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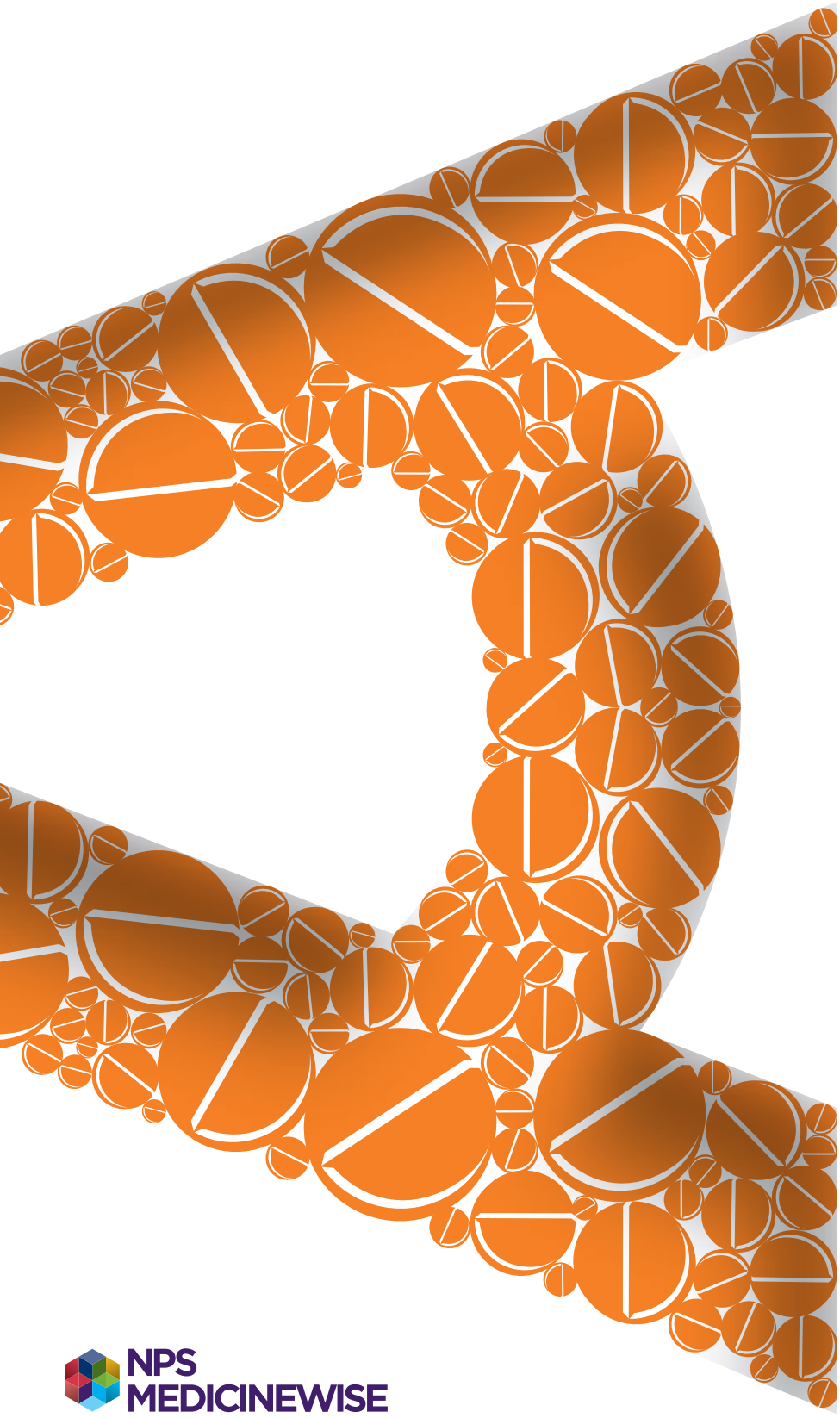

NPS MEDICINEWISE

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EDITORIAL

Metformin: myths, misunderstandings and lessons from history

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Key words
biguanides, lactic acidosis, type 2 diabetes

Aust Prescr 2013;36:38–9

Clinical trials of new drugs may overstate efficacy and not identify adverse effects. It is therefore unusual for the passage of time to reveal that a drug is less toxic, has greater efficacy and a wider range of uses than first claimed. For decades metformin was misunderstood, vilified and banned in many countries, but it is now one of the most prescribed drugs in the world. In 2010 there were more than 100 million prescriptions worldwide for metformin, alone and in combination tablets.

Metformin was developed from a herb, *Galega officinalis**, which was used for centuries to treat many ailments including polyuria. It is a rich source of the toxic substance guanidine. A less toxic alkaloid, galegine, was identified in France just before World War I. Its pharmacology and toxicology were studied in Paris and its structure was identified in Edinburgh. In 1922 metformin (dimethyl biguanide) was synthesised in Dublin and shown to lower blood glucose with fewer gastrointestinal adverse effects than its predecessors. However, in the same year insulin was used for the first time, distracting interest from other glucose-lowering drugs.

In Paris in 1957 metformin, by then called glucophage ('glucose eater'), was studied in trials and shown to lower blood glucose in patients with type 2 diabetes, but not in people without diabetes. Unlike sulfonylureas, metformin did not stimulate insulin release, but increased its peripheral uptake and also reduced the release of glucose from the liver. Metformin had gastrointestinal adverse effects which could be minimised by a 'start low, go slow' approach to dosing.

Also in 1957 an American group published similar results for phenformin (phenylethyl biguanide). Phenformin was energetically marketed worldwide by Ciba-Geigy, but by 1959 an association with lactic acidosis was reported. Unfortunately, this report generated little interest. In contrast, metformin was manufactured by a small French company and, among developed countries, was only the preferred biguanide in France and Scotland.

In the 1970s the number of reports of phenformin-related lactic acidosis and deaths increased. In 1977 it was removed from the market in the USA and also withdrawn from many other countries. The Australian Drug Evaluation Committee recommended severe restrictions on both phenformin and metformin in spite of the different pharmacokinetics of the two drugs. Phenformin is metabolised by the liver and accumulates in patients with a genetic deficiency of the enzyme cytochrome P450 2D6. Metformin is renally excreted and all serious reports of its association with lactic acidosis and deaths are in overdoses or in people with advanced renal failure.[1]

Endocrinologists in France and Scotland, who had considerable experience of using metformin safely, continued to prescribe it extensively. In 1968[2] and 1977[3] Scottish studies comparing metformin with chlorpropamide found that glucose control was the same with both drugs, but patients on metformin had less hypoglycaemia and lost weight, while those on the sulfonylurea gained weight. In spite of similar findings published in leading journals, it took the rest of the world a very long time to reach the same conclusions because of unwarranted fears of lactic acidosis. In 1995 the benefits of metformin were rediscovered in the USA[4] and restrictions were eased in Australia.

Of the many subsequent studies perhaps the most influential has been the UK Prospective Diabetes Study.[5] This was a randomised, multicentre, parallel group trial of 3867 patients over 10 years. Independently of blood glucose control, metformin

* known by many other names including goat's rue, Spanish sanfoin, false indigo, Italian fitch, French lilac and professor-weed

From the Editor

While prescribers are alert for drug–drug interactions, patients may be more interested to know if they can drink alcohol with their medicine. Graham Vernon reviews some drug interactions that consumers are concerned about, and Helen and John Conaglen discuss some of the drugs which can cause sexual dysfunction.

Many people consume nutritional supplements, but these are not always necessary. Serena Parker, Patrick Hanrahan and Claire Barrett consider the harms and benefits of folate.

Concern about the harmful effects of metformin restricted its use for many years. Gillian Shenfield reflects on how this misunderstanding delayed metformin becoming a first-line drug for type 2 diabetes.

reduced the risks of myocardial infarction and all-cause mortality. As a result metformin became the first-choice treatment for obese patients with type 2 diabetes. Later subgroup analyses showed that it had similar vascular protective effects in all patients, but it took another decade for these findings to be translated into official recommendations. In 2012 diabetes experts in the USA and Europe[6] declared that metformin is the drug of first choice for all patients with type 2 diabetes. The Australian National Health and Medical Research Council is considering a similar recommendation.

The story is not yet over. Nephrologists believe metformin is underused in kidney disease. Metformin is now also used to treat polycystic ovary syndrome, gestational diabetes and is showing early promise as a treatment for cancer. Recent meta-analyses controversially suggested that metformin may not prevent macrovascular disease[7], however the risk of cardiovascular events with metformin may be less than with sulfonylureas[8].

There are many lessons from this saga:

- it takes a very long time to collect good population efficacy and safety data
- medications can produce more benefits and harms than first claimed
- drugs marketed by large pharmaceutical companies dominate the market[9] and using new drugs with limited, short-term data from restricted trial populations is a risky activity
- wider understanding of pharmacodynamics and pharmacokinetics could prevent the belief that all drugs in a chemical group have the same actions and adverse effects
- the long delay of translating evidence into practice is occurring with other medicines such as aspirin for preventing cardiovascular disease. <

Conflict of interest: none declared

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Letters to the Editor

Complementary medicines

Editor, – I work regularly in a large public hospital anaesthetic preadmission clinic. I am no longer surprised at how many patients take expensive complementary medicines with little or no validation of their efficacy – for example fish oil to improve vision, ginkgo for Alzheimer's disease, coenzyme Q for cardiac failure. Some patients are on over 10 different products! Can someone please explain the lack of government regulation?

My concerns regarding complementary medicines (and I include here all the usual suspects such as herbals, minerals and vitamins) are:

- some are expensive and could exhaust patients' limited budgets
- some, in fact, may do no good at all or at least there is minimal evidence they do good
- some patients maintain adverse lifestyle choices because they felt, or wanted to believe,

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

LETTERS

these medicines would provide protection (for example, thiamine reverses alcohol-induced liver damage or green tea capsules prevent lung cancer in continuing smokers)

- they may do significant harm (for example vitamin E and increased incidence of prostate cancer).

I do believe that there are some good products out there that will eventually be validated – many current drugs started this way, such as aspirin from willow bark.

How can there be minimal or no regulatory oversight of complementary medicines?

The commonest response in the past when I have raised this issue with the industry was, 'Sure they may not do the job as advertised but at least they are harmless'. This is simply not true!

Bruce Burrow
Deputy director
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Osteonecrosis of the jaw

Editor, – I was very interested in the dental note concerning bone turnover markers (Aust Prescr 2012;35:159). The authors state that the incidence of bisphosphonate-related osteonecrosis of the jaw is 1 in 500 to 1 in 1500. Is this related to oral bisphosphonates used to treat osteoporosis, or does it include intravenous bisphosphonates associated with the treatment of various cancers?

I have recently attended a number of meetings with endocrinologists where they consistently state that the incidence of bisphosphonate-related osteonecrosis of the jaw associated with oral bisphosphonate treatment of osteoporosis is about 1 in 100 000.

There is obviously a wide variation of opinion. I would appreciate comments from the authors regarding this discrepancy on the incidence of osteonecrosis of the jaw.

Graham McNally
General practitioner
Brisbane

Michael McCullough and Alastair Goss, authors of the dental note, comment:

Our dental note on bone turnover markers was specifically quoting the incidence of bisphosphonate-related osteonecrosis of the jaw relating to patients with osteoporosis on oral bisphosphonates.

