated urinary tract infection

The evidence for antibiotic duration in urinary tract infections is sparser than for acute respiratory infections. For uncomplicated urinary tract infections in women there is no significant difference in clinical cure rates, and fewer adverse events in those given 3 days of antibiotics versus 5 days or longer.[23] However, the risk of bacteriological failure is higher in women given a shorter course. Bacterial elimination from the urine is likely to be relevant for women who are pregnant, experience recurrent and painful urinary tract infections or who have urinary tract prosthetic material in situ (e.g. stent or catheter).

Table **Recommended antibiotic prescribing for common bacterial infections** *

Diagnosis	Indications for antibiotic therapy	First-line antimicrobial (if indicated)	Duration	Tablets (for maximum adult dose)
Acute tonsillopharyngitis	2–25 years, high risk of acute rheumatic fever, or rheumatic heart disease, or scarlet fever	Phenoxymethylpenicillin 12-hourly	10 days †	20 x 500 mg
Acute rhinosinusitis	Symptoms >7 days, or high fever >3 days, or biphasic illness	Amoxicillin 8-hourly	5 days †	15 x 500 mg
Acute otitis media	<6 months old, or systemic symptoms, or indigenous community	Non-indigenous: amoxicillin 12-hourly	5 days †	20 x 500 mg
		Indigenous: amoxicillin 12-hourly	7 days †	28 x 500 mg
Community-acquired pneumonia (mild, can review progress in 48 hours)		Adults: amoxicillin 8-hourly, or doxycycline 12-hourly	5–7 days#	30 x 500 mg / 10 x 100 mg
		Children:		
		• 1 month to <3 months: azithromycin daily ‡	3–5 days	–
		• 3 months to <5 years: amoxicillin 8-hourly	3–5 days †	–
		• 5 years or older: amoxicillin 8-hourly §	3–5 days †	–
Uncomplicated urinary tract infection		Non-pregnant women: trimethoprim daily	3 days	3 x 300 mg
		Pregnant women: cefalexin or nitrofurantoin 12-hourly	5 days	10 x 500 mg / 10 x 100 mg
		Men: trimethoprim daily	7 days	7 x 300 mg
		Children ≥1 month: trimethoprim/sulfamethoxazole 12-hourly	3–5 days ¶	–
Cellulitis (mild, low risk for methicillin-resistant *Staphylococcus aureus*)		Dicloxacillin or flucloxacillin 6-hourly, or	5 days ††	20 x 500 mg
		phenoxymethylpenicillin 6-hourly **	5 days †, ††	20 x 500 mg
Impetigo		Non-remote setting:		
		• Localised lesion: topical mupirocin	7 days	–
		• Multiple lesions/recurrent: dicloxacillin or flucloxacillin 6-hourly	3–10 days ‡‡	40 x 500 mg
		Remote setting:		
		• trimethoprim/sulfamethoxazole 12-hourly, or	5 days	10 x 160/800 mg
		• benzathine penicillin intramuscular	single dose	–
Abscess (low risk for methicillin-resistant *Staphylococcus aureus*)	Spreading cellulitis, or systemic symptoms, or large lesion/critical area	Dicloxacillin or flucloxacillin 6-hourly, as an adjunct to incision and drainage	5 days	20 x 500 mg

* As recommended by Therapeutic Guidelines: Antibiotic. Refer to the complete guideline for further information on indications for antibiotic dosing, second-line antibiotics, and when broader spectrum therapy and specialist involvement may be appropriate. Refer also to local guidelines. Use oral regimen unless indicated otherwise.

† Repeat script required only if using liquid formulation for a large child.

‡ *Chlamydia trachomatis* may be the cause in this age group if afebrile and only mildly unwell.

§ Atypical cover with doxycycline, azithromycin or clarithromycin is recommended if *Mycoplasma pneumoniae* or another atypical pathogen is suspected. Doxycycline should not be used in children younger than 8 years of age.

Repeat prescription required only if using amoxicillin.

¶ 5 days for children <1 year, 3 days for children ≥1 year.

** If *Streptococcus pyogenes* clinically suspected or isolated from culture.

†† Up to 10 days if cellulitis more severe.

‡‡ Stop therapy earlier than 10 days if infection has resolved.

Currently 5 days of therapy is recommended for pregnant women and for second-line drugs in non-pregnant women.[8] The first-line 3-day recommendation of trimethoprim in non-pregnant women has been extrapolated from data for trimethoprim/sulfamethoxazole, a drug that is considered equivalent to trimethoprim for this condition.[24]

Short-course therapy has not been adequately evaluated in men and so it is not recommended at present. A Cochrane review of childhood lower urinary tract infection found no difference in persistent bacteriuria or recurrence when comparing 2–4 days with 7–14 days of oral antibiotics.[25]

Oral fosfomycin has recently been registered for use in Australia as a single-dose treatment for uncomplicated urinary tract infections in females over the age of 12 years. However, this antibiotic should generally be reserved for resistant organisms.

Skin and soft tissue infections

There is a lack of systematic review data to guide short-course therapy for skin and soft tissue infection.

Incision and drainage is the primary therapeutic modality for soft tissue abscesses. A recently published systematic review found that for uncomplicated abscesses, adjunctive antibiotic therapy provides a modest benefit in terms of treatment success and prevention of recurrence,[26] but this needs to be balanced against an increased risk of adverse events. Antibiotic courses ranged from 3–14 days and no recommendation on duration was made.[26]

A randomised controlled trial conducted in the remote Australian setting showed that short-course oral trimethoprim/sulfamethoxazole for 3–5 days is effective for impetigo, and equivalent to intramuscular benzathine penicillin.[27]

Stopping antibiotics earlier than the intended standard duration

Since many common infections are spontaneously remitting, the use of antibiotics is often discretionary. Numerous opinions have been published in support of stopping antibiotics earlier.[28-30]

A practical approach in the community setting is to educate patients and advise them that it is safe to cease the antibiotics early if microbiological results exclude a bacterial cause for their symptoms (e.g. negative urine culture or viral acute respiratory infection), or the patient feels better for conditions where the benefit of antibiotics is small and the infection is not severe (e.g. acute respiratory infections).

Patients should be advised to return any remaining antibiotics to the pharmacy for safe disposal, rather than storing them (which risks future inappropriate use) or disposing of them in general household waste (which risks environmental contamination).

Conclusion

There is good evidence that shorter durations of antimicrobials can reduce adverse effects associated with their use. Furthermore, systematic reviews have found that clinical outcomes are similar between short and long courses for many common infections. Given Australia's relatively high rates of prescribing, we can all play a significant role in reducing the burden of inappropriate antimicrobial use by prescribing short-course therapy when appropriate and limiting prescriptions when they are not indicated. ◀

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ARTICLE

Prescribing for transgender patients

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gender dysphoria, gonadal steroid hormones, transgender persons

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SUMMARY

With greater awareness and social acceptance, increasing numbers of transgender individuals are presenting for gender-affirming hormone treatment. There should be a full psychosocial assessment by an experienced clinician before hormone treatment is considered.

People assigned as males at birth who transition to female gender are transgender females. Their management includes an estrogen plus an anti-androgen.

People assigned as females at birth who transition to male gender are transgender males. Their hormone treatment is testosterone.

Treatment is titrated so that hormone concentrations are equivalent to the physiological concentrations of the preferred gender. This aims to minimise adverse effects.

Introduction

Transgender individuals experience incongruity between their sense of gender and their assigned sex at birth. Psychological distress resulting from this incongruity is known as gender dysphoria.

Increasing numbers of transgender individuals are presenting for medical care, probably because of gradually increasing societal acceptance and awareness. Most individuals will have their care started by specialists in transgender health. General practitioners play a valuable role in providing support and managing comorbidities and may contribute to ongoing treatment and monitoring. Transgender people who are comfortable talking to their GP are likely to have better physical and mental health.

Background

No formal estimate of the Australian transgender population is available, but a recent study of high school students in New Zealand found they represented 1% of the population studied.[1] A typical presentation cannot be described, as the journey taken by each individual is highly variable. No specific age group or cultural or socioeconomic background has been associated with an increased likelihood of presentation.

Some transgender individuals elect not to undergo medical treatment, feeling that a change in gender role or expression is, of itself, sufficient. However, many require masculinising or feminising hormones and in some cases surgery to address the psychological distress of their gender dysphoria.

Many decades of experience with gender-affirming hormone treatment have been accumulated and several guidelines published.[2-5] Although prescribing remains off label, treatments are relatively straightforward and safe, resembling those used for postmenopausal women or hypogonadal men.

Treatment in adults

The World Professional Association for Transgender Health advises that medical treatment should only occur after a thorough psychosocial assessment has been undertaken by a clinician experienced in the field. Informed consent must be obtained from the patient.[2] Standard treatment in adults is based on a gender-affirming hormone. This is testosterone for female to male transition and estrogen, supplemented by an anti-androgen, for male to female transition.

Treatment of transwomen (male to female) produces variable changes including:

- breast growth
- softening of the skin
- reduction and fining of body hair
- change in body fat distribution
- reduced muscle mass and strength in the upper body
- emotional change
- decline in libido
- decreased spontaneous erections
- testicular shrinkage and cessation of spermatogenesis.

The effects of testosterone on transmen (female to male) are:

- deepening of the voice
- increased muscle mass and strength (particularly upper body)
- change in body fat distribution
- increased hair growth (body and face)
- increase in skin oiliness and body odour
- atrophy of breasts, vulval and vaginal tissues
- clitoral enlargement
- cessation of menstruation.

In both genders, changes begin to appear in the first few months of treatment and usually reach a maximum after three to five years. Starting treatment after puberty will reverse or regress many primary and secondary sexual characteristics, but obviously some will persist to the extent that reassignment surgery might also be sought by some individuals.

Transwomen

Estrogens in combination with an anti-androgen are the standard first-choice gender-affirming hormone treatments for transwomen.

Estrogen

Estradiol is preferred, as it most closely resembles the hormone produced by the ovaries. It is prescribed in a similar way to hormone replacement therapy for postmenopausal women, but with slightly higher doses. The dose of estradiol valerate tablets starts at 2–4 mg daily, increasing up to 8 mg. Tablets can be given in divided doses if nausea occurs at higher doses.

Patches or implants are preferred for transwomen over 40 years of age (although they can be used in younger people) to minimise the risk of venous thromboembolism. Treatment with patches starts with 100 microgram/24 hours titrated up to 400 micrograms. Implants of 50 and 100 mg are available from compounding pharmacies. Generally, 100 mg is inserted for most transwomen, but a supplementary 50 mg implant can be added for patients with a high body mass index. The duration of drug delivery with implants is on average 6–12 months. Estrogen concentrations should be monitored and a new implant inserted when they fall below physiological levels. Tachyphylaxis can develop with long-term implant use.

Ethinylestradiol and conjugated equine estrogens are generally avoided. They have an increased risk of venous thromboembolism and measurement of their blood concentrations is inaccurate.

