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EDITORIAL

Off-label prescribing

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Key words
Pharmaceutical Benefits Scheme, Therapeutic Goods Administration

Aust Prescr 2013;36:182–3

'Off-label' prescribing occurs when a drug is prescribed for an indication, a route of administration, or a patient group that is not included in the approved product information document for that drug.

Prescribing off label is unavoidable and very common, especially if your practice includes children, pregnant women or palliative care. Off-label prescribing means that the Therapeutic Goods Administration (TGA) has not approved the indication, route of administration or patient group. It does not mean that the TGA has rejected the indication. Commonly the TGA has not been asked to evaluate the indication.

There are many scenarios of off-label prescribing. Examples include meloxicam, a non-steroidal anti-inflammatory drug (NSAID), when used to treat rheumatoid arthritis in children under 18 years, or rosuvastatin, an HMGCoA reductase inhibitor (statin), for the primary prevention of cardiovascular events in a 45-year-old male with a plasma cholesterol of 6 mmol/L and without other risk factors. In the product information meloxicam is contraindicated for children, and rosuvastatin is not indicated for primary prevention in men below the age of 50 years with moderate hypercholesterolaemia and no other risk factors. In the case of meloxicam, studies have probably not been undertaken with the aim of applying to extend the indication to children. In contrast to the product information, the Australian Medicines Handbook does not list treating children with any NSAID as a contraindication or even a 'precaution'. This acknowledges that as a class NSAIDs may be used in children if attention is paid to the dose and the risk factors for adverse effects. Some NSAIDs, for example naproxen, have an indication in the product information for use in children older than two years, and ibuprofen is available over the counter, illustrating the confusion if product information alone is relied upon.

Another reason an indication is not registered is that it is uncommon. Sulfasalazine is used for peripheral joint involvement in ankylosing spondylitis, but there is no such indication or guidance in the product information. This 'current use' is listed in Therapeutic Guidelines.[1] If a drug is 'off patent' and there are a number of generic versions available, there is little motivation for the originator company or any of the generic companies to undertake studies for registering an uncommon indication. The economics simply do not warrant this course of action.

Despite the considerable use of medicines for off-label indications there is little guidance for prescribers. The product information will not include advice about unapproved indications and the drug companies are unable to promote these indications. The older the drug is, the less reliable the product information is for accepted uses of the drug. While a prescriber can ask a drug company for information about using a drug for an unapproved indication, the company needs to tread a fine line to avoid being accused of 'promoting' the indication.

Off-label prescribing does not refer to those indications that are registered by the TGA but not subsidised by the Pharmaceutical Benefits Scheme (PBS). A reasonably common reason for the indication not to be subsidised by the PBS is that the company might not have applied for a subsidy or not reached agreement about the price of the drug. A recent example was gabapentin, a second-line antiepileptic drug with some effect in neuropathic pain. That indication was never subsidised on the PBS, so patients with neuropathic pain had to pay a high price for a month's supply on private prescription unless it was provided through a public hospital. Similarly, disulfiram, prescribed to support abstinence from alcohol in selected patients, is registered by the TGA for this indication. It can only be prescribed

From the Editor

Information about new drugs is an important part of *Australian Prescriber*. We aim to publish this information on the internet as soon as the drug is marketed, and subsequently in print. Although there are five new drugs in this issue, you can find information about other drugs scheduled for release this month at australianprescriber.com.

The internet can provide therapy as well as information. Lisa Lampe includes some of the available online resources in her review of the treatment of anxiety.

Patients are likely to be anxious about having surgery. Anxiety can increase postoperative pain and Philip Corke explains the importance of effective analgesic management. This is an example of the patient-centred prescribing discussed by Andrew Knight. Vasi Naganathan would agree that tailoring therapy to the individual is important when using cardiovascular drugs in older people.

Individualised therapy may be facilitated by increased understanding of a patient's genetics. Aidan McElduff describes some of the genetic changes which contribute to diabetes.

The number of genetically engineered drugs is increasing. Biological therapies are expensive so they are starting to appear in our annual list of Top 10 drugs.

privately in the community as it is not listed on the PBS. This makes it difficult for many patients with alcohol dependency to afford the treatment. Other drugs with a similar indication, such as naltrexone and acamprosate, are listed on the PBS but are very much more expensive to the taxpayer. Some patients are disadvantaged by not having access to a cheaper alternative treatment for alcohol dependency.[2]

If the drug is listed on the PBS with a 'restriction' or a requirement to gain an 'authority', the drug cannot be prescribed or subsidised for a non-PBS listed indication.

There is no legal impediment to prescribing off label, however the onus is on the prescriber to defend their prescription for an indication that is not listed in the product information. If, in the opinion of the prescriber, the off-label prescription can be supported by reasonable quality evidence, for example the indication is identified in the Australian Medicines Handbook, the prescriber should proceed if this is in the patient's best interests.

It is best if your patient knows that their prescription is off label, and why you are recommending the drug. Making a note of this 'conversation' in the patient's records and possibly even recording that the patient 'consented' would be good practice (guidance on approaches to gaining consent for off-label prescribing has recently become available).[3,4] The more uncommon the indication for prescribing the drug, the more important it is that the patient understands and accepts the rationale for your prescription. This approach is not different from what should ideally be done for the prescription of any drug. However, the rationale for an off-label prescription might be subject to more scrutiny in the case of a serious adverse event. This conversation with the patient also helps when the patient cannot find information about the indication in the Consumer Medicines Information (CMI), which is the approved drug information for consumers. You can warn the patient about its absence as many patients will be concerned that 'their' indication is not in the CMI.

the onus is on the prescriber to defend an off-label prescription

It is important to know when you are prescribing off label and it is good that your patients know and understand why. Having evidence or information from the Australian Medicines Handbook, Therapeutic Guidelines or NPS MedicineWise that supports your prescribing decision is very desirable. ◀

Conflict of interest: none declared

REFERENCES

1. eTG complete [internet]. Melbourne: Therapeutic Guidelines Limited; 2013 Mar. www.tg.org.au/index.php?sectionid=71 [cited 2013 Nov 7]
2. Lipworth WL, Wodak AD, Haber PS, Day RO. Why is disulfiram not on the PBS? Med J Aust 2011;195:371-2.
3. Gazarian M, Kelly M, McPhee JR, Graudins LV, Ward RL, Campbell TJ. Off-label use of medicines: consensus recommendations for evaluating appropriateness. Med J Aust 2006;185:544-8.
4. The Council of Australian Therapeutic Advisory Groups. Rethinking medicines decision-making in Australian hospitals: Guiding principles for the quality use of off-label medicines. www.catag.org.au [cited 2013 Nov 20]

Online first – publishing between issues of *Australian Prescriber*

Australian Prescriber is published every two months, in print and online. However, new drugs can become available at any time. We aim to publish information about these drugs as soon as possible at **australianprescriber.com**. We may also publish topical articles here. Online first content will then be incorporated into the next issue of the journal.

From this month, we will send additional e-alerts with links to Online First content. To receive these updates, make sure you are subscribed to an e-alert by visiting **australianprescriber.com/contact_us/mailing_list#email_alert**

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LETTERS

Letters to the Editor

Statins in older adults

Editor, – The recent article (Aust Prescr 2013;36:79-82) suggests statins could be less effective in older patients, may have more adverse effects and should be used in lower doses.

While this may be true in seriously ill patients or those with dementia, we feel that there is insufficient evidence to follow this advice in otherwise fit elderly people. The fact that the relationship of cholesterol to cardiac events in the elderly is less consistent does not negate trials showing a decrease in events no matter what the starting cholesterol is, or the greater decrease in events in higher compared to lower dose statins. With an increased incidence of events in the elderly, the absolute drop with statins may well be greater.

The evidence on loss of memory with statins is minimal in otherwise fit elderly patients. There are anecdotal reports of this only. Myopathy requires drug cessation but this is in the minority of patients. Risks with liver enzyme elevation appear slight at the most.

We feel that following the advice in the article could increase cardiac and other atherosclerotic events in otherwise well elderly people.

Mark Sheppard
Cardiologist

Alistair Begg
Cardiologist

SA Heart
Adelaide

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

We thank Mark Sheppard and Alistair Begg for pointing out the limitations of making clinical judgements based only on chronological age. In older people, in the presence of increasing inter-individual variability, biological age, which is analogous to the degree of frailty, is a much better predictor of outcomes than chronological age. Amongst older people, frailty affects the use, pharmacokinetics, pharmacodynamics, safety and efficacy of medicines.[1,2]

Clinical trials in older people do not show benefits of statins for primary prevention of cardiovascular disease.[3] The participants in these trials are generally fit. The frail are predominantly excluded based on comorbidity, co-medication or impaired physical or cognitive function. In frail older people, we know more about adverse events (from observational studies) than we do about efficacy, which requires randomised controlled trials.[4]

We wish to clarify what is known about adverse effects of statins in fit older people. The majority of the evidence that statins cause cognitive impairment is from case reports and case series, in which the impairment was generally reversible within days to weeks of stopping the statin. Therefore, if statin-associated cognitive decline is suspected, it is reasonable for clinicians to consider a trial of statin withdrawal. Amongst clinical trial participants who were generally fit, myalgias were reported in 5–10%, myositis in 0.1–0.2%, and rhabdomyolysis was rare. A clinician treating one hundred fit older patients, 40% of whom are taking statins, is expected to see 2–4 patients with myalgias. The elevated hepatic transaminases observed with statins are of uncertain clinical significance.

The prescription of statins for primary prevention should be individualised on the basis of clinical judgement.[5] Our article aims to raise awareness of the benefits and risks of statins to help clinicians apply the existing evidence to their patients.

REFERENCES

1. Hilmer SN, Gnjidic D, Le Couteur DG. Thinking through the medication list - appropriate prescribing and deprescribing in robust and frail older patients. Aust Fam Physician 2012;41:924-8.
2. Cerreta F, Eichler HG, Rasi G. Drug policy for an aging population - the European Medicines Agency's geriatric medicines strategy. N Engl J Med 2012;367:1972-4.
3. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet 2005;366:1267-78.
4. Hilmer SN, Gnjidic D, Abernethy DR. Pharmacoepidemiology in the postmarketing assessment of the safety and efficacy of drugs in older adults. J Gerontol A Biol Sci Med Sci 2012;67:181-8.
5. Reiner Z. Statins in the primary prevention of cardiovascular disease. Nat Rev Cardiol 2013;10:453-64.

Prescribing for persistent non-cancer pain

Editor, – I read the article on principles of prescribing for persistent non-cancer pain, anticipating I might get some insight into the management of non-cancer pain in the elderly (Aust Prescr 2013;36:113-5). Unfortunately I was disappointed. I have worked in a residential aged-care facility as a GP for the past nine years and the incidence of non-cancer chronic

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

pain is high – possibly around 60% of our residents aged over 75 years are affected.

The practice I work in prescribes paracetamol up to the maximum advised dose (4000 mg/day) as baseline therapy. Some of our residents require additional pain management. We prescribe quite a lot of opioids, mostly commencing with buprenorphine patches. In a percentage of residents this is insufficient and we mostly use sustained-release oxycontin or even fentanyl patches.

The facility provides physiotherapy, hydrotherapy and occupational therapy but psychotherapy is not readily accessed.

We prefer not to use regular high dose codeine-containing analgesics as we believe there is a problem with metabolites accumulating. Also constipation seems to be a big problem with codeine.

My impression is that dependence and addiction is not a problem in the very elderly, possibly due to some age-related change to the nervous system.

I would be pleased to have some feedback.

John Vanlint
GP
Sinnamon Park
Qld

Milton Cohen, the author of the article, comments:

Thank you for your letter. I appreciate your disappointment as, due to space constraints, the article was limited to principles of prescribing rather than being a more comprehensive treatise on pharmacotherapy for patients with persistent non-cancer pain.