The studies quoted are international, independent and not funded by pharmaceutical companies. They are primarily conducted by oral and maxillofacial surgeons and other specialist dentists who diagnose and treat bisphosphonate-related osteonecrosis of the jaw. They very consistently show an incidence of 1 in 500 to 1 in 1500.[1-3] In specific patient groups having bone invasive procedures, the incidence is more of the order of 1 in 100.[4,5] It should be noted that Osteoporosis Australia, when they met with the Australian Dental Association to develop an instruction pamphlet, agreed that the incidence was at least in the order of 1 in 1500.[6]

Some endocrinologists seem to wish to continue to quote the American Society of Bone and Mineral Research report of the task force in 2007 that indicated an incidence of 1 in 10 000 to 1 in 100 000.[7] This review was published at a time when the only independent published incidence data was the Australian study.[1] The majority of the authors of that task force reported substantial receipt of pharmaceutical company funds. That paper has not been updated in light of the more extensive independent studies.

Another important aspect that has recently received prominence in the medical literature is the length of time a patient with osteoporosis should continue with oral bisphosphonates. In a recent meta-analysis by the US Food and Drug Administration[8] it was shown that for most patients the maximum benefit was achieved by five years. The benefit of continued use beyond this was low with increasing risk of serious complications including bisphosphonate-related osteonecrosis of the jaw, spontaneous femur fracture and oesophageal squamous cell cancer.[8]

Minimising the risk of bisphosphonate-related osteonecrosis of the jaw is straightforward. Prescribers need to be aware of the true incidence of risk and ensure that their patients are dentally fit before commencing oral bisphosphonates. Patients then need to be carefully monitored.

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The seven-year rule for safer prescribing

Editor, – The editorial by Sidney Wolfe (Aust Prescr 2012;35:138-9) suggested that patients should not take any pharmaceutical drugs that have been released until they have been taken by other patients for seven years. By that time, half of the black box warnings or market withdrawals that would ultimately occur for a drug over its lifespan would have already happened.

The logical corollary of this, if it was adopted by all patients, is that the seven-year rule would immediately become an infinite year rule as no patients would be taking any new drugs. Clearly, widespread adoption of this recommendation would have profound effects on achieving any improvement in disease states, let alone the capacity of pharmaceutical companies to continue to exist. The editorial reports that even 25 years is not long enough to exclude the possibility of a new black box warning or market withdrawal.

Perhaps it would be better to outline to patients that changes to medication recommendations can occur and half of these occur within the first seven years and leave it to a harm–benefit discussion between the patient and their prescriber about whether the new medication should be trialled or not.

I do not think that blanket ban approaches are particularly helpful or necessarily balanced.

Marc Russo
Pain medicine physician and specialist
Newcastle
NSW

Sidney Wolfe, the author of the editorial, comments:

Marc Russo's assertions that the seven-year rule, if adopted by all patients, would result in a situation in which 'no patients would be taking any new drugs' and would 'have profound effects on achieving any improvement in disease state' are both incorrect. The editorial clearly states that the rule would not apply to that small proportion of new drugs that represent therapeutic breakthroughs. Patients are not discouraged from using breakthrough drugs, which are defined as offering 'a documented therapeutic advantage over older, proven drugs'. Furthermore, if more patients and their healthcare providers adhered to the rule, there might actually be more incentives for drug companies to develop true breakthrough drugs to improve treatment of diseases, rather than developing a tenth ACE inhibitor, an eighth angiotensin II receptor antagonist or a seventh statin.

Beyond the absence of a documented therapeutic advantage of many new drugs is the increased likelihood of harm from a drug that is statistically much more likely than established, time-tested drugs to have a new risk discovered after marketing – one serious enough to trigger a new black box warning or even market withdrawal.

Russo's proposed alternative to the not 'necessarily balanced' seven-year rule is to 'leave it to a harm–benefit discussion between the patient and their prescriber' to see if the new medication warrants being used. This risks a decision that will likely be tilted toward use because of massively higher promotion of these new drugs to doctors compared with older ones. This decision is therefore more likely to be necessarily unbalanced.

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ARTICLE

Drug-induced sexual dysfunction in men and women

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Key words
antidepressants, antihypertensives, antipsychotics, arousal, erectile dysfunction, hypoactive sexual desire disorder, male impotence, orgasm

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SUMMARY

Many medical conditions and their treatments contribute to sexual dysfunction.

Commonly implicated drugs include antihypertensives, antidepressants, antipsychotics and antiandrogens.

Understanding the potential for drug-induced sexual problems and their negative impact on adherence to treatment will enable the clinician to tailor treatments for the patient and his or her partner.

Encouraging a discussion with the patient about sexual function and providing strategies to manage the problem are critical to good clinical care.

Introduction

Several classes of prescription drugs contribute to sexual dysfunction in men and women (Table 1).[1-3] Patients who develop drug-induced sexual dysfunction are more likely to be non-adherent. This has been found with antihypertensives[4] and antipsychotics[5]. The literature has emphasised male sexual problems with less data available on female or couple problems.

Recreational drugs such as alcohol, narcotics, stimulants and hallucinogens also affect sexual function. Short-term use of alcohol affects sexual desire by decreasing inhibitions, but also diminishes performance and delays orgasm and ejaculation. Many substance abusers report better sexual function, but often their partners report the opposite.[6]

Sexual function consists of the phases of sexual desire, arousal and orgasm. Both men and women can experience problems in any of these phases. Low desire, lack of swelling and lubrication in women, erectile dysfunction, premature, retrograde or absent ejaculation, anorgasmia and painful sex not only affect the individual, but also impact on their partner.

Talking to the patient

Whether patients report their sexual problems depends on several factors, including whether the patient is comfortable disclosing these problems, and whether the clinician is willing to ask about sexual issues and does so in a sensitive way.[7,8]

Patients on long-term medications may not be aware that their sexual problems have developed as a result of their treatment. Conversely some may blame their drugs for sexual problems which are due to relationship difficulties or other stressors. Some doctors consider that asking patients if they had noticed any sexual adverse effects from their drugs may 'suggest' them to the patient, and possibly result in non-adherence. Patients attributing their sexual problems to their drugs are less likely to continue the treatment even when necessary for their health.[9] The consultation should include discussion of the patient's sexual issues so these can be considered in treatment decisions.

Treatments for hypertension

Hypertension is associated with sexual dysfunction.[10] Antihypertensives may also contribute to the problem and lead to low treatment adherence.[4]

Men

In an international survey, 20% of men using beta blockers (beta adrenoreceptor antagonists) for hypertension had erectile dysfunction.[11] Centrally-acting alpha agonists (for example clonidine) and diuretics have also been implicated in impairing sexual function.[4] The aldosterone receptor blocker spironolactone also blocks the androgen receptor and is associated with erectile dysfunction and gynaecomastia.

Women

Sexual dysfunction is more common in women with hypertension (before treatment) compared to normotensive women (42% vs 19%).[12] Although the sexual effects of antihypertensives have been poorly studied in women, these drugs may have similar adverse effects on the arousal phase as in men, leading to failure of swelling and lubrication. Decreased sexual desire (41% of women) and sexual pleasure (34%) have been reported.[13] Alpha adrenergic drugs such as clonidine and prazosin also reduce desire (in a small, randomised trial)[14] and arousal[15]. The angiotensin II receptor antagonist, valsartan, was associated with improved sexual desire and fantasies when compared with the beta blocker atenolol in women with hypertension.[16]

Table 1 **Drugs associated with sexual dysfunction** [1-3]

Drug class	Decreased desire	Decreased arousal	Orgasm or ejaculatory difficulties
Antidepressants	amitriptyline clomipramine fluoxetine imipramine paroxetine phenelzine sertraline	amitriptyline citalopram clomipramine doxepin fluoxetine imipramine nortriptyline paroxetine phenelzine sertraline tranylcypromine	citalopram clomipramine doxepin escitalopram fluoxetine* fluvoxamine imipramine nortriptyline paroxetine* sertraline* tranylcypromine venlafaxine
Other psychotropic drugs	alprazolam chlorpromazine fluphenazine haloperidol lithium risperidone	chlorpromazine fluphenazine lithium risperidone	alprazolam fluphenazine haloperidol risperidone
Cardiovascular drugs	clonidine digoxin hydrochlorothiazide methyldopa spironolactone	beta blockers clonidine digoxin hydrochlorothiazide methyldopa perhexilene spironolactone	
Other drugs	cimetidine	antihistamines cimetidine cyproterone disulfiram gonadotrophin-releasing hormone agonists propantheline pseudoephedrine	naproxen

* common cause of orgasmic difficulty

Psychoactive drugs

Aside from the medicine, it is important to be aware of the effects of psychiatric problems on the patient's relationship and address the psychosocial issues.[17] Up to 70% of patients with depression have sexual dysfunction, which can affect any phase of sexual activity.[18] Reports indicate that 30–80% of women and 45–80% of men with schizophrenia also experience sexual problems.[19] In these patients, it may be difficult to distinguish the effects of the illness on sexual function from the effects of the drugs used for treatment.

Antidepressants

Many antidepressants cause sexual difficulties.[17,20] Selective serotonin reuptake inhibitors and serotonin noradrenaline reuptake inhibitors inhibit desire, cause erectile dysfunction and decrease vaginal lubrication. They also impair orgasm in 5–71% of patients.[18,21,22] This adverse effect is used therapeutically to delay premature ejaculation.

Tricyclic antidepressants inhibit sexual desire and orgasm.[23,24] The effects of specific drugs vary depending on their mechanism of action. For example, clomipramine causes orgasmic difficulties in

up to 90% of patients, while nortriptyline causes more erectile dysfunction but has less effect on orgasm.[25]

Monoamine oxidase inhibitors are also associated with sexual dysfunction. Although moclobemide was reported to increase sexual desire,[24] the doses used in that study were considered subtherapeutic.

Other antidepressants such as venlafaxine and mirtazapine have variable negative effects on all aspects of sexual function. Initial reports on agomelatine in both male and female patients with major depressive disorder suggested significant antidepressant efficacy without significant sexual adverse effects. However, more recent reviews of the sexual effects are conflicting.[26,27]

Antipsychotics

Some antipsychotics may affect sexual function more than others (see Table 2).[19,28] The only Cochrane review of antipsychotic-induced sexual dysfunction has reported a small number of studies relating to men, but none relating to women.[29]

Men taking antipsychotics report erectile dysfunction, decreased orgasmic quality with delayed, inhibited or retrograde ejaculation, and diminished interest in sex. Women experience decreased desire, difficulty achieving orgasm, changes in orgasmic quality and anorgasmia. Dyspareunia, secondary to oestrogen deficiency, can result in vaginal atrophy and dryness. Galactorrhea is experienced in both sexes.[28]

A recent observational study of schizophrenia found that in patients with diminished sexual desire, ziprasidone was preferred over olanzapine.[30] The majority of antipsychotics cause sexual dysfunction by dopamine receptor blockade. This causes hyperprolactinaemia with subsequent suppression of the hypothalamic–pituitary–gonadal axis and hypogonadism in both sexes. This decreases sexual desire and impairs arousal and orgasm. It also causes secondary amenorrhoea and loss of ovarian function in women and low testosterone in men.[31,32] Although poorly understood, other neurotransmitter pathways including histamine blockade, noradrenergic blockade and anticholinergic effects may also be affected by antipsychotics.

Before commencing dopamine receptor antagonists it is useful to establish a baseline prolactin, as subsequent elevation can then be attributed to the drug. Non-drug induced causes of hyperprolactinaemia such as pituitary tumours should be considered in patients on dopamine receptor antagonists.[33]

Table 2 **The relative impact of antipsychotic drugs on sexual function** [19,28]

Effect on sexual function	Antipsychotic
Least	aripiprazole
	quetiapine
↓	clozapine
	olanzapine
	haloperidol
Most	risperidone

Antiepileptics

Sexual dysfunction is common in patients on antiepileptic drugs.[34] Gabapentin and topiramate have been associated with orgasmic dysfunction in both men and women, and reduced libido in women.[35-37]

Contraceptives

Oral contraceptives decrease circulating free testosterone. It is postulated that this decreases desire in women, although there is little evidence to support this.[38] As with other disorders, the impact of social context including the relationship, and fear of pregnancy and sexually transmitted diseases are confounding influences in clinical reports of the impact of oral contraceptives.

