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NPS MEDICINEWISE

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EDITORIAL

Forty and forward?

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Editor
Australian Prescriber

Key words
Australian Prescriber, drug bulletins, PubMed

Aust Prescr 2015;38:146–7

The first edition of *Australian Prescriber* was published in the spring of 1975 by the Australian Department of Health. It aimed to 'assist clinicians, whatever their field, to prescribe the most appropriate treatment'.[1] Forty years on, *Australian Prescriber* has become a trusted part of Australian practice. A whole generation of health professionals has grown up with access to independent information about therapeutics.

Despite its national and international influence, the existence of *Australian Prescriber* has sometimes been in doubt. In 1982, budget cuts led to the brief disappearance of *Australian Prescriber* while plans were made to privatise the journal. One possibility was that *Australian Prescriber* would be taken over by the Australian Medical Association, the publisher of the Medical Journal of Australia. However, the Editor of that journal correctly pointed out that you could not have *Australian Prescriber* associated with advertisements from pharmaceutical companies. It has recently emerged that this comment contributed to that Editor's premature departure from the Medical Journal of Australia.[2]

At the 30th anniversary of *Australian Prescriber* in 2005 the problems of the past appeared to have been resolved.[3] The National Prescribing Service (now known as NPS MedicineWise) had taken over responsibility for the publication of *Australian Prescriber* in 2002. Certain safeguards were built into the contract as the Executive Editorial Board had concerns over editorial independence.[4] The contract included distributing *Australian Prescriber* in print and electronic formats, free of charge and free of advertising, six times a year. This routine is now well established.

Over the past 10 years *Australian Prescriber* has continued to grow. While the print distribution has remained stable, at around 50 000 copies, most of the growth has been in the online readership with approximately 250 000 unique visitors to the *Australian Prescriber* website each month. A website for mobile devices was established in 2013 and this attracts a further 125 000 unique users each month. Social media was in its infancy in 2005, but since 2012 readers have been able to get updates by following *Australian Prescriber* on Twitter.

In 2015 the first *Australian Prescriber* smartphone 'app' was launched. This was a new way to deliver information, about anaphylaxis management and the doses of emergency drugs, that had previously been available in print. The Doctor's Bag app has been well received with over 2500 downloads in the first month.

Work is also underway to meet the new standards of scholarly publication. These standards are partially a response to the recent rise of predatory medical journals.[5] While people value open-access journals, authors usually have to pay fees to have their work published in commercial publications. However, this publishing model has resulted in the emergence of new journals which appear willing to publish anything for money. Predatory journals can exploit people who are desperate to publish their work. There are even alleged cases of fake peer-review.[6]

Although *Australian Prescriber* has always met the standards for MEDLINE listing, the journal has not been given priority for inclusion in that database. To facilitate increased access, we are currently working to make the journal available through PubMed Central. This should make it easier for readers and researchers to find the articles they want.

Maintaining the quality of *Australian Prescriber* requires investment. The growth of *Australian Prescriber* has been achieved despite funding being unchanged for many years. While this has been a challenge over the past decade, the journal is reaching a point where future development may be constrained. In 2005 the *Australian Prescriber* website was considered advanced, but now needs to be upgraded, not least because of the huge numbers of people visiting the website.

In view of the increasing costs of distributing a paper journal, NPS MedicineWise is investigating a range of

From the Editor

Welcome to the 40th anniversary edition of *Australian Prescriber*.

While illicit drugs grab a lot of headlines, the misuse of prescription drugs attracts less attention. Danielle Wood discusses drug diversion, while Jonathan Brett and Bridin Murnion review the management of benzodiazepine misuse.

Many prisoners have a history of drug misuse. While Stephen Hampton, Donna Blomgren, Jill Roberts, Tobias Mackinnon and Gary Nicholls advise on prescribing for people in custody, Alex Wodak calls for reform of the drug laws in Australia.

Prescription drugs can also be used to enhance sporting performance. David Hughes from the Australian Institute of Sport updates us on the anti-doping code in sport.

Health professionals often have to advise whether or not a drug is safe to use during lactation. Neil and Elizabeth Hotham review the principles of prescribing drugs in breastfeeding. Most of the targeted anticancer drugs discussed by Christine Carrington would be unsuitable for use during lactation.

publishing solutions to ensure that health professionals continue to receive the high-quality, evidence-based information they need. This may include seeking additional sources of funding and reducing the print distribution of NPS MedicineWise publications.

Evidence from previous *Australian Prescriber* readership surveys supports the continuation of the print publication. Other publishers have also found that many health professionals prefer a paper journal. Approximately a third of our online readers also like to read *Australian Prescriber* in print. A common scenario is for health professionals to go to the website when they want information quickly and to read the paper copy when they want more detail about a topic. While there is increasing use of the internet, is it too soon to expect health professionals to read only online information?

In a recent readership survey 85% of the readers of the print journal said *Australian Prescriber* had influenced their practice. Significant changes to print distribution may therefore have implications for prescribing. It is important that we continue to provide balance to the printed information supplied directly or indirectly by the pharmaceutical industry.

The Editorial Executive Committee is concerned that all those readers who have opted for the paper journal will not make the switch to the electronic journal. Before making any changes it is essential to seek your views on how *Australian Prescriber* can continue to reach as many health professionals as possible. There will therefore be a survey of a sample of the readers in the coming weeks. Even if you are not part of the readership survey the Editorial Executive Committee will welcome your comments on the future of the journal.

The 21st century has seen a transformation in publishing. *Australian Prescriber* has introduced many innovations over the years and will continue to look for new ways to deliver independent drug information to busy health professionals. However, as *Australian Prescriber* moves forward into its fifth decade, it will be important not to forget the lessons of the past.

John Dowden is the Editor of Australian Prescriber.

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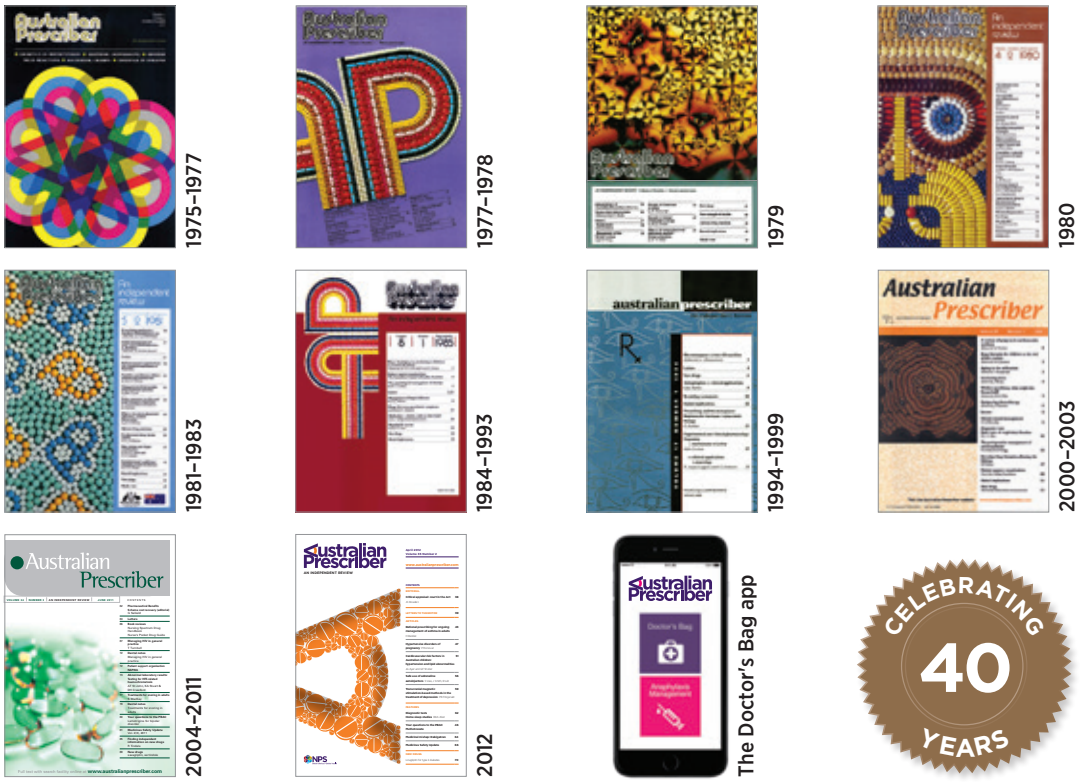
The art of *Australian Prescriber* since 1975



EDITORIAL

The failure of drug prohibition and the future of drug law reform in Australia

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Key words
drug control, drug legislation, drug trafficking, harm reduction

Aust Prescr 2015;38:148–9

Australia's first drug laws, introduced before Federation, banned only the smoking of opium and were aimed at Chinese people working on the goldfields. Since then, like most other countries, Australia has slowly adopted an evolving system of drug prohibition. This included approving three international drug treaties (1961, 1971, 1988) which require signatory nations to pass legislation imposing criminal sanctions on persons convicted of trafficking any of the listed drugs, now numbering approximately 250. A complex UN system has devised and implemented international drug policy and monitored national drug policy. Drugs were defined as a law enforcement issue by the political use of harsh language when referring to people who use drugs and the allocation to the criminal justice system of the overwhelming majority of government expenditure in response to drugs. Politicians have seen benefits in responding to drugs punitively and relying on the criminal justice system.[1]

In recent decades, this approach has been increasingly questioned on the grounds of ineffectiveness, often severe collateral damage and the waste of scarce resources.[2] Former Prime Minister Tony Abbott conceded in 2014 that regarding the war on drugs 'It's not a war we will ever finally win. The war on drugs is a war you can lose.'[3] In recent years, retired (and recently serving) senior police[4] and politicians in Australia and other countries have acknowledged the failure of global drug prohibition.

During the last 50 years, the drug market in Australia and other countries has continued to expand and become more dangerous. The production and consumption of drugs, the number of drug types and the hazardousness of drugs available have all increased. Prices fell, purity often increased and an overwhelming majority of drug users continued to report that obtaining illicit drugs was 'easy' or 'very easy'. Although the aim of our drug laws was to protect the health and well-being of Australians, deaths, disease, property crime, violence and corruption have increased. For example, the rate of heroin overdose deaths in Australia increased 55-fold between 1964 and 1997.[5]

In contrast to the poor record of criminal justice measures, health and social interventions have often had impressive results. Harm reduction measures such as needle and syringe programs, strenuously opposed initially, averted the spread of HIV among and from people who inject drugs, thereby protecting the community. $1 spent on needle and syringe programs saved an estimated $4 of healthcare costs and $27 overall, while $1 spent on methadone treatment saved an estimated $7.[6] The incidence of hepatitis C has declined substantially in Australia in recent years following expansion and improvement of the needle and syringe and drug treatment systems. This trend is likely to continue with further reform of drug laws.

Outcomes for the USA and a number of other countries that have relied on law enforcement have also been poor, costly and have often led to severe unintentional negative consequences. In contrast, countries such as the Netherlands, Switzerland and Portugal that have started to emphasise health and social interventions have achieved improved outcomes including reductions in overdose deaths, HIV infections and crime. Some US states (Colorado, Washington) started taxing and regulating cannabis like alcohol in 2014. Oregon, Alaska, Uruguay and Jamaica are now also committed to this approach. For almost a year from July 2013, New Zealand regulated some new psychoactive substances but stopped because the assessment system was not adequate.[7,8]

The threshold change required for drug law reform is to redefine the problem as primarily a health and social issue.[2] This means that illicit drugs will be treated more like alcohol and tobacco with much more emphasis on expanding and improving the drug treatment system and ensuring that disadvantaged populations have better opportunities in life. Many people with severe drug problems manage to regain control of their lives without help.[9] For those who need assistance to lead normal and useful lives as members of the community, GPs will play an increasingly important role.

If Australia starts moving from criminal to civil penalties for drugs, the thresholds for drug offences will need to be raised and the severity of criminal sanctions reduced. Cannabis, and possibly ecstasy, are among the few drugs that could be taxed and regulated. Drug checking could replace drug sniffer dogs at youth music events. Prescription heroin treatment has proved effective in trials and clinical practice in half a dozen countries and would be helpful in Australia for the small minority of people with severe and treatment refractory heroin dependence.[10] Pressure is now growing in Australia for the medicinal use of cannabis.[11] Like any other medicine, policy and practice should be based on evidence of its effectiveness and safety.[12]

Drug prohibition took many decades to evolve and implement. It is likely that a reformed system based on harm reduction will also evolve slowly over several decades. <

The author began publicly advocating drug law reform in 1987 and has worked on a voluntary basis for drug law reform full time since 2012. He is president of the Australian Drug Law Reform Foundation.

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LETTERS

Letters to the Editor

Warfarin and beetroot

I was interested to read your article 'How to manage warfarin therapy' (Aust Prescr 2015;38:44-8). In the article and subsequent online quiz, it mentions beetroot as being one of the foods that can affect INR, which I found rather unusual. After having worked as a senior pharmacist on a cardiothoracic ward for a number of years, I have counselled countless patients on warfarin and factors that can influence INR and I have never heard of beetroot being one of them. After doing some of my own research, I came across the vitamin K contents of beetroot, which was listed to be approximately 0.3 micrograms per 100 g in comparison with spinach 540 micrograms per 100 g.

Consequently, I believe that consuming beetroot while taking warfarin would have an insignificant effect on INR compared to other foods. I also noted in the quiz that vitamin C was listed as not affecting INR and, although there is limited evidence, there are a number of case reports of vitamin C at high doses affecting INR. Vitamin C is also listed in the Western Australian Department of Health's Living with Warfarin: Information for Patients,[1] so I believe that it is worth mentioning as something that could possibly affect INR.

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Philip A Tideman, Rosy Tirimacco, Andrew St John and Gregory W Roberts, authors of the article, comment:

Louise Vanpraag rightly points out that the beetroot bulb is a negligible source of vitamin K. It was our oversight in not explicitly naming the beetroot leaves as the rich source of vitamin K rather than the bulb.