Your use of opioids for patients in residential aged care when paracetamol and physical measures have been insufficient reflects good quality use of those medicines, especially as you avoid the short-acting prodrugs such as codeine (which about 10% of Caucasians will not convert to morphine). I would however sound a word of caution about transdermal fentanyl, as the lowest dose patch (12 microgram per hour) is approximately equivalent to oral oxycodone 20 mg per day which would be a high dose in that age group.

Addiction is not an issue in the elderly, in contrast to altered cognitive function and constipation which are the main limiting factors. Dependence, as defined by a withdrawal syndrome if the dose is reduced too quickly, can be minimised by keeping doses low and reducing slowly.

For more information on practical pharmacotherapy for managing pain, may I refer you to the following articles:

Cohen ML, Wodak AD. Opioid prescribing in general practice: a proposed approach. Med Today 2012;13:24-32.

Katz B. Pain in older people: often unrecognised and undertreated. Med Today 2012;13:35-38.

Prescribing for refugees

Editor, – Thank you for your editorial on prescribing for refugees (Aust Prescr 2013;36:146-7). Another area of prescription writing can be for immunisations for those in the 'visiting family and friends' category. Many of our refugees who have now been here for years are returning home with their Australian-born children. Keeping these kids on schedule for their government-funded vaccines is important as they may return to their parents' country of origin at a young age.

Adequate preparation with travel immunisations such as hepatitis A and typhoid, and in some cases malaria chemoprophylaxis, is important. The parents themselves may or may not be immune to hepatitis A and many of those returning home as adults are at risk for typhoid. Keeping up to date with new information relating to travel health is fast becoming an area of specialty.

Lani Ramsey
Nurse practitioner
Travel-Bug Vaccination Clinic
Adelaide

Mitchell Smith, one of the authors of the editorial, comments:

Thank you for raising the additional issue of travel health in people with a refugee background. Although by definition refugees are often prevented from returning home even to visit, some are able to do so many years later. Certainly standard immunisations are important, although not a prescribing issue as such. There is good evidence that people returning to a resource-poor country to visit friends and relatives are at increased risk of infectious diseases in particular. Appropriate travel advice and broader community education is therefore important.

ARTICLE

Drug treatment for anxiety

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Key words
antidepressants, benzodiazepines, cognitive behavioural therapy

Aust Prescr 2013;36:186–9

SUMMARY

Antidepressants are recommended as first-line when pharmacotherapy is required for anxiety disorders.

Selective serotonin reuptake inhibitors are effective in all anxiety disorders, and selective and noradrenaline reuptake inhibitors in most anxiety disorders. They are the drugs of first choice.

With the exception of obsessive compulsive disorder, there is little evidence of a dose–response relationship with antidepressants and many patients will respond to standard doses.

Anxiety is generally slower to respond to treatment than depression and clinicians should avoid rapid dose escalation.

The outcomes are likely to be enhanced if patients receive cognitive behavioural therapy in addition to pharmacotherapy.

Benzodiazepines are not the first-line treatment for anxiety disorders.

Introduction

Anxiety is a universal experience. When it becomes persistent, or persists after a triggering stressor has resolved, or is out of proportion to what would be expected and interferes with functioning, it may have reached the level of a disorder.

Both psychological and pharmacological treatment strategies for anxiety disorder have a good evidence base. Established drug treatments for anxiety target serotonin, noradrenaline and gamma-aminobutyric acid (GABA) neurotransmitter systems. They include virtually all classes of antidepressants, as well as benzodiazepines (Table). However, there is more evidence for certain classes of antidepressants over others, and benzodiazepines have a number of disadvantages that preclude their first-line use.

An overview of practice

A stepped-care model for the management of anxiety is recommended. Australian[2] and UK[3] guidelines list non-drug approaches as initial interventions. They include individual non-guided or guided self-help, and psychoeducational groups. For patients who present with marked functional impairment and those who do not respond to the initial interventions, high-intensity psychological interventions (such as cognitive behavioural therapy) or medication are recommended.

Australasian guidelines for panic and agoraphobia[4] identify cognitive behavioural therapy as first-line treatment. As a sole therapy, it can be at least as effective as pharmacotherapy and in some cases more so. Antidepressants alone are less effective than cognitive behavioural therapy alone, or the combination of an antidepressant and cognitive behavioural therapy.[4–6] Additionally, cognitive behavioural therapy is more likely to give lasting benefit. In contrast to depression, efficacy appears to be lost soon after stopping antidepressants, with a recurrence of anxiety being the rule rather than the exception.

Self-help programs

Non-facilitated self-help is available through a number of online resources including:

- www.anxietyonline.org.au – developed by the National eTherapy Centre at Swinburne University of Technology (Victoria) and funded by the Australian Government Department of Health
- www.thiswayup.org.au – an initiative of the Clinical Research Unit for Anxiety and Depression at St Vincent's Hospital (Sydney)
- www.ecentreclinic.org – developed by the Centre for Emotional Health at Macquarie University.

There is increasing evidence to support these web-based programs.[7] Their efficacy has been reviewed by a team at the Australian National University (www.beacon.anu.edu.au). Drop-out rates are reduced by having some contact with a therapist, but this does not have to be an expert. For example, the Clinical Research Unit for Anxiety and Depression program provides verbal scripts that can be used by a practice nurse. Within the stepped-care model, a good quality online anxiety treatment program can be recommended to patients with anxiety disorders of mild to moderate severity if they are comfortable with the technology.

Pharmacotherapy for anxiety

Patients with severe symptoms, those demoralised by their anxiety or those with comorbid depression may benefit from drug treatment. If medication

is likely to be required for more than a few days, an antidepressant should be used. Guidelines[8] recommend selective serotonin reuptake inhibitors (SSRIs) as first-line for all anxiety disorders, and serotonin and noradrenaline reuptake inhibitors (SNRIs) for some disorders (Table).

Choosing an SSRI or SNRI

Clinicians should choose a drug with a favourable tolerability profile and the least potential for drug interactions. Several antidepressants are potent inhibitors of cytochrome P450 enzymes.[9] Combining more than one serotonergic drug, including multiple antidepressants, St John's wort and some analgesics such as tramadol, can give rise to serotonin syndrome. A high index of suspicion is needed for patients who present with hypertension, hyperthermia, autonomic signs and hyperreflexia soon after starting, adding or increasing the dose of a serotonergic drug.[10] Discontinuation syndrome is more common with some antidepressants such as venlafaxine and paroxetine.

Pre-treatment counselling

Most patients with anxiety, and especially those with health concerns, for example in generalised anxiety disorder and panic disorder with or without agoraphobia, are highly sensitive to the physiological effects of medication. Adverse effects commonly seen when commencing antidepressants, such as nausea, headache and dizziness, may be misinterpreted as signs of serious physical illness or impending loss of mental control. Hence, the increased anxiety often observed when starting SSRIs may reflect a combination of normal (though undesirable) physiological effects, heightened cognitive symptoms of anxiety as a result of fears about the seriousness or permanence of these adverse effects, or more rarely, agitation or akathisia or acute suicidality.

Most patients have had their anxiety symptoms for many years before presenting for treatment and will generally tolerate a few more weeks while they wait for a response. Clinical experience suggests that patients most value information about the nature of their illness and its treatment, and do not expect instant alleviation of their symptoms.

To minimise the chances of a patient stopping medication as a result of these factors:

- start the patient on half the minimum strength tablet available. Continue at this dose for a few days to a week, or until the patient feels confident enough to increase the dose.
- give the minimum recommended dose a chance to work before increasing (at least four weeks)

Table **Efficacy of drug treatments for anxiety disorders**

Drug (daily dose)	**Efficacy from meta-analyses or consistent positive findings in more than one randomised controlled trial** *
Selective serotonin reuptake inhibitors	
escitalopram (10–20 mg) †	all anxiety disorders
paroxetine (20–60 mg)	
sertraline (50–150 mg, up to 200 mg in OCD)	
fluoxetine (20–40 mg, up to 60 mg in panic disorder and 80 mg in OCD)	panic/agoraphobia, social phobia, OCD, PTSD
fluvoxamine (100–300 mg)	panic/agoraphobia, social phobia, OCD
citalopram (20–40 mg) †	panic/agoraphobia, social phobia
Serotonin and noradrenaline reuptake inhibitors	
venlafaxine (75–225 mg, higher doses are sometimes used in specialist practice)	all anxiety disorders except OCD
duloxetine (60–120 mg)	GAD
Benzodiazepines	
alprazolam	GAD, panic/agoraphobia
clonazepam	panic/agoraphobia, social phobia
diazepam	GAD, panic/agoraphobia
lorazepam	GAD, panic/agoraphobia
Tricyclic antidepressants ‡ §	
amitriptyline (75–200 mg)	PTSD
clomipramine (75–250 mg)	OCD, panic/agoraphobia
imipramine (75–250 mg)	GAD, panic/agoraphobia
Monoamine oxidase inhibitors	
phenelzine (45–90 mg)	panic/agoraphobia, social phobia
Antipsychotics	
quetiapine (50–150 mg) § #	GAD

GAD generalised anxiety disorder OCD obsessive compulsive disorder
PTSD post-traumatic stress disorder

* If several members of an antidepressant class have demonstrated efficacy, it is highly likely that all members of the class will, however there may be limited studies of individual drugs. Differences in efficacy of benzodiazepines have sometimes been reported between low potency and high potency members of the class.

† Note the maximum dose recommendations have been revised following reports of dose-dependent QT interval prolongation. Citalopram has a greater effect than escitalopram on the QT interval (www.fda.gov/Drugs/DrugSafety/ucm297391.htm).

‡ Relatively few tricyclics have been studied extensively, and there are no studies of this class in social phobia.

§ ECG monitoring of QTc interval may be indicated. Avoid concomitant use with other drugs known to cause electrolyte imbalance or QT prolongation.

The upper limit of the dose range is based on findings that the efficacy of a 300 mg dose was unreliable compared to lower doses in placebo-controlled trials and was associated with more adverse effects and treatment dropouts. Another recent trial found quetiapine 150 mg was effective in generalised anxiety.[1]

- inform the patient about common and expected adverse effects before prescribing. See them again soon and encourage them to telephone should they have any concerns. Appropriate reassurance can be helpful.
- provide information about the expected time frame of response.

Occasionally patients describe intolerable, persistent or unusual adverse effects. In such cases another SSRI (or SNRI) should be tried. The routine use of benzodiazepines when starting SSRIs is not recommended and not usually required if the above strategies are used.

Dose and duration

Approximately 75% of patients respond to the initial minimum dose of antidepressant, with the exception of obsessive compulsive disorder which shows a dose–response relationship.[8] However, for anxiety the onset of action is generally slower than in depression and may take 4–6 weeks.

There is little research about how long treatment should be continued. In practice, I recommend patients take antidepressants for a year in the first instance (similar to guidelines for the first episode of depression). Ideally, patients should also have cognitive behavioural therapy to protect against relapse. In severely anxious patients or those with comorbid depression, cognitive behavioural therapy may be added after some symptomatic improvement has occurred.

a stepped-care model for the management of anxiety is recommended

Other antidepressants

Tricyclic antidepressants are effective in panic disorder, and clomipramine – a relatively serotonergic tricyclic – is effective in obsessive compulsive disorder. There is also some evidence for their use in post-traumatic stress disorder. However, tricyclics have a significant adverse effect profile rendering them far down the list of options. They are highly toxic in overdose, potentiate the sedating effects of alcohol, and can prolong the QT interval. If a general practitioner is considering prescribing a tricyclic, it may be preferable to seek a specialist opinion first.

Similarly, while non-reversible monoamine oxidase inhibitors have been shown to be effective for panic and social anxiety disorders, they carry a high burden of risks and adverse effects and, in general, should only be initiated with specialist review. Common adverse effects include nausea, postural hypotension, insomnia, anticholinergic symptoms and weight gain. They may interact with tyramine or dopa-containing foodstuffs, sympathomimetic drugs, and some alcoholic beverages, with the potential for life-threatening hypertensive crisis. Other serious interactions involving hypertension or hypotension and hyperthermia may be seen with a range of other drugs, including other antidepressants, opioids, levodopa and anaesthetics. For some patients, the foods that must be avoided, such as mature cheese, aged meat or liver products, and yeast extracts, may represent a significant part of their normal diet.