Depot medroxyprogesterone acetate, used as a contraceptive in women, can cause weight gain, depression, vaginal atrophy and dyspareunia with decreased libido in up to 15% of women.[39-41]

Treatments for cancer

The impact of malignancy and its treatment on both the individual and his or her partner can have a significant negative influence on their sexual relationship. Many of the cancer treatments can lead to sexual dysfunction. As common examples, long-acting gonadotrophin-releasing hormone agonists used for prostate and breast cancer result in hypogonadism, with subsequent reduction in sexual desire, erectile dysfunction in men[42], vaginal atrophy and dyspareunia in women as well as orgasmic dysfunction.[34]

Drugs for lower urinary tract symptoms and benign prostatic hyperplasia

Men who present with symptomatic benign prostatic hyperplasia and lower urinary tract symptoms have an increased incidence of sexual dysfunction. Overall, 72.2% of men with lower urinary tract symptoms had erectile dysfunction compared with 37.7% in those without lower urinary tract symptoms.[43] Although surgery and various therapies can improve lower

urinary tract symptoms, some of these treatments also cause or exacerbate erectile dysfunction and ejaculatory dysfunction.[43]

Alpha blockers such as doxazosin, tamsulosin, terazosin and alfuzosin for benign prostatic hyperplasia are reported to be no worse than placebo in their effects on sexual function, although tamsulosin was associated with approximately 10% increase in ejaculatory dysfunction in treated men.[44]

Other drugs that cause sexual dysfunction

Antiandrogens such as cyproterone acetate, cimetidine, digoxin and spironolactone block the androgen receptor. This reduces sexual desire in both sexes,[45] and affects arousal and orgasm.

Steroids such as prednisone used for many chronic inflammatory disorders result in low serum testosterone which reduces sexual desire and causes erectile dysfunction.[46] Immunosuppressive drugs such as sirolimus and everolimus are widely used in kidney transplantation and can impair gonadal function and cause erectile dysfunction.[47] Protease inhibitors for HIV have also been implicated in sexual dysfunction and cause erectile problems in over half of men taking them.[48]

Many other drugs including antihistamines, pseudoephedrine, opioids and recreational drugs may cause sexual dysfunction and should be considered when assessing the patient.

Strategies to manage sexual dysfunction

Non-drug approaches include therapy with a clinical psychologist who understands sexual dysfunction. A variety of strategies have been tried to reverse drug-induced sexual dysfunction, including drug switching, dose reduction and drug holidays. Taking a phosphodiesterase type 5 inhibitor in anticipation of intercourse has become the standard of care for men.[49-51] It improves erections in about 70% of men with hypertension.[52] However, phosphodiesterase type 5 inhibitors are contraindicated in men using nitrates and should be used with caution in those on alpha blockers, where postural hypotension can be a problem. In women, sildenafil has shown promise for reversing the inadequate lubrication and delayed orgasm induced by selective serotonin reuptake inhibitors.[53]

Changing to an alternative drug is recommended for men and women taking antihypertensives. Alpha blockers, ACE inhibitors and calcium channel blockers are not considered to cause erectile dysfunction,[54] while several studies have suggested that angiotensin II receptor antagonists may even improve sexual function. Beta$_1$-selective beta blockers such as nebivolol may have potential advantages in these patients.[55]

In patients taking antipsychotics, establish the cause of the hyperprolactinaemia then consider dose reduction or switching to prolactin-sparing drugs. Relationship counselling and addressing patient-specific concerns can be useful.[28]

In women, oestrogen cream can alleviate local symptoms such as atrophic vaginitis and dyspareunia. If a woman complains of sexual dysfunction while on an injectable progestogen, another form of contraceptive can be considered.[34]

Suggested solutions to gabapentin-induced anorgasmia include dose reduction, timing of dose away from planned coitus until anorgasmia no longer occurs, substitution with a different medication, and co-administration of other medications.[35,36]

Conclusion

Understanding both the impact of a disorder and the effects of its treatment on both the patient and their partner are critical to providing good clinical care. It is important for the clinician to acknowledge and encourage discussion regarding sexual function, as well as enquire about the impact of drugs on sexual function. This will ensure patients and their partners understand their sexual difficulties and treatment options.

Conflict of interest: none declared

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A complete list of the references is available at www.australianprescriber.com/magazine/36/2/42/5

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ARTICLE

Sex, drugs and alcohol

Drug interactions of concern to consumers

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Key words
antibiotics, contraception, drug abuse

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SUMMARY

People often have misconceptions about interactions between alcohol and commonly prescribed drugs. Often there is insufficient evidence to support prohibiting alcohol, but the overall risk needs to be assessed for each individual.

Any drug which suppresses the central nervous system will exacerbate the immediate effects of alcohol and can be expected to increase the risk of alcohol-related harm. Alcohol should not be taken with drugs that can cause a disulfiram-like effect.

Combined hormonal contraceptives are less reliable if taken with drugs which can increase the rate of metabolism of oestrogens and progestogens. The interacting drugs include some antiepileptic drugs and the rifamycins, so action is required to maintain contraception.

Introduction

Patients often express concerns about interactions between their medicines and alcohol and any illicit drugs that they may consume. Doctors and pharmacists are also often asked about interactions, especially short courses of antibiotics, which might reduce the efficacy of oral contraceptives.

There are many misconceptions about which interactions are of clinical concern. While there is information about oral contraceptives and alcohol, it is not possible to predict the safety of consuming any illicit drug. The outcomes of illicit drugs interacting with prescribed medicines cannot be quantified.

Alcohol

Current Australian guidelines do not define 'social drinking' but make recommendations that for healthy people daily alcohol consumption should be limited to two standard drinks* and a maximum of four on a single occasion.[1] However, people asking about alcohol and medicines will generally have some level of ill health. Questions of safety will therefore often need to be in the context of consuming a smaller volume of alcohol. A safer approach would be to think in terms of up to two standard drinks on one occasion – typically, 'Can I have a glass of wine (or beer) when I go out to dinner?'. This can often be addressed in terms of an individual's risk of additive sedation and the circumstances of the occasion, including the support available if the reaction to alcohol was more than expected.

The duration of additive sedation due to an alcohol–drug interaction will depend on the clearance rates of the two components. Blood alcohol concentrations will decline at a predictable rate, but the rate of inactivation of the interacting drug must be considered, for example with long- and short-acting benzodiazepines.

Alcohol (ethanol) is principally metabolised to acetaldehyde by alcohol dehydrogenase in the liver. Other enzymes, including cytochrome P450 (CYP) 2E1, contribute to this conversion and become more significant with higher concentrations of alcohol.[2] Acetaldehyde causes unpleasant symptoms such as headache, flushing and vomiting. These effects are more pronounced if the metabolism of acetaldehyde is inhibited by drugs such as disulfiram (which block aldehyde dehydrogenase). Regular alcohol consumption can induce elevated levels of CYP 2E1, but fortunately this does not result in any clinically significant interactions with other drugs used at therapeutic doses. Consumers can also be assured that metabolic interactions do not lead to elevated (or prolonged) blood alcohol concentrations.

The management of many chronic diseases will be assisted if patients limit their alcohol consumption, regardless of any additional risks from drug interactions. Regularly drinking alcohol may increase the risks in people with chronic diseases, especially if they take drugs which, for example, increase the risk of liver disease, gastric bleeding or falls. A modest level of alcohol consumption is safe in patients who take paracetamol. This is also the case with non-steroidal anti-inflammatory drugs, such as ibuprofen, however the overall long-term risk of gastric bleeding needs to be considered. Regular or occasional consumption of small amounts of alcohol should not affect warfarin control in the absence of liver disease.

* An Australian standard drink contains 10 g of ethanol, for example 375 mL of medium-strength (3.5%) beer or 100 mL of 12.5% wine

Antiepileptic drugs can increase sedation. Intoxication with alcohol can cause seizures, as can alcohol withdrawal syndrome.

The adverse effects of alcohol on illegal 'recreational' drugs only add to the hazards. Any attempt to advise a patient about the outcomes of an interaction between a medicine and an illicit drug will be undermined by a lack of certainty about the actual content of the illicit substance consumed. The possibility of toxic 'contaminants' in an illicit product may be of more concern than a possible pharmacological interaction.

Antimicrobials

Most antibiotics prescribed in general practice do not require abstinence from alcohol. Penicillins, cephalosporins, macrolides and tetracyclines do not present a hazard with alcohol, but the condition being treated may warrant avoiding alcohol.

There are sufficient reports of disulfiram-like reactions with metronidazole to warrant abstinence during therapy. However, the actual danger of the alcohol contained in one or two standard drinks is low. There is no direct evidence with tinidazole but, as with metronidazole, treatment courses are usually short and any risk of an interaction is easily avoided.

Griseofulvin is normally dispensed with an ancillary warning label for alcohol. This is based on a report of an adult who had a severe reaction after consuming a can of beer and one hour later taking his regular dose of griseofulvin.[3] Given the limited evidence and the extended periods of treatment required with griseofulvin, it would be reasonable if patients wanted to test their tolerance to small amounts of alcohol rather than abstain.

Psychotropic drugs

Additional sedation can be anticipated when alcohol is consumed by patients taking benzodiazepines, antipsychotics, sedating antidepressants (especially tricyclics) and many antiepileptic drugs. This potential may not preclude modest levels of alcohol consumption, however some patients who need these drugs may have a history of alcohol abuse. There is also a profound risk if patients overdose with sedative drugs and alcohol. Beverages with a high tyramine content, including some beers and red wine, present an additional hazard with non-selective monoamine oxidase inhibitors (phenelzine, tranylcypromine).

Hormonal contraceptives

Drugs which increase the metabolism of oestrogens and progestogens can reduce the efficacy of oral contraceptives. This occurs when the activity of metabolising enzymes (principally CYP 3A4) in the liver and intestinal mucosa is increased by 'inducing' drugs. These include the complementary medicine St John's wort which can potentially lead to a failure of oral contraception.[4] Although not an enzyme inducer, griseofulvin can potentially reduce the efficacy of hormonal contraceptives. Examples of drugs which can reduce the effectiveness of oral contraceptives are listed in the Box.

Box **Drugs which can reduce the effectiveness of oral contraceptives** [5]

carbamazepine	oxcarbazepine	rifampicin
griseofulvin	phenobarbitone	rifabutin
modafinil	phenytoin	St John's wort

Women taking enzyme-inducing drugs may need to consider other methods of contraception, such as a levonorgestrel intrauterine device, depot medroxyprogesterone or a copper intrauterine device. Depot medroxyprogesterone remains effective when used with enzyme-inducing drugs whereas etonogestrel implants are unreliable (based on reported failures over a shorter period of use).[6] The efficacy of the levonorgestrel intrauterine device is due mainly to local release of progestogen and any increased metabolism in the liver would not be expected to reduce its effectiveness. Vaginal rings (containing ethinyloestradiol and etonogestrel) depend on systemic release of oestrogen and progestogen and cannot be considered a safe option in the presence of enzyme-inducing drugs.

After ceasing an enzyme-inducing drug it may take four weeks for enzyme activity to return to baseline and reliable methods of contraception should be used during this period.[7]

Contraceptive hormones can also affect the metabolism of other drugs. This can be clinically significant with antiepileptic drugs such as lamotrigine.