Anti-androgens

Anti-androgens suppress the production and effect of endogenous androgens and so reduce masculine characteristics. In combination with estrogen they reduce the estrogen dose required to achieve feminising effects. The most commonly used anti-androgens are cyproterone and spironolactone.

Cyproterone is a synthetic progestogen with a potent anti-androgenic effect. The usual starting dose is 25–50 mg daily (but it can be started at 12.5 mg) and can then be increased to 100 mg daily. Rare cases of fulminant hepatotoxicity have been reported with cyproterone use for treatment of metastatic prostate cancer.

Spironolactone is a potassium-sparing diuretic which in higher doses directly inhibits testosterone production and blocks androgen receptors. The usual starting dose is 100 mg daily in one or two doses up to a maximum of 400 mg daily. Blood pressure and potassium concentrations need to be monitored. Possible adverse effects include polyuria, polydipsia and postural hypotension, particularly at higher doses. Hyperkalaemia is also possible, particularly in patients with impaired kidney function or taking potassium-retaining drugs such as ACE inhibitors.

Progesterone

Progesterone is used by some clinicians in addition to estrogens and anti-androgens. Anecdotal reports suggest that progesterone may improve breast development, but there are no well-designed studies of its use in transwomen. Potential adverse effects include depression, weight gain and an increase in lipids.

Transmen

Testosterone is used for masculinising effects for transmen. Menstruation typically ceases in the first 3–6 months of treatment. In cases where this is delayed or distress arises from menstruation, progesterone can be used.

Testosterone

Testosterone is available in a range of formulations, but injected testosterone is the standard first choice. Tablets are unsuitable for gender affirmation as they are unlikely to achieve physiological concentrations or supress menstruation.

Intramuscular injections

Testosterone enantate was, until recently, commonly used, however it is currently unavailable. It is given by intramuscular injection every 2–3 weeks. Suitable patients can be taught to self-inject. The starting dose is 125 mg titrated up to 250 mg with the aim of reaching male physiological concentrations. There

can be cyclical effects of aggression or an expansive mood at the start of the cycle and fatigue and irritability at the end.

Injections of testosterone undecanoate 1000 mg every 10–12 weeks produce similar cyclical effects but with less frequency. This formulation carries a risk of pulmonary microembolism, making it unsuitable for self-injection.

Gels and creams

Testosterone gels and creams are less commonly used, for reasons of practicality. Patients cannot bathe or swim for six hours following application and must avoid contaminating women and children by direct contact. However, for patients who wish to avoid injections or are bothered by their cyclical effects, topical testosterone is a good choice. The standard daily dose is one 50 mg/5 g sachet or 4 actuations of the pump (12.5 mg per actuation) rubbed into the skin of the upper body. Titrate up to 100 mg (2 sachets or 8 actuations). A testosterone cream is also available, with similar dosing. It comes with an applicator which has 0.5 mL gradations.

Patches

Although there is evidence that testosterone patches may eventually achieve similar masculinising effects as injectable formulations, they take a significantly longer time to reach physiological concentrations. For this reason, injectables or topical gels are preferred.

Monitoring

Hormone concentrations are monitored at three-monthly intervals after treatment begins, to assist with titrating the dose to achieve physiological concentrations for the preferred gender. This is based on a presumption that physiological concentrations will produce maximal effectiveness without undue harm. After the first year, monitoring can be reduced to 6–12-monthly.

In transwomen the target range is equivalent to mid-cycle estradiol concentrations of approximately 400–700 pmol/L.[3] Testosterone is also monitored in transwomen to ensure suppression to equivalent female concentrations. Some clinicians monitor prolactin concentrations, as a theoretical risk of prolactinoma exists with estrogen treatment.

In transmen, the target range for testosterone is 8–30 mmol/L. Full blood counts should be monitored in case of polycythaemia. The male, rather than female, haemoglobin reference range should be used.[6]

In both genders, blood pressure, weight, renal and liver function are also regularly monitored. Lipids and blood glucose should be monitored in patients with risk factors.

Transmen should continue to undergo cervical and breast screening as long as they still retain these tissues. Prostate cancer screening should also be discussed with transwomen.

Treatment in children

The treatment of young people is best undertaken by a multidisciplinary team specialised in the area. GPs play an important supporting role for the child and their family. The treatment varies according to the child's stage of puberty. No hormone therapy is required until children reach Tanner Stage 2.

Stage 1 (puberty suppression)

In stage 1 treatment is reversible. A gonadotrophin-releasing hormone analogue (GnRH) will pause the development of secondary sex characteristics. This allows time for the young person to attain cognitive ability and the maturity required to consider consent for stage 2. Should the child change their mind, stage 1 treatment can be discontinued. The default physiology will then resume the development of the characteristics of the child's sex at birth.

In transfemales the ideal time to commence puberty suppression is at the Tanner Stage 2 of puberty. Anti-androgens can be added to minimise male sexual characteristics if a GnRH analogue is started at a later stage of puberty.

In transmales the best results are achieved by starting a GnRH analogue at Tanner Stage 2–3. This will suppress menstruation if menarche has already occurred. However, if treatment begins after menarche, norethisterone will achieve the same results and is cheaper and less invasive than injecting a GnRH analogue.

For both genders, bone health requires attention during stage 1 treatment. Encourage calcium intake and weight-bearing exercise, and monitor bone density and vitamin D concentrations.

Stage 2 (gender-affirming)

Gender-affirming hormone treatment entails the introduction of either estrogen or testosterone to develop the secondary sex characteristics of the preferred gender and minimise those of the birth gender. The timing depends on the cognitive maturity of the adolescent and their ability to consent to the potentially irreversible effects of treatment. Assessment of this is complex, and requires the full cooperation of the adolescent, their family and treatment team. The potential impacts of treatment delay on the child's health and social functioning must also be considered.

Conclusion

Gender-affirming hormone therapy in transgender patients follows similar principles to the treatment of postmenopausal women and hypogonadal men. It is safe if monitored appropriately and delivered with attention to the holistic care of the patient. Specialist care is currently limited and mainly concentrated in metropolitan centres. A supportive GP with knowledge in this area is invaluable to the ongoing care of transgender patients. <

Conflict of interest: none declared

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ARTICLE

Nitrofurantoin and fosfomycin for resistant urinary tract infections: old drugs for emerging problems

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SUMMARY

Uncomplicated urinary tract infection is one of the most common indications for antibiotic use in the community. However, the Gram-negative organisms that can cause the infection are becoming more resistant to antibiotics.

Many multidrug resistant organisms retain susceptibility to two old antibiotics, nitrofurantoin and fosfomycin. Advantages over newer drugs include their high urinary concentrations and minimal toxicity.

Fosfomycin is a potential treatment option for patients with uncomplicated urinary tract infection due to resistant organisms. Nitrofurantoin may be more effective and can be used for urinary infections in pregnant women.

Introduction

Antimicrobial resistance is increasing worldwide, resulting in infections that are more difficult to treat and associated with higher mortality, morbidity and cost.[1-3] In Australia, multidrug resistant Gram-negative bacilli are responsible for a rising proportion of community-acquired uncomplicated urinary tract infections. Consequently, empiric therapy is more likely to fail. This has resulted in increasing numbers of patients with uncomplicated urinary tract infections requiring hospitalisation for intravenous antibiotics because there are no oral treatment options.

Limited Australian data are available for antimicrobial resistance rates in community-onset urinary tract infections.[4,5] One large national survey of urinary isolates from 2015 found resistance rates in *Escherichia coli* of 43% for ampicillin, 9% for amoxicillin with clavulanic acid, 16% for cefazolin, 22% for trimethoprim, and 7% for ciprofloxacin.[6] It is likely that resistance rates have continued to rise since then.

There are few new antibiotics on the horizon and those that have been recently approved are mostly for intravenous use, so older 'forgotten' drugs are being re-explored for the treatment of cystitis.[7-10] Nitrofurantoin and fosfomycin are old antibiotics. They share some important properties including high concentrations in the urinary tract, a minimal impact on gastrointestinal flora and a low propensity for resistance (Table).

Nitrofurantoin

Nitrofurantoin has been available since 1953, and in Australia since the 1970s. Its exact mechanism of action is not well understood and presumably multifactorial. Nitrofurantoin requires reduction by bacterial enzymes producing 'highly reactive electrophilic' metabolites. These then inhibit protein synthesis by interfering with bacterial ribosomal proteins.[11]

Nitrofurantoin has 80% oral bioavailability, and approximately 25% is excreted unchanged in the urine, with only a small portion reaching the colon.[12] Like fosfomycin, therapeutic concentrations are only reached in the urinary tract,[13] so the clinical use of nitrofurantoin is limited to the treatment of uncomplicated urinary tract infection in women. Administration with food results in higher urinary concentrations and fewer gastrointestinal adverse effects.

Antimicrobial activity

Nitrofurantoin is active against common causes of urinary tract infection including *E. coli*, *Citrobacter* and *Enterococcus*. *Klebsiella* and *Enterobacter* are less reliably susceptible. *Serratia*, *Acinetobacter*, *Morganella*, *Proteus* and *Pseudomonas* are usually resistant.[14] Overall, resistance to nitrofurantoin is uncommon and many multidrug resistant organisms retain susceptibility.[15-17] Australian data are limited, but studies suggest resistance rates in *E. coli* of 1–2%.[4,6]

Table **Features of nitrofurantoin and fosfomycin**

Characteristic	Nitrofurantoin	Fosfomycin
Year of discovery	1953	1969
Formulations	Nitrofurantoin macrocrystal 50 mg, 100 mg capsules Slow-release formulation not available in Australia Older microcrystal formulation less available now (more adverse effects)	Fosfomycin trometamol 3 g sachet containing granules to be dissolved in water Intravenous formulation available but for specialised use only
Pharmacokinetics	High urinary concentrations Serum concentrations negligible	Long half-life with high urinary concentrations Serum concentrations inadequate for treatment of systemic infection
Mechanism of action	Not well understood, multifactorial, inhibits ribosomal protein synthesis	Inhibits pyruvyl transferase and therefore cell wall synthesis
Spectrum of activity	Mostly susceptible: *E. coli*, *Enterococcus* Variably susceptible: *Klebsiella*, *Enterobacter*, *Citrobacter* and *Providencia* Typically resistant: *Proteus*, *Serratia*, *Acinetobacter*, *Morganella* and *Pseudomonas*	Mostly susceptible: *E. coli* Variably susceptible: *Klebsiella*, *Proteus*, *Citrobacter*, *Enterobacter*, *Pseudomonas* and *Enterococcus* Typically resistant: *Morganella* and *Acinetobacter*
Resistance	Uncommon	Uncommon
Indications	Uncomplicated urinary tract infection in women	Uncomplicated urinary tract infection in women
Dosing	50–100 mg 4 times a day for 5 days	Single 3 g oral dose
Adverse events	Infrequent, mainly gastrointestinal Rare reports of pulmonary or liver toxicity, peripheral neuropathy	Infrequent, mainly gastrointestinal (9% diarrhoea, 4% nausea)
Pregnancy and breastfeeding	Category A, although not recommended beyond 38 weeks gestation due to risk of haemolytic anaemia in neonates. For this reason it is also best to avoid during the first month of breastfeeding	Category B2, small amounts excreted in breast milk so not recommended in breastfeeding
Children	Avoid <1 month of age	Avoid <12 years of age
Interactions	Few significant drug interactions	Co-administration with metoclopramide can lower serum and urine concentrations
Renal impairment	Contraindicated if CrCl <30 mL/min Cautious use between CrCl 30–60 mL/min if benefits outweigh risks	Dose reduction required if CrCl <50 mL/min