While there have been two separate case reports of a possible interaction between high doses of vitamin C and warfarin causing an elevated INR, three separate crossover trials using daily vitamin C doses of 1–10 g for periods of one week to six months have failed to reveal an interaction.

Warfarin brands

Although a comprehensive guide to managing warfarin, the article in the April 2015 issue (Aust Prescr 2015;38:44-8) did not mention the problem of brand confusion with warfarin. Transition of care, such as hospital admission, is a time when warfarin management may be compromised. In Australia we have two brands – Coumadin and Marevan. Both are manufactured by Aspen Pharmaceuticals, and are available in different strengths and tablet colours. Recently reported incidents involving warfarin brand confusion at our hospital resulted in dose omissions due to Marevan not being available on the ward and inadvertent switching from Marevan to Coumadin. Although no patient harm resulted, time was spent in sourcing the 'right' brand and managing the incidents.

The Pharmaceutical Benefits Scheme notes that the brands have not been shown to be bioequivalent and should not be interchanged.[1] However, a systematic review comparing the bioequivalence of six international warfarin brands found that switching brands was relatively safe.[2] In 44 years of reporting adverse drug reactions in Australia, only three reports, all from 1977, implicate brand switching.[3]

The manufacturer has previously been approached to phase out one brand, with a recommendation that Coumadin be primarily used.[4] We call for either bioequivalence testing of Coumadin and Marevan by the manufacturer or, in the interests of medication safety, for only one brand of warfarin to be available.

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

Philip A Tideman, Rosy Tirimacco, Andrew St John and Gregory W Roberts, authors of the article, comment:

We agree that brand continuity for warfarin is preferred. While it seems unlikely there would be clinically significant differences in the two brands, which vary by a single excipient, there has been no formal bioequivalence testing. The availability of a single brand in Australia would simplify warfarin management and remove any confusion about brand swapping for both patients and clinicians.

Naltrexone and liver disease

In the good review on long-term drug treatment of patients with alcohol dependence (Aust Prescr 2015;38:41-3), the important issue of underuse of pharmacotherapy for alcohol dependence is identified and an outline of treatment is given. However, the article states that naltrexone is contraindicated in acute hepatitis or liver failure. In my clinical practice, varying degrees of chronic liver disease are commonly encountered when treating an alcohol-dependent population. Continued heavy drinking is much more likely to pose a greater risk to liver function than naltrexone. Arguably, the risk–benefit assessment likely favours naltrexone treatment. Naltrexone can be prescribed in patients with stable or compensated cirrhosis but is not recommended in acute liver failure. It carries a low risk of hepatotoxicity. However, in my experience, many potentially suitable patients are not given the drug because of concerns about hepatotoxicity.

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Philip Crowley, the author of the article, comments:

Precautions listed in naltrexone's product information include saying it may cause hepatocellular injury when given in excessive doses, and its use in patients with active liver disease must be carefully considered in light of its hepatotoxic effects. The product information also states that naltrexone is contraindicated in acute hepatitis or liver failure. This is based on a study in which 300 mg/day naltrexone was administered to obese patients. Five of 26 naltrexone recipients, and none of the placebo group, developed elevated serum transaminases after 3–8 weeks of treatment.[1]

Data on aspartate aminotransferase (AST) and alanine aminotransferase (ALT) have been used as an indicator of hepatotoxicity, with concentrations indicating both the effects of medication on hepatotoxicity, and reduced hepatotoxicity due to reduced alcohol consumption. Twelve of 1383 participants (0.9%) in the COMBINE study[2] had elevated liver enzymes greater than five times the upper levels of normal. (Most cases were in the naltrexone group.) These effects resolved following discontinuation of the drug. This is the one study large enough to detect an adverse effect at this low level of incidence.

The study that Dr Mike McDonough refers to supports other smaller studies[3,4] indicating that naltrexone was not hepatotoxic at the recommended dose in a trial of 74 participants.

I agree that often patients do better in a risk–benefit assessment when taking naltrexone compared to not taking it (because of concerns about minor liver enzyme changes).

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ARTICLE

Management of benzodiazepine misuse and dependence

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Key words
benzodiazepines, diazepam, drug abuse, drug dependence

Aust Prescr 2015;38:152–5

SUMMARY

There are well-recognised harms from long-term use of benzodiazepines. These include dependency, cognitive decline and falls.

It is important to prevent and recognise benzodiazepine dependence. A thorough risk assessment guides optimal management and the necessity for referral.

The management of dependence involves either gradual benzodiazepine withdrawal or maintenance treatment. Prescribing interventions, substitution, psychotherapies and pharmacotherapies can all contribute.

Unless the patient is elderly, it is helpful to switch to a long-acting benzodiazepine in both withdrawal and maintenance therapy. The dose should be gradually reduced over weeks to lower the risk of seizures.

Harms from drugs such as zopiclone and zolpidem are less well characterised. Dependence is managed in the same manner as benzodiazepine dependence.

Introduction

Despite a modest decrease in the annual number of benzodiazepine prescriptions dispensed, the current level of prescribing probably represents significant overuse. Over the last 20 years the quantity of benzodiazepines on each prescription has increased. Alprazolam became the second most popular drug, increasing more than eightfold.[1] Of particular concern are the patients who have been using benzodiazepines for more than six months. There are few indications for long-term therapy and they are generally controversial.[2]

Benzodiazepine-related problems include diversion, misuse, dependency, driving impairment, and morbidity and mortality related to overdose and withdrawal. In older patients they have been associated with cognitive decline, dementia[3] and falls.[4,5] There is evidence of increased mortality with long-term use.[6]

In February 2014, in response to increasing illicit use, alprazolam was rescheduled to Schedule 8. It has greater toxicity in overdose,[7] and associated mortality[8] relative to other benzodiazepines. The public health impact of this rescheduling is yet to be determined. This barrier to prescribing has placed renewed focus on benzodiazepine dependence. However, there is a paucity of research on the optimal management of benzodiazepine dependence, so practice has to be guided by general principles.

Prevention

Any patient who has taken a benzodiazepine for longer than 3–4 weeks is likely to have withdrawal symptoms if the drug is ceased abruptly. The risk of inducing dependence can be reduced by issuing prescriptions limited to 1–2 weeks supply.

Benzodiazepines are often prescribed for insomnia and anxiety. In general, the optimal treatment of these conditions in primary care is non-pharmacological, particularly psychological and behavioural, therapies. Because of tolerance and withdrawal symptoms, long-term use of benzodiazepines can lead to dose escalation and worsening of the underlying condition.

Recognition and assessment

The benzodiazepine-dependent population is heterogeneous and this influences management. A frail 70 year old with falls prescribed flunitrazepam as a sedative hypnotic for 20 years requires a different management approach from a 25-year-old intravenous drug user buying street alprazolam. The principles of management of dependence with 'z-drugs' such as zolpidem and zopiclone are the same as the management of benzodiazepine dependence.

Benzodiazepine substance use disorder can be diagnosed using DSM-5 criteria,[9] but the Severity Dependence Scale is a simple screening tool validated for use in the community.[10] Some patients prescribed benzodiazepines may have aberrant drug-related behaviours, ranging from double dosing to selling medicines illicitly or injecting them. Systems limitations in prescription monitoring in Australia reduce our ability to identify 'doctor shopping' so the

presence of any aberrant drug-related behaviours should prompt further assessment and treatment.

The assessment determines the severity of misuse and informs the risk of relapse and of harm. It should include the indication for prescribing, dose, duration of use, age and any history of psychiatric or medical comorbidity as well as any other past or current substance misuse. Assess for benzodiazepine substance use disorder and the severity of aberrant drug-related behaviours. Supportive social networks and stable housing are positive prognostic indicators. Assessing the patient's readiness to change guides the initial management.

Management

Patient engagement in management is essential as without this any attempts to address harmful use may be hindered by non-adherence or even doctor shopping. If the patient is not ready to change, or is just considering change, then motivational interviewing techniques are recommended. If the patient is ready for change, there are two approaches to the management of dependence:

- benzodiazepine withdrawal with the aim of abstinence
- benzodiazepine maintenance therapy.

The choice of approach depends on an assessment of the risk of harm and relapse. Low-risk patients can be managed in general practice and may benefit most from attempting withdrawal. High-risk patients are best managed with initial stabilisation and maintenance therapy in specialist residential or outpatient addiction services. There are general principles that apply to both groups.

Prescribing interventions

Staged dispensing is effective in both withdrawal and maintenance. This can be done by regular dispensing of small quantities at a local pharmacy with clinical review, for example daily dispensing with fortnightly clinical review. Liaison with a community pharmacist is a useful strategy.

Benzodiazepine substitution

Some benzodiazepines, notably alprazolam, appear to have a greater propensity for misuse and are more dangerous in overdose. The reasons for this are multifactorial, including perception of intoxication, potency relative to formulation (e.g. a single 2 mg alprazolam tablet is equivalent to four 5 mg diazepam tablets), shorter half-life and risk of withdrawal phenomena. A common approach is substituting these shorter half-life drugs, such as alprazolam, with longer half-life drugs, such as diazepam.[11] Conversion tables are available to guide conversion to diazepam equivalents (Table). When tapering benzodiazepines, fewer patients taking longer half-life drugs drop out, however there is a lack of robust evidence supporting substitution. Studies in older patients have found gradual withdrawal without substitution can be successful.[12,13]

Monitoring

When treatment is offered, ensure the patient is not doctor shopping to obtain more prescriptions. Doctors can register with Medicare's Prescription Shopping Information Service which provides a limited telephone report. However, this relies on doctors calling the program rather than being alerted automatically. With written patient consent, authority can be gained to release information on Pharmaceutical Benefits Scheme prescriptions over a given time period.[14]

Urine drug screening is complicated by the presence of benzodiazepine metabolites. Care should be taken in interpreting the results as some metabolites are themselves parent compounds. For example, temazepam and oxazepam are metabolites of diazepam, which may lead the practitioner to conclude that the patient had been taking other benzodiazepines during diazepam treatment. Urine drug screening should be used as a tool to engage the patient rather than as a punitive measure.

Table **Benzodiazepine and z-drugs half-life and conversion table**

Drug	Approximate half-life (hours)	Dose of oral benzodiazepine approximately equivalent to diazepam 5 mg
Short- to intermediate-acting benzodiazepines		
Triazolam	1–3	0.25 mg
Oxazepam	4–15	15 mg
Temazepam	5–15	10 mg
Lorazepam	12–16	1 mg
Bromazepam	20	3 mg
Alprazolam	6–25	0.5 mg
Flunitrazepam	20–30	0.5 mg
Nitrazepam	16–48	5 mg
Clobazam	17–49	10 mg
Long-acting benzodiazepines (includes effects of active metabolites)		
Clonazepam	22–54	0.5 mg
Diazepam	20–80	5 mg
Z-drugs		
Zolpidem	2.4	10 mg
Zopiclone	5.2	7.5 mg

Discontinuation with the aim of abstinence

Long-term abstinence rates following discontinuation vary greatly. These range from 25% at 12 months for those with complicated dependence[15] to 80% for older adults in general practice.[16] Abrupt cessation of benzodiazepines after a period of 1–6 months of use can cause life-threatening seizures so the dose should be gradually reduced.

The duration of weaning depends on tolerability and the starting dose. While not specifying a withdrawal period, most studies in primary care have found that gradual withdrawal over at least 10 weeks is successful in achieving long-term abstinence.[12]

Box **Benzodiazepine withdrawal syndrome – clinical features**

General

Headache

Palpitations

Sweating

Musculoskeletal

Tremor, fasciculations

Muscle pain, stiffness and aches (limbs, back, neck, jaw)

Neurological

Dizziness, light-headedness

Paraesthesia, shooting pains in neck and spine

Visual disturbances (blurred vision, diplopia, photophobia, vision lags behind eye movements)

Tinnitus

Faintness and dizziness, sense of unsteadiness

Confusion, disorientation (may be intermittent) – a common cause of confusion in older patients

Delirium (in the absence of autonomic hyperactivity) – particularly in older patients

Delusions, paranoia

Hallucinations (visual, auditory)

Grand mal seizures 1–12 days after discontinuing benzodiazepines

Gastrointestinal

Nausea

Anorexia

Diarrhoea (may resemble irritable bowel syndrome)

Psychological

Rebound insomnia, nightmares

Anxiety, panic attacks

Irritability, restlessness, agitation

Poor memory and concentration

Perceptual distortions – sensory hypersensitivity (light, sound, touch, taste), abnormal sensations (e.g. 'cotton wool' sensations)

Metallic taste

Distortions of body image

Feelings of unreality, depersonalisation, derealisation

Depression, dysphoria

Patients with a lower risk of relapse are those taking a daily dose of 10 mg diazepam equivalent or less at the start of tapering, and those who have made a substantial dose reduction themselves before the start of tapering. Other low-risk characteristics are less severe benzodiazepine dependence (measured on a dependence scale), no previous withdrawal attempts, high life satisfaction and no use of alcohol.[15,17] Patients without unstable psychiatric or medical comorbidity, no history of seizures and no concurrent drug abuse or dependence are also at a lower risk of harm from benzodiazepine withdrawal.

Patients may find that the symptoms of withdrawal (see Box) are typical of their previous problems such as insomnia or anxiety. This should be discussed with them, and psychotherapy or appropriate pharmacotherapy offered.

There are no standard tapering regimens and the rate of tapering depends on the starting dose, duration of therapy, risk of relapse and how well tapering is tolerated by the patient. In general, at higher doses (e.g. greater than 10 mg diazepam equivalents per day) the dose may be tapered more rapidly. Once the patient achieves 10 mg the dose should be tapered more slowly (e.g. 5 mg twice daily for two weeks, then once daily for two weeks, and then 2 mg daily for two weeks and then cease).

Pharmacotherapy

Anticonvulsants have some efficacy in benzodiazepine withdrawal if the patient is not dependent on other drugs. Carbamazepine has a modest benefit[12] and pregabalin can be effective.[18] Antidepressants and beta blockers have no proven benefit.