Antimicrobials

Guidelines published in the UK and USA no longer recommend additional contraceptive precautions when non-enzyme inducing antibiotics are taken with oral contraceptives, regardless of the duration of therapy.[7,8] This applies to commonly prescribed drugs such penicillins, cephalosporins, macrolides, tetracyclines, trimethoprim and azole antifungals. These recommendations reflect the limited evidence of contraceptive failure associated with antibiotics which do not induce liver enzymes. The theory that oral antibiotics could interrupt enterohepatic reabsorption of oestrogens has not been substantiated.

Additional contraceptive precautions may be warranted if the antibiotic or infection causes

vomiting or diarrhoea. This is particularly important with progestogen-only oral contraceptives.

Enzyme-inducing antimicrobials include rifampicin, rifabutin, efavirenz, nevirapine, ritonavir and tipranavir. Women must use a reliable form of contraception with these drugs. There are no data on the effects of short courses of rifampicin on hormonal contraceptives. Additional methods of contraception should be used if rifampicin is taken for prophylaxis of meningitis due to *Neisseria meningitidis* or *Haemophilus influenzae*. Four weeks of additional cover will be required even after two days of exposure to rifampicin. Also, an active pill should be taken each day during the course and for seven days after the last rifampicin dose.[5]

Enzyme-inhibiting antibiotics, such as erythromycin and fluconazole, can increase oestrogen and progestogen concentrations, but have limited potential to cause adverse effects. The duration of antibiotic therapy will rarely warrant reducing the dose of oral contraceptive.

Antiepileptic and psychotropic drugs

Enzyme-inducing drugs such as phenytoin, carbamazepine, oxcarbazepine and phenobarbitone can cause failure of oral contraceptives. Topiramate is a weaker inducer and a change in contraception may only be required with doses of more than 200 mg daily.[7] Lamotrigine can cause slight reductions in progestogen concentrations, but this should not lead to a reduction in the efficacy of combined oral contraceptives.[7] However, ethinyloestradiol can increase the clearance of lamotrigine and reduce control of seizures. Combined oral contraceptives may therefore be unsuitable for women taking lamotrigine for epilepsy.

Conclusion

The potential significance of interactions depends on both the drugs involved and an individual's susceptibility to suffering an adverse outcome. Clinicians often appeal for drug interaction alerts to define a severity rating. However, the severity of the outcome will usually depend as much on a patient's medical risk as on the drugs in question. The best approach is to identify a potential problem and then assess its significance for the patient. Practical advice on clinically significant interactions can be found in the Australian Medicines Handbook,[5] and guidelines for managing interactions with contraceptives are provided in Contraception: an Australian clinical practice handbook[9]. If in doubt seek advice from a pharmacist or a medicines information centre. ◁

Conflict of interest: none declared

Q:

SELF-TEST QUESTIONS

True or false?

1. Additional contraception is needed by women who take oral contraceptives, when they are prescribed a short course of penicillin.
2. Patients should not drink alcohol while being treated with metronidazole.

Answers on page 67

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Dental note

Sex, drugs and alcohol

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Amongst the misconceptions, or 'urban legends', that exist in dental practice is the potential for an unwanted pregnancy because of an interaction between the antibiotics we prescribe and oral contraceptives. The lack of evidence for this interaction has resulted in a change in overseas guidelines and we should be advising our patients accordingly.

Dentists should discuss with patients potential problems with any adverse reaction to prescribed medicines, particularly diarrhoea or vomiting. If they develop any reaction or are otherwise concerned, they should be told to cease the drug and contact us as the prescribing clinician, or their doctor, as soon as possible.

Of particular note for dentists is the interaction between alcohol and metronidazole. We should warn our patients of this possibility and recommend that they abstain from alcohol.

ARTICLE

Skin glues for wound closure

SUMMARY

Skin glues are a safe and effective method to close selected wounds.

They are also cost-effective and help prevent infection.

Ideally, wounds should be less than 4 cm, not contaminated or infected and have skin edges that are not under tension. Wounds should be closed within 12 hours.

Most patients will be children with short clean wounds.

Dehiscence is slightly higher with skin glues than with sutures, but the cosmetic outcome is comparable and skin glues are painless.

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Key words
children, emergency treatment, skin adhesives, sutures

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Introduction

Closure of wounds is often needed to promote wound healing and to produce an acceptable cosmetic result. Traditionally sutures and also adhesive strips have been used. Skin glues are safe and effective but wound selection is important.[1-4]

Skin glues are cyanoacrylates. Derivatives with long chains are less reactive and stronger. They are available in liquid monomer formulations which react with formaldehyde on contact with skin or other surfaces. This polymerisation produces an exothermic reaction to create a bridge while becoming adherent to the skin.

Today's products are all effective and non-toxic and produce strong bonds.[5] One study has shown that the current adhesive properties have a bursting strength equivalent to 4/0 nylon in an intracuticular wound closure.[2]

Wound selection

Not all wounds are suitable for skin glues (Box 1) – it is likely that they are only appropriate for 15–20%.[2] In particular, bites should not be treated with glues. Wounds should be less than 12 hours old, clean and free of debris.

Most wounds studied, particularly in emergency departments, were 1–6 cm. Some experts believe that wounds greater than 4 cm should not be closed with skin glue alone[6] while others believe up to 10 cm is acceptable[7,8]. A general agreement is that for optimum results, wounds should be less than 4 cm in length. Longer wounds have increased rates of dehiscence.

Skin glues should be used only for superficial approximation of skin. With surgical incisions, wound closure of layers should be performed and ideally glue should only be used in the skin approximation. Similarly in all other wounds which are gaping, it is vital to have skin approximation before applying the skin glue.

Variable results with some wounds

Without deeper sutures to approximate the skin, using skin glues to close excision sites is associated with increased rates of dehiscence.[2,9] Glues may be used over joints only when accompanied by deeper tension sutures and splinting.[1,2] They are generally acceptable for the treatment of skin flaps.[2] Glues do not appear to compromise circulation further given that the circulation is often already compromised. Nail bed repair has been successfully reported.

Advantages of skin glues

Applying skin glue is painless. In about 20% of patients there is a report of a sensation of mild heat but no actual pain.[1] Wound infection rates are low (less than 3%) and are not increased with skin glues.[5]

Procedure time is reduced.[1,2,5,8] Studies reported that the time of the actual wound repair in all settings was less than formal suturing. Sedation, which is sometimes used in children having sutures, is not needed with skin glues.

Cosmetic appearance with skin glues is comparable to outcomes with sutures and strip approximation.[1,2,5,7,10] Most of the trials have used a blinding method with photographs assessed by plastic surgeons, other doctors and patients themselves. Comparisons were made of appearance, absence of step-off, margin irregularities, separation, edge inversion and wound

Box 1 **Wounds not suitable for skin glue**

Deeper wounds requiring sutures to approximate the skin edges
Contaminated wounds from animal or human bites
Crushed or infected wounds
Skin over joints or other high tension areas
Wounds which cross muco-cutaneous borders
High friction areas such as perineum, buttocks
High moisture areas
Wounds over 12 hours old

distortion. The results universally recorded that final cosmetic appearance for skin glues was similar to sutures, and both were better than adhesive strips.[8,9]

Skin glues are expensive. However, when compared with equipment and labour costs as well as the need for follow-up for suture removal, the overall cost is felt to be equivalent to sutures.[11]

Patient satisfaction with skin glues was higher than with sutures in most studies. Reasons included lack of pain, ease of wound care and no need for follow-up and suture removal.

There is no chance of needle-stick injury with skin glues. They provide a barrier for short-term exposure to water. Swimming is generally not recommended.

Disadvantages of skin glues

In studies, 4% of wounds reopen with skin glues compared to 1–2% with sutures. This was thought to be due to a combination of poor technique, poor wound selection, but most importantly breakage of bonds or sloughing from the skin surface.[1,2] Dihescence may cause delayed healing, poor cosmetic result and possible infection.

Patients may not feel that glue alone is adequate.[7] This was found generally in active males who felt there was a higher chance of wound breakdown. Some patients are allergic to the cyanoacrylate or residual formaldehyde.

Tips for using skin glues

Accurately applying skin glues is easy (Box 2) and takes less than an hour to learn. In contrast, optimising suture usage takes about two years.[12] The wound still needs to be irrigated and prepared before applying skin glues.

Antibiotic ointments should not be used in conjunction with the application of skin glues. Care should be taken not to get the glue near or in the eye. Eyes should be protected with gauze to prevent eyelid attachment or corneal deposition. Antibiotic ointment or petroleum jelly can facilitate removal of glue if corrections are required.

Box 2 Steps for applying skin glue

1. Select wound carefully
2. Apply antiseptic solution to clean wound as usual
3. Oppose skin edges, usually by pulling slightly on both ends of the wound
4. Apply adhesive to the wound plus 5–10 mm either side. It usually needs three coats.
5. Allow 30–45 seconds for polymerisation with 10–15 seconds between layers. Fanning the wound will not speed up polymerisation.
6. Once dry, cover the wound if the child is likely to pick at it, otherwise leave open
7. Glue will peel off in 5–8 days

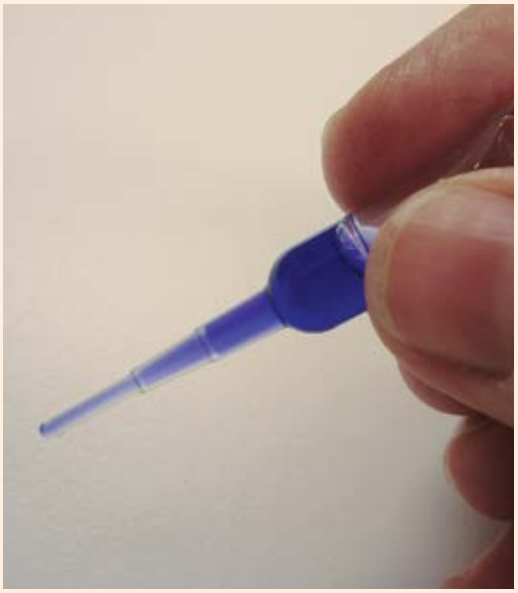
Applying the glue

The two most common applicators for skin glues involve pressure on the container with gravity assisting. They are difficult to apply upwards on a wound. In one type (Fig. 1A), the inner glass container is crushed between the fingers which starts the polymerisation process. The liquid flows easily from the bottom of the container by gravity and pressure feed to an outward nozzle which allows continuous application due to lower viscosity. The other type (Fig. 1B) requires scissors to open the feeder and has larger droplets with higher viscosity to allow droplet application. The nozzle is then used to spread the coating.

Fig. 1 Skin glue applicators

A Continuous applicator

B Droplet applicator



The skin edges are approximated with fingers of the other hand, taking care not to include the gloves in the application process. It is important to practise controlling the applicator and get used to adhesive viscosity. The glue should cover the wound plus about 5–10 mm of skin on either side. Polymerisation takes 30–45 seconds. Two additional layers should be used, with 10–15 seconds between each layer. Full strength is achieved after 2.5 minutes.

Conclusion

Careful wound selection and practice of the technique make wound closure with skin glue acceptable in up to 20% of wounds. An increased rate of wound dehiscence is a potential drawback.

Conflict of interest: none declared

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Book review

Therapeutic Guidelines: Ulcer and wound management. Version 1.

Melbourne: Therapeutic Guidelines Limited; 2012.
87 pages

The prevalence of ulcers in the community has been estimated to be up to 2% and contributes a significant impost on the health budget. This has led to a general realisation of the importance of not only managing, but preventing this potentially chronic problem. This handbook highlights the importance of not treating the ulcer in isolation, but also considering factors that influence healing and the effects of the ulcer on the patient.