CrCl creatinine clearance

Efficacy and safety

A meta-analysis of 27 older controlled trials (4807 patients) found clinical cure rates of 79–92%, similar to comparator antibiotics. Only mild toxicities (most commonly gastrointestinal) and no cases of pulmonary fibrosis or hepatotoxicity were reported.[18] Dosing recommendations for the standard formulation are 50–100 mg four times daily. There is a long-acting formulation available overseas, but not in Australia, which can be dosed twice daily. This slow-release formulation (100 mg three times daily) was used in a recent open-label comparison with fosfomycin. The cure rate was 70% in the nitrofurantoin group.[19]

Historically nitrofurantoin was thought to be contraindicated if the creatinine clearance was less than 60 mL/minute due to an increased risk of toxicity. However, recommendations have been changing to allow cautious, short-term use in patients with mild renal impairment (30–60 mL/min) if there are no alternative antibiotics.[20,21] Nitrofurantoin can be used to treat cystitis in pregnancy (although not beyond 38 weeks gestation due to the risk of haemolytic anaemia in the neonate).

Nitrofurantoin became a preferred drug in the international consensus guidelines for urinary tract infection in 2010.[22] These emphasised the lower rates of 'collateral damage' on gastrointestinal flora.[23-24]

It remains to be seen if resistance rates increase as a consequence of this recommendation and the subsequent rise in nitrofurantoin prescribing. The true incidence of major hepatic and pulmonary toxicity is unclear, but this appears to be more common with long-term use in the elderly.[14] For the short-term treatment of uncomplicated urinary tract infection in otherwise healthy young women, nitrofurantoin is a safe and effective choice, and overall efficacy and rates of adverse events appear similar to comparator antibiotics. In patients with infections due to multidrug resistant organisms and therefore few alternative treatment options, we recommend using 100 mg four times daily for five days, administered with food to optimise absorption and efficacy.

Fosfomycin

Fosfomycin was first isolated in Spain in 1969, and was introduced in Europe throughout the 1970s.[25] It is a small molecule from a unique drug class that acts by inhibiting pyruvyl transferase. This enzyme is responsible for synthesising the precursors of peptidoglycan, the key component of the bacterial cell wall. Uptake in the USA was initially limited due to problems with susceptibility testing, but this was standardised in 1983.

Fosfomycin trometamol, an oral formulation that can be taken as a single 3 g dose, was introduced in 1995. In many countries it is now a first-line treatment option for uncomplicated urinary tract infection in women.[22] This single-dose regimen is attractive due to better adherence and is generally well tolerated. While transient gastrointestinal disturbance can occur, serious adverse events are rare.[26]

In Australia, fosfomycin was only previously available via the Special Access Scheme. The Therapeutic Goods Administration has now approved it for acute uncomplicated lower urinary tract infection, in females more than 12 years of age, caused by susceptible organisms (Enterobacteriaceae including *E. coli*, and *Enterococcus faecalis*).

Antimicrobial activity

Susceptibility testing for fosfomycin is available, but can be complicated and is not necessarily routine in Australian microbiology laboratories. Fosfomycin is most active against *E. coli*, and minimum inhibitory concentrations are typically low.[27-29] Other urinary pathogens such as *Klebsiella*, *Proteus*, *Citrobacter*, *Enterobacter*, *Pseudomonas* and *Enterococcus* have variable susceptibility.[30-32] *Morganella morganii* and *Acinetobacter* are typically resistant.[28] Urinary concentrations following a single 3 g dose are generally sufficient to treat patients infected with susceptible organisms, although some recent data suggest more variability in urinary concentrations than previously thought.[33,34]

As fosfomycin has a unique structure there is minimal cross-resistance with other antibiotics. At present, many multidrug resistant isolates remain susceptible to fosfomycin, even in geographic regions where there has been widespread use of the drug.[35,36] No comprehensive studies examining fosfomycin susceptibility have been conducted in Australia.

While resistant subpopulations of bacteria may develop with fosfomycin exposure, resistant strains do not seem to easily survive in vivo.[32,37-40] However, there are multiple resistance mechanisms and there are reports of increasing resistance correlating with higher fosfomycin usage in Spain.[32,41-43] Plasmid-mediated resistance, which could disseminate more readily, has been described in Japan,[44] and among livestock[45] and pets[46] in China.

Efficacy and safety

Historically, the clinical efficacy of fosfomycin was thought to be similar to antibiotics such as trimethoprim, trimethoprim/sulfamethoxazole, fluoroquinolones, beta-lactams and nitrofurantoin, with reported cure rates of 75–90%.[47-51] However, methodological flaws in the older studies may have resulted in clinical efficacy being overestimated. A recent large randomised trial found a lower clinical cure rate with fosfomycin compared with nitrofurantoin (58% vs 70%, p=0.004).[19] While some recent observational studies have demonstrated fosfomycin efficacy in uncomplicated urinary tract infection caused by resistant organisms,[52-56] including non-inferiority to carbapenems,[57,58] there are reports of treatment failures particularly with *Klebsiella*.[59]

As low serum concentrations lead to treatment failures, fosfomycin is not appropriate for patients with bacteraemia or upper urinary tract infections such as pyelonephritis. Occasionally, longer courses have been used to treat complicated urinary tract infection, for example as completion therapy when there are no oral alternatives to intravenous antibiotics.[57] There is also an emerging role in prostatitis and perioperative prophylaxis for urological procedures in men.[60-62] Specialist infectious diseases input should be sought for these complex cases if off-label use or prolonged courses of therapy are being considered.

Fosfomycin is generally well tolerated, with adverse events rare and usually transient. Gastrointestinal events (9% diarrhoea, 4% nausea) have been most commonly reported with rare reports of other more serious problems.[26] Co-administration with metoclopramide can lower serum and urinary concentrations and should be avoided, but there are few other problematic drug

interactions. Fosfomycin is classified in pregnancy category B2. It is not recommended in breastfeeding as small amounts are excreted in breast milk. Given there are minimal data on use in children under 12 years of age, it is not advised for this group.

In Australia, we currently recommend reserving fosfomycin for the treatment of uncomplicated urinary tract infection in patients when the standard first-line drugs are not an option. Part of the rationale behind this is to minimise the emergence of resistance and prolong the usefulness of fosfomycin for patients without alternative options.[35] As resistance to other drugs inevitably rises and local experience increases, fosfomycin may become a first-line option in the future.

Antibiotic resistance

While re-exploring older 'forgotten' drugs like nitrofurantoin and fosfomycin is a useful strategy, it represents only part of the multifaceted response required to tackle the complex problem of antimicrobial resistance and 'preserve the miracle' of antimicrobials over the coming decades.[63] As we have seen historically with virtually all other antibiotics, resistance is likely to emerge as usage increases. It remains to be seen how long this will take, to what extent it will occur and whether it will be via dissemination of existing resistance mechanisms or evolution of new ones. The increasing failure of standard empirical therapy for urinary tract infection is foreseeable, and it is likely that more patients will require microbiological testing before starting antibiotics, not only for individualised patient management but also for broader epidemiological surveillance to inform guideline recommendations.

Consultation with an infectious diseases specialist can assist with the management of patients with multidrug resistant infections and leads to better outcomes.[64] Other important strategies include the development of new antimicrobial drugs, preserving those currently available by judicious use, implementation of comprehensive antimicrobial stewardship programs and stringent infection control practices worldwide to reduce the spread of resistant organisms.

Conclusion

Nitrofurantoin is suitable for uncomplicated lower urinary tract infections. Bacterial resistance is uncommon.

Fosfomycin is a safe and effective antibacterial drug for urinary tract infections, but its use should be limited to delay the development of resistance. It will prove to be a useful treatment option for community-based treatment of patients with resistant organisms. ◁

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ARTICLE

Prescribing for adolescents

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SUMMARY

The process of prescribing changes as children move into adulthood. For some medicines, such as psychotropic drugs, safety and efficacy are less well understood in adolescents.

As adolescents mature they attain the capacity to consent to their own medical treatment. An assessment of their competency will need to take into account the nature of the treatment being proposed.

Parental involvement is usually beneficial particularly for adolescents with chronic or complex conditions, but increasing adolescent autonomy needs to be respected.

Adherence to treatment can be supported by understanding adolescent development and involving adolescents in management plans.

Introduction

The challenges in prescribing for adolescents fall into four main categories:

- medicine safety and efficacy, taking into account the physiology of puberty
- the increasing autonomy of the adolescent patient
- conscious or unconscious clinician bias regarding young people
- concerns about adherence.

Prescribing decisions will involve clinical judgement, the adolescent's preferences, parent's or carer's wishes and the medicolegal framework.

Prescribing patterns for adolescent patients

Adolescents are defined by the World Health Organization as those aged 10–19 years. There are very little up-to-date data on prescription rates specifically for the adolescent population. An analysis of general practice surveillance data from 1998 to 2005 found the most frequently prescribed drugs in this age group were antibiotics for respiratory infections, antidepressants for anxiety or depression, and bronchodilators and corticosteroids for asthma.[1] Among 14–17-year-old females, contraception is the second most commonly managed problem. Less than two-thirds of contraceptive prescriptions in this age group are for contraception, with menstrual problems and acne accounting for the rest.[2]

Safety and efficacy

It is important not to view adolescents as 'mini adults' when it comes to prescribing, although in general, the more advanced an adolescent is in puberty, the more similar their body composition and organ functions are to adults. This makes pharmacokinetic considerations simpler than they are in children.[3] Nevertheless, physiological phenomena such as growth plate fusion and bone mass accrual which occur during puberty have implications for some prescribing decisions. For example, long-term use of depo-medroxyprogesterone is associated with osteoporosis, and long-term oral corticosteroids have the potential to affect growth. It is also important for clinicians who may have been prescribing drugs such as antiepileptics for adolescents when they were children to consider their sexual maturation and the possibility of pregnancy. Issues such as sexuality should be raised in a sensitive and confidential manner.