Moclobemide, a reversible monoamine oxidase inhibitor, has been associated with inconsistent findings in efficacy studies for anxiety. A relatively small number of trials support the use of mirtazapine. It might be considered for anxious patients given its relatively sedating profile, but once anxiety has been relieved and the patient is in the maintenance phase, weight gain and persistent sedative effects can be a problem. There is no robust literature for reboxetine or agomelatine.

Benzodiazepines

Benzodiazepines reduce the somatic and psychological symptoms of anxiety in panic disorder, generalised anxiety disorder and, for high potency benzodiazepines, in social anxiety disorder. However, some evidence suggests that patient function may not improve to a similar extent.[11] Because they can cause cognitive impairment and have a potential for dependence, benzodiazepines are not first-line treatments. Alprazolam may have a greater potential for dependence than other benzodiazepines because of its rapid onset of anxiolysis and short half-life. Its use has increased in recent years, even while use of other benzodiazepines has declined or remained stable.[12] Clinicians intending to prescribe alprazolam should carefully consider how likely it is that its use will remain restricted to the very short term – that is, a few days to a week – to see a patient through a crisis.

An additional consideration when using benzodiazepines is that the withdrawal syndrome is frequently mistaken by patients as indicating that the anxiety for which the drug was originally started has returned. In the case of alprazolam, the short half-life means that some regular users may begin to experience withdrawal symptoms in the morning following the last night-time dose, thus seeming to confirm the continuing need for the drug. Benzodiazepines do have a place for patients for whom other drugs and non-pharmacological interventions have failed to bring relief.

Other drugs

There is some evidence of efficacy for buspirone in generalised anxiety disorder, although results

are inconsistent. Nausea is common and dosing is inconvenient at three times daily.

Several randomised controlled trials have shown quetiapine to be effective in relieving symptoms of generalised anxiety disorder over the eight-week period of the studies.[1] However, given the risk of weight gain, metabolic adverse effects, the low but real risk of tardive dyskinesia, and concerns regarding possible adverse cardiac effects of atypical antipsychotics,[13] long-term use of antipsychotics is inadvisable.

Pregabalin has been shown to be effective in generalised anxiety disorder and was included as a second-line drug in UK guidelines. However, it is not subsidised for this indication in Australia. Beta blockers have little evidence to support their use in anxiety disorders, including social anxiety disorder.

Failure to respond

If a patient does not respond to treatment, the first step is to review their diagnosis and any changes in their medications (for example drugs recently started or stopped). Patients with anxiety disorders may be particularly susceptible to the anxiogenic effects of caffeine. Substance abuse (including alcohol) can exacerbate or cause anxiety. As anxiety is frequently seen in major depression, consider the possibility of an agitated depression.

Personality style can be a potent cause of anxiety, and is unlikely to respond to drug treatment alone. For example, individuals with an obsessive compulsive personality style (perfectionistic, hypermoral, need for routine and certainty) may become anxious when their normal routine is disrupted. Those with a dependent personality style may become highly anxious if there is a threat to an important relationship.

Secondly, review medication adherence and whether sufficient time has been allowed to see a response. Also ask about their environment – is there a source of chronic worry? Finally, consider adding or revisiting cognitive behavioural therapy or other non-pharmacological strategies, such as mindfulness-based strategies. Specialist assessment is advised before employing medication augmentation strategies.

Suicide risk and anxiety

Patients with anxiety disorders may experience suicidal ideation, so this risk should always be assessed. Research suggests that the risk of a suicide attempt is most likely to be elevated when there is a comorbid depression. Agitation and akathisia are potential adverse effects of SSRIs and may also be associated with an increased risk of suicide.

Conclusion

Anxiety occurs on a spectrum from normal and short-lived to persistent, distressing and disabling. Effective treatments are available and a stepped-care model is advocated, linked to the severity of the anxiety and any comorbidity. SSRIs are recommended as first-line pharmacotherapy for all anxiety disorders, with SNRIs also a valuable first-line treatment for many of them. Response is typically slower than is seen in depression. Benzodiazepines should be reserved for short-term use or treatment refractoriness, and are not routinely required as adjunctive therapy when starting antidepressants. ≺

In the past three years, Dr Lampe has received speakers' honoraria from AstraZeneca, Lundbeck, Pfizer and Servier.

Q:

SELF-TEST QUESTIONS

True or false?

1. Antidepressants used on their own are less effective than cognitive behavioural therapy for anxiety disorders.
2. Benzodiazepines are first-line therapy for anxiety disorders.

Answers on page 219

REFERENCES

1. Stein DJ, Bandelow B, Merideth C, Olausson B, Szamosi J, Eriksson H. Efficacy and tolerability of extended release quetiapine fumarate (quetiapine XR) monotherapy in patients with generalised anxiety disorder: an analysis of pooled data from three 8-week placebo-controlled studies. Hum Psychopharmacol 2011;26:614-28.
2. Australian Centre for Posttraumatic Mental Health. Australian guidelines for the treatment of adults with acute stress disorder and posttraumatic stress disorder. Melbourne: ACPMH; 2007.
3. National Institute for Health and Clinical Excellence. Clinical guidelines CG113. Generalised anxiety disorder and panic disorder (with or without agoraphobia) in adults. London: NICE; 2011.
4. Royal Australian and New Zealand College of Psychiatrists. Australian and New Zealand clinical practice guidelines for the treatment of panic disorder and agoraphobia. Aust N Z J Psychiatry 2003;37:641-56.
5. Bandelow B, Seidler-Brandler U, Becker A, Wedekind D, Ruther E. Meta-analysis of randomized controlled comparisons of psychopharmacological and psychological treatments for anxiety disorders. World J Biol Psychiatry 2007;8:175-87.
6. Watanabe N, Churchill R, Furukawa TA. Combination of psychotherapy and benzodiazepines versus either therapy alone for panic disorder: a systematic review. BMC Psychiatry 2007;7:18.
7. Lampe LA. Internet-based therapy: too good to be true? Aust N Z J Psychiatry 2011;45:342-3.
8. Bandelow B, Sher L, Bunevicius R, Hollander E, Kasper S, Zohar J, et al. Guidelines for the pharmacological treatment of anxiety disorders, obsessive-compulsive disorder and posttraumatic stress disorder in primary care. Int J Psychiatry Clin Pract 2012;16:77-84.
9. Snyder BD, Polasek TM, Doogue MP. Drug interactions: principles and practice. Aust Prescr 2012;35:85-8.
10. Boyer EW, Shannon M. The serotonin syndrome. N Engl J Med 2005;352:1112-20.
11. Munjack DJ, Baltazar PL, Bohn PB, Cabe DD, Appleton AA. Clonazepam in the treatment of social phobia: a pilot study. J Clin Psychiatry 1990;51 Suppl:35-40; discussion 50-3.
12. Moylan S, Giorlando F, Nordfjaern T, Berk M. The role of alprazolam for the treatment of panic disorder in Australia. Aust N Z J Psychiatry 2012;46:212-24.
13. Kuehn BM. FDA panel issues mixed decision on quetiapine in depression and anxiety. JAMA 2009;301:2081-2.

ARTICLE

Cardiovascular drugs in older people

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Key words
aged 80 and over, atrial fibrillation, heart failure, hypertension

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SUMMARY

Cardiovascular drugs are the most frequently prescribed medicines for older people. However, it can be difficult to find a regimen that does more good than harm, especially if the patient is frail.

Prescribers should determine the goals of treatment, understand the limitations of the evidence and be vigilant for the adverse effects of cardiovascular drugs.

Regimens for common cardiovascular diseases, such as hypertension, chronic heart failure and chronic atrial fibrillation, need to be tailored to the individual patient, taking into account factors such as comorbidity and life expectancy.

Introduction

The prevalence of diseases such as hypertension, coronary heart disease, chronic heart failure and chronic atrial fibrillation increases with age, so cardiovascular drugs are the most frequently prescribed treatments for older people. These drugs are also responsible for a large proportion of the adverse drug reactions suffered by older people.

Important considerations when prescribing

There are some general principles to apply when prescribing cardiovascular drugs to older people (Box). It is important to tailor a regimen for each individual patient.

Determine the goals of treatment

Prescribers should ask themselves, 'What outcome do I hope to achieve for this patient?' The prescriber should also consider what their patient hopes to achieve by following the treatment regimen. In general, cardiovascular drugs are helpful for symptom control, prevention of cardiovascular events or life extension. In a healthy 80-year-old person all three goals may be applicable. In contrast, symptom control may be the only goal for an 80-year-old with severe dementia.

In frail older people with multiple comorbidities and functional limitations, it is important to prioritise the goals of treatment. These priorities should guide prescribing. A common dilemma faced by clinicians is the combination of supine hypertension and symptomatic postural hypotension in a frail older person. In this situation, if the hypotension results in falls, dizziness and impairment of everyday function then avoiding postural hypotension should be the priority even at the expense of less than ideal control of blood pressure. High blood pressure may have to be accepted as long as it is not causing symptoms. The consequences of a fractured hip as a result of a fall due to postural hypotension can be more devastating than the vascular events one was aiming to prevent by lowering blood pressure.

Table 1 gives examples of how priorities may differ between a well older person and a frail older person for the treatment of specific cardiovascular diseases. Avoiding adverse effects is important in both groups, but the risk of harm is greater in frail older people. In addition, mortality benefits are less likely to be seen in frail older people.

Be aware of the limited evidence

Older people are poorly represented in clinical trials,[1] so there are limited data about the benefit and harm

Box **Guidelines for prescribing cardiovascular drugs to older people**

1. Take into account all the information obtained from a comprehensive assessment (e.g. postural hypotension, cognitive status, life expectancy)
2. Set goals of treatment – symptom control vs life prolongation
3. Understand and apply the evidence appropriately
4. Avoid under-prescribing drugs that are likely to have symptomatic and functional benefits (e.g. diuretics for chronic heart failure)
5. Be vigilant for adverse effects (see Table 2)
6. Specifically look for drug–drug and drug–disease interactions
7. Discuss the potential benefits and harms with patient, family and carers
8. Choose drugs wisely, start at a low dose and then increase the dose slowly
9. Try to avoid starting several drugs simultaneously
10. Conduct regular drug reviews
11. Stop drugs that are unlikely to be of benefit or are likely to result in more harm than good
12. Take a multidisciplinary approach to achieving optimal regimens (e.g. pharmacists can advise on simplifying the regimen and the best delivery system)

Table 1 **Priorities of treatment for cardiovascular diseases in healthy and frail older people**

Disease	Healthy older person	Frail older person
Hypertension	Decrease risk of vascular events Decrease mortality	Avoid symptoms of hypertension and hypotension
Chronic heart failure	Symptomatic relief Decrease admissions to hospital for decompensated acute heart failure Potential mortality benefit	Symptomatic relief Decrease admissions to hospital for decompensated acute heart failure Avoid symptomatic hypotension and other adverse effects
Anticoagulation for chronic atrial fibrillation	Harm–benefit ratio usually favours anticoagulation	Harm–benefit ratio may favour antiplatelet drug over anticoagulant
Dyslipidaemia	Decrease risk of vascular events	Maintaining nutrition and treating malnutrition takes priority over dyslipidaemia

of giving cardiovascular drugs to frail older patients. Clinical guidelines for cardiovascular diseases rarely provide any details on how they should apply to older frail people with multiple comorbidities. Given these limitations, prescribers should choose a regimen which is appropriate for the individual patient and minimises the risk of harm. Prescribing purely on evidence from younger patients or disease-specific guidelines leads to polypharmacy, pill burden and often harm. However, the lack of direct evidence should not be a reason to deny older people treatments that have the potential to improve their quality of life. For example, treatment to minimise the breathlessness of heart failure can have a big impact on the everyday function and overall quality of life of an older person.