The handbook covers the causes of ulcers and wounds and their management in an easy-to-read and informative manner. It gives guidance on the role of investigations, antibiotics, dressings and, in particular, management for particular ulcer beds. Importantly, less commonly addressed issues such as pain management are outlined.

The text is supplemented with boxes and figures which summarise assessment and treatment plans for individuals with ulcers. The photos used are true representations of the pathologies described.

The information within the handbook has been extensively researched and is in keeping with international consensus guidelines. The handbook would serve as an excellent adjunct for the specialist, medic and paramedic who has an interest in wound and ulcer management.

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ARTICLE

Folate for therapy

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Key words
cancer, cardiovascular disease, methotrexate

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SUMMARY

Folate is a B vitamin which is needed for DNA synthesis, replication and repair. It is found in leafy green vegetables.

Folic acid supplementation in pregnancy reduces the risks of neural tube defects. In the general population, supplements have no clear benefit in reducing the risk of cardiovascular disease or dementia.

There is conflicting evidence about cancer prevention. Some studies suggest folic acid supplements increase the risk of malignancy.

Routine folic acid supplementation in patients receiving low-dose methotrexate for rheumatic diseases reduces the risk of some adverse effects.

Introduction

Folate is vitamin B_9. It was named after the Latin word folium (leaf) and it was first isolated from spinach in 1941. Folate-rich foods include green leafy vegetables (broccoli, spinach, salad greens), chickpeas, nuts, orange juice and some fruits. Many foods are fortified with folic acid including some breakfast cereals, bread and products containing wheat flour.

The active form of folate is tetrahydrofolate. This has a role in the synthesis, replication and repair of DNA. A deficiency of folate can lead to megaloblastic anaemia.

Supplements

Synthetic folate used as a supplement differs from the main naturally occurring folate. In its oxidised state folic acid has a significantly higher bioavailability. A dose of more than 200 microgram saturates normal intestinal absorptive mechanisms. Raised total folate and unmetabolised folate in the serum may interfere with the regulatory functions of natural folates by competing for binding with enzymes, carrier proteins and binding proteins.[1]

Taking supplements around the time of conception reduces the risks of neural tube defects. As the neural tube is closed by embryonic day 26, folic acid supplementation needs to begin one month before conception and be maintained for at least three months after. The Australian Government recommendation is that all pregnant women take a folic acid supplement of at least 400 microgram/day and aim for a dietary intake of 600 microgram. Australian wheat flour is fortified to 120 microgram/100 g of bread (about three slices).[2]

Supplementation has also been purported to prevent some types of cancer, cardiovascular disease and dementia. More recently there has been concern that folic acid supplements may increase the risk of some cancers.

Cardiovascular disease

In 1969 a connection between homocysteine and cardiovascular disease was proposed. Patients with homocystinuria, an inherited enzyme deficiency, leading to elevated plasma concentrations of homocysteine, were noted to develop severe cardiovascular disease in their early twenties. It was speculated that high homocysteine concentrations could contribute to atherosclerosis.

Homocysteine elevation also occurs in people with diets deficient in folate, vitamin B_6 or B_{12}. Regardless of the cause, supplementation with folate, vitamin B_6 or B_{12} can lower plasma homocysteine. In patients with homocystinuria, lowering homocysteine reduced the risk of cardiovascular events.[3]

Folic acid supplementation reduces homocysteine concentrations typically by 25% in those with hyperhomocysteinaemia. Maximum responses are seen with 800 microgram/day over six weeks. Higher doses do not result in further significant lowering.[4]

Randomised controlled trials in people without homocystinuria are inconclusive regarding the benefit of folic acid supplementation. There was no significant evidence of change in the risk of cardiovascular events, stroke or all-cause mortality in those with a history of cardiovascular disease.[3] Lowering homocysteine does not confer a secondary prevention benefit, but some studies show a primary prevention benefit for stroke.[5] The benefit of folic acid supplementation in cardiovascular disease in patients with rheumatoid arthritis is unknown.[6]

Dementia

The effect of folic acid supplements on cognitive impairment is uncertain. Higher concentrations of homocysteine have been associated with worse function across a number of cognitive domains[7] and a study of 818 patients aged 50 to 70 years with hyperhomocysteinaemia found improvement in cognitive tests in those taking supplements.[8] However,

the role of folic acid in lowering homocysteine for the primary prevention of dementia is not established.

A study in the USA after the introduction of fortification found an association between increased cognitive decline and increased folic acid intakes (greater than 400 microgram/day).[9] In a Cochrane review of eight trials there was no evidence that folic acid improved the cognitive function of unselected elderly people with or without dementia.[10]

Cancer

Although folic acid supplementation had been considered safe, there has been increasing concern that it may raise the risk of cancer. In Norway, where food is not fortified with folic acid, two randomised controlled trials found an increased incidence of cancer among patients taking supplements for secondary prevention of cardiovascular events. The Norwegian Vitamin Trial (NORVIT) and Western Norway B Vitamin Intervention Trial (WENBIT) included 6837 Norwegians taking supplementary folic acid 800 microgram/day, vitamin B_{12} and vitamin B_6 in various combinations. In those taking folic acid for a median of 39 months, with a further 38 months of post-trial follow-up, there was an increase in cancer incidence (hazard ratio 1.2) and mortality (hazard ratio 1.38). The predominant cancer was lung cancer.[11]

Other observational studies have shown source-specific effects, with dietary folate being protective while folic acid supplements were harmful or without effect in relation to cancer risk.[12] A Swedish study found the risk of pancreatic cancer was reduced by diets rich in folate, but not by supplements.[13]

The dose and timing of folic acid supplementation relative to the development of premalignant lesions may be important, but the mechanism by which supplementation may promote cancer development is unknown.[14] After a review of the risk, the UK Scientific Advisory Committee on Nutrition considered that, despite uncertainties, the mandatory fortification of flour was supported, with controls to limit excessive folic acid intake.[15]

There is no evidence that folic acid supplementation reduces the risk of colorectal, breast or prostate cancer. Some reported studies suggest an increased risk of breast, prostate, colorectal and endometrial cancer with folic acid supplementation.

Breast cancer

An observational study found that folic acid supplementation of at least 400 microgram/day led to a 20% increased risk of breast cancer.[16] However, the Women's Antioxidant and Folic Acid Cardiovascular study found no association with breast cancer.[17] Similarly, another study found no association with breast cancer when folic acid supplementation was 200 microgram/day or less.[18]

Colorectal cancer

A randomised controlled trial for the prevention of colorectal cancer in genetically predisposed patients found folic acid 1 mg/day for six years did not prevent recurrence of colorectal adenoma. However it reported a 67% increased risk of advanced lesions with malignant potential and a twofold increased risk of having three adenomas.[19]

An intake below 200 microgram daily is recommended in those with a history of colorectal adenomas and those more than 50 years old, due to the increased risk of developing colorectal cancer after this age.[15]

Prostate cancer

There has been a meta-analysis of 10 randomised controlled trials of oral folic acid supplementation of at least 400 microgram/day. This showed a small but significant increase in prostate cancer compared with controls.[12]

Methotrexate and folic acid

Methotrexate is a cornerstone of disease-modifying antirheumatic drug therapy for rheumatoid arthritis. It is an analogue of folic acid and thus classed as an antimetabolite. Methotrexate inhibits dihydrofolate reductase (which converts dihydrofolate to tetrahydrofolate), but the mechanism of action in rheumatoid arthritis is unclear.

On average, 30% of patients cease methotrexate within one year due to adverse effects and 60% experience mild adverse effects.[20] Gastrointestinal intolerance and transaminase elevation are the main reasons for dose reduction or cessation. The risk factors for methotrexate toxicity include alcohol use, obesity (≥ 8% hepatotoxicity with body mass index 20–25; ≥ 20% hepatotoxicity with body mass index 30–35), older age and folate deficient status.

Concurrent folic acid supplementation reduces elevations of hepatic transaminases, gastrointestinal intolerance and stomatitis, and may increase the maximum tolerated dose of methotrexate.[21] Supplementation does not appear to have a protective effect on the development of cytopenia or liver disease, such as cirrhosis.

Folinic acid is a metabolically active reduced form of folate that bypasses dihydrofolate reductase.[20] It is a stronger methotrexate antagonist than folic acid, as folic acid must be enzymatically converted to a fully reduced form. However it seems to have no greater effect than folic acid in the prevention of methotrexate-related adverse effects. As folinic acid

may reduce the effectiveness of methotrexate and is more expensive, its routine use is not recommended.[22] It has an important role in the treatment of methotrexate overdose and acute bone marrow toxicity, due to its faster action and independence of dihydrofolate reductase.

Studies have shown no reduced efficacy of methotrexate with a folate:methotrexate dose ratio of 3:1, that is, the dose of folate can be at least three times that of methotrexate before there is any effect on efficacy. For a once-weekly dose of 15 mg methotrexate, up to 45 mg of folic acid could be prescribed concurrently if required. There is no difference in benefit between folic acid 1 mg/day or 5 mg/week during methotrexate therapy.[23]

Recommendations for the use of folic acid with methotrexate are varied. Patients with a normal mean corpuscular volume and no adverse effects from methotrexate may not require prophylactic folic acid.[24] If the red blood cell folate is low, 1 mg/day folic acid is recommended (except on the day of the methotrexate dose to avoid competing for absorption). When the red blood cell folate is persistently low the folic acid dose should be gradually escalated up to a maximum folate:methotrexate ratio of 3:1. The British Society for Rheumatology[25] recommends a single weekly dose of folic acid 5 mg the morning following the day of the methotrexate dose. A consensus statement from 751 rheumatologists from 17 countries in 2008 recommended at least 5 mg/week of folic acid during methotrexate therapy.[22]

It is unknown if patients with rheumatoid arthritis who take folic acid supplements have increased rates of cancer. Theoretically, they may incur a higher risk of cancer because of the doses of folic acid prescribed concurrently with methotrexate.

The role of folic acid supplementation when methotrexate is used in juvenile idiopathic arthritis and psoriatic arthritis is uncertain. Folic acid supplementation in patients with psoriasis possibly reduces the efficacy of methotrexate.[26]

Conclusion

Supplementation with folic acid has a clear role to correct folate deficiency and in the prevention of neural tube defects. Prophylactic folic acid is recommended with low-dose methotrexate for rheumatic diseases, to reduce the risk of some adverse effects.

The routine use of more than 5 mg/week folic acid exceeds many formal recommendations. The harm versus benefit of higher doses is unclear. There is a limited benefit in vascular disease and a possible increase in malignancy.

Conflict of interest: none declared

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Q:

SELF-TEST QUESTIONS

True or false?

3. Folic acid supplements increase the efficacy of methotrexate.

4. To reduce fetal neural tube defects, folic acid supplements should be started before conception.

Answers on page 67

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Book review

Bad Pharma: How drug companies mislead doctors and harm patients

Ben Goldacre
London: Fourth Estate; 2012.
364 pages

The stated aims of this openly polemic book are to explain how the relationship between the pharmaceutical industry and the field of medicine has distorted the practice of medicine.

The author strongly emphasises the important issue of missing data. He describes how negative clinical trial data, that are not published due to strong industry bias and some academic journal bias, distort the evidence regarding the benefits and adverse effects of drugs.