In younger adolescents whose peak growth velocity is still underway, paediatric dose calculations may be needed for some drugs, especially those with significant adverse effects. While several classes of drugs are safe to use in adult doses for adolescents aged 12 years and over, many have not been studied in this population, including psychotropic drugs.[4] Clinicians often prescribe medicines off label with decisions based on research from adults because of limited knowledge about dosing, efficacy and safety in adolescents.[5]

For antidepressants, current evidence shows a modest benefit for only one drug in this age group (fluoxetine).[6] There are also concerns about the risk of harm. Mild to moderate depression should be treated with non-pharmacological therapy. Decision making regarding psychotropic drugs requires careful consideration. A thorough assessment of mental health symptoms, a comprehensive biopsychosocial assessment,[7] and a risk and safety assessment are warranted. Drug therapy is more likely to be indicated

in moderate to severe depression or anxiety, in conjunction with non-pharmacological therapy,[6] and is a shared process with the adolescent (and parent or caregiver). Collaboration with others involved in care, such as a psychologist and school counsellor, is important, as well as considering the need for a psychiatric opinion.

Capacity to consent to medical treatment

Adolescents attain cognitive capacity for reasoning and abstract thinking that, under Australian law, can afford them the legal status of 'mature minor'. All jurisdictions in Australia allow for the Common Law test of 'Gillick competence' which recognises that an adolescent under the age of 18 may have the capacity to consent to medical treatment on their own behalf and without their parents' knowledge.[8] Additional legislation in South Australia and New South Wales grants adolescents aged 16 years and over (rather than 18 years) the right to consent to their own treatment as adults.[9]

An assessment of the adolescent's competency needs to be assessed in each case on a continual basis, and should consider the maturity of the adolescent as well as the nature and the complexity of the treatment. To be competent the adolescent should be able to understand:[7]

- what the treatment is for and why it is necessary
- any treatment options or alternatives
- what the treatment involves
- likely effects and possible adverse effects
- seriousness of the treatment
- consequences of not treating.

Options including the benefits and harms of treatment versus those of non-drug treatment should be discussed. Asking the adolescent to explain their own understanding of this can be helpful. It should be noted however that adults also have misunderstandings about medicines – this is not unique to adolescents. For example, a large household survey in the UK found substantial misinformation about antibiotics.[10] If unsure of an adolescent's capacity to consent, it is important to seek advice from a clinician with expertise in this area. In very complex cases a medical defence organisation may be able to provide advice.

Confidentiality

If adolescents ask for their parents not to be informed about their prescription, it is important to enquire about this wish. The concept of safety is understood by adolescents and is the basis for explaining exceptions to confidentiality. Discussing the adolescent's safety regarding drug treatment, as well as their health problem as the initial and primary concern, can be a useful way to encourage more openness with the parents. It can be revealing as well as practical to discuss with an adolescent what would happen if a family member were to discover their medicines. This can be a 'reality check' as well as an opportunity to anticipate reactions. Importantly, even though an adolescent may not want to involve a parent initially, this can change and it is important to maintain an ongoing dialogue about this. It is essential also that the adolescent understands confidentiality and its limits, and that if there are concerns about safety with risk to themselves, or others, there would be a need to inform their parent or caregiver.

If there are circumstances where an adolescent decides not to inform their parents, the context behind this should be explored and the reasons documented by the prescriber, as well as documenting having offered to speak with a parent.

The shifting power dynamics in the adolescent–parent–clinician triad is a challenge for many clinicians. Difficulties reported by GPs include, on the one hand, negotiating time alone with adolescents to facilitate engagement, while on the other hand, feeling that adolescents are not sufficiently responsible to manage their health alone.[11] What is unknown is whether clinicians change their prescribing behaviour as a result of these difficulties. For example, there is no published research that has explored prescribing decisions on the basis of parental presence or absence during consultations, whether parental consent is sought when prescribing for minors, and how often and for which drugs, or whether competency assessments are made.

Possible bias

There is also a dearth of information about the influence of conscious or unconscious bias towards young people in prescribing decisions, although interesting evidence is emerging in the area of contraception. A study among young Australian women (18–23 years) found that they perceived that doctors provided incomplete information about, and limited their options for, contraception because they were young.[12] A recent qualitative study involving young women (16–24 years) of culturally diverse backgrounds also suggested that clinicians may be selective about the contraception options they offer.[13] The uptake of long-acting reversible contraceptives has been slow among Australian women, despite them being recommended as first-line options for nulliparous

women in Australia, the USA and the UK.[14] This may be because Australian women and clinicians are unfamiliar with long-acting reversible contraceptives, compared to the combined oral contraceptive pill.[14] However, there is a need to understand whether clinicians are consciously 'gatekeeping' and if so what influences this. Young women have the right to be informed about the full range of contraception options.

Adherence

Adherence to treatment is another challenge when prescribing for adolescents, particularly for those with a chronic illness such as diabetes. Rather than make assumptions about non-adherence among adolescents, it is the role of clinicians to work with adolescents to optimise adherence just as they would with adults. Understanding adolescent brain development, and how this influences behaviour, risk-taking and decision making, can inform approaches to self-management.

In adolescence, peers have an impact on the processing of social information, resulting in a heightened sensitivity to peer attitudes. Adolescents are also more likely than adults to seek out situations that are arousing, exciting or stressful and they have greater difficulty than adults in overriding 'high emotions'.[15]

Understanding neurodevelopmental phenomena can help clinicians as well as the designers of programs intended to support adolescents with chronic illness as they transition from paediatric to adult care. Shared decision making is a goal in the management of chronic health conditions and enhances adherence, as do strategies such as motivational interviewing and pharmacist support.[16] As children move into adolescence, the process of shared decision making needs to be supported by clinicians in consultation with the patient and their parents or carers. Listening to the adolescent's concerns can identify previously unconsidered barriers that may be amenable to change, such as dosage regimens interfering with school timetables, or concerns about adverse effects based on (mis)information on the internet or among peers. After identifying these concerns, additional strategies may include:

- education – providing accurate information and repeating at regular intervals in a variety of formats, for example verbal, written information, websites, books
- organisational – simple dosing, once-daily, extended-release formulations, alarms on watches, reminders on phones
- behavioural and problem solving, for example pairing taking medicines with other well-established behaviours
- peer and family support
- motivational interviewing techniques.

Evaluation of adherence is important at regular intervals when the adolescent and family have an opportunity to ask questions and discuss any treatment-related concerns.[17]

Conclusion

Adolescents are a group who are in a dynamic process of acquiring autonomy in all areas of life, including health care and self-management. Clinicians play a vital role in supporting this process and engaging adolescents in a provider–patient relationship that can have a positive impact on their health. Challenges around medicine safety, medicolegal concerns, clinician awareness about treatment bias, navigating the shifting dynamics in the parent–patient–clinician relationship, and finding strategies for improving adherence and self-management can all be addressed by first understanding adolescent development. Assessing psychosocial as well as medical histories should be routine and helps to build an empathic and trusting relationship with adolescent patients. <

Conflict of interest: none declared

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ARTICLE

The hot patient: acute drug-induced hyperthermia

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SUMMARY

Drugs can cause dysregulation of the hypothalamic–pituitary–adrenal axis which can result in a rise in core temperature. This type of hyperthermia is unresponsive to antipyretics and can be complicated by rhabdomyolysis, multi-organ failure and disseminated intravascular coagulation.

Organic causes of fever such as infection must be ruled out. Syndromes associated with drug-induced fever include neuroleptic malignant syndrome and anticholinergic, sympathomimetic and serotonin toxicity.

The class of offending drugs, as well as the temporal relationship to starting or stopping them, assists in differentiating between neuroleptic malignant syndrome and serotonin toxicity.

Immediate inpatient management is needed. The mainstay of management is stopping the drug, and supportive care often in the intensive care unit.

Introduction

Drugs that alter the neurotransmitters noradrenaline (norepinephrine), dopamine and serotonin can affect thermoregulation by the hypothalamic–pituitary–adrenal axis.[1,2] In drug-induced hyperthermia the core temperature is at least 38.3 °C.[3] Hyperthermia can be complicated by peripheral factors such as increased heat production (e.g. with 3,4-methylenedioxymethamphetamine (MDMA/ecstasy) and other sympathomimetics) and decreased heat loss (e.g. with anticholinergic drugs). Excessive heat production can result in life-threatening complications such as rhabdomyolysis and secondary hyperkalaemia, metabolic acidosis, multi-organ failure and disseminated intravascular coagulation.[1]

The most commonly used drugs that affect thermoregulation include antipsychotic drugs, serotonergic drugs (especially when taken in combination), sympathomimetic drugs, anaesthetics and drugs with anticholinergic properties (Table 1).

Non-drug-induced causes of hyperthermia

There are numerous causes of complicated hyperthermia that are not due to drug exposure (Table 2). Non-drug causes should always be considered and excluded. Lethal catatonia (which can develop over weeks), central nervous system lesions or infections, and tetanus can all cause hyperthermia associated with muscle rigidity. The diagnosis is based on the history and clinical picture.

Thyrotoxicosis and phaeochromocytoma should be considered in the differential diagnosis of hyperthermia. However, they are rarely associated with muscle rigidity.

Table 1 **Drugs commonly known to cause hyperthermia and associated muscle rigidity**

Drug-induced syndrome	Associated drugs
Neuroleptic malignant syndrome	Antipsychotics (haloperidol, olanzapine), some antiemetics (metoclopramide), withdrawal of antiparkinson drugs
Serotonin toxicity	Serotonin reuptake inhibitors, monoamine oxidase inhibitors, dextrometorphan, tramadol, tapentadol, linezolid, St John's wort (toxicity most often occurs when the drugs are used in combination)
Anticholinergic toxicity	Antispasmodics, anticholinergic drugs, plant alkaloids (such as belladonna, *Brugmansia*) and mushrooms (e.g. *Amanita*)
Sympathomimetic syndrome	Phenthylamines, e.g. amphetamines, methamphetamines (MDMA), cocaine, monoamine oxidase inhibitors
Malignant hyperthermia	Volatile anaesthetics and depolarising muscle relaxants, e.g. suxamethonium
Uncoupling of oxidative phosphorylation	Salicylates in overdose, dinitrophenol

Table 2 **Non-drug causes of hyperthermia and muscle rigidity**

Non-drug-induced causes	Associated features
Severe catatonia	Severe rigidity accompanied by psychosis, severe affective disorder, stupor
Heat stroke	Extreme dehydration, exercise or stress in hot, humid environments particularly in patients taking diuretics
Central nervous system infection	General malaise, neurological deterioration, meningeal irritation
Tetanus	Trismus, muscle spasm starting from the neck down, profuse sweating, spasticity intensified by stimuli
Thyrotoxicosis	Tachycardia, tremor and hypertension
Phaeochromocytoma	Tachycardia, hypertension and tremor, diaphoresis, agitation

Drug-induced hyperthermia and hypermetabolic state

Differentiating the conditions associated with drug-induced hyperthermia can be difficult, however the time course of symptom development can assist in diagnosis (Table 3). The drug history is vital.