Flumazenil, a $GABA_A$ receptor antagonist, has been used as a low-dose intravenous or subcutaneous infusion over four days to help patients rapidly withdraw from benzodiazepines to a lower dose or to abstinence without significant withdrawal symptoms. A proposed mechanism is reversal of receptor desensitisation and down regulation. There are some data showing effectiveness, albeit in small groups of patients.[19] Although relatively uncommon, seizures can occur with low-dose flumazenil infusion and so it should only be considered in a specialised unit.[20]

Psychotherapy

A meta-analysis of treatment for benzodiazepine discontinuation found that gradual dose reduction combined with psychological treatment was superior to gradual dose reduction alone.[21] A recent Cochrane review assessed randomised controlled trials of many different psychosocial interventions. It found only moderate evidence that adding cognitive behavioural therapy during taper was more effective than just

tapering the dose. There was insufficient evidence to make any conclusions regarding motivational interviewing. Interventions that could reduce benzodiazepine use include a tailored letter from the patient's GP advising reducing or quitting the drug, standardised interviews and relaxation techniques.[22]

Stabilisation and maintenance therapy

Some patients are reluctant to consider ceasing their benzodiazepine and are at high risk of relapse or harm. A harm reduction strategy may be more appropriate for this group. This involves using a long half-life substitute to prevent intoxication and withdrawal phenomena, and allowing the patient to engage in holistic treatment of their dependence, before slowly reducing the dose.

Patients who may need maintenance therapy are those who are on a high diazepam equivalent dose, have a range of aberrant drug-related behaviours (especially doctor shopping) and have a chaotic social setting or unstable psychiatric diagnoses. Patients who are alcohol or drug dependent may also benefit from this approach.[23] These people are often difficult to manage and should be referred to a specialist addiction service. To support management in rural and remote settings, health professionals in all states and territories have access to 24-hour phone support services.[24]

Patients on maintenance therapy may eventually reach a period of stability in which withdrawal to a lower dose or abstinence may be considered. High-risk patients or those with unstable medical conditions or a significant seizure history may benefit from admission to an inpatient service for stabilisation or withdrawal.

Conclusion

There is significant concern regarding overprescribing of benzodiazepines and the resultant harms. People who are benzodiazepine dependent or at risk because of misuse should be identified and appropriately assessed to determine their risk of harm. Depending on patient characteristics, benzodiazepines can be withdrawn or the patient stabilised on a maintenance program.

Prescribing interventions, substitution, psychotherapies and pharmacotherapies all contribute to the management of benzodiazepine dependence. However, some of these interventions have limited supporting evidence. There is therefore a need to develop a better evidence base and treatment paradigm for these patients.

Conflict of interest: none declared

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ARTICLE

Drugs in breastfeeding

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CPD FOR PHARMACISTS

This article has a continuing professional development activity for pharmacists available at www.australianprescriber.com/continuing-professional-development

SUMMARY

Most commonly used drugs are relatively safe for breastfed babies. The dose received via milk is generally small and much less than the known safe doses of the same drug given directly to neonates and infants.

Drugs contraindicated during breastfeeding include anticancer drugs, lithium, oral retinoids, amiodarone and gold salts.

An understanding of the principles underlying the transfer into breast milk is important, as is an awareness of the potential adverse effects on the infant.

Discussion with the mother about the possibility of either negative product information or ill-informed advice from others will reduce the confusion and anxiety that may be generated.

Good resources about medicines and breastfeeding are available and include state-based medicines information services.

Introduction

Although the National Health and Medical Research Council recommends exclusive breastfeeding for around six months, continued alongside complementary food until a minimum of 12 months, current breastfeeding statistics show Australia falling well below these recommendations. While 96% of women start breastfeeding, exclusive breastfeeding rates drop off to 39% of babies at three months and 15% at five months.[1] Faced with these statistics, it is important to be able to give accurate advice on the safety of drugs so that breastfeeding is promoted whenever possible.

Most drugs are not of concern in breastfeeding.[2-4] In addition, most lactating women take few medicines, and then only occasionally. Further, even though virtually all drugs are transferred into breast milk to some extent, the amount of drug is usually small and unlikely to cause an adverse effect on the baby. Considering the number of drugs available, relatively few known adverse effects occur in babies and it is generally not necessary to suspend breastfeeding because of the mother's medication. This concept is not new. It was suggested over 100 years ago that '... it is possible to show that drugs ... when given to a mother, rarely affect the milk injuriously, and almost never the babe to a marked degree'.[5]

Although the number of drugs available now is much greater, the same approach can apply. If ongoing medication use is necessary, only a few drugs warrant the cessation of breastfeeding (see Table). However, given the vulnerability of infants, vigilance is required.

What affects the concentration of a drug in milk?

It is important to be aware of how drugs transfer into breast milk and what factors can influence this.

Table **Examples of drugs contraindicated in breastfeeding**

Drug	Comment
Amiodarone	Long half-life, iodine-containing molecule, and may affect thyroid function in infant
Antineoplastics	Leukopenia, bone marrow suppression
Gold salts	Rash, nephritis, haematological abnormalities
Lithium	Breastfeeding only feasible with rigorous monitoring
Radiopharmaceuticals	Contact obstetric information service
Retinoids (oral)	Potential for serious adverse effects

Maternal plasma concentration

Passive diffusion is the primary pathway by which drugs enter milk. There is a good concordance between the time-course of maternal plasma-drug concentration and milk-drug concentration. Maternal plasma concentration is also affected by the drug's distribution into different tissues. A high volume of distribution (as for sertraline) will contribute to a lower maternal plasma concentration and a subsequent lower concentration in milk.

Maternal plasma protein binding

Transfer into breast milk is also influenced by the extent to which the drug is bound by maternal plasma proteins. Free unbound drug diffuses readily while highly protein-bound drugs like ibuprofen or warfarin (both 99% protein bound) are unable to diffuse in significant amounts.[6] Sertraline is highly protein bound (98%) so overall it will be minimally transferred to the breastfed baby.[6] By comparison, venlafaxine has much lower protein binding and so more of the drug will be present in milk.[6]

Size of the drug molecule

Most drug molecules, including alcohol, nicotine and caffeine, are small enough to enter milk. Exceptions are drugs with high molecular weights such as heparins and insulin.

Degree of ionisation

Drugs cross membranes in an un-ionised form. Milk is generally slightly more acidic (pH 7.2) than the mother's plasma (pH 7.4) so it attracts weak organic bases such as oxycodone and codeine.[7] Such drugs become ionised and 'trapped' in the milk. Conversely, weak organic acids such as penicillin tend to be ionised and held in maternal plasma.

Lipid solubility

In addition to the passive diffusion into the aqueous phase, lipid-soluble drugs such as citalopram[8] may have co-secretion by dissolution in the fat droplets of milk.[2] In practical terms, this may not be of concern. It would not be an indication to change therapy if citalopram has been effective, but infant drowsiness should be monitored. Although the fat content of the milk varies according to infant age and phase of the feed, this is unlikely to impact on the choice of drug therapy.

Maternal pharmacogenomics

A growing understanding of the influence of pharmacogenomics is well exemplified with codeine which is variably metabolised to morphine by the cytochrome P450 (CYP) 2D6 enzyme. The ultra-rapid metaboliser phenotype occurs in up to 10% of Western Europeans and up to 30% of North Africans. Repeated codeine doses in these women produce significant amounts of morphine. Rapid transfer from maternal plasma to the milk may result in central nervous system depression and potentially infant death.[9] Codeine should be avoided during breastfeeding[10] and alternative analgesia is recommended, such as paracetamol or ibuprofen.

What influences the risk of adverse effects on the baby?

If the baby is exposed to a drug in milk, several factors determine if there is an effect.

Timing of the dose

Feeding the baby just before the mother takes a drug results in the baby receiving the lowest possible drug concentration. However, this principle clearly does not apply for drugs with a long half-life, such as diazepam. For these drugs, there should be an even more rigorous assessment of whether they are needed.

Toxicity

Premature babies and neonates have a lower capacity to metabolise and excrete drugs.[2] In addition, for babies who may already have been exposed to a drug in utero just before delivery, further exposure via breast milk will augment the existing drug concentration.

The Table lists drugs that are contraindicated in breastfeeding. Some drugs are inappropriately regarded as unsafe. Metronidazole, despite unfounded fears of carcinogenicity and mutagenicity, is safe in breastfeeding for short-term use.[11] However, anecdotally, its bitter taste in milk may lead to fussiness in the feeding infant. Valproate is regarded as safe, especially in monotherapy when the risk of infant sedation is low.[11] Monitoring the infant for liver and platelet changes may be advisable.[12]

The immunosuppressant azathioprine is excreted into breast milk as an active metabolite 6-mercaptopurine. Cautious use is advised in lactating women, and monitoring of the infant for signs of immunosuppression and other toxicity is recommended.[6,11,12]

Oral bioavailability

The drug's presence in breast milk does not necessarily lead to significant exposure for the baby. The infant gut may degrade or destroy a drug, for example omeprazole (for which the standard formulation is enteric-coated). Gentamicin is given intravenously to the mother. As it is poorly absorbed orally by the baby, drug concentrations will not be reflected in infant plasma.

Volume of breast milk

The amount of milk a baby receives varies. The estimated intake by an exclusively breastfed baby is 150 mL/kg/day. However, if the breast is being offered only as a comfort to an older baby, for example at night, the volume ingested is likely to be small.

Relative infant dose

The relative infant dose is the dose received via breast milk (mg/kg/day) relative to the mother's dose (mg/kg/day). It is expressed as a percentage. A relative dose of 10% or above is the notional level of concern,[6] but this is rare. An example is lithium,[6,12] which is generally contraindicated in breastfeeding.[13]

Age of infant

A review found that most adverse effects of drugs in breast milk occurred in newborns under two months and rarely in those older than six months.[14] An infant's metabolism and excretion capacity at birth is only a third of what it is at 7–8 months.[15]

Drugs used to stimulate milk production

Domperidone and metoclopramide are galactogogues and have both been used off-label to stimulate prolactin and enhance milk supply. However, these drugs do not have high evidence of efficacy for this indication.[11,16] Also, there are concerns about the overuse of domperidone given that it may be prescribed on discharge from obstetric hospitals and used long term, sometimes at high doses. Non-pharmacological approaches to boost milk supply, such as correct advice, support and more frequent breastfeeding, are preferable.

Practice points for prescribing in breastfeeding

- If a drug is needed, prescribe it at the lowest effective dose. Temporarily suspend breastfeeding (and express milk) for potentially toxic drugs, such as cytotoxics and radiopharmaceuticals (see Table). Reinstatement of a drug will be determined by its half-life. It may not be possible to continue breastfeeding if lengthy treatment with a toxic drug is needed.
- Select alternative routes or products to minimise systemic exposure in the mother. For example, choose a poorly absorbed fibre laxative over a stimulant laxative.
- Choose drugs with a relatively short half-life, such as sertraline rather than fluoxetine, to minimise drug exposure in milk.
- Advise the mother to feed the infant before taking her medicine so that the drug concentration in milk will be at its lowest. Reassure her that the drug will return to her bloodstream from the milk as her blood concentration falls and will not 'store' in the milk until the next feed. This advice does not apply to drugs with a long half-life. The need for these drugs should be reassessed, especially in the neonatal period.

Advice on social drugs

Advise mothers to delay a glass of alcohol until after a feed and wait for two hours before the next feed to minimise infant exposure. Nicotine replacement therapy is not an absolute contraindication to breastfeeding and is preferable to smoking, although short-acting forms should be selected. Smoking, including passive smoking, has been associated with sudden infant death syndrome. High maternal intake of caffeine is associated with irritability and poor sleep patterns in the infant.

Breastfeeding in the context of illicit drug use is likely to be problematic. A follow-up study of one-year-old breastfed infants of mothers who used cannabis found some impairment in motor development, although the researchers found it difficult to determine whether in utero exposure was a greater influence.[17] Women should be encouraged to stop using cannabis and avoid exposure of the baby to second-hand smoke.

Finding information and advice

If unsure, seek advice on the use of a drug during breastfeeding. There are a number of different information sources available.

Drug information services

State-based obstetric drug information services provide detailed advice on the use of drugs during lactation and should be able to advise about past clinical experience with the drug (see Box).

LactMed

LactMed[11] is a freely accessible, well-resourced and peer-reviewed online database that can be downloaded as an app for mobile devices. It is updated to keep pace with new information, including published studies and drug approvals. It also incorporates information on complementary treatments.

Australian Medicines Handbook

The Australian Medicines Handbook (AMH)[16] also provides information on prescribing during lactation. It includes advice about drugs that may suppress lactation and those that are contraindicated or should be used with caution. However, lack of evidence of harm does not mean that a drug is safe.

The Women's Pregnancy and Breastfeeding Medicines Guide

The Women's Pregnancy and Breastfeeding Medicines Guide, originally published in book format, is now available as an online subscription.[12] The online version is constantly updated, providing evidence-based recommendations on the use of medicines during pregnancy and breastfeeding.

Product information

Be aware that the drug's product information sometimes contains advice that is contrary to recommended treatment.[18] An example is the treatment of mastitis with cephalexin: 'Alternative feeding arrangements for the infant should be considered.' Explanation should be given to the mother (and, if appropriate, her partner) that, while taking any antibiotic for mastitis, it is recommended to breastfeed more frequently and perhaps also express milk, to prevent stasis in the milk ducts and to maintain supply.

Conclusion

Most commonly used drugs are relatively safe for breastfed babies. The dose received via milk is generally small and much less than the known safe doses of the drugs used in neonates and infants. Further, most lactating women take few medications and often only occasionally. For women on chronic medications, most can be reassured, but some drugs will be contraindicated and others not yet adequately studied. Good resources are available, including state-based drugs and medicines information services.

Neil Hotham is a specialist editor for the Australian Medicines Handbook.