This book has chapters covering the flaws in the drug development process, in the design and reporting of drug trials, and in the ability of regulators to carry out their roles. There is also an extensive discussion of drug marketing practices. He goes on to describe the role prescribing doctors and key opinion leaders play in the practice of medicine, which is now strongly influenced by pharmaceutical companies. The author, Dr Ben Goldacre, who has also published a book called Bad Science, has referenced his points well and illustrated them using examples.

The author accurately introduces this book as pop science. I found the writing style colloquial and repetitive. The examples and explanations are too simplistic for healthcare practitioners. This is a shame because the book provides important evidence of the ongoing problems in the relationship between medical practitioners, healthcare systems and the pharmaceutical industry, and offers concrete actions that could be taken. However, given the redundancy, digressions and patronising exposition, it is likely that this book will mainly be of interest to a motivated lay audience.

Dr Ahmad is a member of the Editorial Executive Committee of Australian Prescriber.

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FEATURE

Medicinal mishap

Incorrectly dropped in the eye

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Case 1

A 70-year-old woman rang the Poisons Information Centre with complaints of stinging and redness in one eye. She had instilled a drop of mometasone lotion instead of prednisolone with phenylephrine drops, prescribed after surgery for glaucoma. She was advised to flush the eye thoroughly with running water and to present to a doctor if symptoms persisted.

Case 2

A person called about a colleague who had rinsed his eyes with chlorhexidine and cetrimide irrigation solution, instead of normal saline, from a first aid kit. The eye was stinging. He was advised to flush his eyes thoroughly for 15 minutes and to present to a doctor if symptoms persisted.

Case 3

A general practitioner called regarding a man who presented following referral from the NSW Poisons Information Centre. The man was complaining of persistent redness and discharge after accidentally applying ear drops (acetic acid, isopropyl alcohol) into his eyes eight hours earlier. The general practitioner found corneal ulceration after fluorescein staining and referred the patient to an ophthalmologist.

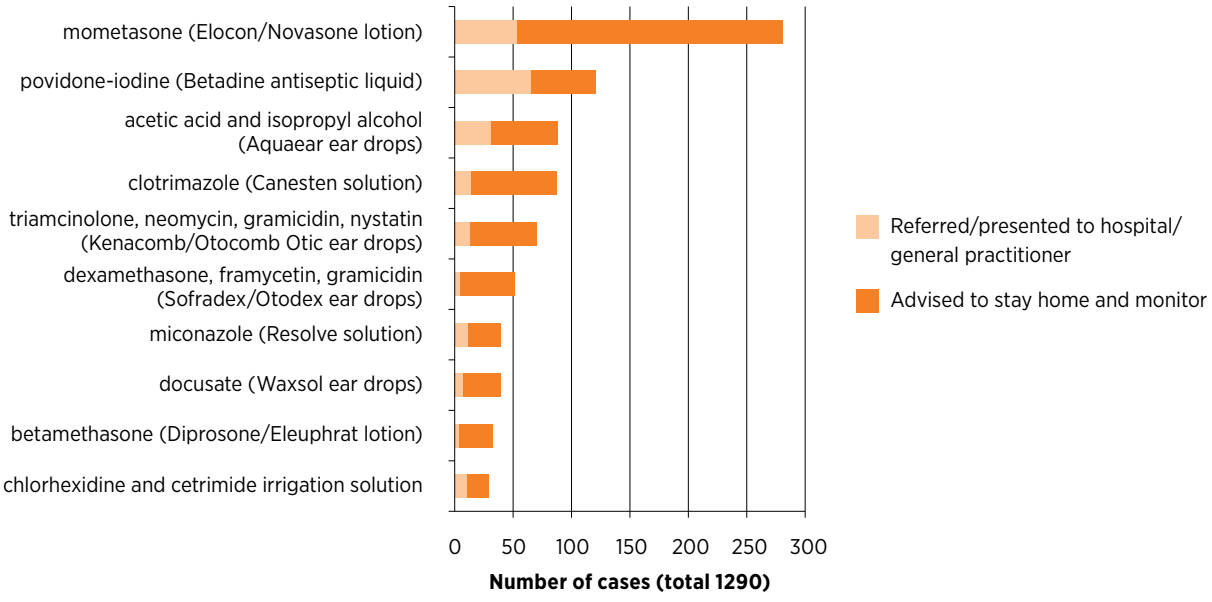
Comment

Medication administration errors are well known in the hospital environment,[1] but little is known about these errors in the community.[2] In particular, eye administration of non-ocular medications is under-recognised. Conversely, accidental eye administration of 'superglue' (cyanoacrylates) mistaken for eye drops is well documented.

A recent retrospective review of calls to the NSW Poisons Information Centre between 2004 and 2011 found 1290 cases of accidental ocular administration of pharmaceutical products not intended for use in the eye. More than 75% of the cases were adults and 60% were female.

The main products involved were a mixture of prescription and over-the-counter steroids, antiseptics, antifungals, antibacterials, ear wax removal, ear drying and nasal decongestant products (Fig. 1). The vast majority of products applied to the eye were in dropper bottles, although 92 involved application of creams, gels or ointments (mostly intended for use on cold sores). In 31 cases dermal irrigation solutions were used and 16 cases involved salbutamol or ipratropium nebules. In comparison, there were around 900 cases of superglue being accidentally applied to the eye.

Fig. 1 **Most common pharmaceuticals accidentally administered into the eye and reported to the NSW Poisons Information Centre, 2004–11** [3]



Follow-up data were unknown for the majority of cases but 342 people (27%) presented to, or were referred to, a medical practitioner or hospital. In addition, three cases had corneal ulceration. One was the result of application of a lotion containing mometasone with isopropyl alcohol and propylene glycol, and two cases were due to ear drops for swimmers ear containing acetic acid and isopropyl alcohol.

Recommendations

Mistaken identity of similar looking products appears to be the most common cause of errors (Fig. 2). Safety tips to prevent accidental eye administration, particularly of ear drops, have been highlighted by the Institute for Safe Medication Practices.[4] Suggestions include:

- keep the drops in the original box
- separate the drops – store different types of drops in separate locations
- discard leftover drops
- examine the product closely before administering
- warnings at the time of prescribing, dispensing or sale can help to remind consumers of the potential dangers of mixing up medicines.

Further research into the product packaging and labelling of topical pharmaceuticals is needed to help stop these preventable errors. Poisons centres can play an important role in pharmacovigilance and represent an underused resource of adverse event reports. Research could be conducted by obtaining follow-up information on exposures. It could help to identify a range of problems, such as confusing product packaging and labelling. <

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Fig. 2 **Similarities in product appearance of two commonly used topical pharmaceuticals**

Chloramphenicol is for ocular use

Mometasone is for dermal use

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Poisons Information Centre

Phone 131 126 from anywhere in Australia – 24 hours – for information and advice on the treatment of poisoning, bites and stings

Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Medicines Safety Update

Volume 4, Number 2, April 2013

In this issue

Montelukast – neuropsychiatric risks

Health professionals are reminded of the possibility of neuropsychiatric adverse events, including suicidal ideation, in children, adolescents and adults treated with montelukast. Health professionals should be aware of these potential adverse effects and advise patients and parents to seek medical advice should they occur.

Montelukast is a leukotriene receptor antagonist approved for the prophylaxis and treatment of chronic asthma in adults and children aged 2 years and older, and for the symptomatic treatment of seasonal allergic rhinitis.

It is available on the Pharmaceutical Benefits Scheme (streamlined authority) as a 'first-line preventer medication, as the single preventer agent for children aged 2 to 5 years with frequent intermittent or mild persistent asthma, as an alternative to sodium cromoglycate or nedocromil sodium'.

The Product Information (PI) for montelukast contains a precaution describing the possibility of multiple neuropsychiatric adverse events, including suicidal ideation, depression, agitation, aggressive behaviour, hallucinations, insomnia, somnambulism and tremor, as well as others.

Reported cases

Suspected neuropsychiatric adverse events in adult, adolescent and paediatric patients taking montelukast have been reported to the TGA.

Between 1 January 2000 and 1 January 2013, the TGA received reports of neuropsychiatric adverse events in 58 children and adolescents being treated with montelukast. Among the adverse events were five reports of suicidal ideation, five reports of depression and eight reports of agitation. Other neuropsychiatric reactions reported included nightmares, altered mood and insomnia. In many cases, patients experienced multiple neuropsychiatric reactions.

Although the number of reports is small, the inherent difficulty in establishing psychiatric diagnoses in children could contribute to under-reporting of related effects to the TGA.

Information for health professionals

Health professionals are reminded of the potential for neuropsychiatric adverse effects during treatment with montelukast, particularly when initiating therapy and increasing the dose. This is especially important if the patient is a child.

Health professionals should consult the PI for further information on potential neuropsychiatric adverse events and carefully evaluate the risks and benefits of continuing treatment with montelukast if such events occur.

In the case of children, caregivers should also be made aware of these potential adverse effects and instructed to seek medical advice if they have any concerns.

Health professionals are encouraged to report any suspected adverse events to the TGA.

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

TGA Health Safety Regulation

MEDICINES SAFETY UPDATE

Use of 2013 seasonal influenza vaccines in children

The TGA advises health professionals that, for the 2013 influenza season, there are four influenza vaccines registered for use in children from the age of 6 months – Agrippal, Fluarix, Influvac and Vaxigrip. An additional influenza vaccine, Fluvax, is registered for use in children from the age of 5 years. Fluvax should not be used in children under 5 years and should only be used in children aged 5 to under 9 years based on careful consideration of potential benefits and risks in the individual child.

During the 2010 influenza season, an excess number of febrile reactions and febrile convulsions occurred in children under 5 years after immunisation with one of the registered seasonal influenza vaccines, Fluvax.[1] As a result, the approved indication for Fluvax was changed to 5 years and over, with special precautions in children aged 5 to under 9 years.

Vaccine changes

Following a review of the strains of influenza that were circulating in the Southern Hemisphere, the Australian Influenza Vaccine Committee recommended changes to two of the strains in the 2013 vaccine compared with the 2012 vaccine. Details of the strains were announced on the TGA website.

The influenza strains in the 2013 vaccines are the same as the strains in the influenza vaccines used in the recent Northern Hemisphere winter. The TGA is reviewing surveillance data from the Northern Hemisphere to ensure there have been no unexpected adverse events related to these strains and, with the States and Territories, will be closely monitoring adverse event reports once the vaccination program commences.

Recommendations for use

For the 2013 influenza season, the TGA has registered five vaccines for use in children, with the indications shown in the table. An additional vaccine, Intanza (Sanofi Pasteur), is only registered for use in adults aged 18 to 59 years.

Adverse events following 2012 influenza vaccination

There were 435 adverse events reported to the TGA following vaccination with 2012 influenza vaccines, including 66 cases that were classified as serious.

Of these, 28 reports were of adverse events in children aged under 5 years and 9 reports were of adverse events in children aged 5 to under 9 years.

The TGA is aware that there were cases of inadvertent administration of Fluvax to children aged under 5 years, including four cases that resulted in adverse event reports. To minimise the risk of inadvertent administration in 2013, Fluvax's sponsor, bioCSL, has worked with the TGA to implement clearer warnings on the label and packaging, as well as in the black box warning in the Product Information (PI).

For further information about individual vaccines, please refer to the relevant PI document.

Reporting of adverse events following influenza vaccination

Please report all adverse events associated with influenza vaccination in patients of any age to the TGA or through the current requirements in their State or Territory.

Table
2013 seasonal influenza vaccines approved for use in children

Vaccine	Sponsor	Approved indication
Agrippal	Novartis Vaccines and Diagnostics	6 months and over
Fluarix	GlaxoSmithKline	6 months and over
Influvac*	Abbott Australasia	6 months and over
Vaxigrip*	Sanofi Pasteur	6 months and over
Fluvax**	bioCSL	5 years and over

* These vaccines also have a paediatric 0.25 mL ('junior') presentation registered for use in children aged 6 to 35 months.