Be vigilant for adverse effects

Over the past 20 years there has been an increase in hospital admissions due to adverse drug reactions particularly in people over 80 years old.[2] Cardiovascular drugs are responsible for about 20% of these reactions in this age group. Adverse drug reactions can occur even at recommended adult doses. As people become frailer and acquire new diseases a previously safe and tolerated regimen may result in harm. Age-related changes in drug receptors, impairments in homeostatic mechanisms and postural autonomic function are just some of the reasons why older people are more sensitive to the hypotensive effects of many cardiovascular drugs.

Older people are likely to have diseases that result in disease–drug interactions. For example, people with dementia may become more confused if they are prescribed drugs that can cause confusion such as beta blockers. Frail older people with Parkinson's disease often have orthostatic hypotension due to disease-related autonomic dysfunction. They are therefore more likely to come to harm from hypotension when prescribed cardiovascular drugs which lower blood pressure. This problem can be exacerbated by the blood pressure lowering effects of drugs for Parkinson's disease.

In addition, older people on many different drugs (polypharmacy) are at increased risk of adverse events, in part because of the increased likelihood of drug–drug interactions.

To minimise the possibility of adverse drug reactions it is a good idea to take a 'start low, go slow' approach when prescribing. If possible, start only one new drug at a time, at the lowest dose possible and increase the dose slowly while being vigilant for possible adverse effects.

It is important to question and examine older people for possible adverse drug reactions. Often the symptoms can be non-specific such as falls, tiredness or confusion. An adverse drug reaction such as postural hypotension can easily be missed if not looked for. It is important to be aware of the common problems that could be the adverse effects of cardiovascular drugs (see Table 2). Ask specifically about, and look for, these adverse effects. Be particularly aware of drugs that have a narrow therapeutic window or a long half-life such as digoxin and warfarin.

The drug regimen should be easy to follow and, with the help of pharmacists, have packaging, labels and dose administration aids that are easy to use. A general practitioner can order a home medicine review for people living in the community. A similar scheme is funded to encourage a medication management review for patients in residential aged-care facilities.

Hypertension

The Hypertension in the Very Elderly Trial (HYVET) found that treating hypertension (systolic blood

pressure above 160 mmHg) in patients over 80 years old is beneficial in terms of all-cause mortality, episodes of heart failure and deaths from strokes.[3] However, it is important to be aware that participants were screened carefully for comorbidity including postural hypotension (systolic blood pressure less than 140 mmHg after two minutes of standing was an exclusion criteria). Although patients in the trial were healthier than the general population of the same age, antihypertensive therapy should be considered in this age group if their life expectancy is more than one or two years. However, there will be a proportion of patients, particularly the frail, who will not tolerate treatment or in whom a decision will be made not to treat after weighing up the harms and benefits.

Table 2 **Problems with cardiovascular drugs**

Problem	Drug
Confusion	beta blockers digoxin HMGCoA reductase inhibitors (statins)*
Cough	ACE inhibitors less common with angiotensin receptor antagonists
Gout	thiazide diuretics loop diuretics
Headache/flushing	calcium channel blockers
Hyperkalaemia	ACE inhibitors angiotensin receptor antagonists aldosterone antagonists
Hypokalaemia	thiazide diuretics loop diuretics
Hyponatraemia	ACE inhibitors thiazide diuretics loop diuretics
Lethargy	beta blockers
Oedema	calcium channel blockers
Postural hypotension	antihypertensive drugs diuretics nitrates
Bleeding	antiplatelet drugs e.g. aspirin, clopidogrel anticoagulants e.g. warfarin, dabigatran and rivaroxaban
Renal failure	diuretics ACE inhibitors angiotensin receptor antagonists
Myalgia and myopathy	statins
Constipation	calcium channel blockers

* based on case reports

The current National Heart Foundation hypertension guidelines[4] recommend treating patients with grade 2 and 3 hypertension (systolic >160 mmHg or diastolic >100 mmHg). For patients aged 80 and over, the results from HYVET would support this recommendation. However, it is not clear if antihypertensive therapy should be prescribed to patients with grade 1 hypertension (systolic 140–159 mmHg or diastolic 90–99 mmHg). There is no direct clinical trial evidence in people aged 80 and over showing a benefit for treating this range of blood pressure.

The guidelines also recommend antihypertensive treatment regardless of blood pressure in patients with associated conditions such as diabetes, strokes and chronic kidney disease, or evidence of end-organ damage such as proteinuria from chronic kidney disease. It may be reasonable to follow this recommendation, but it is based on extrapolating the evidence from trials in much younger patients. Clinical judgement and common sense are required. For example, most patients over 80 years old will not live long enough for proteinuria to ever progress to clinically significant renal failure.

The National Heart Foundation correctly says that all patients aged 75 years and over can be assumed to have a high absolute cardiovascular risk (more than 15% probability of a cardiovascular event within the next five years) without needing to use a cardiovascular risk calculator. This could be interpreted as a recommendation that all patients aged over 75 years should be prescribed antihypertensives, but there is no direct evidence to support treatment regardless of blood pressure. There is also little evidence that treating hypertension in old age prevents dementia or slows progression in patients with dementia.

Target blood pressure

HYVET had a target blood pressure of 150/80 mmHg. The National Heart Foundation recommends less than 140/90 mmHg and less than 130/80 mmHg in patients with associated conditions or end-organ damage. 'Lower is better' may not apply to blood pressure in the very old. There is evidence from epidemiological studies in older people that low blood pressure is associated with poorer survival. These studies suggest there is a threshold blood pressure, which varied by study, below which mortality increases.

Choice of drug

Coexisting conditions, tolerability and the potential for adverse effects should guide the choice of

antihypertensive drug. In many patients other conditions such as ischaemic heart disease or chronic heart failure will determine what is prescribed. Avoiding the adverse effects of high doses of a single drug is a reasonable rationale for adding a second drug. However, there is no evidence that combination antihypertensive drugs are more effective or safer in older people.

Chronic heart failure

A study in the USA suggests that many older patients would have been excluded from clinical trials in heart failure.[5] Only 18%, 13% and 25% of more than 20 000 patients aged over 65 years from a heart failure cohort would have met the enrolment criteria of three major trials in heart failure – SOLVD (ACE inhibitor),[6] MERIT-HF (beta blocker)[7] and RALES (aldosterone antagonist).[8] For example, impaired systolic function was an entry criterion for these trials. However, a large proportion of older people have heart failure with preserved systolic function for which there is little evidence that 'standard' treatments are of benefit.

Choice of drug

In a robust older person with systolic heart failure it is reasonable to try to achieve optimal doses of ACE inhibitors and beta blockers, but start at low doses and watch for adverse effects. In frail patients with systolic heart failure the best approach is to try one drug at a time, starting at a low dose, and observe closely for benefit and harm. In many cases, the recommended doses will not be achievable and measured renal function may decline. If the patient's function and health improves, the uncertainty about whether there are mortality benefits at lower doses is less important. In addition, the decline in measured renal function may not be clinically significant.

In patients with preserved left systolic function, the regimen should focus on minimising the symptoms and signs of heart failure. Diuretics are the mainstay of treatment for relieving symptoms of fluid retention. Age-related decreases in renal function may reduce the efficacy of conventional doses of diuretics so careful upward titration of the dose may be needed. This needs to be balanced with the fact that older people are more at risk of electrolyte disturbances and volume depletion from diuretics. Older people and their carers can sometimes learn to self-adjust the dose of diuretic using weight as a guideline.

Atrial fibrillation

Atrial flutter or fibrillation can occur in older people as the result of a transient condition such as an infection. This is important to recognise, as a long-term antiarrhythmic drug may not be required. Chronic atrial fibrillation usually, but not always, requires rate control. Symptomatic improvement should be the goal rather than a specific heart rate. Digoxin and beta blockers are commonly used for rate control in atrial fibrillation.

Digoxin

Digoxin has a narrow therapeutic window. Reduced renal function and a lower lean body mass increase serum digoxin concentrations. A number of commonly used drugs, such as verapamil, amiodarone and diltiazem, can also increase serum digoxin. Electrolyte abnormalities such as hypokalaemia, hypomagnesaemia, hypercalcaemia as well as conditions such as hypothyroidism and myocardial ischaemia can aggravate digoxin toxicity. Health professionals need to be aware that symptoms of digoxin toxicity can occur in the target range. The prescriber should therefore be vigilant in checking for adverse effects such as anorexia, nausea, vomiting, visual disturbances, depression and confusion.

Beta blockers

In patients with renal impairment, use beta blockers with predominantly hepatic elimination (for example metoprolol). For patients with hepatic impairment, use beta blockers with predominantly renal elimination (for example atenolol). Even if liver function tests are normal, there is an age-related decrease in liver blood flow. So if adverse effects such as confusion are thought to be possibly due to a predominantly hepatically eliminated beta blocker, it may be worth a trial of changing to a renally eliminated beta blocker. Less lipid soluble beta blockers (atenolol and bisoprolol) may be less likely to enter the brain so may cause fewer sleep disturbances and nightmares.

Anticoagulation

In carefully selected older patients with non-valvular atrial fibrillation, there is good evidence that oral anticoagulation is better than antiplatelet therapy in reducing the risk of stroke. The clinical dilemma is that older people are at a higher risk of bleeding during anticoagulation. The decision on anticoagulation versus antiplatelet therapy is best made by a doctor who has a comprehensive understanding of the whole patient and is able to take into account factors such as falls risk, bleeding history, potential drug interactions and likely compliance with dose adjustments and INR monitoring. There are a number of bleeding risk scoring systems,[9] but they are not used much in

SELF-TEST QUESTIONS

True or false?

3. An INR below 2.0 is effective in preventing stroke in an elderly patient being anticoagulated for atrial fibrillation.

4. Diuretics should not be prescribed for patients over 80 years old with fluid retention due to heart failure.

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everyday practice. There is no evidence that a lower target INR (<2) is effective or has a lower risk of bleeding than a target of 2–3.

The newer oral anticoagulants, such as dabigatran, may seem to be an attractive alternative to warfarin in older people as regular blood tests are not required. However, there is no antidote or reversal drug if bleeding occurs. In addition, severe renal impairment is a contraindication and any decrease in renal function can increase the risk of bleeding.

Conclusion

Appropriate and safe prescribing of cardiovascular drugs for older people can be challenging. There are many things to take into account when prescribing for older people, especially if they are frail. Tailoring treatment to the individual patient with the aim of doing more good than harm, should be the guiding principle when prescribing cardiovascular drugs to older people.

Conflict of interest: none declared

REFERENCES

1. Nair BR. Evidence based medicine for older people: available, accessible, acceptable, adaptable? Australas J Ageing 2002;21:58-60.
2. Burgess CL, Holman CD, Satti AG. Adverse drug reactions in older Australians, 1981-2002. Med J Aust 2005;182:267-70.
3. Beckett NS, Peters R, Fletcher AE, Staessen JA, Liu L, Dumitrascu D, et al. Treatment of hypertension in patients 80 years of age or older. N Engl J Med 2008;358:1887-98.
4. National Heart Foundation of Australia (National Blood Pressure and Vascular Disease Advisory Committee). Guide to management of hypertension 2008. Updated December 2010. National Heart Foundation; 2010.
5. Masoudi FA, Havranek EP, Wolfe P, Gross CP, Rathore SS, Steiner JF, et al. Most hospitalized older persons do not meet the enrollment criteria for clinical trials in heart failure. Am Heart J 2003;146:250-7.
6. SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med 1991;325:293-302.
7. MERIT-HF Investigators. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet 1999;353:2001-7.
8. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al; Randomized Aldactone Evaluation Study Investigators. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. N Engl J Med 1999;341:709-17.
9. NPS MedicineWise. Good anticoagulant practice. Medicinewise News 2013 Feb 4. www.nps.org.au/publications/health-professional/medicinewise-news/2013/good-anticoagulant-practice [cited 2013 Nov 7]

FURTHER READING

Hilmer S, Gnjidic D. Statins in older adults. Aust Prescr 2013;36:79-82.