Box **Obstetric drug information services in Australia**

Australian Capital Territory	Medicines Information Service Canberra Hospital and Health Service Phone: 02 6244 3333
New South Wales	MotherSafe Royal Hospital for Women Phone: 02 9382 6539 Toll free (NSW): 1800 647 848
Northern Territory	Northern Territory Drug Information Centre Royal Darwin Hospital Phone: 08 8922 8424
Queensland	For health professionals: Queensland Medicines Advice and Information Service (QMAIS) Royal Brisbane and Women's Hospital Phone: 07 3646 7599 or 07 3646 7098
South Australia	SA Pharmacy Obstetric and Paediatric Medicines Information Service Women's and Children's Hospital Phone: 08 8161 7222
Tasmania	No drug information centre currently available
Victoria	Medicines Information Services Pharmacy Department, Royal Women's Hospital Phone: 03 8345 3190 Medicines Information Centre Monash Health Phone: 03 9594 2361
Western Australia	Drugs in Pregnancy and Breastfeeding Information Service King Edward Memorial Hospital Phone: 08 9340 2723

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FURTHER READING

The full list of further reading references is in the online version of this article at www.australianprescriber.com/magazine/38/5/156/9.

ARTICLE

Prescribing for people in custody

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drug dependence, prescription drug diversion, prisoners

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SUMMARY

People who are, or have been, in custody often have multiple morbidities and multi-dimensional disadvantage.

A thorough clinical evaluation and multidisciplinary approach will assist in managing these patients. Treatment plans should be pragmatic and simple, and explained in an understandable manner.

Caution should be used in the prescription of any medicines that have the potential for abuse. There is also a risk of drug diversion.

There is an increase in mortality after prisoners are released into the community. Preparations should therefore be made before release to ensure continuity of care.

Introduction

In Australia at any one time there are about 30 000 people in custody (i.e. in police cells, on remand or in sentenced correctional facilities),[1] which is 170 adult prisoners per 100 000 people. During 2013 imprisonment rates for males were 318 per 100 000 men, and for females 26 per 100 000 women. These people may require medical treatment while in custody and this may need to continue when they return to the community.

Patient characteristics

Imprisonment provides a window of opportunity to identify the health needs of a vulnerable and disadvantaged group of people with a high level of morbidity. Statistics vary considerably between states, but there are a number of distinct features of the prison population in Australia.[2] There is an over-representation of Aboriginal and Torres Strait Islander people and culturally and linguistically diverse people in custody (see Table).

Prisoners have a high prevalence of mental illness, chronic disease, substance abuse and blood-borne virus infections. In an Australian study, approximately 50% reported having been told they had a mental illness and 25% were referred for mental health assessment on admission into custody. About 32% reported having a chronic disease and approximately 22% had tested positive for hepatitis C.[2]

In addition to the burden of illness, there are a number of factors and barriers that influence the delivery of care to people in custody. These include poor literacy, intellectual disability, a history of limited access to health services, challenging behaviours and poor decision making.

Systems are in place to screen patients for chronic diseases, mental health problems, substance abuse and infectious diseases such as blood-borne viruses. Patients identified with these problems are then channelled into programs that manage their specific concerns.

Table **Approximate percentage of people in custody with indicators of social disadvantage and risk behaviours in Australia** [2]

	Indicator	Approximate percentage of people in custody
Social disadvantage	Aboriginal and Torres Strait Islander	33%
	Culturally and linguistically diverse	20%
	Unemployed before incarceration	50%
	Homeless before incarceration	33%
Risk behaviour	Smokes	80%
	Drinks alcohol to excess	50%
	Uses illicit drugs	75%

Prison environment

The prison environment impacts on the delivery of health care, as security requirements coexist alongside the medical requirements of the prisoners. This often provides additional challenges to the provision of health care. Health in prisons and forensic facilities is managed by state government agencies or private corporations. There is no access to the Pharmaceutical Benefits Scheme so medicines are purchased through contract arrangements. On admission, medicines may be changed to

alternatives that are available on the approved formulary. This may mean minor adjustments in medication, for example discontinuation of combination antihypertensive products in favour of individual drugs. Medicines are usually provided to patients daily and administration may be supervised depending on the potential for drug diversion. This may result in adjustments to the timing and dosing of some drugs, for example insulin.

General approaches to prescribing

There are a number of approaches to the management and prescription of medicines to prisoners. As always, prescribing should occur after proper assessment, even in this challenging environment. Use appropriate language and information when providing advice on treatments or disease states. The information provided must be easy to understand, culturally appropriate and may require the use of Aboriginal health workers or an interpreting service. Tailoring and simplifying the regimen to meet patients' needs is also a practical consideration in prison.

Addiction and abuse

Approximately 75% of people in custody have used illicit substances before incarceration.[2] There is concern about the potential of prescription medicines to be used as 'currency', either voluntarily or under duress.

Working in a multidisciplinary team ensures the best care and involves obtaining advice from, or working with, a variety of professionals. This may include pharmacists, nurses, psychologists, physiotherapists, Aboriginal health workers, interpreters, occupational therapists, addiction medicine specialists, psychiatrists, pain management specialists, physicians and surgeons. This particularly applies to chronic disease states, chronic pain and palliative care. The team may need to include representatives from the custodial service as well as representatives from a local hospital.

In general, a practitioner should approach prescribing in custody with the following in mind:

- The basis for a safe and effective treatment is thorough assessment which includes seeking information from GPs, hospitals and other health professionals who have treated the patient.
- The prescription of psychoactive medicines needs to be based on a formal diagnosis.
- It is vital to communicate with others providing care because of the risk of prisoners playing individual clinicians off against one another.
- Always be cognisant of potential drug-seeking behaviours. These include requests for specific drugs, aggressive and unreasonable behaviours, and giving information that is not consistent with objective findings.
- All patients with complex needs should have formal management plans in place.

Cautions

Some prescription drugs, such as benzodiazepines, opioids and GABA analogues, are likely to be misused or diverted. Many others are abused for real or perceived effects. Some reported examples are:

- drugs with anticholinergic effects, like hyoscine, are abused for a 'high' that occurs when smoked
- nicotine patches are boiled up in water to release the nicotine, and the water is then consumed to get an immediate stimulant effect
- mirtazapine and quetiapine are used for their sedative effects.

Benzodiazepines

In all medical practices, including prison, there is the potential for abuse and diversion of benzodiazepines. All prisoners should be supervised when given a dose. Many people enter custody stating they require benzodiazepines, which they say are for epilepsy, but are actually substances of dependence. Benzodiazepines have a place in the management of acute epileptic seizures, however they are rarely indicated for long-term management. If a prisoner is received into custody and is taking a benzodiazepine, in particular clonazepam, for epilepsy, a referral to a neurologist should be made to ensure the treatment is appropriate. In regard to specific drugs:

- diazepam is useful in the management of withdrawal from alcohol, opioids or other shorter acting benzodiazepines
- temazepam is useful for people in some rare acute situations, for example when people are first arrested or in the treatment of insomnia associated with interferon treatment.

Alprazolam should only be used in exceptional circumstances and never in the long term.

Opioids

Prescribing opioids presents a particular challenge in custody. Prisoners known to be dependent should be assessed for placement in an opioid substitution program where available. People who are withdrawing should be managed using established protocols under the supervision of a practitioner experienced in the management of opioid withdrawal.

Many prisoners are taking oral opioids that have been prescribed inappropriately for chronic pain. Opioids work well in acute pain, but their role in chronic non-malignant pain is limited,[3] so a high degree of scepticism should be used when prisoners say they are using opioids for chronic pain. In the first instance a thorough history and examination must be undertaken, including gathering information from other practitioners and looking for drug-seeking behaviours. It is particularly useful to develop skills in examination of the back. Investigations can be difficult to organise in custody and are often less helpful than expected. A multidisciplinary team approach is important. A small number of patients may require opioids for chronic pain, but this treatment needs to be supervised and regularly reviewed.

The National Drug and Alcohol Research Centre has produced useful resources for GPs on opioid prescribing.[4] Currently a real-time system, the Electronic Recording and Reporting of Controlled Drugs, is being trialled in some states. When developed this will assist prescribers in managing patients seeking drugs of addiction in the community and in custody.

GABA analogues

GABA analogues such as pregabalin and gabapentin were originally developed for epilepsy. They have a role in the management of chronic neuropathic pain,[3] however the benefits are limited. These drugs are very frequently abused and have a high currency value in prison.[5]

Psychiatric prescribing in custody

Many people in custody have mental health problems and unfortunately many people who have mental illness only receive treatment when they are imprisoned. People should receive comprehensive team management for their mental health problems. Local protocols that follow accepted standards are used to promote consistent practice throughout the custodial health service. These should be followed for starting and maintaining antipsychotics. The protocols prompt checking for cardiac adverse effects, prolactin elevation and metabolic adverse effects.

Amphetamine stimulants such as dexamphetamine and methylphenidate should be prescribed for indications such as attention deficit hyperactivity disorder only by an approved specialist prescriber.

Many people in custody are prescribed antidepressants. Tricyclics should rarely be started because of their adverse effects and toxicity in overdose. Some patients may apply pressure for antidepressants to be used for sedative purposes, but this should be avoided.

Preparation for release from custody

It is important that patients are prepared for release as there is a higher mortality after release.[6] Patients should be medically discharged with a discharge summary. This can be challenging as release dates may not be predictable. Many prisoners released into the community have complex medical histories, so medical practitioners who see them without a discharge summary should contact the medical records section of the local correctional health service for a copy of the relevant information.

All discharged prisoners should be linked to a GP for follow-up. This can be difficult as many people in prison do not have a GP, do not want the GP to know they were in prison, or will live in a different location on release. Indigenous people can be referred to an Aboriginal medical service.

People with a known addiction to opioids have better outcomes in the community if they are treated in an opioid substitution program. When discharged they need to be connected to a relevant community service.

Patients with mental illness should be stabilised and referred to a community mental health service for follow-up. As they may be released on high doses due to their psychiatric morbidity they require careful monitoring.

Specific arrangements must be made for people undergoing treatment for blood-borne viruses or receiving opioid substitution therapy, to ensure continuity of care following release into the community.

Conclusion

Medical practitioners will treat people who are, or who have been, in prison. It is helpful to realise that these people tend to be from disadvantaged groups, are likely to have significant and multiple morbidity, are less likely to seek help and may have a limited ability to adequately care for themselves. Thoroughly assess these patients and manage their health needs with simple regimens and clear, contextually appropriate explanations. It is best to avoid drugs that are subject to abuse or diversion, and to seek collaboration from colleagues in other disciplines. Managing these patients will not only improve their lives, but also reduce the burden of disease in the population. <

Conflict of interest: none declared

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ARTICLE

Drug diversion

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Key words
benzodiazepines, drug dependence, opioids, prescription drug diversion

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SUMMARY

Prescription drug diversion has significant health, legal and social implications. Deaths from misuse of prescription drugs account for a significant proportion of overdose deaths.

The drugs most commonly involved are analgesics, particularly opioids, and psychoactive drugs, particularly benzodiazepines.

Diverted drugs are most often sourced from a family member or friend, but are also sourced from overseas pharmacies or laboratories, or bought from drug dealers.

Drug diversion can be mitigated by good prescribing practices. Systems for monitoring the prescribing and dispensing of medicines are being instituted across Australia.

Introduction

Prescription drug diversion is defined as the unlawful channelling of regulated pharmaceuticals from legal sources to the illicit marketplace.[1] This includes transferring drugs to people they were not prescribed for.

Scope

The diversion of prescription drugs has been a problem in Australia and globally for over 25 years. The impacts extend across many areas, from incarcerations of people under the influence of prescription drugs[2] to confrontation and conflict in healthcare settings. This leaves healthcare professionals unsupported when managing patients who may be misusing prescriptions.

Among the most concerning manifestations of drug diversion is the increasing number of overdose deaths related to prescription pharmaceuticals. It is difficult to quantify exactly how many deaths result from drug diversion as opposed to complications arising from prescribed use. A study published from coronial data looked specifically at whether oxycodone detected on post-mortem analysis was known to be prescribed to the deceased. It found that only 39% had a legitimate prescription for oxycodone.[3]

Quantifying the extent of the problem is difficult. It has been shown that, for opioids, diversion is proportional to the number of prescriptions issued without supervised dosing and inversely proportional to the availability of heroin.[4] Concerningly, the number of opioid dispensings in Australia increased from 500 000 in 1992 to 7.5 million in 2012.[5]

Data from needle and syringe programs show the proportion of users reporting the injecting of pharmaceutical opioids increased from 9% in 2005 to 16% in 2009.[6] Diverted pharmaceuticals are taken alone or combined with alcohol or other illicit recreational drugs such as cannabis.

The pharmacological properties of a drug influence its desirability on the illicit market. Drugs with a rapid onset of effect and those that produce greater effects from a single tablet are more desirable, for example a single 2 mg alprazolam will produce a similar effect to four 5 mg tablets of diazepam.[7] Other commonly diverted drugs are listed in the Table.

Points of diversion

The sources of diverted pharmaceuticals are difficult to evaluate. Diversion can occur at any point along the supply chain, although the most common point is at or beyond the point of practitioner–patient interface. Primary health care is the main target in prescription drug diversion, although drugs provided on hospital discharge can be diverted or used to influence ongoing prescribing by the GP.

Table **Commonly diverted drugs**

Class	Drugs
Benzodiazepines	all
Opioids	all
Stimulants	dexamphetamine pseudoephedrine methylphenidate
Antipsychotics	olanzapine quetiapine
Anaesthetic drugs	ketamine propofol
GABA agonists	gabapentin pregabalin

Studies of prison inmates' self-reported use in the year before incarceration found that 21% obtained prescriptions directly from a doctor in their name and 43% had been given them by a friend or family member. Other sources were drug dealers, and purchasing from friends or family. Only a small number of inmates reported forging or stealing scripts.[2] A similarly small number of prescription drugs are obtained through forced entry into pharmacies, warehouses and laboratories. There are scattered reports of prescription drugs being salvaged from clinical waste (sharps bins), diverted by healthcare workers within hospitals and sourced illicitly from patients in aged-care facilities, but the proportion they contribute to diversionary use is difficult to quantify.