Neuroleptic malignant syndrome

Neuroleptic malignant syndrome can be a life-threatening idiosyncratic reaction to therapeutic doses of all antipsychotics. The risk is thought to be higher with high-potency antipsychotics (e.g. haloperidol). Neuroleptic malignant syndrome can also be caused by dopamine antagonists (e.g. domperidone) or the sudden withdrawal of dopaminergic drugs (e.g. bromocriptine, levodopa). Men are affected twice as often as women.[4] It is characterised by:

- autonomic instability (systolic blood pressure changes ≥30 mmHg and heart rate changes ≥30 beats/min within the first 24 hours)
- hyperthermia (without another cause, although hypothermic variants have been described)
- encephalopathy (which can range from mild delirium to coma)
- extrapyramidal syndrome (there can be cog-wheel rigidity, or lead-pipe rigidity where the same level of muscle resistance is felt in all directions).

Along with the time course of onset, the presence of diaphoresis, rigors, fever, tremor, in combination with laboratory evidence of muscle injury (elevated creatinine kinase) and leucocytosis, can help distinguish neuroleptic malignant syndrome from other drug toxicities.[5,6]

Neuroleptic malignant syndrome can emerge any time from starting the drug to many years later. Symptoms develop gradually over a period of days and can take a similar time to resolve.

Risk factors include dehydration, agitation, exhaustion, escalation of an antipsychotic dose and previous episodes of neuroleptic malignant syndrome. Organic brain injury and polypharmacy with other psychotropic drugs have also been identified as risk factors.

Morbidity and mortality result from secondary medical complications. These include sepsis, aspiration pneumonia, pulmonary embolism, myoglobinuric renal failure secondary to rhabdomyolysis,[7] metabolic acidosis and electrolyte abnormalities including hyperkalaemia and hypo- or hypernatraemia.

Serotonin toxicity

Symptoms of serotonin toxicity (or serotonin syndrome) can range from mild to severe. The onset of toxicity is normally rapid and apparent within six hours of taking serotonergic drugs. The extent of symptoms relates directly to synaptic serotonin concentrations. Toxicity is usually not severe following an overdose of a single serotonergic drug, but is more serious with a combination of serotonergic drugs. Combinations of a single tablet of monoaminoxidase inhibitor with a serotonin reuptake inhibitor are potentially fatal.[8]

Severe serotonin toxicity is a medical emergency and is characterised by a triad of:

- neuromuscular excitation (manifesting as ankle and/or ocular clonus, hyperreflexia, myoclonus and rigidity)
- autonomic excitation (tachycardia, hyperthermia)
- altered mental state (e.g. agitation, confusion).[9]

The presence of clonus helps in differentiating serotonin toxicity from sympathomimetic or anticholinergic toxicity or neuroleptic malignant syndrome. The Hunter Serotonin Toxicity Criteria can be used to predict cases likely to progress to severe toxicity and guide treatment.[10]

Other non-serotonergic drugs such as some opioids (e.g. tramadol) or over-the-counter medicines such

Table 3 **Clinical features of neuroleptic malignant syndrome, serotonin toxicity, anticholinergic syndrome and sympathomimetic syndrome**

	Neuroleptic malignant syndrome	Serotonin toxicity *	Anticholinergic toxicity	Sympathomimetic syndrome
Onset	Slow (1–3 days)	Rapid (minutes–hours)	Rapid	Rapid
Autonomic system: †				
Instability	♦♦♦	♦	–	–
Hypertension	Labile (SBP >30 mmHg above baseline)	♦	♦♦	♦♦
Tachycardia	Labile (>30 bpm above baseline)	♦♦♦	♦♦	♦♦♦
Diaphoresis	♦♦♦	♦♦	–	♦♦
Hyperthermia	♦♦♦	♦♦	♦♦♦ ‡	♦♦
Mental state:				
Confusion	♦♦♦	♦ (late stage)	♦♦♦	♦
Agitation/restlessness	Akathisia	♦♦♦	♦♦♦	♦♦♦
Coma	♦♦	–	♦	–
Motor system:				
Bradykinesia	♦♦	–	–	–
Tremor	♦	♦♦♦	–	♦♦♦
Rigidity	♦♦	♦	–	–
Hypertonia	–	♦♦	♦	–
Hyperreflexia	–	♦♦♦	♦	♦♦♦
Clonus (ankle/eye)	–	♦♦♦ (lower limb more than upper limb)	–	♦
Myoclonus	–	♦	–	–
Seizures	–	♦ (rare)	–	♦♦
Others:				
Rhabdomyolysis	♦♦♦	♦♦	–	♦♦
Mydriasis	–	♦♦♦	♦♦	♦♦

– No effect
♦ mild
♦♦ moderate
♦♦♦ severe
SBP systolic blood pressure

* Mechanism is excess serotonin.
† These features are non-specific and do not assist in differentiation between syndromes.
‡ Mechanism is inability to sweat and unopposed dopamine centrally leading to dysregulation.
bpm beats per minute

as St John's wort can precipitate serotonin toxicity (Table 1). A thorough history is imperative to identify contributing drugs that may have been stopped weeks earlier but have a long half-life (e.g. fluoxetine).

Anticholinergic toxicity

Anticholinergic toxicity occurs either as a result of antagonism at the muscarinic receptors or a reduction in cholinergic transmission. Toxicity can be caused by eating plants containing atropine-like alkaloids. It is also associated with multiple classes of drugs, such as antiparkinson drugs and tricyclic antidepressants, both in acute overdose or chronic use. The result is central and peripheral clinical effects that are a consequence of the relative cholinergic deficiency at the muscarinic receptors.[11]

The most commonly observed peripheral effects include dry mucous membranes, tachycardia, urinary retention, blurred vision and reduced gastrointestinal motility (ileus). Fever may result from decreased heat loss (due to the absence of sweating), increased heat production (due to agitation and activity) and central nervous system temperature dysregulation.[12] Central symptoms are predominantly agitation, confusion and hallucinations.

Sympathomimetic syndrome

Psychostimulants such as methamphetamines cause an increase in the effects of the neurotransmitters nor/adrenaline (nor/epinephrine), dopamine and serotonin by increasing their release or blocking their reuptake (such as methylphenidate).[13] Toxicity results from an excess of these catecholamines.

Patients may present with agitation, repetitive movements, akathisia, delirium, pressured speech, hypertension, tachycardia and hyperthermia. Additional sympathomimetic features include mydriasis, diaphoresis and neuropsychiatric manifestations such as paranoid psychosis. Complications can damage almost all organ systems. For example, they may involve the cardiovascular, central nervous and gastrointestinal systems (causing myocardial vasospasm, seizures and mesenteric ischaemia).

The degree of monoamine release is substance specific so presentations can be variable. For example, amphetamines release a greater degree of noradrenaline (norepinephrine) compared to MDMA/ecstasy which causes a greater increase in serotonin and therefore carries a greater risk of serotonin toxicity.

Hyperthermia results from central dysregulation, as well as increased heat production from increased physical activity. It is exacerbated by stimulation of peripheral alpha-adrenergic receptors and impaired vasodilation. Rhabdomyolysis is thought to be multifactorial and related to possible overuse of skeletal muscles as a result of excited delirium or repetitive behaviours as well as extreme vasoconstriction.[14]

Management

In all cases of drug-induced hyperthermia with associated rigidity, the principal management is prompt discontinuation of the offending drug and supportive management of the symptoms in hospital. Specifically, this includes active cooling in intensive care, correction of electrolyte abnormalities, intravenous fluids, early thromboprophylaxis and monitoring for aspiration. Muscle rigidity and agitation are responsive in most cases to judicious use of benzodiazepines. Antipyretics have no therapeutic benefit in drug-induced hyperthermia, as the central controlling mechanisms for temperature are not functioning normally.[15]

In the case of neuroleptic malignant syndrome, pharmacotherapy is reserved for complicated cases with moderate rigidity and hyperthermia. The dopamine agonist, bromocriptine, has been reported to be useful in case reports. Dantrolene should be considered in extreme cases of hyperthermia and muscle rigidity. Patients should be monitored for its adverse effects of hepatitis and respiratory impairment.[5,16] A cautious reintroduction of an alternative antipsychotic can be considered after two weeks, once symptoms have completely resolved. However, recurrence has been reported in up to a third of cases of neuroleptic malignant syndrome.[17,18]

Serotonin toxicity is managed largely supportively, as most symptoms subside based on the half-life of the offending drugs. Symptoms therefore usually resolve within 24–72 hours of stopping the drug. In severe cases of toxicity, management consists of sedation (with benzodiazepines), paralysis and intubation to reduce muscle activity, and adequate cooling. These measures need to be started before the patient deteriorates. Chlorpromazine and cyproheptadine (serotonin ($5HT_{2a}$) antagonist) are recommended in moderate to severe cases of toxicity.[9]

Moderate to severe anticholinergic toxicity may require pharmacological intervention based on the persisting symptoms. The reversal of toxicity can be achieved by increasing acetylcholine concentrations with physostigmine. This requires specialist advice from a toxicologist and has the adverse effects of bradycardia and potential seizures. Droperidol can be used for severe agitated delirium.

Conclusion

Drug-induced hyperthermia and rigidity can be a medical emergency and usually requires hospital admission. The clinical assessment and differential diagnosis should always rule out other causes. Stop the offending drug and give supportive care. Severe cases may require adjunctive pharmacotherapy. Specialist toxicological support will be required in most cases. ≺

Nazila Jamshidi was the editorial registrar for Australian Prescriber *in 2018.*

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New drugs

Alirocumab

Approved indication: hypercholesterolaemia

Praluent (Sanofi-Aventis)
pre-filled syringes containing 75 mg/mL and 150 mg/mL
Australian Medicines Handbook section 6.5, Drugs for dyslipidaemia

Following evolocumab, alirocumab is the second inhibitor of proprotein convertase subtilisin/kexin type 9 (PCSK9) to be approved in Australia.[1] Like evolocumab, alirocumab is a monoclonal antibody that binds to PCSK9. This leads to an increase in the number of low-density lipoprotein (LDL) receptors, enabling them to remove more LDL cholesterol from the circulation.[2,3] Alirocumab can therefore have a role in patients with hypercholesterolaemia that is not controlled by statins, or those who cannot tolerate statins.

Alirocumab is injected subcutaneously every two weeks or once a month. The maximum serum concentration is not reached until 3–7 days after injection. The median half-life of the antibody is 17–20 days, but this is reduced to 12 days if the patient is taking a statin. No data are available for patients with severe hepatic or renal disease, or in pregnancy and lactation.