Medicinal mishap

When is child-resistant packaging not child resistant?

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Case

A six-year-old boy presented to hospital after accessing his father's lithium tablets. It was unclear how many tablets were in the container and whether the child had taken any.

The lithium was stored in a plastic bottle with a child-resistant cap. On examining the cap, it was noted that the child-resistant mechanism would not engage unless downward pressure was applied while closing the cap. Without the downward pressure, the cap spun freely and would not engage to a fixed closure point. When this occurred, the cap could then be opened in the same manner as a simple screw cap. There were no instructions on the cap to say that downward pressure was required to activate the child-resistant mechanism. This procedure is not required for the majority of other child-resistant caps used on the Australian market.

The child needed to be observed for six hours. No adverse events emerged so he was discharged.

Comment

Young children gaining access to medicines is a frequently overlooked aspect of medication safety. The use of child-resistant packaging is a proven strategy for preventing poisoning, but it is only one layer of a multifaceted approach which includes supervision and limiting access.

Personal clinical experience suggests that families are not given preventive advice by the prescribing doctor or dispensing pharmacist about the potential toxicity to young children of drugs within their household. To compound this, there is confusion in the general

population about the effectiveness of child-resistant packaging in preventing poisoning in young children and in particular the functionality of child-resistant closures. There are several problems:

- child-resistant closures are used on products which have toxicity ranging from mild (such as penicillin-based syrups) to major
- the Therapeutic Goods Administration (TGA) Order 80 determines products requiring child-resistant packaging, yet a number of potentially toxic drugs fall outside this order and are marketed in non-child-resistant packaging (such as essential oils sold in bottles with standard screw caps, and calcium channel blockers sold in blister packs)
- child-resistant closures are often referred to as 'child-proof' caps, even by medical professionals, yet the Australian Standard AS 1928-2007 effectively allows up to one in five children in the testing range (42–51 months) to access the product. This is a compromise between keeping children out and making child-resistant closures so effective that adults cannot access them. The child-resistant closures are tested to ensure that 80% of adults can get in.
- the child-resistant mechanism is often assumed to be engaged, when it is not, either due to failure to fully close the cap or a dysfunction of the child-resistant closure.

An ad hoc survey of local and interstate pharmacies in relation to this incident revealed that several other batches of lithium tablets had similarly dysfunctional child-resistant closures. This matter has been reported to the manufacturer and the TGA.

With an increasing number of drugs stored in the home, it is important that child-resistant packaging performs as well as intended. Product failures need to be identified by appropriate surveillance and then promptly addressed.

Recommendations

Currently, there is no requirement for companies marketing medicines in Australia to perform post-production quality assurance testing of the functionality of child-resistant caps, although a few companies do perform these tests. Minor alterations to the bottle, cap or wadding can have significant impacts on the functionality of the child-resistant cap, and these defects can only be discovered at the end of the manufacturing chain. Ideally, they should be detected before the product is marketed.

The collation of reports of failures of child-resistant packaging is hampered by the lack of national standardisation of poisons information data in Australia and the inconsistency of product and packaging specific detail within those data. There are currently efforts underway to address this.

Patients should ensure that their medicines are kept out of reach of children, for example by storing the drugs in a locked container. However, this is only feasible when medication is not in use, and anecdotally, some exposures occur in the brief interval when the medication is being accessed to take a dose, or when it is being packed for travel. Effective child-resistant packaging is an important secondary prevention strategy in these scenarios. Consumer awareness of medication toxicity and poisoning prevention in young children could also be improved at the point of prescription and dispensing.

Conflict of interest: none declared

Comment by the Therapeutic Goods Administration

The TGA and the sponsor company investigated this case and found no evidence that the packaging of the relevant batch was defective when released for sale. As such, the reported issue of the child-resistant mechanism failing to engage unless downward pressure was applied while closing was found to be an isolated defect, the cause of which is unknown and may have occurred after purchase.

Child-resistant closures for medicines marketed in Australia are manufactured and tested to very high standards. However, like any mass-produced good, there may be the occasional defective unit.

All suspected child-resistant packaging defects should be reported to the TGA or sponsor so that they can be investigated.

Scheduled medicines are required to carry the warning 'KEEP OUT OF REACH OF CHILDREN' in bold text, placed prominently at the top of the label. The container of the lithium carbonate tablets referred to in the report carried this warning.

It is important to note that child-resistant closures are not child-proof. If they were, it would be difficult or impossible for many elderly people and arthritis sufferers to open them.

Child-resistant closures are tested on four-year-old children. The child in the report was six years old.

The requirements for child-resistant packaging of medicines are set out in Therapeutic Goods Order No. 80 'Child-Resistant Packaging Requirements for Medicines'.

Health professionals who receive a report of a suspected child-resistant packaging defect from a patient should consider sending the packaging to the TGA or sponsor so that the defect can be verified and properly assessed.

DIAGNOSTIC TESTS

Non-type 1, non-type 2 diabetes: what's in a name?

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Key words
glucokinase, insulin, maturity-onset diabetes of the young, sulfonylurea

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SUMMARY

Most patients who develop diabetes are classified as having either type 1 or type 2 diabetes. However, a small proportion of patients do not fit these classifications and are said to have non-type 1, non-type 2 diabetes.

Type 1 diabetes usually presents in childhood and adolescence, but if pancreatic function fails slowly it may present in later life. This has been called latent autoimmune diabetes in adults.

Type 2 diabetes usually presents in later life, but a few people develop its features at an early age. They may have maturity-onset diabetes of the young, which is now known to be caused by specific genetic defects.

The genetic defects of maturity-onset diabetes of the young are autosomal dominant, so there is a strong family history. Knowing which gene is affected is important as this may influence treatment.

Introduction

Diabetes mellitus is most often a result of the combination of insulin resistance and insulin deficiency. Hyperglycaemia occurs because there is an inadequate concentration of insulin (insulin deficiency) to overcome the degree of insulin resistance present.

In type 1 diabetes there is autoimmune destruction of pancreatic beta cells. The rate of this destruction varies, being more rapid in children and adolescents and slower in adults. This explains why it classically presents before the age of 30 years and patients quickly become insulin dependent. The slower onset type 1 diabetes in adults is sometimes referred to as latent autoimmune diabetes.

In type 2 diabetes the patient secretes insulin, but there is a decrease in insulin sensitivity which is usually called insulin resistance. Ageing, obesity and physical inactivity are commonly associated with insulin resistance. The natural history of type 2 diabetes is that insulin secretion falls with duration of the disease and can result in absolute insulin deficiency.

The biochemical mechanisms underlying insulin resistance or a poor insulin secretory response by the beta cells of the pancreas are not fully understood. There is evidence for a genetic contribution to both.[1] In the past, patients with insulin deficiency were considered to have type 1 diabetes while those with insulin resistance had type 2 diabetes. However, not all patients present with classical phenotype. There are young people who have features of type 2 diabetes and there are older people with slowly progressing insulin-dependent diabetes. The classification of diabetes has therefore been revised (see Box).

Box **Types and causes of diabetes**

Type 1 – insulin deficiency predominantly due to autoimmunity (includes latent autoimmune diabetes in adults)

Type 2 – predominantly insulin resistance with relative insulin deficiency

Genetic defects (includes maturity-onset diabetes of the young (MODY) and mitochondrial diabetes)

Pancreatic diseases e.g. pancreatitis

Endocrinopathies e.g. Cushing's disease

Gestational diabetes

Drugs e.g. corticosteroids, olanzapine

Clinical classification

Diabetes can be diagnosed by a high concentration of glucose or glycated haemoglobin (HbA1c) in the blood. Every time you see a patient with newly diagnosed diabetes, you should ask yourself the question 'What is the underlying cause of this diabetes?' Sometimes the answer is obvious, but often it is unclear.

Type 1 diabetes accounts for 5–10% of cases. There is usually no family history of diabetes. Type 1 diabetes presents classically with weight loss, polyuria, polydipsia and ketosis in a younger patient, however it can be detected at any stage in its evolution. The presence of a variety of autoantibodies confirms the diagnosis of type 1 diabetes. These include autoantibodies to islet cells, insulin and glutamic acid decarboxylase, but their absence does not exclude the diagnosis.

Type 2 diabetes accounts for 90–95% of cases. It can be considered as a disease for which the cause has not yet been identified. There is often a family history of diabetes. The patients are usually over 30 years old with a high body mass index. If not obese, they have central obesity. This is more common in Asian patients.

Within the classical type 2 group of older, overweight, non-ketotic patients, about 5% have evidence of beta cell autoimmunity.[2] This means that they have type 1 diabetes, but with a much slower onset than the classical presentation. This has been called latent autoimmune diabetes in adults. These patients will require insulin earlier than patients without autoantibodies, however, many practitioners are slow to start insulin in patients who have not been diagnosed as having type 1 diabetes, even when treatment for type 2 diabetes does not achieve a target concentration of HbA1c.

Treatment should be guided by the clinical picture predominantly and not the diagnosis. Clinical features include the degree of hyperglycaemia, the presence or absence of ketosis, symptoms and the patient's body mass index and physical activity.

Finding the cause of hyperglycaemia

Clinical questions are 'Does this person have a significant, identifiable contributor to the diabetes in addition to age, physical inactivity and obesity?' and 'How will this alter my management?' To answer these questions requires clinical skill and judgement. Doing every possible test in every patient would be inappropriate.

During the history and physical examination, consider if the patient is on any drugs such as olanzapine which could contribute to hyperglycaemia, or has a disease which is associated with diabetes.[3,4] Endocrinopathies such as acromegaly, Cushing's syndrome or hyperthyroidism and conditions such as pancreatic cancer and haemochromatosis can cause hyperglycaemia.

Genetics

More recently, the search for an explanation of the patient's hyperglycaemia has been expanded to include the question 'Does this patient have a genetic contributor to the diabetes which can be identified and which would alter management?'.

Genetic mutations have been found in young people who present with features of type 2 diabetes. These conditions are collectively known as maturity-onset diabetes of the young (MODY). They are different from the type 2 diabetes which is now occurring in obese young people. The mutations cause dysfunction of pancreatic beta cells, but autoantibodies are usually absent.

MODY accounts for 1–2% of cases of diabetes. It is usually diagnosed before the age of 25 years. As there is autosomal dominant inheritance, there is a strong family history of diabetes present in every generation. The six genes listed in the Table account for most cases of MODY. The most common conditions are MODY 2 and 3. Identifying the mutation may significantly alter treatment.

MODY 1 and 3

Mutations in the hepatic nuclear factor genes result in MODY 1 and 3. These mutations are associated with hyperglycaemia that leads to microvascular complications so these patients require treatment. They may have been born large, and experienced postnatal hypoglycaemia, and they have glycosuria. The mutations produce an insulin deficiency picture which is likely to be mistaken for type 1 diabetes, but the patients do not become totally insulin deficient with time.

The patients may be particularly sensitive to therapy with sulfonylureas. Early in the disease, glycaemic control may be better with a sulfonylurea than with insulin.

MODY 2

In MODY 2 a mutation causes a defect in glucokinase – a glycolytic enzyme. This results in fasting hyperglycaemia, but little postprandial hyperglycaemia. During a glucose tolerance test, despite the fasting hyperglycaemia, the rise in blood glucose after a glucose load is less than 3 mmol/L.

Recognising MODY 2 is important as it is not associated with microvascular complications and so it does not require any treatment to control blood glucose. However, there are two major caveats.