One study in the USA found that the primary sources of prescription drugs on the street included older people and patients with chronic pain.[7] Obtaining drugs via the internet from overseas vendors is becoming more frequent, with quantities seized by Australian customs doubling over the past four years.[8]

Prevention strategies

Limiting the misuse and diversion of prescription drugs requires a coordinated approach between regulatory bodies, governments, pharmacies and individual prescribers. There are several guidelines aimed at reducing prescription drug diversion.

The National Pharmaceutical Drug Misuse Framework for Action is a strategy that was developed in response to the rising misuse of prescription opioids.[9] This aims to improve the quality use of medicines and reduce potential misuse. It addresses several key areas including improved systems for medication management, greater support for prescribers and pharmacists, education and improvement of health literacy, harm reduction and improved regulation.

Drug monitoring

A key element of the Framework is the Electronic Recording and Reporting of Controlled Drugs system. Introduced in 2012, it is currently only in use in Tasmania, but plans are in place to extend it nationally. The aim of the medication monitoring system is to provide prescribers and pharmacists with real-time access to information on prescriptions of controlled substances.

Currently, Medicare runs a Prescription Shopping Information Service* that can be accessed by registered prescribers without patient consent. Its limitations are that it only identifies patients who present to more than five prescribers, or obtain in excess of 50 prescriptions or 25 restricted items in a three-month period. Other monitoring systems are in place, but require patient consent and are retrospective in nature. With patient consent, the exact number of prescriptions can be tracked from all prescribers, yet the reports issued to the requesting physician only reflect the previous three months of prescription use.

Drug monitoring systems have their shortcomings and their effectiveness in limiting drug diversion is the subject of national and international debate.[10] However, they can be viewed as one element of a coordinated approach to support prescribers.

Reformulation of pharmaceuticals at risk of diversion

Reformulation of a drug into an abuse-deterrent preparation is a strategy that has been adopted to mitigate the diversion of pharmaceuticals. The primary aim of reformulation is to prevent the intravenous use of oral preparations. Temazepam was previously available in gel caps and tablets. The gel caps were deemed easier to inject than the tablet formulation and they were withdrawn from the market in 2004 following numerous reports of abscesses, thrombophlebitis and cellulitis associated with their use.

A tamper-resistant formulation of oxycodone was introduced in Australia in 2014, several years after it was introduced in the USA. At this preliminary stage, there are conflicting reports on whether this has stemmed the misuse of one of the most commonly diverted opioids or simply shifted use to other formulations. Early findings from the National Opioid Medication Abuse Deterrence study show a decline in pharmacy sales of oxycodone 80 mg following the introduction of the abuse-deterrent formulation.[11] Previously this was the most commonly diverted dose by people who inject drugs. In addition, there are various means of overcoming the tamper-resistant formulation to facilitate intravenous use.

Training

Improved training of doctors in identifying and treating addiction has been acknowledged as a key area in minimising pharmaceutical diversion. Specialist bodies such as the Royal Australasian College of Physicians and the Royal Australian College of General Practitioners have policies guiding good prescribing practices for drugs of dependence. To overcome the limited exposure to addiction training, a system of prescriber credentialing has been suggested. This already exists in some states, such as the NSW Opioid Treatment Accreditation course, but is mostly directed towards prescribing in the context of opioid treatment programs.

* Prescription Shopping Information Service 1800 631 181

Good prescribing practice

There are several measures that health professionals can put in place to minimise drug diversion. The first is to seek to identify current or previous addictive behaviours in all patients to whom potentially addictive drugs are prescribed.

Good prescribing practice involves an assessment of the indication for the drug, a discussion of its adverse effects, an appraisal of functional status, and constructing realistic expectations in the form of a treatment agreement, before prescribing. These precautions also emphasise regular review and defined treatment periods with the aim of identifying any potential misuse or diversion during treatment.[12] Such principles can be extended to any drug with the potential for misuse.

The Box lists other practice points to identify misuse and minimise diversion.[13]

Conclusion

The diversion of prescription pharmaceuticals is a recognised problem with severe adverse consequences. Importantly, the source of most diversion appears to be at the level of the patient–prescriber interaction or after the prescription is dispensed. The diversion of drugs within healthcare settings constitutes a much smaller proportion of overall drug diversion, but holds significant risks for both patient and healthcare provider.

Various organisations have developed plans to address the problem and there is a push toward improvements in drug monitoring systems. There is a need for more awareness and specialised training in the area of addiction to ameliorate drug diversion. Meanwhile there is a range of actions health professionals can take to combat medication misuse and achieve the quality use of medicines.

Conflict of interest: none declared

Box Strategies to reduce drug diversion[13]

Limit forged and illicit scripts

Ensure tamper-resistant scripts are written and all prescription paper is kept secure.

Prescriber–pharmacist interaction

Communicate with pharmacists about exact quantities to be prescribed and enquire as to the possibility of concerns regarding drug-seeking behaviour.

Limit quantities of medication dispensed

Mandate restricted dispensing (i.e. issue of a daily or weekly supply) in cooperation with a pharmacy.

Local policy

Develop a local policy on prescribing drugs of addiction to new patients.

Adhere to legislation

Ensure prescriptions for patients recognised to be drug dependent are registered with the relevant state governing body.

Refer to treatment

Use the support of drug and alcohol or chronic pain services as part of a treatment agreement for patients who demand an increasing number or frequency of scripts.

Enforce treatment boundaries

In response to violent or threatening behaviour, terminate treatment and involve senior clinicians or management. Further advice on management can be accessed via local addiction services.

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ARTICLE

The World Anti-Doping Code in sport

Update for 2015

SUMMARY

Some athletes cheat by using drugs or medical methods such as transfusion to enhance their performance. However, this may put their health at risk.

The World Anti-Doping Agency prohibits certain methods and drugs that may enhance performance, harm the athlete or violate the spirit of sport. Some may be banned only during competitions, but others are banned at all times.

Prohibited substances include over-the-counter and prescription medicines. It is therefore important for athletes and health professionals to check what is permitted.

There are many resources available through organisations such as the Australian Sports Anti-Doping Authority and the World Anti-Doping Agency.

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Key words
doping in sport, drugs in sport, performance-enhancing drugs

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Introduction

The World Anti-Doping Agency (WADA) was established in 1999 as an independent, international agency with the aim of creating an environment in world sport that is free of doping. WADA and associated anti-doping organisations such as the Australian Sports Anti-Doping Authority (ASADA) strive to ensure that there is a 'level playing field' in high-performance sport and to optimise the safety and welfare of athletes. The World Anti-Doping Code (the Code) is the document that provides consistency of anti-doping policies across sports and across international boundaries. It is based on five international standards aimed at bringing consistency among anti-doping organisations. It covers:

- testing and investigations
- laboratories
- therapeutic use exemptions
- the list of prohibited substances and methods
- protection of privacy and personal information.

The world of sports doping is constantly changing. One of the key functions of WADA is to support high-quality research in order to stay abreast and ahead of individuals and organisations who seek to illegally enhance sporting performance. The Code also requires frequent updating to adapt to changing knowledge and the changing doping environment. A new Code was introduced in 2015 with ramifications for athletes, sporting organisations and medical practitioners who deal with high-level athletes.

Athletes bear strict liability for any substances found within their bodies. As some commonly prescribed drugs are prohibited in sport, it is crucial that medical practitioners and others advising athletes have access to up-to-date anti-doping information. Exemptions may need to be obtained if the athlete requires the therapeutic use of a drug.

Important considerations when treating athletes

Medical practitioners need to be aware that, when treating athletes who are subject to drug testing, certain medicines that are not illegal to prescribe to the general community could result in the athlete breaching anti-doping rules. Some of these prohibited medicines are likely to stand out as being of concern for athletes, for example anabolic steroids, growth hormone and stimulants. Other medicines may not be so obvious, for example insulin, probenecid, diuretics, beta blockers and terbutaline.

Some medicines such as insulin are banned for their direct anabolic effects while other medicines such as diuretics and probenecid are banned because they can be used to mask banned substances in the urine. Beta blockers can reduce tremor in particular sports such as golf and shooting. Methylphenidate, a phenethylamine derivative, is banned in sport because of its stimulant effects.

There are some drugs that are banned during competition, but are not banned out of competition, for example oral corticosteroids. Other drugs, such as salbutamol and pseudoephedrine, are permitted, but are prohibited above a threshold serum concentration. Salbutamol can be taken by inhaler without incurring an anti-doping rule violation, but nebulised salbutamol could put the serum concentration beyond

the prohibited level. An athlete taking more than 1600 microgram of salbutamol by inhaler, within a 24-hour period, may potentially exceed the threshold serum concentration.[1] Athletes who have a therapeutic use exemption for a diuretic and are also using inhaled salbutamol may require another therapeutic use exemption for their salbutamol. This is because the diuretic could increase their salbutamol concentration above the prohibited threshold.

Most medical practitioners working with high-performance athletes refrain from prescribing pseudoephedrine on the day of competition. While an athlete could feasibly take a moderate dose of pseudoephedrine on the day of competition and remain below the threshold, there is high inter-individual variability in the urinary concentration of pseudoephedrine. WADA advises athletes to refrain from taking pseudoephedrine 24 hours before competing.

Of particular note for medical practitioners should be the rules about the use of intravenous fluids in athletes. As a result of the abuse and inappropriate use of intravenous fluids in sporting environments, the Code lists as a prohibited method:

> Intravenous infusions and/or injections of more than 50 mL per 6 hour period except for those legitimately received in the course of hospital admissions, surgical procedures or clinical investigations.

This effectively means that high-performance athletes should not be administered intravenous fluids except for medical indications.

Medical practitioners need to remember that not all athletes are young. Some international athletes in sport are aged over 50 years and are more likely to be taking prescription medicines. Drugs prescribed to older athletes may therefore require consideration of the anti-doping regulations.

The 2015 Prohibited List

Each year WADA specifies substances and doping methods that are not permitted in sport. The Prohibited List is the international standard that outlines the substances and methods that are prohibited in sport.

For a substance or method to be prohibited, it must meet at least two of the following conditions:

- The substance or method has the potential to enhance, or does enhance, performance in sport.
- The substance or method has the potential to risk the athlete's health.
- WADA has determined that the substance or method violates the spirit of sport.

The Prohibited List is complex and detailed. Even experienced sports medicine practitioners refer to the list carefully when dealing with potential doping matters. The Prohibited List is divided into broad sections (see Box).[2]

The 2015 Prohibited List came into effect on 1 January. There are some important changes from the previous list:

- Mimetics have been included in the section on peptide hormones and growth factors (S2) to reflect the fact that synthetic analogues are also prohibited substances.
- Non-erythropoietic EPO-receptor agonists have been added.
- Hypoxia-inducible factor stabilisers have been included because of their growing importance in doping, particularly in relation to the use of inhaled xenon and argon.
- Examples of chorionic gonadotrophin and luteinising hormone-releasing factors such as buserelin have been added.
- Corticorelin has been included as an example of corticotropin-releasing factor.
- Growth hormone-releasing factors have been divided in a more precise categorisation to illustrate the varying biological properties.
- The wording in relation to diuretics has been altered to clarify that diuretics are not only masking agents but can be abused for other purposes such as rapid weight loss.
- The whole family of phenethylamine derivatives has been identified to address the growing number of illegal, designer stimulants derived from phenethylamine.

Changes to the monitoring program

Certain drugs, while not prohibited, are monitored to assess their use and to guide future changes to the list. The following changes have been made to the monitoring program for 2015:

- Monitoring of pseudoephedrine will cease, but urinary concentrations above 150 microgram/mL are prohibited during competition.
- Telmisartan (angiotensin II receptor antagonist) has been added to the monitoring program as it may enhance endurance by inducing metabolic changes such as mitochondrial biogenesis and changes in skeletal muscle fibre type.
- Meldonium (Mildronate) has been added as it has potential cardiac stimulant effects.

Therapeutic use exemptions

Sporting authorities and medical practitioners working in high-performance sport are cognisant of the need to ensure that anti-doping rules do not impact negatively upon the health of the athlete. To ensure that athletes can be treated for a legitimate medical condition, WADA can provide a therapeutic use exemption for an otherwise banned substance. International and national athletes should apply for a therapeutic use exemption prospectively. In cases where a medical emergency necessitates the use of an otherwise prohibited substance, an athlete may apply for a retrospective therapeutic use exemption. Athletes should check with their sporting organisation in the first instance.

Most sporting organisations will have a chief medical officer who can assist with the therapeutic use exemption process, or the sport's administrators should be able to direct the athlete appropriately. Further advice regarding therapeutic use exemptions can be obtained by contacting the Australian Sports Drug Medical Advisory Committee (www.asdmac.gov.au/about/contact.html).

Sports supplements

The sports supplements industry is largely unregulated. The vast majority of the many ingredients found in sports supplements have not been subject to scientific scrutiny to support their use. Efficacy and safety data are lacking for many ingredients.[3]

Many sports supplements have been found to contain little or none of the active ingredients claimed by the manufacturer.[4] Even more concerning is that several studies have found a substantial proportion of sports supplements contain ingredients which are not mentioned on the label but which could result in an anti-doping rule violation.[5]

In 2013 the Australian Crime Commission reported that performance-enhancing and image-enhancing drugs, including peptides and hormones, were being used in some sections of professional sport.[6] Section S2 of the Prohibited List addresses this issue by including growth hormone, erythropoietin and 'other substances with similar chemical structure or similar biological effects'.

During 2013–14, ASADA conducted an assessment of sanctioned athletes and found that 54% of publicly disclosed anti-doping rule violations involved a prohibited stimulant found in a supplement.[7] Athletes and the professionals supporting them need to be vigilant about the dangers of an inadvertent violation of anti-doping rules occurring as a result of taking sports supplements.

Box World Anti-Doping Code Prohibited List 2015 [2]

Substances and methods prohibited at all times (in and out of competition)

Prohibited substances

S0. Non-approved substances

This includes veterinary drugs and those which have not been approved by regulatory bodies such as the Therapeutic Goods Administration.