** Febrile events have been observed in children aged 5 to under 9 years after immunisation with Fluvax. Therefore, in this age group, a decision to vaccinate with the 2013 Southern Hemisphere formulation of Fluvax vaccine should be based on careful consideration of potential benefits and risks in the individual.

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MEDICINES SAFETY UPDATE

Denosumab and severe hypocalcaemia

Health professionals are reminded to closely monitor patients being treated with denosumab for signs of severe hypocalcaemia, which in some cases can be fatal. Pre-existing hypocalcaemia must be corrected before initiating therapy with denosumab.

Denosumab is available in Australia as two brands, Prolia and Xgeva, which have different indications.

Prolia (60 mg) is given once every 6 months for the treatment of osteoporosis in postmenopausal women, and for the treatment of men with osteopenia who are receiving androgen deprivation therapy for non-metastatic prostate cancer.

Xgeva (120 mg) is given once every 4 weeks for the prevention of skeletal-related events in adults with bone metastases from solid tumours.

Denosumab is a fully human monoclonal antibody to the receptor activator of nuclear factor-κB ligand (RANKL) that blocks its binding to receptor activator of nuclear factor-κB (RANK), inhibiting the development and activity of osteoclasts, decreasing bone resorption, and increasing bone density.[1]

Hypocalcaemia is a known risk with denosumab, especially in patients who:

- are predisposed to hypocalcaemia (for example, those with a history of hypoparathyroidism, thyroid surgery, parathyroid surgery, malabsorption syndromes and excision of small intestine)
- have severe renal impairment (creatinine clearance < 30 mL/min)
- are receiving dialysis.

Signs and symptoms of hypocalcaemia include altered mental status, tetany, seizures and QTc prolongation.

Hypocalcaemia as a result of denosumab most commonly occurs in the first 6 months of treatment, but can occur at any time. The risk of severe hypocalcaemia is greater with use of Xgeva, although cases have also been reported in patients using Prolia.

Detection and reporting

Last year, a review of international postmarket data by the sponsor, Amgen, found that severe symptomatic hypocalcaemia occurred at an estimated rate of 1–2% in patients treated with Xgeva.[2] Some of these cases were found to be fatal. Amgen wrote to health professionals in September 2012, advising them of this information.

From 1 January 2011 to 25 October 2012, the TGA had received eight reports of hypocalcaemia in patients being treated with Xgeva. In all but one case, Xgeva was the sole suspect. During the same period, the TGA received 10 reports of hypocalcaemia with Prolia. In eight of those cases, Prolia was the sole suspect.

Changes to the Product Information

The precaution in the Xgeva Product Information (PI) regarding hypocalcaemia has been updated to advise health professionals that severe symptomatic hypocalcaemia has been reported in the postmarketing setting. Similar text has also been added to the adverse effects section.

The adverse effects section of the Prolia PI has been updated to advise health professionals that rare events of severe symptomatic hypocalcaemia have been reported in patients at increased risk of hypocalcaemia. The PI was also updated to specify that atypical femoral fractures have been reported in patients being treated with Prolia.

Advice for health professionals

Pre-existing hypocalcaemia must be corrected before initiating therapy with denosumab.

It is recommended that health professionals monitor the calcium levels of patients being treated with Prolia, especially if they are predisposed to hypocalcaemia. To reduce the risk of hypocalcaemia, patients must be adequately supplemented with calcium and vitamin D.

Supplementation with calcium and vitamin D is required for all patients receiving Xgeva (unless hypercalcaemia is present).

For full prescribing details, refer to the Xgeva and Prolia PIs, available on the TGA website.

Patients being treated with denosumab should be informed about the signs and symptoms of hypocalcaemia (for example, altered mental status, tetany and seizures) and of the need to seek immediate medical attention if they experience any of them.

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MEDICINES SAFETY UPDATE

Thank you for reporting

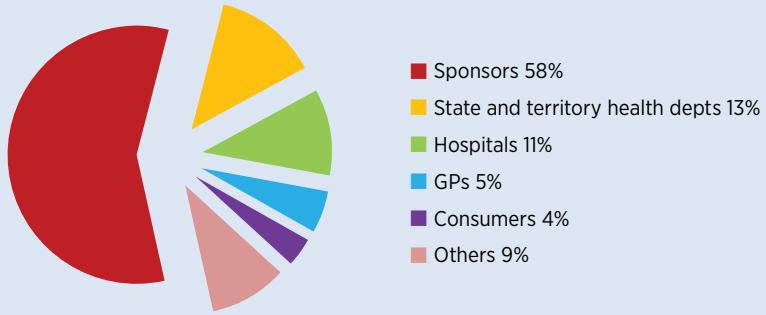
The TGA received approximately 14 500 adverse event reports during 2012. This was a similar number to those received during the previous year.

In recent years, sponsors have become the predominant reporter of adverse events. In 2012, sponsors were responsible for approximately 8350 reports (58% of all reports received) – demonstrating their commitment to meeting pharmacovigilance requirements, which support the TGA's mission to ensure ongoing medicine, vaccine and medical device safety in Australia.

Meanwhile, general practitioners (GPs) and consumers made a comparatively small number of reports in 2012. GPs contributed 5% of reports received last year, which was a decrease on the 7% they contributed in 2011.

The TGA aims to stimulate greater reporting from GPs and consumers in the future, with greater promotion of reporting avenues (such as the 'blue card') and other initiatives under the TGA's blueprint reforms that will support easier reporting. As part of the TGA's aim to increase transparency, it is working towards making information about medicines and medical devices that are being monitored publicly available. Further information about these activities will be provided as they develop.

Figure
Sources of adverse event reports made to the TGA in 2012



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

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

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

Reports may be submitted:

- **using the 'blue card'** available from the TGA website and with the October issue of *Australian Prescriber*
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Medicines Safety Update is written by staff from the Office of Product Review

DISCLAIMER

ABNORMAL LABORATORY RESULTS

Urinary drug screening

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Key words
drug abuse, opioids, saliva

Aust Prescr 2013;36:62–4

SUMMARY

Urinary drug screening can detect substances including over-the-counter and prescription drugs. The focus of screening is often illicit drugs.

Simple point-of-care tests, largely immunoassays, can rapidly detect a class of drugs or specific drugs in urine. More complex large scale laboratory screens and confirmatory tests can also be used.

Urine tests can often provide evidence of previous drug consumption. Screening is therefore useful in monitoring abstinence from drug use, the use of drugs in the workplace and in legal disputes.

Introduction

Drugs, chemicals and other substances consumed by humans are often excreted in the urine, where they may be detected with screening tests. The detection of these compounds is limited only by the assay and cost.

In hospital or pathology laboratories the emphasis is typically on drugs of abuse, screening either for compliance to (e.g. methadone) or abstinence from (e.g. cannabis) particular substances. Hospital screening can also give the clinician additional help in the differential diagnosis and treatment of a patient, but the availability of toxicological analyses varies between hospitals.

Most commonly used drug screening tests involve immunoassay techniques.[1] These range from so-called bedside or point-of-care testing to more sophisticated laboratory-based immunological tests. Immunoassay can provide fast and reliable results, however the results must be interpreted with caution.

What can be tested?

The most common drugs tested in urine include amphetamines, benzodiazepines, cannabis, cocaine and opioids. Other tests can screen for more specific compounds, rather than drug classes, such as alcohol, methadone, buprenorphine, phencyclidine and other stimulants (for example cathinones) and designer drugs. Alcohol metabolites such as ethylglucuronide can now be detected in urine and, importantly, for much longer periods than alcohol itself (up to several days). Ethylglucuronide screening has been used clinically as evidence of abstinence from alcohol for patients awaiting liver transplant.[2]

Urinary drug screening can be quite complex with detection of a comprehensive list of targeted and unknown substances. For example, forensic laboratories have the capability to detect a wide range of compounds using immunoassays and other chromatographic techniques (that is gas chromatography/mass spectrometry or liquid chromatography/mass spectrometry). The methods used in these laboratories often aim for a wide range of drugs and metabolites to try to detect as many forensically relevant compounds as possible.

Other laboratories, such as sports testing facilities, can screen for drugs (including steroids and biomarkers). Screens for unknown compounds have been made possible by the advent of new technologies. These laboratories are more specialised than the typical hospital or pathology laboratories and are strictly regulated for the detection of these compounds by accrediting bodies such as the National Association of Testing Authorities, Australia[3] and the World Anti-Doping Agency[4].

Standards

An Australian/New Zealand Drug testing standard (AS/NZS 4308:2008) provides guidance on the most common classes of drugs to be tested in urine.[5] The Australian Standard (AS 4308) was the world's first national standard for medicolegal drug testing. It is designed to ensure the standardisation of procedures for specimen collection and the detection of drugs of abuse. These include cannabis metabolites, cocaine metabolites, benzodiazepines, sympathomimetic amines (amphetamines) and opioids. Urine for medicolegal testing should be collected and analysed by an AS/NZS 4308:2008 accredited organisation. Consultation with the laboratory is useful to find out which compounds can be tested as well as for interpretation of negative or positive findings.

Why test urine for drugs?

Urine screening can provide an indication that someone has consumed drugs at some point before sampling. Most drugs typically have a detection window of up to 48 hours (Table). This may be shorter for some drugs which are eliminated relatively quickly from the body such as alcohol or gamma-

hydroxybutyrate. Drugs such as diazepam and cannabis can persist in urine for days or even weeks and so can be detected for longer periods.

The frequency of drug consumption will also have an impact on the effectiveness of urine screening. Acute or once-off use, as in the case of drug-facilitated crime where a drug is used to render someone incapacitated, is more difficult to detect and may challenge the sensitivity of urine screening. People who use drugs more regularly will typically have higher concentrations of drugs in their urine leading to easier detection with possibly longer timeframes.

In chronic users, drugs of abuse can be detected in urine for approximately one week after last use, and in extreme cases even longer in cocaine (22 days) and cannabis users (up to three months).[6] Urine testing will not show when a drug was used, or how much. Importantly, a positive drug result cannot infer impairment at the time the urine was collected.

Results

Urine testing typically involves a screening test followed by a confirmation test. Confirmation is usually performed on the sample taken for screening.

Screening tests

Most drugs of interest are first detected by simple immunoassays. These are broad screening tests that are quick, often cheap and effective for showing a positive or negative result. However, as with all screening tests there are limitations to the degree of interpretation that can be inferred from the result. The limitations of immunoassay techniques include false positives as well as false negative results.

A false positive is a screening test that fails to be confirmed using other more sensitive and specific techniques such as gas chromatography/mass spectrometry or liquid chromatography/mass spectrometry. This means that the immunoassay has cross-reacted with some other substance in the urine leading to a false positive result for the substance of interest. Other drugs can trigger such false positive results and the laboratory should have a list of compounds which can cross-react with the screening test. For example, ranitidine can produce a false positive result for amphetamines. It is also worth noting that some foodstuffs can also produce positive results such as poppy seeds for opioids.

A false negative result is possible when the screening test is negative but the confirmatory test is positive. This is less common as negative screening tests are not usually confirmed. When a screening test is negative that is usually the end of the investigation. In a workplace, a false negative test can have far-reaching ramifications if an incident occurs after screening and a urine sample test then finds drugs which were missed by the initial screening process. On-site or point-of-care devices must therefore be rigorously tested and validated before use in the field. AS/NZS 4308 states that on-site screening devices be evaluated at 25% above and 30% below the level considered positive (these are typically referred to as cut-offs). The Standard also specifies that failure of no more than 10% of on-site devices is permitted.