Table **The genetics of maturity-onset diabetes of the young (MODY)**

Condition	Gene affected	Chromosome affected
MODY 1	HNF-4 alpha	Chromosome 20
MODY 2*	glucokinase	Chromosome 7
MODY 3†	HNF-1 alpha	Chromosome 12
MODY 4	IPF-1	Chromosome 13
MODY 5	HNF-1	Chromosome 17
MODY 6	NeuroD1	Chromosome 2

* 13% of MODY cases
† 70% of MODY cases
HNF hepatocyte nuclear factor
IPF insulin promoter factor

The hyperglycaemia is often first detected during pregnancy and may require treatment. The risk to the fetus depends on whether the fetus also has the mutation or not. Unaffected fetuses are at risk of being oversized, while affected fetuses may be undersized if the mother's hyperglycaemia is treated.[‡] The other caveat is that a glucokinase mutation does not protect against developing type 2 diabetes. The risk is thought to be the same as in the general population. People with MODY 2 should be monitored (using HbA1c) to detect worsening hyperglycaemia.

Mitochondrial diabetes

In mitochondrial diabetes a mutation is inherited from the mother. It is usually associated with hearing impairment. The mutation in mitochondrial DNA results in a gradual functional decline in the pancreatic beta cells.

A practical approach

A stepwise approach to a patient with newly diagnosed diabetes, or a patient with diabetes who you are seeing for the first time, might be:

- does the person have type 1 diabetes? (younger, thinner, acute onset hyperglycaemia)
  - if uncertain, consider measuring autoantibodies to confirm the diagnosis
- if not type 1 diabetes
  - is this simply type 2 diabetes or is there another obvious contributing factor such as a disease or drugs either known or not yet recognised?
  - consider other aetiologies including MODY (identify them as antibody negative for further possible investigation as more information on aetiology appears in the future)
- if MODY is suspected use the diabetesgenes.org website calculator[§] and refer to a specialist.

Future developments

It is not cost-effective to do genetic testing on everyone with diabetes. Research is looking for markers which may suggest MODY. One example is high-sensitivity C-reactive protein. Its concentration may be lower in patients with HNF-1 alpha mutations.

The general use of the term MODY is likely to decline with increased understanding of the underlying genetic disorders.

Conclusion

The diagnosis of diabetes can usually be made by using the information obtained from history and physical examination. A few patients who were previously thought to have type 1 or type 2 diabetes have been found to have a genetic disorder. These patients have by definition non-type 1, non-type 2 diabetes.

Patients with MODY have a strong family history of diabetes, but no autoantibodies or features of insulin resistance. These patients are often misdiagnosed – identifying the mutation may change the way they are managed. ◀

Conflict of interest: none declared

Q:

SELF-TEST QUESTIONS

True or false?

5. Diabetes due to a glucokinase mutation needs to be treated with insulin.

6. Type 1 diabetes can be excluded if the patient has no autoantibodies.

Answers on page 219

[‡] www.diabetesgenes.org/content/glucokinase

[§] see www.diabetesgenes.org/content/mody-probability-calculator for the prototype MODY Probability Calculator

REFERENCES

1. Frayling TM. Genome-wide association studies provide new insights into type 2 diabetes aetiology. Nat Rev Genet 2007;8:657-62.
2. Zinman B, Kahn SE, Haffner SM, O'Neill MC, Heise MA, Freed MI; ADOPT Study Group. Phenotypic characteristics of GAD antibody-positive recently diagnosed patients with type 2 diabetes in North America and Europe. Diabetes 2004;53:3193-200.
3. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2004;27 Suppl 1:S5-S10.
4. World Health Organization. Definition, diagnosis and classification of diabetes mellitus and its complications. Geneva: WHO Department of Noncommunicable Disease Surveillance; 1999.

ARTICLE

Patient-centred prescribing

SUMMARY

Patients' requests and expectations, and prescribers' perceptions of these, are strong influences on prescribing behaviour.

Prescribers often overestimate patients' expectation of a prescription and so may overprescribe. Exploring patient expectations may reduce this.

Strategies for improving the quality of prescribing include clarifying the patient's concerns, goals and expectations of treatment, discussing management options, and the explicit use of evidence to inform shared decision making.

Introduction

Patients influence the behaviour of prescribers. What do we know about the complex interaction between patients and prescribers, and how can we use this knowledge to make us better prescribers in practice?

One of the goals of a consultation with a patient is to reach a shared understanding of their illness, and the underlying disease process and its effect on their lives. The treatment options need to be discussed, including their pros and cons. From this, a treatment plan can be negotiated taking into account the patient's goals and expectations of treatment.

Patient expectations

Patients may declare their preference for a medication. Sometimes this is through a direct request or it may be by mentioning a particular disease. Occasionally patients may present a set of symptoms typical of a condition which they believe should result in a prescription.

Persistence of symptoms ('Can't seem to shake this one, doctor') and life circumstances ('I am going overseas next week') may be offered as a reason for a prescription. Previous experience with a particular drug may also be used to influence a prescriber's decision.[1,2] Many patients present with information gained from internet searches informing their requests. This is to be welcomed as evidence of an engaged patient and is an opportunity to discuss sources of quality information such as NPS MedicineWise.

Patient requests and expectations influence a prescriber's behaviour. An expectation of a prescription increases the likelihood that a drug will be prescribed.[3-7] A request may contribute to overprescribing but can be beneficial by alerting a doctor to a problem and increasing the attention paid to it. For example, in one study patients asking for antidepressants increased and improved history-taking for depression.[8]

Patients may be dissatisfied if they expect a prescription and do not receive one. This experience has been found to double the likelihood that a patient will consult another doctor for the same problem.[9] Consumers' expectations are not, however, fixed. The doctor should explore the reasons why the patient wants a particular medicine and a mutually agreed decision can be made based on the benefits or otherwise of a prescription.

Direct-to-consumer advertising, common in the USA, influences patients to request medication. This in turn strongly increases the likelihood of prescription.[6]

Prescriber perceptions

The perception that a patient expects a prescription is a strong driver to prescribe, increasing the likelihood by 10 times in one study.[7] In other studies, it was identified as the strongest factor affecting prescribing behaviour.[3,7,9,10] Prescribers may perceive the patient's expectation as 'pressure' to prescribe.[5] Doctors report concerns that failing to prescribe may damage the doctor–patient relationship and decrease the likelihood of an effective therapeutic alliance.[2,11]

About two thirds of the time, prescribers correctly identify a patient's expectation of a prescription.[10,12] If a prescriber responds to this expectation by providing a prescription, the patient's belief that a prescription is the appropriate response is reinforced. In this way the doctor's behaviour may influence the patient's future expectations, increasing the likelihood of future prescriptions.[2] Doctors tend, however, to overestimate these expectations and many studies have shown a tendency to overprescribe because of this.[2,5,12-14] On the other hand, a perception that a patient does not want a medicine may lead to under-prescribing.

Other patient factors that influence prescribing

A study of insulin prescribing for older patients found that doctors may adjust their prescribing depending

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on many factors including the perceived health literacy of the patient, their social supports as well as their socio-economic status.[15] There is evidence that patients with lower socio-economic status receive poorer quality prescribing with more drugs, increased polypharmacy and decreased prescription of preventive drugs such as statins for lowering cholesterol.[16] Older patients may experience similar problems.[17] An Australian study found location to be an important factor with less statin prescribing in remote and rural populations compared with urban patients.[18]

Models

Understanding and discussing a patient's concerns, goals and expectations helps to optimise prescribing.[5] A number of influential models of the doctor–patient interaction have emerged which incorporate the patient's influence on medical decision making including the decision to prescribe.

The content: evidence-based medicine

Perhaps the most influential model for treatment decision making has been evidence-based medicine, defined in Box 1.[19] Patient values are often forgotten in the discussion of evidence, but were rightly included as a core component of the original model. Understanding a patient's ideas about their medicines and what has or has not worked in the past is invaluable for making effective future prescribing decisions. It is also important to explain the evidence base for treatment options.

A person is unlikely to take a prescribed drug, even under the best guideline, if they expect no benefit, or even harm, from it. Similarly a patient's goals and expectations may mean that treating to a guideline-based target is not appropriate. Clinical expertise enables the prescriber to explore the common ground between the best evidence and the patient's values and sometimes to select other treatments or influence the patient if required. Evidence-based practice acknowledges and incorporates the influence of the patient in decisions about treatment.[19]

The consultation: the Patient-Centred Clinical Method

Evidence of factors which improve outcomes in the patient–doctor interaction led to the description of the Patient-Centred Clinical Method model, summarised in Box 2.[20] A clinician should seek to fully understand the disease and the illness including the patient's ideas, concerns and expectations about their illness. They should also aim to understand the patient as a person and their life context. Preventive care and being realistic about what is achievable are important. Try to find common ground with the patient, clarify and agree goals and share decision making about investigations and treatment. Finally, effective interactions involve attention to improving the doctor–patient relationship. This model provides an evidence-based approach to making the best use of patient influence within the consultation to maximise outcomes.

Conclusion

Clinicians seeking to base their decisions on best evidence will take into account patients' values and goals. In consultations, a prescriber will be aware of a tendency to overestimate patient expectation of a prescription. By asking and understanding a patient's concerns and expectations, common ground is more likely to be found allowing shared decision making and maximising the effectiveness of medicine use. ◁

Andrew Knight is a board member of NPS MedicineWise.

Box 1 **Evidence-based practice** [19]

Evidence-based practice is the integration of clinical expertise, patient values, and the best research evidence into the decision-making process for patient care.

Clinical expertise refers to the clinician's cumulated experience, education and clinical skills.

The patient brings to the encounter his or her own personal and unique concerns, expectations and values.

The best evidence is usually found in clinically relevant research that has been conducted using sound methodology.

Box 2 **The six interactive components of the Patient-Centred Clinical Method** [20]

Exploring both the disease and the illness experience

Patient history, physical examination, investigations

Dimensions of illness (feelings about being ill, ideas about the illness, effects of the illness on their function, and their expectations of the doctor)

Understanding the whole person

The person (e.g. their life history, personal and developmental issues)

The proximal context (e.g. family, employment, social support)

The distal context (e.g. culture, community, ecosystem)

Finding common ground

Defining the problems and priorities

Establishing goals of treatment/management

Identifying the roles of patient and doctor

Incorporating prevention and health promotion

Health enhancement, risk avoidance/reduction, early identification, complication reduction

Enhancing the patient–doctor relationship

Including compassion and trust, sharing power and healing. Building self-awareness in patient and doctor, and being aware of unconscious aspects of relationship such as transference and counter transference.

Being realistic

Clinicians need to be realistic about their own time and about building the capacity of the practice team. Wise stewardship of resources is important.