S1. Anabolic drugs

- S1.1 Anabolic androgenic steroids
  - a. exogenous e.g. danazol
  - b. endogenous e.g. testosterone and its metabolites
- S1.2 Other anabolic agents e.g. tibolone

S2. Peptide hormones, growth factors, related substances and mimetics

- S2.1 Erythropoietin-receptor agonists
  - i. erythropoiesis-stimulating agents e.g. erythropoietin (EPO)
  - ii. non-erythropoietic EPO-receptor agonists
- S2.2 Hypoxia-inducible factor stabilisers, and activators e.g. argon
- S2.3 Chorionic gonadotrophin and luteinising hormone and their releasing factors in males
- S2.4 Corticotropins and their releasing factors
- S2.5 Growth hormone and its releasing factors

S3. $Beta_2$ agonists

Inhaled drugs, such as salbutamol, can be used within specified limits.

S4. Hormone and metabolic modulators

- S4.1 Aromatase inhibitors e.g. anastrozole
- S4.2 Selective oestrogen receptor modulators e.g. tamoxifen
- S4.3 Other anti-oestrogenic substances e.g. clomiphene
- S4.4 Drugs modifying myostatin function
- S4.5 Metabolic modulators e.g. insulin

S5. Diuretics and masking agents

The masking agents include drugs such as probenecid.

Prohibited methods

M1. Manipulation of blood and blood components

This includes retransfusion of the athlete's own blood.

M2. Chemical and physical manipulation

This includes tampering with samples.

M3. Gene doping

This includes normal as well as genetically modified cells.

Substances prohibited in competition

S6. Stimulants e.g. amphetamines, pseudoephedrine

S7. Narcotics e.g. methadone

S8. Cannabinoids

S9. Glucocorticosteroids

Substances prohibited in particular sports

P1. Alcohol (banned in air sports, archery, motor sport, motorcycling and powerboating)

P2. Beta blockers (banned in archery, motor sport, billiards, darts, golf, shooting, some skiing and snowboarding events, and some underwater events)

Harmful effects of doping

Medical practitioners need to be aware of the potential adverse effects of doping behaviour by athletes. Drugs such as anabolic steroids are associated with aggression, hypertension, impotence and infertility. Abuse of growth hormone can result in acromegaly and an increased risk of cancer. Use of erythropoietin for sporting purposes increases the risk of hypertension, thrombus formation and thromboembolic events. Athletes who decide to dope are by nature risk-takers and will often underestimate the potential health risks associated with doping behaviour.

Anti-doping resources

There are many resources available to medical practitioners to assist when there is any doubt about a medicine being prohibited. Perhaps the most useful of these is the online 'Check Your Substances' tool, hosted on the ASADA website. This site (https://checksubstances.asada.gov.au) allows medical practitioners, coaches and athletes to enter the name of the drug and receive advice about its status. The substance will be deemed to fall under one of four categories:

- permitted for use (e.g. paracetamol, amoxycillin)
- prohibited (e.g. testosterone, amphetamine)
- permitted in females only (e.g. human chorionic gonadotrophin)
- subject to certain conditions (e.g. prednisolone, pseudoephedrine hydrochloride).

The Australian Sports Drug Medical Advisory Committee website (www.asdmac.gov.au/athletes/conditions.html) contains advice relating to specific medical conditions such as asthma, attention deficit hyperactivity disorder and hypertension. There is also advice for medical practitioners on therapeutic use exemptions. In addition, there are several online educational resources that allow individuals to inform themselves about anti-doping rules (www.asada.gov.au/education/index.html).

The ASADA E-Learning webpage provides medical practitioners and others involved in sport with up-to-date educational resources to assist them when dealing with athletes on matters of anti-doping compliance (http://elearning.asada.gov.au). There is an online update covering the 2015 World Anti-Doping Code and the changes from the 2009 Code, and how this affects athletes and their support personnel. This site requires registration, but the learning module only takes a maximum of 15 minutes to complete.

Some sources of drug information, such as MIMS, provide a symbol against drugs that have potential ramifications for athletes.

Conclusion

For medical practitioners and others who are not regularly dealing with high-performance athletes, the WADA Code can appear to be a long, confusing and cumbersome document. WADA and national anti-doping organisations attempt to strike a balance between providing equity and fairness in sport, and ensuring that athletes have access to appropriate treatment for legitimate medical conditions.

The ASADA website is a useful resource. In particular, the 'Check Your Substances' page provides an easy reference for medical practitioners when there is doubt regarding the status of a particular drug. If any doubt persists and the medical problem is not urgent, the athlete should be urged to consult with their national sporting organisation. All national sporting organisations have appropriate contacts through which they can provide advice. If a medical practitioner, coach, athlete or parent has further questions that cannot be answered via the ASADA website, they can ring ASADA on 1300 027 232.

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ARTICLE

Oral targeted therapy for cancer

SUMMARY

Oral targeted therapies are increasingly being used to treat cancer. They work by interfering with specific molecules or pathways involved in tumour growth.

It is essential that health professionals managing patients taking these drugs have appropriate training and skills. They should be aware of potential adverse effects and drug interactions, and be able to manage toxicities when they occur.

Despite the selectivity of these targeted therapies, they still have serious adverse effects including skin reactions, diarrhoea and altered organ function.

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Key words
adverse effects, drug interactions, targeted cancer therapies, tyrosine kinase inhibitors

Aust Prescr 2015;38:171–6

Introduction

Targeted therapies block the spread or growth of cancer by interfering with specific molecules or pathways involved in the growth and progression of cancer. The target molecule may be present in normal tissue, but is overexpressed or mutated in the cancer. These drugs can be more effective than cytotoxic chemotherapy as they are specific to the cancer.

Targeted therapies do not damage normal cells in the way cytotoxic chemotherapy does. Nevertheless they are still associated with some toxic adverse effects. These effects are often unique to the therapy and can be severe requiring close monitoring and clinical management. Targeted therapies can also be used in combination with chemotherapy and radiation therapy, and synergistic toxicities such as diarrhoea and skin effects can occur.

Small-molecule inhibitors are given orally. Although treatment is initiated and managed by a cancer specialist, ongoing therapy may not always need to be administered in an oncology setting and patients taking these drugs are increasingly being seen in general practice.

Monoclonal antibodies are another type of targeted therapy for cancer. However, these drugs are given parenterally because they are proteins and would be destroyed by the gut.

Small-molecule inhibitors

Table 1 lists current oral small-molecule inhibitors for specific cancers that are reimbursed by the Pharmaceutical Benefits Scheme (PBS). A large number are also under investigation in clinical trials so it is expected that more will be approved over the next few years.

Mode of action

Small-molecule inhibitors are able to cross the cell plasma membrane and interfere with intracellular targets. They often act on multiple pathways in the cell.

Protein kinases play an important role in regulating cellular activity and are often found to be mutated in cancer. A number of therapies have been developed that block kinase activity and hence block cell growth. These drugs carry the suffix -nib.

BCR-ABL inhibitors

Imatinib was one of the first targeted therapies to be developed for the treatment of chronic myeloid leukaemia. It blocks the BCR-ABL protein kinase which results from a chromosomal translocation (the Philadelphia chromosome) in chronic myeloid leukaemia. Imatinib inhibits the proliferation of leukaemia cells and results in durable responses in over 80% of patients.[1] Imatinib is also active against gastrointestinal stromal tumours and certain types of acute leukaemia.

Epidermal growth factor receptor inhibitors

The epidermal growth factor receptor (EGFR) exists on the outside of cells and is activated by growth factor ligands. Once activated, intracellular tyrosine kinase activity occurs and several signal transduction cascades are initiated which lead to cell proliferation. In many cancers the EGFR activity is increased due to mutations in the receptor or tyrosine kinase protein domains. EGFR tyrosine kinase inhibitors, such as erlotinib and gefitinib, act on the EGFR tyrosine kinase domain. They are used to treat advanced non-small cell lung cancers that have the EGFR mutation.[2,3]

Lapatinib inhibits the tyrosine kinase activity associated with EGFR and human epidermal growth factor receptor 2 (HER2).[4] The HER2 receptor is overexpressed in about 25–30% of breast cancers.

Table 1 **Oral targeted therapies subsidised by the Pharmaceutical Benefits Scheme** [7-11]

Target	Medicine (brand name)	Indication
BRAF	dabrafenib (Tafinlar)	melanoma
BCR-ABL	imatinib (Glivec)	chronic myeloid leukaemia, gastrointestinal stromal tumour
	dasatinib (Sprycel)	chronic myeloid leukaemia
	nilotinib (Tasigna)	chronic myeloid leukaemia
EGFR	erlotinib (Tarceva)	non-small cell lung cancer
	gefitinib (Iressa)	non-small cell lung cancer
	lapatinib (Tykerb)	metastatic breast cancer
MEK	trametinib (Mekinist)	melanoma
mTOR	everolimus (Afinitor)	metastatic breast cancer, renal cell carcinoma
Multi-targeted, including VEGF	pazopanib (Votrient)	renal cell carcinoma, soft tissue sarcoma
	sunitinib (Sutent)	renal cell carcinoma, pancreatic neuroendocrine tumour
	sorafenib (Nexavar)	hepatocellular carcinoma
Immune system (immunomodulators)	thalidomide (Thalomid)	myeloma
	lenalidomide (Revlimid)	myeloma, myelodysplastic syndrome
	pomalidomide (Pomalyst)	myeloma

BRAF Intracellular protein kinase that forms part of the mitogen-activated protein (MAP) kinase pathway and drives cell proliferation
BCR-ABL BCR = breakpoint cluster region, ABL = abelson murine leukemia oncogene-1 (BCR-ABL is a fusion gene created by the ABL1 gene on chromosome 9 to the BCR gene on chromosome 22)
EGFR Epidermal growth factor receptor (member of the ErbB family of receptors that promotes cell proliferation)
MEK MAPK/ERK kinase (MAPK = mitogen activated protein kinase, ERK = extracellular-signal-regulated kinase)
mTOR Mammalian target of rapamycin (protein kinase that regulates cell growth)
VEGF Vascular endothelial growth factor (protein produced by cancer cells that stimulates angiogenesis)

BRAF and MEK inhibitors

Other targeted drugs inhibit pathways that occur downstream of the EGFR receptor. Dabrafenib inhibits the activity of BRAF, an intracellular protein kinase of the RAF kinase family that drives cell proliferation and can be mutated in melanoma cells (Aust Prescr 2014;37:28-35). Dabrafenib significantly improves progression-free survival (by approximately two months) in melanoma compared to standard chemotherapy.[5]

Trametinib inhibits the MEK pathway and has been combined with dabrafenib in an effort to reduce resistance to dabrafenib, and to reduce some of the adverse effects associated with BRAF inhibition.[6]

Multi-targeted drugs including vascular endothelial growth factor inhibitors

Sunitinib, sorafenib and pazopanib are kinase inhibitors that affect multiple pathways involved in cancer cell growth. In addition to blocking tyrosine kinase pathways they block the vascular endothelial growth factor (VEGF) protein which promotes angiogenesis. These drugs are active in a variety of cancers due to their diverse activity (Table 1).[7-11]

Adverse effects

Despite their selectivity, targeted therapies still have adverse effects, ranging from mild skin reactions to fatal gastrointestinal perforation (see Table 2). Toxicity depends largely on the target of the drug and the drug's individual properties. Most targeted therapies, with the exception of immunomodulatory drugs, are known to cause nausea, diarrhoea and skin problems. Adverse effects of individual drugs and the management of these can be found in the eviQ Cancer Treatments Online website (www.eviq.org.au).[12]

Patients require constant monitoring while on therapy. All healthcare professionals who see the patient should be aware of the toxicity profile of the therapy and the appropriate management. Many targeted therapies can adversely affect liver and renal function so laboratory results should be monitored regularly. It is usual for the treating haematologist or oncologist to review blood tests monthly.
Some targeted therapies are used in combination with cytotoxic chemotherapy. For example, the

Table 2 **Common adverse affects associated with oral cancer therapies**

Adverse effect	Drug (affects >1% of patients)
Diarrhoea	dabrafenib, dasatinib, erlotinib, gefitinib, lapatinib, nilotinib, pazopanib, sorafenib, sunitinib
Hypertension	pazopanib, sorafenib, sunitinib
Prolongation of QT interval	dabrafenib, dasatinib, lapatinib, nilotinib, pazopanib, sorafenib, sunitinib
Bleeding	dasatinib, erlotinib, gefitinib, pazopanib, sorafenib, sunitinib
Constipation	lenalidomide, thalidomide
Fever	dabrafenib
Hypothyroidism	imatinib, pazopanib, sunitinib
Oedema	dasatinib, everolimus, imatinib, nilotinib
Pulmonary complications	dasatinib, imatinib, erlotinib, gefitinib, lapatinib
Venous thromboembolic events	lenalidomide, pazopanib, sorafenib, sunitinib, thalidomide
Reduction in left ventricular ejection fraction	dasatinib, lapatinib, pazopanib, sorafenib, sunitinib, trametinib

combination of lapatinib and capecitabine is used in breast cancer and these patients require a regular check of their blood counts before each cycle of chemotherapy.

Dermatological effects

Skin reactions are common with targeted therapies that affect the EGFR pathways since the EGFR is found in the skin. These effects tend to develop a few weeks after starting therapy and include rash, itching, and changes in hair and nails.[13] Table 3 details common dermatological effects of targeted therapies.

Patients taking EGFR inhibitors should use a mild soap that is free from alcohol and perfume, and apply a bland moisturiser as a preventive measure at least twice a day. Skin can be extra sensitive to the sun and patients should be advised to use a broad spectrum sunscreen (SPF 30+). Hydrocortisone cream and oral antibiotics such as doxycycline which have an anti-inflammatory action are alternatives for skin rashes not responsive to moisturising creams.

The BRAF inhibitors have a potential to cause skin malignancies. These patients should be regularly checked for signs of malignant skin changes such as the development of a squamous cell carcinoma.