Heterozygous familial hypercholesterolaemia

Patients with heterozygous familial hypercholesterolaemia have very high concentrations of LDL cholesterol. The placebo-controlled ODYSSEY FH I and II trials studied 735 patients whose LDL cholesterol was elevated despite treatment with high-dose statins. The 490 patients allocated to alirocumab injected 75 mg twice weekly, increasing to 150 mg if the LDL-cholesterol concentration remained elevated after eight weeks. In the FH I trial the mean cholesterol concentration after 24 weeks had fallen from 3.7 mmol/L to 1.8 mmol/L with alirocumab, but rose to 4 mmol/L with placebo. In FH II the reduction was from 3.5 mmol/L to 1.8 mmol/L with no change in the placebo group.[4]

Hypercholesterolaemia

Alirocumab has been studied in patients with a high risk of cardiovascular events who had hypercholesterolaemia despite statin therapy. It has been compared with placebo and ezetimibe.

Placebo-controlled trials

One trial, ODYSSEY COMBO I, recruited patients who were taking maximally tolerated doses of statins. It randomised 209 patients to inject alirocumab and 107 to inject placebo every two weeks. After 24 weeks the mean concentration of LDL cholesterol had fallen from 2.6 mmol/L to 1.3 mmol/L with alirocumab, but only from 2.7 mmol/L to 2.6 mmol/L in the placebo group.[5]

The ODYSSEY LONG TERM trial randomised 1553 patients taking high doses of statins to inject alirocumab and 788 to inject a placebo. After 24 weeks the LDL cholesterol fell from 3.17 mmol/L to 1.25 mmol/L compared with a fall from 3.15 mmol/L to 3.08 mmol/L with placebo. The trial continued for 78 weeks. At that time the mean LDL-cholesterol concentration was 1.5 mmol/L in the alirocumab group and 3.17 mmol/L in the placebo group.[6]

The feasibility of giving alirocumab every four weeks was studied in the ODYSSEY CHOICE 1 trial. This enrolled patients with hypercholesterolaemia who had a moderate to very high risk of cardiovascular disease. There were 458 patients randomised to inject alirocumab 300 mg every four weeks, 115 to inject 75 mg every two weeks and 230 patients had injections of placebo every two weeks. Most of these patients were already taking statins. By 24 weeks the four-weekly injections had reduced LDL cholesterol by 58.8% in patients taking statins and by 52.7% in patients not taking statins. The corresponding reductions with two-weekly injections were 51.6% and 50.2%, while there was almost no change in the placebo group.[7]

Trials with ezetimibe

The ODYSSEY MONO trial studied 103 patients with a 10-year risk of cardiovascular death of 1–5%. They were not taking statins. At the start of the trial the concentration of LDL cholesterol was approximately 3.6 mmol/L in both groups. After 24 weeks this was reduced by 47% with alirocumab and by 16% with ezetimibe.[8]

The ODYSSEY COMBO II trial enrolled patients with a high cardiovascular risk who had hypercholesterolaemia that was not controlled by maximally tolerated doses of statins. They continued this treatment, but 479 added alirocumab and 241 added ezetimibe. After 24 weeks the concentrations of LDL cholesterol had fallen from 2.8 mmol/L to 1.3 mmol/L with alirocumab and from 2.7 mmol/L

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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.

to 2.1 mmol/L with ezetimibe. At 52 weeks LDL cholesterol was 1.4 mmol/L in the alirocumab group and 2.2 mmol/L in the ezetimibe group.[9]

The ODYSSEY OPTIONS I trial compared alirocumab with ezetimibe and increased statin treatment. It involved 355 patients with a 10-year risk of cardiovascular death of at least 5%. These patients started a daily baseline regimen of atorvastatin 20 mg or 40 mg. They then added alirocumab or ezetimibe or doubled their statin dose. Patients taking atorvastatin 40 mg daily could also be randomised to switch to rosuvastatin 40 mg daily. After 24 weeks, the LDL-cholesterol concentration had fallen by 44.1% in patients taking alirocumab with atorvastatin 20 mg and by 54% in those taking it with atorvastatin 40 mg. The corresponding figures for added ezetimibe were 20.5% and 22.6%. Doubling the atorvastatin dose only reduced LDL cholesterol by about 5%, but it fell by 21.4% in patients switched to rosuvastatin 40 mg.[10]

To compare treatment options for patients with statin intolerance, the ODYSSEY ALTERNATIVE trial randomised 126 patients to take alirocumab, 125 to take ezetimibe and 63 to take atorvastatin 20 mg in a rechallenge group. Their mean baseline LDL cholesterol was approximately 5 mmol/L. After 24 weeks this had reduced by 45% with alirocumab and by 14.6% with ezetimibe.[11]

Safety

In the clinical trials 5–9% of patients stopped alirocumab because of a treatment-related adverse event. The most common adverse events with alirocumab were upper respiratory tract symptoms, pruritus and injection-site reactions. Although 6.1% of patients had injection-site reactions, only 0.2% stopped treatment because of them. Some patients will have hypersensitivity reactions and 4.8% will develop antibodies against alirocumab. Alirocumab had more musculoskeletal adverse effects than placebo. In the ODYSSEY ALTERNATIVE trial 15.9% of the patients taking alirocumab stopped treatment because of these effects. This was less than the 22.2% of the control group who stopped treatment when rechallenged with atorvastatin, but the difference was not statistically significant.[11] A small proportion of patients experienced confusion or memory impairment so there will be a need for neurocognitive adverse effects to be monitored after marketing. Similarly, alirocumab may have ophthalmological adverse effects in a small number of patients.

Discussion

The clinical trials show that alirocumab significantly reduces LDL cholesterol in a variety of patients. The percentage reductions are larger than with oral ezetimibe (see Table). However, patients who have high LDL-cholesterol despite taking a statin may prefer a daily tablet to an injection. If an injectable treatment is preferred then it is a choice between alirocumab and evolocumab. There is evidence that alirocumab 300 mg monthly has similar efficacy to 75 mg every two weeks. However, there were more injection-site reactions when alirocumab was given monthly.[7,12] For most patients in the trials LDL cholesterol was reduced by using 75 mg every two weeks, but the dose can be increased

Table **Examples of alirocumab efficacy**

Patient group	Trial	Percentage change in LDL cholesterol at 24 weeks (%)		
		Alirocumab	Ezetimibe	Placebo
Heterozygous familial hypercholesterolaemia (n=486)	ODYSSEY FH I[4]	−48.8	–	9.1
Heterozygous familial hypercholesterolaemia (n=249)	ODYSSEY FH II[4]	−48.7	–	2.8
Patients at increased cardiovascular risk not taking statins (n=103)	ODYSSEY MONO[8]	−47	−16	–
Patients at increased cardiovascular risk intolerant of statins (n=314 including atorvastatin control group)	ODYSSEY ALTERNATIVE[11]	−45	−14.6	–
Patients at increased cardiovascular risk on maximally tolerated statin dose (n=314)	ODYSSEY COMBO I[5]	−48.2	–	−2.3
Patients at increased cardiovascular risk on maximally tolerated statin dose (n=720)	ODYSSEY COMBO II[9]	−50.6	−20.7	–
Patients at increased cardiovascular risk on maximally tolerated statin dose (n=2341)	ODYSSEY LONG TERM[6]	−61.0	–	0.8

n number of randomised patients

to 150 mg if needed. At present there is not an option to increase the dose of evolocumab for primary hypercholesterolaemia. A systematic review concluded that for patients with a high cardiovascular risk who have high concentrations of LDL cholesterol despite statin therapy there is stronger evidence for alirocumab than for evolocumab.[13] However, cholesterol concentrations are a surrogate outcome and the effect of alirocumab on cardiovascular outcomes is not yet known. The long-term adverse effects of what could be a lifelong treatment are also unknown.

TT manufacturer provided additional useful information

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NEW DRUGS

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Apalutamide

Approved indication: prostate cancer

Erlyand (Janssen-Cilag)
60 mg film-coated tablets
Australian Medicines Handbook section 14.3.1, Anti-androgens

Apalutamide has been approved in Australia for non-metastatic, castration-resistant prostate cancer. It is an oral anti-androgen which binds to the androgen receptor, reducing cell proliferation and increasing apoptosis.

The approval of this drug is mainly based on a placebo-controlled phase 3 trial (SPARTAN) in 1207 men who had prostate cancer with a high risk of developing metastatic disease.[1] This was defined as a prostate-specific antigen (PSA) doubling time of 10 months or less while they were receiving androgen-deprivation therapy. Metastatic disease was ruled out with imaging before randomisation. The men were randomised to receive apalutamide (240 mg a day) or placebo in a 2:1 ratio. They also continued androgen-deprivation therapy.

The primary end point of the study was metastasis-free survival. This was defined as the time from randomisation to first detection of a distant metastasis on imaging, or death from any cause. Median metastasis-free survival was significantly longer with apalutamide compared to placebo (40.5 vs 16.2 months). Median progression-free survival was also significantly longer. At the final analysis, median overall survival had not been reached with apalutamide.[1]

Serious adverse events (grades 3–4) were more common with apalutamide than with placebo – the most frequently reported were hypertension (14.3 vs 11.8%), rash (5.2 vs 0.3%), fracture (2.7 vs 0.8%), falls (1.7 vs 0.8%), diarrhoea (1 vs 0.5%), fatigue (0.9 vs 0.3%) and weight loss (1 vs 0.3%).[1] Although not serious, hypothyroidism was much more common with apalutamide than with placebo (8.1 vs 2%) and was considered to be related to treatment.[1] Dysgeusia, pruritus, depression, heart failure and ischaemic heart disease were also more frequent with apalutamide and three patients died of myocardial infarction. Treatment had to be stopped because of an adverse event in 11% of men receiving apalutamide and 7% of men receiving placebo. About a third of the discontinuations with apalutamide were due to a rash.

There is evidence that apalutamide prolongs the QT interval so prescribers should consider an electrocardiogram and electrolyte monitoring in patients with a history of QT prolongation or who are taking other drugs that prolong the QT interval.

Two patients taking apalutamide had a seizure even though people with a predisposition to seizures were excluded from the study. Patients should be warned of this risk and apalutamide should be permanently discontinued if seizure occurs.

People on prolonged androgen-deprivation therapy have an increased risk of osteopenia and osteoporosis. As apalutamide adds to this risk, patients should be monitored for fall and fracture risk and treated if necessary.

The recommended dose of apalutamide is 240 mg taken once a day. Tablets should be swallowed whole (with or without food). Dose adjustment is not required in patients with mild or moderate hepatic or renal insufficiency (eGFR ≤29 mL/1.73 m^2). However, there is no experience of the drug in those with severe impairment.

Following administration, maximum plasma concentrations are reached within 1–5 hours. Oral bioavailability is 100% and the drug is excreted in the urine (65%) and faeces (24%). Apalutamide is metabolised by cytochrome P450 (CYP) 2C8 and 3A4 so concomitant use of strong inhibitors of these enzymes (e.g. gemfibrozil, clarithromycin) may increase apalutamide exposure. Apalutamide is a strong inducer of CYP3A4 and 2C19 and a weak inducer of CYP2C9 so it may decrease the efficacy of substrates of these enzymes such as midazolam, omeprazole and warfarin respectively. It also weakly induces P-glycoprotein, breast cancer resistance protein (BCRP) and organic anion transporting polypeptide 1B1 (OATP1B1).