REFERENCES

1. Scott JG, Cohen D, DiCicco-Bloom B, Orzano AJ, Jaen CR, Crabtree BF. Antibiotic use in acute respiratory infections and the ways patients pressure physicians for a prescription. J Fam Pract 2001;50:853-8.
2. Stevenson FA, Greenfield SM, Jones M, Nayak A, Bradley CP. GPs' perceptions of patient influence on prescribing. Fam Pract 1999;16:255-61.
3. Webb S, Lloyd M. Prescribing and referral in general practice: a study of patients' expectations and doctors' actions. Br J Gen Pract 1994;44:165-9.
4. Fischer T, Fischer S, Kochen MM, Hummers-Pradier E. Influence of patient symptoms and physical findings on general practitioners' treatment of respiratory tract infections: a direct observation study. BMC Fam Pract 2005;6:6.
5. Little P, Dorward M, Warner G, Stephens K, Senior J, Moore M. Importance of patient pressure and perceived pressure and perceived medical need for investigations, referral, and prescribing in primary care: nested observational study. BMJ 2004;328:444.
6. Tentler A, Silberman J, Paterniti DA, Kravitz RL, Epstein RM. Factors affecting physicians' responses to patients' requests for antidepressants: focus group study. J Gen Intern Med 2008;23:51-7.
7. Cockburn J, Pit S. Prescribing behaviour in clinical practice: patients' expectations and doctors' perceptions of patients' expectations - a questionnaire study. BMJ 1997;315:520-3.
8. Feldman MD, Franks P, Epstein RM, Franz CE, Kravitz RL. Do patient requests for antidepressants enhance or hinder physicians' evaluation of depression? A randomized controlled trial. Med Care 2006;44:1107-13.
9. Macfarlane J, Holmes W, Macfarlane R, Britten N. Influence of patients' expectations on antibiotic management of acute lower respiratory tract illness in general practice: questionnaire study. BMJ 1997;315:1211-4.
10. Britten N, Ukoumunne O. The influence of patients' hopes of receiving a prescription on doctors' perceptions and the decision to prescribe: a questionnaire survey. BMJ 1997;315:1506-10.
11. Corbett M, Foster N, Ong BN. GP attitudes and self-reported behaviour in primary care consultations for low back pain. Fam Pract 2009;26:359-64.
12. Cutts C, Tett SE. Do rural consumers expect a prescription from their GP visit? Investigation of patients' expectations for a prescription and doctors' prescribing decisions in rural Australia. Aust J Rural Health 2005;13:43-50.
13. Salmon P, Ring A, Dowrick CF, Humphris GM. What do general practice patients want when they present medically unexplained symptoms, and why do their doctors feel pressurized? J Psychosom Res 2005;59:255-60.
14. Lado E, Vacariza M, Fernandez-Gonzalez C, Gestal-Otero JJ, Figueiras A. Influence exerted on drug prescribing by patients' attitudes and expectations and by doctors' perception of such expectations: a cohort and nested case-control study. J Eval Clin Pract 2008;14:453-9.
15. Agarwal G, Nair K, Cosby J, Dolovich L, Levine M, Kaczorowski J, et al. GPs' approach to insulin prescribing in older patients: a qualitative study. Br J Gen Pract 2008;58:569-75.
16. Odubanjo E, Bennett K, Feely J. Influence of socioeconomic status on the quality of prescribing in the elderly - a population based study. Br J Clin Pharmacol 2004;58:496-502.
17. Ryan C, O'Mahony D, Kennedy J, Weedle P, Byrne S. Potentially inappropriate prescribing in an Irish elderly population in primary care. Br J Clin Pharmacol 2009;68:936-47.
18. Stocks N, Ryan P, Allan J, Williams S, Willson K. Gender, socioeconomic status, need or access? Differences in statin prescribing across urban, rural and remote Australia. Aust J Rural Health 2009;17:92-6.
19. Sackett DL, Straus SE, Richardson WS, Rosenberg W, Haynes RB. How to practice and teach EBM. Edinburgh: Churchill Livingstone; 2000.
20. Stewart M, Brown JB, Weston WW, McWhinney IR, McWilliam CL, Freeman TR. Patient-centered medicine: transforming the clinical method. 2nd ed. Oxford: Radcliffe Medical Press Ltd; 2003.

ARTICLE

Postoperative pain management

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Key words
analgesia, gabapentin, neuropathic pain, pregabalin, surgery

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SUMMARY

Postoperative pain management aims to minimise patient discomfort, facilitate early mobilisation and functional recovery, and prevent acute pain developing into chronic pain.

Mental health can affect a patient's recovery and psychological vulnerability is predictive of severe postoperative pain. Education before surgery reduces anxiety and improves patient satisfaction.

The choice of analgesia depends on the type of surgery the patient is having. Using procedure-specific pain guidelines within an enhanced rehabilitation program is recommended.

Different types of analgesia can be combined for additive or synergistic pain relief. Regional analgesic techniques are being increasingly incorporated into multimodal analgesic regimens.

The diagnosis of acute neuropathic pain following surgery is often delayed.

Introduction

The amount of pain a patient suffers after surgery is related to the extent of tissue damage and the site of surgery. Operations on the thorax and upper abdomen are more painful than procedures on the lower abdomen which in turn are more painful than operations on limbs.[1] Joint replacement is associated with severe postoperative pain.[2]

Pain has both sensory and emotional components that interact to produce an overall 'pain experience'. Unrelieved pain after surgery can interfere with sleep and physical functioning and can negatively affect a patient's well-being on multiple levels.[3] This may extend into the rehabilitation period and delay hospital discharge and functional recovery.[4,5] Good pain control is important to prevent negative outcomes such as hypertension, myocardial ischaemia, arrhythmias, respiratory impairment, ileus and poor wound healing.

Preparing patients before surgery

Pre-admission consultation 1–2 weeks before surgery allows for the formulation of an individualised analgesic plan. For example, patients using opioids chronically can be identified and preoperative consultation organised. A multidisciplinary approach involving specialists in pain and addiction medicine is often required with these patients.

The preoperative consultation is also an opportunity to discuss pain relief options including invasive techniques such as epidural, spinal opioids and peripheral nerve blocks.

Written information with diagrams and simple descriptive terms helps to inform, educate and psychologically prepare patients for surgery.[6] This has been shown to shorten hospital stay and reduce the need for postoperative pain relief.[7]

Predictors of postoperative pain

Preoperative pain, anxiety, young age, obesity, fear of surgery, psychological distress and type of surgery (abdominal, orthopaedic and thoracic surgery, long duration) have been identified as predictors of postoperative pain (Box).[5,8] Early identification of these allows for more effective intervention and improved postoperative management.[1]

Psychological vulnerability

Pre-existing anxiety and psychological distress such as depression are predictors of severe postoperative pain. A patient who has previously experienced severe postoperative pain may be anxious about subsequent surgery. Addressing the patient's fears can reduce the severity of pain and suffering.[9]

Catastrophising (that is, magnifying the threat of pain) and hypervigilance (that is, a strong attention toward pain) have emerged as strong predictors of acute postoperative pain.[10,11]

Multimodal analgesia

Opioids delivered by patient-controlled analgesia are the mainstay of systemic analgesia for the treatment of moderate to severe postoperative pain. Unfortunately opioid-related adverse effects limit their use in many patients. Analgesics that act by different mechanisms and at different receptor sites can be combined to produce additive or synergistic

pain relief and can reduce opioid use.[12] Regimens that use non-opioid analgesics include:

- paracetamol
- non-steroidal anti-inflammatory drugs (NSAIDs), including cyclo-oxygenase inhibitors
- alpha$_2$ agonists (clonidine, dexmedetomidine)
- gabapentin and pregabalin[13]
- ketamine
- lignocaine infusions
- peripheral nerve blocks, local anaesthetic wound infiltration and continuous wound infusion techniques.

Despite evidence showing the benefit of multimodal analgesia, it is still underused.[14] For example, NSAIDs are valuable adjuvant drugs, with the potential benefits outweighing the potential disadvantages in most surgical patients.[15,16]

Box **Risk factors for chronic postsurgical pain**

Preoperative factors

Pain, moderate to severe, lasting more than a month
Repeat surgery
Psychological vulnerability
Preoperative anxiety
Female gender
Younger age (adults)
Workers' compensation
Genetic predisposition
Inefficient diffuse noxious inhibitory control *

Intraoperative factors

Surgical approach with risk of nerve damage

Postoperative factors

Pain (acute, moderate to severe)
Radiation therapy to area
Neurotoxic chemotherapy
Depression
Psychological vulnerability

* Diffuse noxious inhibitory control (also called conditioned pain modulation) is an endogenous descending pain-modulating pathway which is activated when two concomitant painful stimuli are applied ('pain inhibits pain'). Inefficient diffuse noxious inhibitory control is associated with functional pain syndromes (fibromyalgia, irritable bowel syndrome) and is thought to be a risk factor for developing chronic pain following surgery.

Source: Adapted from references 5, 43 and 45

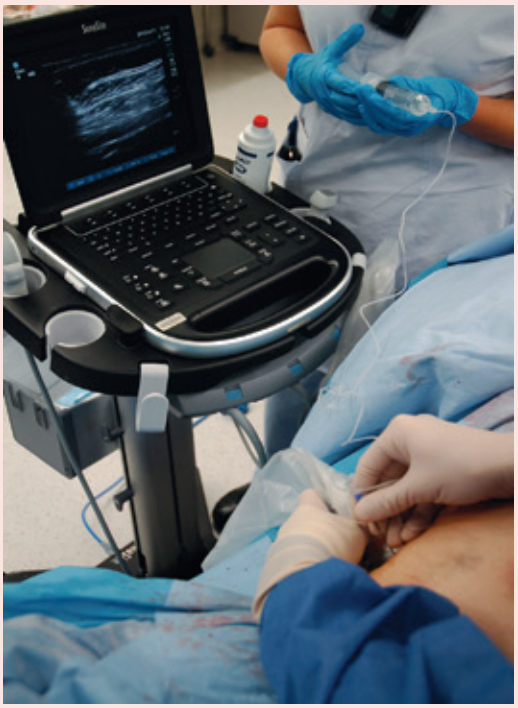
Regional analgesia

Although epidural techniques can provide excellent analgesia following major surgery, there is increasing evidence that less invasive regional analgesia can be as effective.[17] This includes paravertebral block for thoracotomy, pre-peritoneal local anaesthetic infusion following laparotomy and caesarean section, and local infiltration analgesia for knee replacement.[18-22]

Local anaesthetic wound infusions can have significant benefits in procedures as diverse as open nephrectomy, mastectomy and inguinal hernia repair.[23-25] The transversus abdominis plane block (Fig. 1) reduces pain scores and opioid requirement in inguinal hernia repair, open appendicectomy, laparoscopic cholecystectomy, laparotomy, lower segment caesarean section, hysterectomy and laparoscopic gynaecological procedures.[26] Wound infusions are typically continued for 2–5 days postoperatively.

Ultrasound-guided peripheral nerve blocks are increasingly being used for postoperative pain.[27] Commonly used sites include the brachial plexus to manage shoulder and upper limb pain, femoral nerve block for knee surgery pain, and sciatic nerve block

Fig. 1 **Ultrasound guided transversus abdominis plane (TAP) block**



Normal saline injected by an assistant is used to locate the TAP before catheter placement and instillation of a local anaesthetic solution

for foot and ankle pain. The duration of analgesia can be extended from hours to days by connecting a catheter to an elastomeric or electronic infusion device next to the peripheral nerve or plexus.[28] Patient-controlled regional analgesia provides equivalent or superior pain relief with less anaesthetic compared to continuous infusions alone with a variety of perineural techniques.[29] With appropriate support, portable patient-controlled regional analgesia can be managed at home.[30]

Procedure-specific analgesia

Each type of surgical procedure has its own unique postoperative pain characteristics and clinical consequences. The choice of analgesia should be based on the evidence for that particular surgical procedure. For example, thoracic epidural reduces movement-related pain, ileus and postoperative nausea and vomiting compared to other analgesia after open colorectal procedures. However, it is clearly not appropriate for minimally invasive laparoscopic abdominal procedures with limited tissue injury.[14] Ideally, multimodal procedure-specific analgesia should be incorporated into a rehabilitation program after surgery to improve patient outcomes.[31-34] Guidelines for procedure-specific analgesia are available online.[35,36]

Discharge planning

Pain management for day surgery patients remains the responsibility of the anaesthetist or the surgeon. The severity and likely duration of the pain should be assessed before discharge. Analgesic regimens to address the pain include:

- mild to moderate pain – paracetamol and/or ibuprofen
- moderate to severe pain – oxycodone (5–10 mg 4–6 hourly) is preferable to codeine-containing medicines.

Acute neuropathic pain

Neuropathic pain is caused by a lesion or disease of the somatosensory nervous system.[37] It can result from surgery and is a condition that is under-recognised, often difficult to treat and one that may progress to persistent pain and disability.[38]

Unfortunately there are no guidelines on how to diagnose a significant neuropathic component to postoperative pain. Operations that damage peripheral nerves have a relatively high risk of producing neuropathic pain (for example amputation, thoracotomy, mastectomy, inguinal herniorrhaphy) and it is often a component of burn injury pain.[39,40]

The diagnosis of neuropathic pain is based on the patient's description of pain (burning, shooting, spontaneous) and altered sensation (pins and needles, numbness), and on simple bedside tests for hyperalgesia (an exaggerated response to a painful stimulus) and allodynia (pain evoked by light touch or gentle pressure to deep tissues).