The Multinational Association of Supportive Care in Cancer (www.mascc.org) provides useful clinical practice guidelines for the prevention and treatment of EGFR inhibitor-associated dermatological toxicities.[14] Therapy may need to be interrupted or reduced for severe reactions. This decision will be made by the treating haematologist or oncologist in consultation with the patient.

Gastrointestinal effects

Gastrointestinal-related toxicity is prominent with many targeted therapies. Complications include diarrhoea, constipation and nausea.

Diarrhoea affects up to 80% of patients. In many cases the diarrhoea can be managed with antidiarrhoeal medication, such as loperamide. If not controlled, it can quickly develop into serious dehydration and electrolyte imbalance. Patients must be educated about self-monitoring and self-treatment of diarrhoea when they start therapy. It is usual to provide the patient with a supply of loperamide to use should diarrhoea develop. Patients must be advised to seek advice from their specialist if diarrhoea lasts for longer than 24 hours or does not respond to medication.[15] Patients who develop severe diarrhoea may require a dose adjustment, treatment interruption or even discontinuation of the therapy.

Bleeding risk and implications for surgery

Because angiogenesis inhibitors (e.g. pazopanib, sorafenib, sunitinib) affect blood vessels, patients can have problems with bleeding and wound healing.

These drugs should be stopped before any planned surgery or invasive procedures including dental surgery. It is generally recommended that therapy is stopped a week before major surgery and at least 3–4 days before minor surgery. Treatment is generally restarted four weeks after surgery to reduce complications with wound healing, but this may vary according to the therapy, surgery and the patient. Advice should always be sought from the treating oncologist or haematologist with regard to stopping and starting of therapy and for surgical or dental procedures.

Table 3 **Common skin problems with oral cancer therapies**

Skin problems	Presentation
Papulopustular (acneiform) rash	Erythematous pustules with or without pruritus Occurs on scalp, face, upper chest and back Onset occurs 1–6 weeks after treatment commences
Xerosis (dry skin) and fissures	Dry, scaly, itchy skin Often follows the acneiform rash Painful fissures on tips of fingers and toes Onset 1–2 months after treatment commences
Pruritus	Often accompanies acneiform rash and dry skin
Paronychia	Tender and oedematous inflammation of the nail folds of fingers and toes Lesions can become infected Onset about 6 weeks after treatment commences
Hand–foot syndrome	Redness in the palms of the hands and soles of feet Blisters and cracked peeling skin can develop May be accompanied by painful paraesthesia Onset 1–2 months after treatment commences
Hair changes	Trichomegaly (elongation and curling of the eyelashes) Hypertrichosis (usually as facial hair) Hyperpigmentation Scalp hair changes including brittle hair, slowed growth and alopecia Onset 2–5 months after treatment commences

Immunomodulatory drugs

Lenalidomide, thalidomide and pomalidomide are immunomodulatory drugs mainly used in the treatment of myeloma in combination with steroids.[16] They may also be combined with cytotoxic chemotherapy. They block several pathways that drive the progression of myeloma and have anti-angiogenic properties.

Due to the well-documented risk of birth defects associated with these drugs, only specialists and pharmacists registered with the Pharmion Risk Management Program are allowed to prescribe and dispense thalidomide, lenalidomide and pomalidomide.

There is an increased incidence of thromboembolic events in patients treated with the combination of dexamethasone and lenalidomide, thalidomide or pomalidomide, and prophylactic antithrombotic therapy is routine for these patients.[17] These drugs are associated with constipation and diarrhoea. Haematological toxicities are more common with lenalidomide, while dose-dependent peripheral neuropathy is associated with prolonged therapy with thalidomide.

All-trans retinoic acid

All-trans retinoic acid is an oral therapy used in the treatment of acute promyelocytic leukaemia,[18] usually in combination with arsenic trioxide and/or cytotoxic chemotherapy. It is a derivative of vitamin A with a distinct mode of action. All-trans retinoic acid binds to the retinoic acid gene receptor and induces the differentiation of acute promyelocytic leukaemia cells into normal mature cells. Common adverse effects include headache, fever, weakness and fatigue. All-trans retinoic acid should only ever be prescribed by a haematologist experienced in managing acute promyelocytic leukaemia.

Drug interactions

Interactions between targeted therapy and other prescribed and over-the-counter medicines, complementary medicines and food can affect the efficacy and safety of both the targeted therapy and other therapy. It is important that an assessment is made of potential interactions when a patient is started on therapy, or when any new medications are started.

The bioavailability and absorption of many tyrosine kinase inhibitors is affected by food and the acidity

of the stomach environment. The concomitant use of acid suppressive treatment decreases absorption of dasatinib, erlotinib, gefitinib, lapatinib and pazopanib.[19] The combination of these drugs and an H_2 antagonist, proton pump inhibitor or antacid should be avoided. Food can enhance the absorption of lapatinib in an unpredictable manner and lapatinib should be taken on an empty stomach.

A number of targeted therapies are substrates for the cytochrome P450 (CYP) 3A4 enzyme.[20-22] Simultaneous use with other CYP3A4 inhibitors, such as grapefruit juice, can increase concentrations of many targeted drugs and cause toxicity. A warning label alerting the patient not to consume grapefruit-containing products is required on many targeted therapies including lapatinib, nilotinib, pazopanib and sunitinib.

Other CYP3A4 inhibitors that patients with cancer may be taking include:

- azole antifungals – fluconazole, itraconazole, posaconazole, voriconazole
- macrolide antibiotics – clarithromycin, erythromycin
- antiemetics – aprepitant.

Concomitant use of CYP3A4 inducers can reduce concentrations of tyrosine kinase inhibitors and lower their efficacy. CYP3A4 inducers include:

- antiepileptic drugs – carbamazepine and phenytoin
- oral dexamethasone
- rifampicin
- St John's wort.

$5HT_3$ antagonists (for nausea), antibiotics (clarithromycin, erythromycin) and azole antifungals (such as fluconazole) are commonly used by patients with cancer and these can have a fatal interaction with targeted therapies by prolonging the QT interval (Aust Prescr 2015;38:20-4). QT prolongation with the serotonin $5HT_3$ antagonist ondansetron occurs in a dose-dependent manner. Single intravenous doses of ondansetron should not exceed 16 mg in patients under 75 years and 8 mg in patients over 75 years. If concurrent use of these drugs cannot be avoided then an ECG should be obtained before, and one week after, starting concomitant medication.

Targeted therapies with anti-angiogenic activity can increase the risk of bleeding. Any co-administered drug or complementary therapy that interferes with blood clotting adds to this risk. Caution should be used when prescribing or dispensing antiplatelet medication, and anticoagulants including dabigatran, rivaroxaban and apixaban.

Vaccination

Live vaccines are contraindicated in patients with impaired immune function and those who have poorly controlled malignant disease. Inactivated vaccines are generally safe, but patients may have a diminished immune response to the vaccine. The recommended schedule of vaccination for cancer patients is outlined in the 10th edition of the Australian Immunisation Handbook.[23]

Patient information and labelling

The majority of oral targeted therapies will be self-administered at home by the patient. As with oral cytotoxic therapy, patients should be given verbal information and a written plan that includes when the drug should be taken and if it should be taken before or after food, adverse effects and any drugs or foods that need to be avoided.

The labelling of oral targeted therapy, like cytotoxic therapy, should clearly state the dose and the number of tablets to be taken. It is important that the patient understands when continuous dosing may be required or when the drug is given on a cyclical basis. For example, in renal cell cancer, sunitinib is taken as a daily dose for four weeks followed by a two-week break, whereas pazopanib is taken continuously. In pancreatic neuroendocrine tumours, sunitinib is taken continuously.

Targeted therapies are not cytotoxic and do not require cytotoxic handling precautions. Some are known to be teratogenic, for example thalidomide, while for others there is limited or no evidence of safety. The product information should always be consulted.

Adherence to treatment

Many targeted therapies are taken continuously for a number of months or years until disease progression or resistance occurs. Adherence to treatment plays a pivotal role in the success of therapy. Treatment failure can develop with some therapies, such as imatinib for chronic myeloid leukaemia, if they are not taken as prescribed.[24] This is due to the loss of the cytogenetic response because of the inconsistent exposure to imatinib.

Non-adherence increases with longer duration of therapy and when patients experience adverse effects. Adherence should be discussed regularly with the patient to identify any difficulties they may be having complying with the dosing.

Drug resistance

Acquired resistance to molecularly targeted drugs can develop over time and occurs with almost all therapies. Specific mutations often contribute directly to this, however cellular and physiological mechanisms also play a significant role. Resistance to therapy remains a significant challenge in the clinical management of cancer with targeted therapy.

Conclusion

As with oral cytotoxic therapy, the delivery of oral targeted therapy requires a multidisciplinary approach.[25,26] Treatments should only be initiated by a cancer specialist who has experience with these drugs.

It is essential that health professionals managing these patients have appropriate training and skills in the use of these therapies in cancer care. They should be aware of the adverse effects and the potential for drug interactions. Healthcare professionals should seek advice from the prescribing cancer specialist when required. If a patient unknown to the doctor or pharmacist presents for therapy, a full patient review must be conducted and the oncologist or haematologist who initiated treatment should be contacted for further advice. ◁

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New drugs

Apremilast

Approved indications: psoriasis, psoriatic arthritis
Otezla (Celgene)
30 mg film-coated tablets
Australian Medicines Handbook Appendix A

Psoriatic arthritis affects at least 25% of patients with psoriasis. Although there may be differences in the pathogenesis, both conditions involve immune-mediated inflammation. Immunosuppressant drugs such as methotrexate and cyclosporin have therefore been used to treat severe cases.

Phosphodiesterase 4 is an enzyme involved in inflammatory processes. When it is inhibited by apremilast there is a decrease in pro-inflammatory cytokines, such as tumour necrosis factor, and an increase in anti-inflammatory cytokines such as interleukin 10. In psoriatic skin, this results in less infiltration by inflammatory cells and reduced epidermal thickness.

The dose of apremilast is increased over six days from 10 mg on the first day to reach the recommended dose of 30 mg every 12 hours. The tablets can be taken with food, but should not be divided. After the drug is absorbed it is extensively metabolised. Some of the metabolic pathways involve the cytochrome P450 (CYP) system including CYP3A4. The concentration of apremilast will be reduced by inducers of CYP3A4, such as phenytoin, rifampicin and St John's wort, but inhibitors of CYP3A4, such as ketoconazole, do not significantly increase the concentration. Most of the metabolites are excreted in the urine. A dose reduction is required in severe renal impairment (creatinine clearance <30 mL/min). The elimination half-life is about nine hours.

Apremilast has been studied in moderate to severe psoriasis and in psoriatic arthritis but, at the time of writing, not all of the phase III trials have been published in full.

In a phase II placebo-controlled, dose-ranging study, 88 patients were randomised to take apremilast 30 mg twice daily. The outcome of this study was the proportion of patients who had at least a 75% improvement on the Psoriasis Area and Severity Index (PASI 75). After 16 weeks, 41% of the patients had this response compared with 6% (5/88) of the patients given a placebo.[1]

Two phase III trials enrolled 1257 patients with moderate to severe plaque psoriasis. Results at 16 weeks showed that the PASI 75 outcome was achieved by 28.8–33.1% of the patients taking apremilast, but only by 5.3–5.8% of those taking a placebo. In one of the trials 77 patients, who had achieved a PASI 75 response, continued treatment for 52 weeks. This response was sustained in 47 of these patients.[2]

There were four main trials of apremilast in psoriatic arthritis. They had similar designs with 24 weeks of placebo-controlled treatment followed by at least 28 weeks of active treatment for all patients and then an open-label safety phase. The primary outcome of these trials was the proportion of patients having a 20% improvement in their condition as assessed by the American College of Rheumatology criteria (ACR 20).

The first of these trials (PALACE 1) randomised 168 patients who had experienced an inadequate response to disease-modifying antirheumatic drugs, to take apremilast 30 mg twice daily and 168 to take a placebo. After 16 weeks an ACR 20 response had been achieved by 38.1% of those taking apremilast and 19% of the placebo group. For the patients who had psoriasis affecting at least 3% of their skin surface there was some improvement – a 75% reduction in the PASI was achieved by 21% of patients taking apremilast 30 mg twice daily and 4.6% of the placebo group.[3] The two other trials of previously treated patients had similar ACR 20 results (see Table).

A fourth trial with a similar design studied 528 patients with psoriatic arthritis who had not previously been treated with a disease-modifying drug. At 16 weeks an ACR 20 response had been achieved by 30.7% of the patients taking apremilast and 15.9% of the placebo group.

The advantage of apremilast over placebo was sustained in patients who continued to take it for psoriatic arthritis. In the PALACE 1 trial, 130 of the 168 patients randomised to take apremilast 30 mg twice daily continued it for a year. An ACR 20 response was achieved by 54.6%.[4] In the other two trials of previously treated patients the response was 52.6–63% while for untreated patients it was 57%.

Adverse events with apremilast led to 5.2% of the patients dropping out of the psoriasis studies and 4.9% dropping out of the psoriatic arthritis studies. Common adverse effects included diarrhoea, nausea, upper respiratory tract infections and headaches. Over a year there was an average weight loss of

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.

Table **Efficacy of apremilast in psoriatic arthritis**

Trial	Response rates at 16 weeks ‡	
	Placebo	Apremilast 30 mg 12-hourly
PALACE 1[3]	19% (32/168)	38.1% (64/168)
PALACE 2	18.9% (30/159)	32.1% (52/162)
PALACE 3	18.3% (31/169)	40.7% (68/167)

‡ Proportion of patients previously treated with a disease-modifying antirheumatic drug who had at least a 20% improvement in the criteria of the American College of Rheumatology

1.86 kg. There is a question about whether there is an increased incidence of depression with apremilast.

Apremilast is contraindicated in pregnancy. It is unknown if the drug is excreted in human breast milk.