Apalutamide provides a new treatment option for men with castration-resistant prostate cancer who have not yet started chemotherapy. It prolongs metastatic-free survival by a median of two years when added to androgen-deprivation therapy. However, treatment comes with some serious adverse effects and numerous potential drug interactions.

T T manufacturer provided additional useful information

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FURTHER READING

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NEW DRUGS

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Baricitinib

Approved indication: rheumatoid arthritis

Olumiant (Eli Lilly)
2 mg, 4 mg film-coated tablets
Australian Medicines Handbook section 15.1.2, Immunosuppressants

Methotrexate is the drug of choice for most patients with rheumatoid arthritis. However, in some patients, other drugs may be needed to control the disease. There is now a range of options, such as tumour necrosis factor (TNF)-alpha antagonists (e.g. adalimumab) and Janus kinase (JAK) inhibitors (e.g. tofacitinib).[1,2] Baricitinib is another JAK inhibitor that selectively inhibits the enzymes JAK1 and JAK2. As these enzymes are involved in the production of cytokines, inhibiting them has anti-inflammatory effects.[1]

The film-coated tablets are well absorbed. Although there is some metabolism by cytochrome P450 3A4, most of the drug is excreted unchanged in the urine. The half-life is 12.5 hours. Baricitinib is not recommended for patients with severe hepatic or renal impairment (glomerular filtration rate <30 mL/min/1.73 m^2). There are not thought to be any clinically significant pharmacokinetic drug interactions.

A phase II placebo-controlled trial studied baricitinib in daily doses of 1 mg, 2 mg, 4 mg or 8 mg. The 301 patients in this trial had moderate to severe rheumatoid arthritis despite treatment with methotrexate. The primary outcome of the study was the proportion of patients in the 4 mg and 8 mg groups who achieved a 20% response, on the American College of Rheumatology Index (ACR20), after 12 weeks of treatment. This outcome was achieved by 76% of the patients taking baricitinib and 41% of those taking placebo. The benefits of baricitinib were maintained after a further 12 weeks of treatment.[3]

The phase III RA-BEGIN trial studied baricitinib in patients who had not previously been treated with disease-modifying antirheumatic drugs (DMARDs). The 584 patients were randomised to take baricitinib 4 mg once daily, methotrexate weekly, or both drugs. When efficacy was assessed after 24 weeks of treatment, the response to baricitinib monotherapy was statistically superior to methotrexate. In the baricitinib group, 77% of the patients had an ACR20 response versus 62% in the methotrexate group. Combining the two drugs did not improve the response rate more than baricitinib alone. The response was maintained in patients who continued treatment for a total of 52 weeks.[4]

The RA-BUILD trial involved 684 patients who were intolerant of, or had an inadequate response to, at least one DMARD. They were randomised to receive baricitinib 2 mg, baricitinib 4 mg or a placebo for 24 weeks. When efficacy was evaluated after 12 weeks, an ACR20 response had been achieved by 66% of the patients taking 2 mg and 62% of those taking baricitinib 4 mg. These responses were significantly greater than the 39% seen in the placebo group. This advantage was sustained over the next 12 weeks of the trial. After 24 weeks there was radiological evidence of less disease progression in patients taking baricitinib.[5]

The option of using baricitinib instead of adalimumab to treat patients who have had an inadequate response to methotrexate was assessed in the RA-BEAM trial. A total of 1307 patients were randomised to take baricitinib 4 mg daily, adalimumab injections every two weeks, or a placebo. After 24 weeks the patients taking placebo were switched to baricitinib. Efficacy was assessed after 12 weeks, at which time there was an ACR20 response in 70% of the baricitinib group. This was statistically superior to the 61% who responded to adalimumab and the 40% response to placebo. After 52 weeks the ACR20 responses were 71% with baricitinib and 62% with adalimumab. Both drugs reduced radiological progression more than placebo.[6]

The RA-BEACON trial studied 527 patients who had discontinued treatment with, or had been unable to tolerate, TNF antagonists, other biological DMARDs or both. They were randomised to either add baricitinib (2 mg or 4 mg) or a placebo. After 12 weeks 55% of the baricitinib groups had an ACR20 response versus 27% of the placebo group. This advantage was still present after another 12 weeks of treatment. The difference between baricitinib 2 mg and placebo was not significant at 24 weeks for symptoms such as joint swelling and tenderness.[7]

Drugs that modulate the immune system are associated with an increased risk of infections. Patients should be screened for tuberculosis and viral hepatitis before treatment. Reactivation of herpes virus can lead to disseminated herpes zoster. Over 52 weeks, infections were more frequent with baricitinib than with adalimumab (48 vs 44%).[6] There is a possibility that the risk of malignancy could be increased. Baricitinib may also be associated with deep vein thrombosis.

Full blood counts, liver enzymes and lipids should be monitored during treatment. This is because patients can develop anaemia, neutropenia, liver injury and elevated lipids, and treatment may need to be suspended.

Baricitinib is approved for use in patients with moderate to severe arthritis who have had an inadequate response to other treatments. However, it can also be used earlier in treatment if the patient cannot tolerate other drugs. Although the recommended dose is 4 mg daily, a 2 mg dose may help some patients. It is not clear how baricitinib and tofacitinib compare. Tofacitinib appears to cause a reduction in lymphocyte counts more often than baricitinib.

Some of the patients in the clinical trials have continued in an extension study (RA-BEYOND). This should provide more information on the long-term safety and efficacy of baricitinib.

T T manufacturer provided additional useful information

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

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NEW DRUGS

Migalastat

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Approved indication: Fabry disease

Galafold (Amicus)
123 mg capsules
Australian Medicines Handbook Appendix A

Fabry disease is one of the lysosomal storage disorders. Many X-linked mutations can cause a deficiency of the enzyme alpha-galactosidase A. This results in an accumulation of its substrates such as globotriaosylceramide (GL–3). A build-up of these substrates, particularly in the vascular endothelium, leads to damage in the heart, kidneys and nervous system. Death occurs mainly because of renal failure and cardiac or cerebrovascular complications. Enzyme replacement therapy, with infusions of agalsidase, has been available for several years.

Although alpha-galactosidase A is mutated, it may still retain some enzyme activity. Migalastat works by binding to the active site of the defective enzyme. This stabilises the enzyme enabling it to enter the lysosome. Once inside the lysosome migalastat dissociates from the enzyme allowing alpha-galactosidase A to catabolise the accumulated substrate.

Migalastat should not be taken within two hours of a meal as food reduces absorption by 40%. Most of the dose is excreted unchanged in the urine with a half-life of 3–5 hours. Renal impairment will increase drug exposure so migalastat is not recommended if the glomerular filtration rate is below 30 mL/min/1.73 m^2.

Migalastat has been compared to placebo in adults with Fabry disease. Only 22% had been treated (more than six months previously) with enzyme replacement therapy. In the double-blind trial 28 patients took oral migalastat every other day and 22 took placebo. They had kidney biopsies at baseline and at six months. After six months 41% of the migalastat group had a reduction of at least 50% in the number of GL-3 inclusions in the interstitial capillaries of the kidney. This response was seen in 28% of the placebo group. The median reduction in GL-3 from baseline was 40.8% with migalastat and 5.6% with placebo.[1]

Statistical analysis showed that, overall, migalastat was no different from placebo. The drug was more effective in some mutations than others, so if the results are analysed according to the mutation there is an advantage for migalastat. Post hoc analysis of 45 patients with suitable mutations taking migalastat showed a significant reduction in GL-3 inclusions in renal interstitial capillaries at six months. However, there were no significant differences in glomerular filtration rates at six months. Open-label follow-up at 24 months showed the mean estimated glomerular filtration rate had reduced by 0.3 mL/min/1.73 m^2 with migalastat and by 1.51 mL/min/1.73 m^2 with placebo.[1]

Similarly, treatment with migalastat had no significant overall effects on left ventricular mass in the first six months of the trial. However, when the patients with suitable mutations were analysed there was a significant decrease in left ventricular mass at 24 months.[1]

Another trial compared migalastat to enzyme replacement therapy with agalsidase in adults with suitable mutations. They had been receiving therapy for at least a year. In this open-label trial 36 patients were randomised to oral migalastat every other day and 24 to continue infusions of agalsidase every other week. After 18 months the decline in glomerular filtration rate was similar in both groups. For example, using the estimated glomerular filtration rate method, the annual decline was 0.4 mL/min/1.73 m^2 with migalastat and 1.03 mL/min/1.73 m^2 with agalsidase (>50% overlap of the 95% confidence interval). On echocardiography, there was a significant reduction in left ventricular mass with migalastat. In a composite clinical outcome of renal, cardiac or cerebrovascular events there was an event in 29% of the migalastat group and 44% of the agalsidase group.[2]

Fabry disease can cause debilitating gastrointestinal symptoms. Compared to placebo migalastat decreased diarrhoea and reflux.[1] Other adverse reactions include headache, dizziness, paraesthesia, muscle spasms, rash and weight gain. As for other patients with Fabry disease, there should be regular monitoring of renal and cardiac function.

Fabry disease is rare so the trials only had small numbers of patients. It would therefore be difficult to show a significant difference in effectiveness between migalastat and enzyme replacement therapy. The difference in events was not statistically significant.[2] An oral treatment is likely to be preferred by patients, but only those with suitable mutations seem to benefit. There are over 800 different mutations of which 268 are suitable for treatment with migalastat. At present the benefits of migalastat are based largely on surrogate markers. It remains to be seen whether, for example, by slowing the decline in glomerular filtration rate long-term treatment will lead to less renal failure.

TT manufacturer provided additional useful information

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NEW DRUGS

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Rufinamide

Approved indication: seizures

Inovelon (Eisai)
100 mg film-coated tablets
Australian Medicines Handbook section 16.1.3, Other antiepileptics

Rufinamide is indicated as adjunctive therapy for seizures associated with Lennox-Gastaut syndrome in patients aged four years and older. This is a severe and rare form of epilepsy which typically develops between 3 and 5 years of age and can continue into adulthood. Patients with this syndrome have multiple different types of seizures, developmental delays, intellectual disability and behavioural problems. They also have characteristic electroencephalogram patterns.

Rufinamide is a triazole derivative which is structurally unrelated to other antiepileptics. It modulates the activity of sodium channels and prevents them from switching to the active state.