When using immunoassay techniques, samples can easily be adulterated to provide a false result. Adulterations are common in patients who undergo clinical compliance testing, for example abstinence control in drug users. Adulterations can include water (leading to dilution of urine), bleach and masking agents (such as diuretics) or other substances that interfere with the screening test. Adulterant checks are also part of a laboratory's capability to detect an invalid specimen. The Standard provides guidance on what to do to avoid adulteration and how to test for adulterants (for example temperature and creatinine checks).

Table **Detection of drugs in urine**

Drug or drug class	Detection times in urine
Benzodiazepines (e.g. alprazolam, diazepam, temazepam)	1–7 days or longer depending on half-life of drug*
Cannabinoids	3–28 days depending on frequency of use
Cocaine	1–3 days
Methamphetamine/amphetamine	2–5 days
Methylenedioxymethamphetamine	2–5 days
Opioids (e.g. morphine, codeine)	1–2 days
Steroids (e.g. testosterone, stanozolol)	Days to months depending on the half-life of the steroid

* may be longer in chronic users

Confirmatory tests

Confirmation tests are usually required for medicolegal purposes when drug testing is used in the workplace or for family custody disputes in which parents are allegedly using drugs at home in the presence of children. An initial urinary screening test must be confirmed for evidence of drug use. Confirmatory testing is more sensitive and specific than screening tests and confirms the drug of interest as opposed to the drug class.

Clinical laboratories have relied on gas chromatography/mass spectrometry for confirmation, however developments in liquid chromatography/mass spectrometry technologies over the last 10 years have meant a wider range of compounds can be confirmed simultaneously. Laboratories must demonstrate compliance with requirements to either International Organization for Standardization (ISO) 17025 (for chemical/forensic testing) or ISO 15189 for medical/pathology testing and must be accredited by the National Association of Testing Authorities.

Screening tests other than urine

The evolution of oral-fluid testing (saliva) both from a policy and technology viewpoint has grown rapidly in recent years. This testing has been used primarily to test drivers for illicit drugs (amphetamines and cannabis) and is now being used in the workplace.

Saliva is easier and safer to collect than urine. Unlike urine, not all drugs are easily detectable in oral fluid, either because of the low concentrations or the short time that drugs are present in saliva. The detection of a drug in oral fluid is normally associated with recent use (up to 24 hours) as the drugs can be related to blood or plasma concentrations and therefore physiological effect. This cannot be inferred from urine as the concentration in urine can only be related to previous consumption and not any effect of the drug.

Conclusion

Urine screening is an effective tool for monitoring abstinence from drug use, assessing the use of drugs in the workplace and for legal disputes. A number of laboratories can provide testing for drugs of abuse and prescription drugs (for example benzodiazepines and some opioids). Point-of-care tests can provide similar information, however knowledge of which drugs and compounds can be detected as well as interpretation of what the test results mean is essential in maximising the information that can be gained from urinary screening. ◁

Conflict of interest: none declared

Q:

SELF-TEST QUESTIONS

True or false?

5. Urinary drug screening can identify previous intoxication with illicit drugs.

6. Cannabis may be present in the urine for up to a month following chronic use.

Answers on page 67

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New drugs

Ingenol mebutate

Approved indication: actinic keratoses
Picato (Leo Pharma)
tubes containing 0.015% or 0.05% gel
Australian Medicines Handbook section 8.7

Actinic or solar keratoses, which are precancerous skin lesions, are very common in older Australians with fair skin. Current treatments include surgery or cryotherapy, and topical treatments such as fluorouracil and imiquimod (Aust Prescr 2011;34:6-7).

Ingenol mebutate is a topical treatment derived from the sap of the plant *Euphorbia peplus*. The gel is thought to work by inducing local cell death and by promoting an inflammatory response that attracts immune cells such as T cells, neutrophils and macrophages. After skin application, systemic absorption is below detectable limits so little is known of its pharmacokinetic profile. However, as a precautionary measure, ingenol mebutate use during pregnancy should be avoided.

This product has been tested in four phase III randomised placebo-controlled trials.[1] Enrolled patients had 4–8 typical, discrete actinic keratoses within a 25 cm^2 field. Those with lesions on the face and scalp were randomised to ingenol mebutate 0.015% gel or vehicle gel once daily for three days, and those with lesions on the trunk or extremities were randomised to ingenol 0.05% gel or vehicle gel once daily for two days (see Table). The gel was self-applied to a defined treatment area of 25 cm^2. Blinding in the trials was limited because of skin reactions to the active treatment.

After eight weeks, lesions had completely cleared in more people receiving the active treatment compared to those receiving placebo (see Table). For one patient with face and scalp lesions to have complete resolution, 2.6 patients needed to be treated. For patients with trunk and extremity lesions, the number needed to treat was 3.4.

Patients whose lesions had resolved after eight weeks were enrolled in observational follow-up studies. After 12 months, actinic keratoses recurred in 53.9% of patients who had had face and scalp lesions and 56% of patients with trunk and extremity lesions.

The most common adverse reactions were pain, pruritus, irritation, and infection at the application site. Skin reactions included erythema, flaking, crusting, swelling, pustulation and ulceration which were generally transient. Eye problems (eyelid and periorbital oedema) were more common with ingenol mebutate than with placebo. Patients are advised to avoid the eye area and wash their hands after applying the gel.

Three treatment-related serious adverse events have been reported – one case of Bowen's disease (mild) and two cases of squamous cell carcinoma (mild and moderate).

Ingenol should not be applied immediately before or after having a shower or within two hours of bedtime. After the gel has been applied, touching the area should be avoided for six hours. It is important to store ingenol at 2–8° C at all times.

In conclusion, ingenol mebutate is more effective than placebo for treating actinic keratoses. However, lesions are likely to recur in over 50% of patients after a year. Although this gel has not been directly compared to other topical treatments, a Cochrane review found its short-term efficacy was similar to diclofenac, fluorouracil and imiquimod.[2] The advantage of ingenol mebutate is that only 2–3 applications are needed, whereas other creams and gels must be applied for weeks or months.

T T manufacturer provided additional useful information

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

Table **Efficacy of ingenol mebutate gel in patients with actinic keratoses** [1]

	Face and scalp lesions		Trunk and extremity lesions	
Treatment	ingenol mebutate 0.015%	placebo	ingenol mebutate 0.05%	placebo
Number of patients	277	270	226	232
Patient response*	42.2%	3.7%	34.1%	4.7%

* complete resolution of lesions 8 weeks after treatment

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NEW DRUGS

Live Japanese encephalitis vaccine

Approved indication: prevention of Japanese encephalitis

Imojev (Sanofi Pasteur)

vials containing one dose of freeze-dried powder for reconstitution

Australian Medicines Handbook section 20.1

The currently approved vaccine for Japanese encephalitis in Australia is an inactivated vaccine given in two doses (Aust Prescr 2009;32:82-6). This new product is a live attenuated vaccine using the yellow fever vaccine virus – strain 17D-204 – as a vector. In this virus, two of the yellow fever genes have been replaced by Japanese encephalitis genes (strain SA_{14} 14-2) encoding a premembrane and an envelope protein. This chimeric virus is propagated in tissue culture before being freeze-dried for use.

Vaccination is recommended for people who live in or are travelling to areas where Japanese encephalitis is endemic, such as Papua New Guinea and parts of Asia. It is also recommended for people who work with the virus in laboratories. The vaccine is indicated from 12 months of age as a single subcutaneous injection.

In an early dose-finding trial, most of the 87 adults who were given the live vaccine (1.8–5.8 $\log_{10}$ plaque-forming units subcutaneously) developed neutralising antibodies to the chimeric vaccine strain and, to a lesser degree, to the wild-type Japanese encephalitis strains Beijing-1, Nakama and 902/97. A second dose of the vaccine 30 days later did not boost this immune response.[1]

In a phase III immunogenicity trial of 820 adults (enrolled from Australia and the USA), one dose (4 $\log_{10}$ plaque-forming units) of the live vaccine was comparable to three doses of an inactivated Japanese encephalitis vaccine. A month after vaccination, 99% of people in the live vaccine group were considered to have protective levels of neutralising antibody to the vaccine strain compared to 74.8% of people in the comparator group.[2]

In a paediatric trial, almost all children (aged 1–5 years) developed seroprotective antibody levels after a single dose of the vaccine, regardless of whether they had been previously vaccinated with an inactive vaccine. Many of the children developed neutralising antibodies that cross-reacted with other Japanese encephalitis strains.[3]

It is not currently known if a booster of the live vaccine will be needed, but from longer-term immunogenicity studies it seems antibody responses last for at least four years in adults and six months in children.

In adults, the most common adverse reactions to the vaccine included headache (23.9%), fatigue (21%), malaise (17%), myalgia (14.7%) and injection-site pain (11.8%). These were also common in children as well as irritability (28.5%), loss of appetite (25.9%), fever (20.7%), vomiting (19.2%) and abnormal crying (19.1%).

Vaccination should be postponed in the event of a fever or acute illness. The vaccine is contraindicated in people with impaired cellular immunity, including those on immunosuppressive therapies such as chemotherapy or high-dose steroids (for 14 days or more), and people with symptomatic HIV infection.

This vaccine should not be given to women during pregnancy and lactation as there is a theoretical risk that the virus could cross the placenta or be secreted in breast milk.

In children, other vaccines should not be given at the same time. However, in adults concomitant yellow fever vaccine can be administered in the opposite arm or leg. Prescribers should be aware that plasma products such as immunoglobulins could potentially neutralise the live virus so vaccination after receiving blood products should be avoided for at least six weeks.

This live vaccine seems to produce durable immune responses to Japanese encephalitis but its actual efficacy will not be known until after marketing. It may be preferable to the current inactivated vaccine as it is approved for use in children and only one dose is indicated.

T T manufacturer provided additional useful information

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

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

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

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

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5	False	6	True

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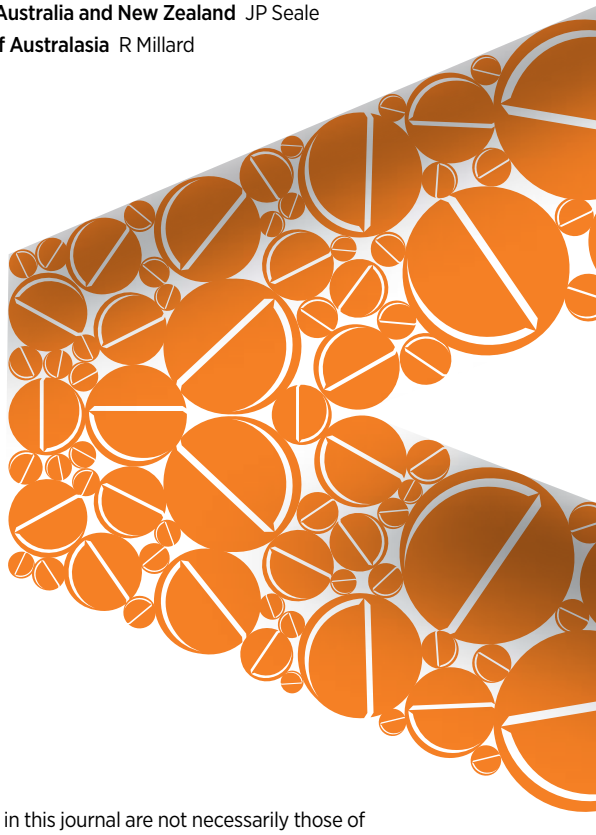

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