While apremilast is more effective than a placebo for patients with moderate to severe plaque psoriasis, it needs to be compared to other oral therapies. It is unknown whether apremilast has a disease-modifying effect in joints affected by psoriatic arthritis. Until more data are available, it would seem prudent to reserve apremilast for patients with active psoriatic arthritis who do not respond or cannot tolerate other drugs, however this restriction has not been included in the marketing approval.

T T manufacturer provided additional useful information

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First published online 26 August 2015

Ibrutinib

Approved indication: chronic lymphocytic leukaemia, mantle cell lymphoma

Imbruvica (Janssen-Cilag)

140 mg tablets

Australian Medicines Handbook section 14.2.3

Ibrutinib is an oral small-molecule drug for B-cell malignancies. It works by binding to Bruton's tyrosine kinase and blocking signalling through the B-cell receptor and cytokine receptor pathways. This inhibits the proliferation of B cells.

Ibrutinib has been registered for the following indications:

- first line for chronic lymphocytic leukaemia in patients with the 17p deletion
- second line for chronic lymphocytic leukaemia and small lymphocytic lymphoma (after at least one previous therapy)
- second line for mantle cell lymphoma (after at least one previous therapy).

Ibrutinib should be taken once a day. The recommended daily dose is 420 mg for chronic lymphocytic leukaemia and small lymphocytic lymphoma, and 560 mg for mantle cell lymphoma.

The safety and efficacy of ibrutinib were assessed in several trials.[1-3] In general, patients were heavily pre-treated (2–4 previous therapies) and their median ages were 66–68 years. Patients taking warfarin were excluded.

Chronic lymphocytic leukaemia and small lymphocytic lymphoma

The approval is based on a single-arm phase II trial[1] and a comparative phase III trial with ofatumumab.[2] Most enrolled patients had chronic lymphocytic leukaemia with only 5% having small lymphocytic lymphoma. Approximately a third of those in each trial had an abnormal chromosome 17 (17p deletion), which is associated with a poorer prognosis.

Patients were given daily ibrutinib until their disease progressed or they developed unacceptable adverse effects. In the phase II trial, patients were given 420 mg or 840 mg. Overall, 71% of patients responded to treatment (Table 1). These were mainly partial responses. At 26 months, the progression-free survival rate was estimated at 75% and overall survival was 83%.

In the phase III trial, ibrutinib 420 mg significantly improved rates of progression-free survival, overall survival and treatment responses compared to ofatumumab (Table 1).[2] The efficacy of ibrutinib was similar in patients with and without the 17p deletion.[1,2]

Mantle cell lymphoma

The approval of daily ibrutinib 560 mg for mantle cell lymphoma is based on an open-label, uncontrolled phase II trial of 111 patients with relapsed or refractory disease.[3] Over two-thirds of patients responded to ibrutinib – 23 patients had a complete response and 35 had a partial response (Table 2). The response rate seemed to be independent of age, previous bortezomib exposure and prognosis at baseline. The estimated median duration of response was 17.5 months and the estimated median progression-free survival was just under 14 months.

Adverse effects and precautions

In a cohort of 357 patients, 6% discontinued treatment because of an adverse event (including infection and subdural haematoma). The most common adverse events were diarrhoea, musculoskeletal pain, upper respiratory tract infection, bruising, rash, nausea, fever, neutropenia and constipation. These were reported in at least 20%

Table 1 **Efficacy of daily ibrutinib in chronic lymphocytic leukaemia and small lymphocytic lymphoma**

Phase II trial [1]	**Ibrutinib 420 mg (51 patients)**	**Ibrutinib 840 mg (34 patients)**
Response rate‡	71% (2 complete and 34 partial responses)	71% (24 partial responses)
Progression-free survival estimated at 26 months	75%	
Overall survival at 26 months	83%	
Phase III trial [2]	**Ibrutinib 420 mg (195 patients)**	**Ofatumumab§ (196 patients)**
Response rate‡	43% (all partial responses)	4% (all partial responses)
Progression-free survival at 6 months	88%	65%
Median duration of progression-free survival	Not reached (at 9.4 months)	8.1 months
Overall survival at 12 months	90%	81%

‡ Assessment included blood counts, physical and radiological examinations to determine lymph node, spleen and liver size, and bone marrow biopsy to confirm a complete response.

§ Intravenous ofatumumab 300 mg was given at week one followed by 2000 mg each week for seven weeks and then monthly for 16 weeks.

Table 2 **Efficacy of daily ibrutinib in mantle cell lymphoma** [3]

	Ibrutinib 560 mg (111 patients)
Overall response rate#	68% (23 complete responses, 52 partial responses)
Estimated median duration of progression-free survival	17.5 months
Estimated median progression-free survival	13.9 months
Estimated overall survival at 18 months	58%

Response was assessed by regular physical and radiological examinations (CT and PET scans) and bone marrow biopsy. A PET scan was needed to confirm complete responses.

of patients. Anaemia, neutropenia, pneumonia and thrombocytopenia were the most common serious adverse effects (grade 3 or 4) and occurred in 5% or more of patients.

In total, 26 patients died during the trials. Apart from progressive disease, causes included pneumonia (5 patients), sepsis (2 patients), secondary malignancy (2 patients), cardiac arrest (1 patient) and hypovolaemic shock (1 patient).

Bleeding-related adverse events were common with ibrutinib and ranged from bruising and nosebleeds to blood in the urine, gastrointestinal bleeding and intracranial haemorrhage. Warfarin, fish oil and vitamin E should not be given concomitantly with ibrutinib.

Atrial fibrillation is a risk with ibrutinib, particularly during acute infections or in people with a history of atrial fibrillation or other cardiac risk factors. Regular cardiac monitoring is recommended. Alternatives to ibrutinib should be considered in patients who need oral anticoagulants.

Blood counts should be monitored every month as severe neutropenia, thrombocytopenia and anaemia can occur. Skin cancers have been reported with ibrutinib so regular skin examination is important.

Ibrutinib caused a transient increase in lymphocyte count at the beginning of treatment in 75% of patients with chronic lymphocytic leukaemia and 35% of patients with mantle cell lymphoma. Lymphocytosis often occurred at the same time as a reduction in lymph node and spleen size and is thought to be a pharmacodynamic effect unrelated to progressive disease. Leukostasis (clumping of white blood cells) was occasionally reported and may be related to an increase in circulating lymphocytes. It can cause local hypoxaemia and bleeding which can present as headache, blurred vision, transient ischaemia, cerebrovascular accident and dyspnoea. Patients should be monitored closely and ibrutinib may need to be interrupted if this occurs.

Pharmacology and drug interactions

Ibrutinib is rapidly absorbed after oral administration and metabolised in the liver by cytochrome P450 (CYP) 3A4. The half-life is 4–6 hours and metabolites are eliminated in the faeces (90%) and urine (10%).

Co-administration of moderate or strong CYP3A4 inhibitors such as ketoconazole, clarithromycin, erythromycin or verapamil should be avoided. If they are needed, the ibrutinib dose should be reduced to 140 mg or interrupted for up to a week. Avoid grapefruit and Seville oranges as they can inhibit CYP3A4.

Strong CYP3A4 inducers and drugs that increase the pH of the stomach can decrease ibrutinib concentrations and are not recommended. St John's wort should also be avoided. As ibrutinib could theoretically inhibit intestinal P-glycoprotein, substrates of this transporter with a narrow therapeutic index (e.g. digoxin) should be taken at least six hours before or after the ibrutinib dose.

Conclusion

Ibrutinib offers another option for people with chronic lymphocytic leukaemia or mantle cell lymphoma, particularly those who have relapsed after previous treatments. Adverse effects are common and sometimes severe so patient monitoring is very important with this drug.

T T manufacturer provided additional useful information

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First published online 26 June 2015

Pembrolizumab

Approved indication: metastatic melanoma
Keytruda (MSD)
vials containing 50 mg powder
Australian Medicines Handbook section 14.2.1

Along with vemurafenib[1], dabrafenib[2] and trametinib[3], pembrolizumab is approved for metastatic melanoma. Like ipilimumab[4], it is an immune checkpoint inhibitor that works by modulating the patient's own immune response to tumour cells.[5]

Pembrolizumab was formerly known as MK3475 and lambrolizumab. It is a humanised monoclonal antibody that blocks the interaction between programmed death 1 (PD-1) on T cells with its ligands PD-L1 and PD-L2 on immune and tumour cells. Blocking this interaction boosts the immune response and potentially leads to tumour regression.

This antibody is indicated as monotherapy for inoperable or metastatic melanoma. It is given intravenously (over 30 minutes) every three weeks. The drug's terminal half-life is approximately 26 days. The drug is catabolised and its clearance is not affected by mild–moderate renal impairment or mild hepatic impairment. Pembrolizumab has not been studied in patients with more severe renal or hepatic impairment.

Pembrolizumab has been assessed in a number of clinical trials. A phase I non-randomised trial enrolled 135 patients with advanced disease. The majority of participants (69%) had received previous systemic treatment, including chemotherapy, immunotherapy, or a BRAF inhibitor. Patients were given pembrolizumab 10 mg/kg every two or three weeks, or 2 mg/kg every three weeks. Across all doses, 38% of patients who could be evaluated had a confirmed response to treatment (see Table). The estimated median progression-free survival was over seven months and median overall survival was not reached.[6]

This phase I trial was expanded to include another cohort of patients who were refractory to ipilimumab and, if they had the BRAF mutation, had previously been treated with a BRAF or MEK inhibitor, or both. They were randomly assigned to pembrolizumab 2 mg/kg or 10 mg/kg every three weeks. Just over a quarter of patients responded to treatment and 58–63% were still alive after a year (see Table).[7] The efficacy of pembrolizumab in the phase I trial seemed to be independent of the dose.[6,7]

An analysis of 146 patients who received pembrolizumab 2 mg/kg found that response rates were better in those who had not previously been treated with ipilimumab compared with those who had (37% vs 26%). The median duration of progression-free survival was also longer (36 vs 22 weeks). At six months, overall survival was similar in ipilimumab-naïve and pre-treated patients (79% vs 83%). This analysis has not yet been published in full.

A randomised phase III trial compared pembrolizumab to ipilimumab. All enrolled patients had advanced melanoma but only 34% had been previously treated with systemic therapy. Pembrolizumab 10 mg/kg every two or three weeks improved progression-free and overall survival compared to ipilimumab. Response rates were also better with pembrolizumab (see Table).[8]

In the safety cohort of 411 patients, the most common treatment-related adverse events included arthralgia (14.8%), diarrhoea (14.8%), fatigue (30.2%), nausea (10%), pruritus (22.8%), cough (11.1%) and rash (19.8%). Albumin (36.7%), haemoglobin (51.6%) and lymphocytes (28.2%) went down with pembrolizumab. Decreased calcium (28.5%) and sodium (32.6%) concentrations were also observed. Liver function should be monitored as increases in alanine aminotransferase (23.6% of patients), alkaline

Table **Efficacy of pembrolizumab in metastatic melanoma**

Phase I trial[6]			
	Pembrolizumab 10 mg/kg every 2 weeks (52 patients)	**Pembrolizumab** 10 mg/kg every 3 weeks (45 patients)	**Pembrolizumab** 2 mg/kg every 3 weeks (20 patients)
Response rate‡	52%	27%	25%
Phase I trial – expanded cohort[7]			
	Pembrolizumab 10 mg/kg every 3 weeks (76 patients)	**Pembrolizumab** 2 mg/kg every 3 weeks (81 patients)	
Response rate‡	26% (1 complete and 19 partial responses)	26% (1 complete and 20 partial responses)	
Median progression-free survival	14 weeks	22 weeks	
Overall survival at 12 months	63%	58%	
Phase III trial[8]			
	Pembrolizumab 10 mg/kg every 2 weeks (279 patients)	**Pembrolizumab** 10 mg/kg every 3 weeks (277 patients)	**Ipilimumab** 3 mg/kg every 3 weeks (278 patients)
Response rate‡	33.7% (14 complete, 80 partial responses)	32.9% (17 complete, 74 partial responses)	11.9% (4 complete, 29 partial responses)
Median progression-free survival	5.5 months	4.1 months	2.8 months
Overall survival at 12 months	74.1%	68.4%	58.2%

‡ Complete and partial responses were based on assessment of target and non-target lesions according to the RECIST 1.1 criteria.[6]

phosphatase (22.6%) and aspartate aminotransferase (27.7%) were common.

Because of pembrolizumab's mechanism of action, immune-mediated adverse reactions are a concern. In the safety cohort, these included pneumonitis (12 patients), colitis (4 patients), hepatitis (2 patients) and nephritis (3 patients). Immune-mediated endocrinopathies have also been reported including hypophysitis (2 patients), type 1 diabetes, hyperthyroidism (5 patients) and hypothyroidism (34 patients). Monitoring blood glucose and thyroid function at the start and during pembrolizumab therapy is recommended. Depending on severity of these events, pembrolizumab should be interrupted or stopped and patients should be treated with corticosteroids. Severe infusion-related reactions have occasionally been reported with pembrolizumab and this is a contraindication to further treatment.

More patients discontinued the 10 mg/kg dose than the 2 mg/kg dose because of an adverse event.[7] The most common reasons for stopping pembrolizumab were pneumonitis, renal failure and pain.

Pembrolizumab is a category D drug in pregnancy. Although there are no data in pregnant women, blocking PD-1 in animals increases fetal loss. Contraception should be used during and for four months after treatment has finished.

The recommended dose of pembrolizumab is 2 mg/kg every three weeks. Around a quarter of patients with pre-treated metastatic melanoma responded to this dose. Response rates were better in those who had not previously been treated with ipilimumab. Autoimmune adverse reactions are a problem with this drug and regular patient monitoring is vital. Patients do not need to carry the BRAF mutation to be eligible for pembrolizumab.

T T manufacturer provided additional useful information

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The Transparency score (T) is explained in 'New drugs: transparency', Aust Prescr 2014;37:27.

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

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

Correction

Long-term drug treatment of patients with alcohol dependence

Aust Prescr 2015;38:41-3

Naltrexone is contraindicated in acute hepatitis or liver failure, and liver function should be monitored during therapy – not necessarily monthly, as the article states, but according to need.

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