Its approval in Australia is mainly based on a randomised, placebo-controlled trial in 138 patients aged 4–30 years old. To be eligible, they had to be having a minimum of 90 seizures a month and a recent history of a slow spike-and-wave pattern on electroencephalogram. After a four-week run-in baseline period in which patients continued taking their usual antiepileptic drugs, rufinamide (n=74) or matched placebo (n=64) was added and treatment was continued for 12 weeks.[1]

Rufinamide was more effective at reducing total seizure frequency than placebo (by 33 vs 12%, p=0.0015) after four weeks of treatment. In particular, it reduced tonic and atonic seizures or 'drop attacks' by a median of 43% while placebo increased them by 1.4% (see Table).[1]

In the trial, somnolence (24 vs 13%) and vomiting (22 vs 6%) were significantly more common with rufinamide than with placebo. Some patients discontinued treatment because of these adverse events. Status epilepticus was reported in three patients taking rufinamide but in no patients taking placebo.

Rufinamide shortens the QTc interval and should not be given to those with hereditary short QT syndrome. Care should also be taken in people taking concomitant medicines with the same effect.

The recommended dose of rufinamide is 45 mg/kg/day. It should be given with food in two equal doses – in the morning and the evening – and tablets can be crushed and given in water. Maximum plasma concentrations are reached within six hours of administration and the elimination half-life is 6–10 hours. After being metabolised, most of the dose is excreted in the urine. Careful dose titration is recommended in mild–moderate hepatic impairment and the drug should not be used in people with severe impairment. Dose adjustment is not needed in renal impairment, but haemodialysis can reduce rufinamide concentrations by 30%.

Exposure to rufinamide can be affected by concomitant antiepileptic drugs. Valproate increases plasma concentrations of rufinamide, so a lower initial rufinamide dose is needed in patients already taking valproate. Concurrent phenytoin, primidone, phenobarbital (phenobarbitone) or carbamazepine can decrease rufinamide concentrations, but it is not known if these decreases are clinically significant. Rufinamide is a mild inducer of cytochrome P450 (CYP) 3A4 so it may reduce concentrations of CYP3A4 substrates.

Rufinamide is not recommended in pregnancy. The drug may reduce ethinylestradiol and norethindrone, so women taking the combined pill should be advised to use additional contraception.

Rufinamide appears to be an effective adjunctive treatment of refractory seizures, particularly drop attacks, in patients with Lennox-Gastaut

Table **Efficacy of rufinamide in patients with seizures associated with Lennox-Gastaut syndrome**[1]

	Rufinamide*			Placebo		
	Before treatment	**After treatment**	**Median reduction in seizures**	**Before treatment**	**After treatment**	**Median reduction in seizures**
Total seizures over 4 weeks (median)	290 (n=74)	204	33%	205 (n=64)	205	12%
Tonic and atonic seizures over 4 weeks (median)	92 (n=64)	61	43%	93 (n=60)	76	-1.4%

n number of patients
* The maximum target dose of rufinamide was 45 mg/kg/day in two divided doses or matched placebo.

syndrome. However, dose titration is required at the beginning of treatment because of the risk of drug interactions with other antiepileptic drugs.

TT manufacturer provided additional useful information

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NEW DRUGS

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Tildrakizumab

Approved indication: psoriasis

Ilumya (Sun)
pre-filled syringes containing 100 mg/mL
Australian Medicines Handbook section 8.2, Drugs for psoriasis

Immune mechanisms are involved in the inflammation seen in psoriasis. Several pro-inflammatory cytokines, such as the interleukins, are implicated and this has led to the use of cytokine modulators when the psoriasis is severe enough to require systemic therapy. These include tumour necrosis factor alpha antagonists, such as etanercept, and the monoclonal antibodies ixekizumab, secukinumab and ustekinumab. Tildrakizumab is a monoclonal antibody which blocks the interaction of interleukin 23 with its receptor and this inhibits the release of pro-inflammatory cytokines.

Tildrakizumab has to be given by subcutaneous injection. The drug is slowly absorbed. In the recommended regimen of one injection followed by another after four weeks and then every 12 weeks, steady-state concentrations are reached at 16 weeks. The antibody is catabolised with a half-life of 23 days. No studies have been done in patients with hepatic or renal impairment.

A phase II trial studied several different doses of tildrakizumab in 355 patients with moderate–severe plaque psoriasis. To be included in the trial the patients had to have a Psoriasis Area and Severity Index (PASI) score of at least 12 (moderate severity). After 16 weeks this score had reduced by at least 75% in 33–74% of the patients. This response was significantly better than the 4% rate seen in a placebo group. At the recommended dose of tildrakizumab 100 mg, 62% of the patients had cleared or minimal psoriasis.[1]

The main trials of tildrakizumab (reSURFACE 1 and 2) studied doses of 100 mg and 200 mg in patients with moderate–severe plaque psoriasis (PASI score ≥12). The participants in reSURFACE 1 were randomised to tildrakizumab or placebo, while in reSURFACE 2 patients were randomised to tildrakizumab, etanercept or placebo (see Table). After 12 weeks the patients in the placebo groups were re-randomised to one of the tildrakizumab groups. The PASI score fell by at least 75% (PASI 75) in 6% of the placebo groups at 12 weeks. In contrast, this outcome was achieved by 61–64% of the patients given tildrakizumab 100 mg, 62–66% of those given 200 mg and 48% of the etanercept group. At 28 weeks the PASI 75 outcome was achieved by 73–82% of the patients who continued tildrakizumab and 54% of those taking etanercept. Favourable responses were also seen in 55–86% of the patients who switched from placebo. With tildrakizumab 100 mg, the psoriasis was clear or minimal in 55–58% of the patients at 12 weeks and in 65–66% of those who were treated for 28 weeks.[2]

During the phase III trials only about 1% of the patients discontinued tildrakizumab 100 mg because of adverse effects.[2] Common effects included injection-site reactions, nasopharyngitis and fatigue. Injecting an antibody that alters the immune response has some potentially serious adverse effects. Cancer was more frequent with tildrakizumab than placebo (0.2 vs 0%). During treatment 6.5% of the patients developed antibodies to tildrakizumab. This led to minor decreases in efficacy, but no apparent increase in adverse events. Tuberculosis should be excluded before treatment. Live vaccines should not be given during treatment and for at least 17 weeks afterwards.

In all clinical trials, 1994 people received tildrakizumab and the mean duration of treatment was 53.9 weeks. As psoriasis is a chronic disease, longer term safety data will be needed, including safety in pregnancy

Table **Twelve-week efficacy of tildrakizumab in psoriasis**[2]

	Trial						
	reSURFACE 1			reSURFACE 2			
Treatment	Tildrakizumab 100 mg	Tildrakizumab 200 mg	Placebo	Tildrakizumab 100 mg	Tildrakizumab 200 mg	Placebo	Etanercept 50 mg
Number of patients	309	308	155	307	314	156	313
PASI 75 response*	64%	62%	6%	61%	66%	6%	48%
Clear or minimal disease†	58%	59%	7%	55%	59%	4%	48%

* Proportion of patients achieving at least a 75% improvement in the Psoriasis Area and Severity Index
† Based on physician's global assessment

and lactation. Although the efficacy of tildrakizumab is probably similar to that of other monoclonal antibodies, its onset of action is slower. More patients will achieve a PASI 75 response with tildrakizumab than with etanercept, but the difference in patients with minimal or cleared psoriasis at 12 weeks is not statistically significant.[2]

TT manufacturer provided additional useful information

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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, and the European Medicines Agency.

NEW DRUGS

Aust Prescr 2019;42:42
https://doi.org/10.18773/austprescr.2019.010

Emicizumab

Approved indication: haemophilia A

Hemlibra (Roche)
Vials containing 105 mg/0.7 mL
Australian Medicines Handbook Appendix A

Patients with haemophilia A lack coagulation factor VIII. In the coagulation cascade this factor interacts with factor IX to activate factor X. A deficiency of factor VIII puts the patient at risk of prolonged bleeding. This can be addressed by infusions of factor VIII, however they can cause the development of antibodies which then inhibit factor VIII. One approach to this problem has been to treat the patient with factor VIII inhibitor bypassing fraction. A new approach is using emicizumab. This genetically engineered monoclonal antibody overcomes the lack of factor VIII by bridging factors IX and X to restore haemostasis.

Emicizumab is given by subcutaneous injection. There is some variation in bioavailability according to the injection site, but injections can be rotated around the abdomen, thighs and upper outer arms. The drug has an absorption half-life of 1.7 days and an elimination half-life of 28 days. It is probably catabolised. Age and the presence of factor VIII inhibitors have no clinically important effects on the pharmacokinetics of emicizumab. As the drug alters coagulation it will affect tests based on intrinsic clotting, such as the activated partial thromboplastin time.

The main trial of emicizumab in patients with factor VIII inhibitors enrolled patients aged 12 years and above. Those randomised to receive prophylaxis with emicizumab were injected with a weekly dose of 3 mg/kg for four weeks followed by 1.5 mg/kg every week. The main outcome of this open-label trial was assessed in patients who had previously had episodic treatment, rather than prophylaxis, with bypassing products. After 24 weeks the annualised rate of bleeds requiring treatment was 2.9 events in 35 patients receiving emicizumab prophylaxis. This was significantly lower than the rate of 23.3 events in a control group of 18 patients. There was no bleeding at all in 63% of the emicizumab group. In another group of 24 patients who had previously used bypassing products for prophylaxis, the bleeding rate fell from 15.7 events/year to 3.3 events/year with emicizumab prophylaxis.[1]

The full results of an open-label, paediatric trial have not yet been published. An interim efficacy analysis included 57 children younger than 12 years. In 23 children who had prophylaxis with emicizumab for at least 12 weeks the annualised bleeding rate was 2.9. There were no bleeds in 64.9% of the children.[2]

Emicizumab has also been studied as prophylaxis for patients who have haemophilia A but no factor VIII inhibitors. The trial focused on patients who had previously been managed with episodic factor VIII, given when required. After the loading doses, patients who had been randomised to receive prophylaxis with emicizumab were given either 1.5 mg/kg every week or 3 mg/kg every two weeks. After a study period of at least 24 weeks, the annualised rate of bleeds requiring treatment was 1.5 in the 36 patients given weekly injections and 1.3 in the 35 patients given fortnightly injections. The rate was 38.2 in a group of 18 patients who received no prophylaxis. There was no bleeding at all in 50% of those treated weekly and 40% of those treated fortnightly.[3]

In the main trial of patients with inhibitors the most frequent adverse effect of emicizumab was injection-site reactions. Other common reactions included headache, fatigue and arthralgia.[1] As emicizumab acts on the clotting system there is a risk of thrombotic adverse effects. In the trial these included thrombotic microangiopathy, thrombophlebitis and cavernous sinus thrombosis. The thrombotic microangiopathy could be related to the patients also being treated with activated prothrombin complex.[1] Patients can develop antibodies against emicizumab.

Although data are currently limited, emicizumab appears to be an advance. As it can be given once a week it has an advantage over other prophylactic regimens. Less frequent dosing is being studied in children.

T T manufacturer provided additional useful information

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