Unfortunately, the diagnosis is often made retrospectively when there has been a poor response to opioids and a good response to anti-neuropathic analgesics.[41] As few studies have investigated acute neuropathic pain, treatment guidelines are based on the experience in chronic pain.[5] Intravenous ketamine (0.1 mg/kg/hour) or lignocaine (1–1.5 mg/kg/hour) can be used initially in patients who are 'nil by mouth'. This can be followed by amitriptyline (10–25 mg orally) at night and gabapentin or pregabalin titrated to response.[38,42,43]

Acute to chronic pain transition

Acute postoperative pain can develop into chronic pain. This is defined as pain still present three months after surgery. The overall incidence of chronic postsurgical pain is estimated to be 10–50%. In some patients (approximately 6%) the pain may be severe and disabling and referral to a pain clinic is needed.[44-46]

Predisposing risk factors for chronic postsurgical pain can be patient- or surgery-specific (see Box).[5] Severe acute postoperative pain is a major predictor for chronic postsurgical pain and effective analgesia may reduce this.[47] In at-risk patients, the duration of analgesia may need to be extended for as long as the nociceptive input from the wound persists (sometimes weeks).[48,49] Drugs such as gabapentin and pregabalin, which have an effect on surgically-induced central sensitisation, may prevent chronic postsurgical pain.[50,51] Early referral to a pain clinic is recommended for at-risk patients with pain that persists or those who are using complex analgesics (high doses of opioids or gabapentinoids) before discharge.[52]

Conclusion

A patient-specific approach to pain management is recommended, taking into account the surgical procedure, preoperative medical and psychological status, age, concurrent opioid use and patient preference. Using regional analgesia (for example, epidural or peripheral nerve analgesia) with a local anaesthetic is associated with significantly lower pain scores than is seen with systemic opioids. It also facilitates earlier rehabilitation and reduced hospital stay.[53] There is increasing evidence of an association between the severity of the acute pain and the risk of developing chronic postsurgical pain. <

Conflict of interest: none declared

Q:

SELF-TEST QUESTIONS

True or false?

7. Patients with neuropathic pain usually respond well to opioid analgesia.

8. Severe acute pain after surgery is a major risk factor for chronic pain.

Answers on page 219

REFERENCES

A complete list of the references is available at www.australianprescriber.com/magazine/36/6/202/5

1. Ip HY, Abrishami A, Peng PW, Wong J, Chung F. Predictors of postoperative pain and analgesic consumption: a qualitative systematic review. Anesthesiology 2009;111:657-77.
2. Ekstein MP, Weinbroum AA. Immediate postoperative pain in orthopedic patients is more intense and requires more analgesia than in post-laparotomy patients. Pain Med 2011;12:308-13.
3. Sinatra R. Causes and consequences of inadequate management of acute pain. Pain Med 2010;11:1859-71.
4. Strassels SA, Mcnicol E, Wagner AK, Rogers WH, Gouveia WA, Carr DB. Persistent postoperative pain, health-related quality of life, and functioning 1 month after hospital discharge. Acute Pain 2004;6:95-104.
5. Macintyre PE, Schug S, Scott DA, Visser EJ, Walker SM. Working Group of the Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine 2010. Acute Pain Management: Scientific Evidence. 3rd ed. Melbourne: ANZCA, FPM; 2010.
6. Practice guidelines for acute pain management in the perioperative setting: an updated report by the American Society of Anesthesiologists Task Force on Acute Pain Management. Anesthesiology 2012;116:248-73.
7. Carr DB, Goudas LC. Acute pain. Lancet 1999;353:2051-8.
8. Sommer M, De Rijke JM, Van Kleef M, Kessels AG, Peters ML, Geurts JW, et al. Predictors of acute postoperative pain after elective surgery. Clin J Pain 2010;26:87-94.
9. Daniel HC. Psychological therapies – adult. In: Macintyre PE, Walker SM, Rowbotham DJ, editors. Clinical Pain Management: Acute Pain. 2nd ed. London: Hodder Arnold; 2008.
10. Papaioannou M, Skapinakis P, Damigos D, Mavreas V, Broumas G, Palgimesi A. The role of catastrophizing in the prediction of postoperative pain. Pain Med 2009;10:1452-9.
11. Lautenbacher S, Huber C, Kunz M, Parthum A, Weber PG, Griessinger N, et al. Hypervigilance as predictor of postoperative acute pain: its predictive potency compared with experimental pain sensitivity, cortisol reactivity, and affective state. Clin J Pain 2009;25:92-100.
12. Buvanendran A, Kroin JS. Multimodal analgesia for controlling acute postoperative pain. Curr Opin Anaesthesiol 2009;22:588-93.
13. White PF. The changing role of non-opioid analgesic techniques in the management of postoperative pain. Anesth Analg 2005;101:S5-22.
14. White PF, Kehlet H. Improving postoperative pain management: what are the unresolved issues? Anesthesiology 2010;112:220-5.
15. White PF, Raeder J, Kehlet H. Ketorolac: its role as part of a multimodal analgesic regimen. Anesth Analg 2012;114:250-4.
16. Marret E, Kurdi O, Zufferey P, Bonnet F. Effects of nonsteroidal antiinflammatory drugs on patient-controlled analgesia morphine side effects: meta-analysis of randomized controlled trials. Anesthesiology 2005;102:1249-60.
17. Rawal N. Epidural technique for postoperative pain: gold standard no more? Reg Anesth Pain Med 2012;37:310-7.
18. Kotze A, Scally A, Howell S. Efficacy and safety of different techniques of paravertebral block for analgesia after thoracotomy: a systematic review and metaregression. Br J Anaesth 2009;103:626-36.
19. Beaussier M, El'Ayoubi H, Schiffer E, Rollin M, Parc Y, Mazoit JX, et al. Continuous preperitoneal infusion of ropivacaine provides effective analgesia and accelerates recovery after colorectal surgery: a randomized, double-blind, placebo-controlled study. Anesthesiology 2007;107:461-8.
20. O'Neill P, Duarte F, Ribeiro I, Centeno MJ, Moreira J. Ropivacaine continuous wound infusion versus epidural morphine for postoperative analgesia after cesarean delivery: a randomized controlled trial. Anesth Analg 2012;114:179-85.
21. Fowler SJ, Symons J, Sabato S, Myles PS. Epidural analgesia compared with peripheral nerve blockade after major knee surgery: a systematic review and meta-analysis of randomized trials. Br J Anaesth 2008;100:154-64.
22. Ganapathy S. Wound/intra-articular infiltration or peripheral nerve blocks for orthopedic joint surgery: efficacy and safety issues. Curr Opin Anaesthesiol 2012;25:615-20.
23. Forastiere E, Sofra M, Giannarelli D, Fabrizi L, Simone G. Effectiveness of continuous wound infusion of 0.5% ropivacaine by On-Q pain relief system for postoperative pain management after open nephrectomy. Br J Anaesth 2008;101:841-7.
24. Sidiropoulou T, Buonomo O, Fabbi E, Silvi MB, Kostopanagiotou G, Sabato AF, et al. A prospective comparison of continuous wound infiltration with ropivacaine versus single-injection paravertebral block after modified radical mastectomy. Anesth Analg 2008;106:997-1001.

Dental note

Postoperative pain management

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Dental treatment can result in varying degrees of postoperative pain depending on the nature and extent of the treatment, the anatomical site involved and the individual patient's pain threshold and coping behaviour. Routine dental treatment may result in mild pain while more invasive treatment, such as dentoalveolar surgery, can result in moderate to severe postoperative pain.

It is important to determine that the pain is a sequel to dental treatment. Other causes, such as incomplete treatment or other untreated dental pathology, should be excluded.

Recommendations for pain management following dental treatment have been published.[1] In general, this involves drugs taken orally. Mild pain is usually managed with ibuprofen or aspirin or, if non-steroidal anti-inflammatory drugs (NSAIDs) are contraindicated, paracetamol. For moderate to severe pain, a combined dosing protocol of ibuprofen and paracetamol is recommended or, if NSAIDs are contraindicated, paracetamol plus codeine.

Comparisons of oral analgesic drugs are found on the Oxford league table of analgesic efficacy.[2] The information has been obtained from systematic reviews of randomised, double-blind, single-dose studies in patients with moderate to severe pain and the results have been validated.

Conflict of interest: none declared

REFERENCES

1. Oral and Dental Expert Group. eTG complete [internet]. Melbourne: Therapeutic Guidelines Limited; 2012.
2. Bandolier. Oxford league table of analgesics in acute pain. 2007. www.medicine.ox.ac.uk/bandolier/booth/painpag/Acutrev/Analgesics/Leagtab.html [cited 2013 Nov 7]

Australian Government
Department of Health
Therapeutic Goods Administration

Medicines Safety Update

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Pioglitazone risk–benefit review

A recently completed TGA review of pioglitazone (Actos and generics) has found that the drug has a favourable long-term risk–benefit balance. However, health professionals should weigh the known risks against the benefits of pioglitazone therapy and discuss these with patients.

The TGA's review was prompted by the identification of an increased risk of bladder cancer with long-term use of pioglitazone.[1,2] In light of ongoing safety concerns with rosiglitazone, another drug in the same class, the TGA conducted a full risk–benefit review of pioglitazone.

Pioglitazone is a thiazolidinedione (TZD) oral antidiabetic drug that has been registered in Australia since 2001.

To 1 September 2013, the TGA has received 212 adverse event reports involving pioglitazone. The most commonly reported events were cardiac failure, oedema and weight gain, but there were also 11 reports of bladder cancer. Before June 2011, no such cases had been identified.

Risk–benefit evaluation

The TGA review found that pioglitazone lowers HbA1c by a similar amount to that seen with other classes of oral antidiabetic drugs. Where pioglitazone was added to current therapy, HbA1c was lowered by 0.8–1.3% after 16 weeks.

In the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) study, risk was reduced from 13.6% over three years with placebo to 11.6% with pioglitazone, equating to a 16% reduction of the risk of a combined end point of death, myocardial infarction and stroke.[3]

In terms of risks, the TGA found the potential for bladder cancer increased by 40% (3 in 10 000 person-years) after two years of use. The risk appears to increase with duration of use.

Other identified risks associated with pioglitazone therapy included:

- the fracture risk for women is doubled (from 0.5 to 1.0 per 100 patient years) when weighed against non-TZD comparators
- compared to placebo there is an increased incidence of heart failure (11% vs 7.5%) and oedema (22% vs 13%), as well as dose-related weight gain.

Information for health professionals

The existing evidence shows pioglitazone has a favourable long-term risk–benefit balance. The absolute risks are likely to vary with age. Take these factors into account when considering treatment with pioglitazone.

REFERENCES

1. FDA Drug Safety Communication. Update to ongoing safety review of Actos (pioglitazone) and increased risk of bladder cancer. US Food and Drug Administration; 2011.
2. Therapeutic Goods Administration. Pioglitazone and risk of bladder cancer. Med Saf Update 2011;5.
3. Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study. Lancet 2005;366:1279-89.

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

TGA Health Safety Regulation

5-alpha reductase inhibitors and risk of high-grade prostate cancer

New warnings regarding the risk of high-grade prostate cancer have been added to the Product Information documents for the 5-alpha reductase inhibitors finasteride and dutasteride.

5-alpha reductase inhibitors (5ARIs) are a class of drug primarily used to treat symptomatic benign prostatic hyperplasia (BPH) in men.

The two 5ARIs registered in Australia are finasteride (Proscar [5 mg] and Propecia [1 mg]) and dutasteride (Avodart [0.5 mg] and Duodart [0.5 mg in combination with 0.4 mg tamsulosin]). Propecia is only indicated for the treatment of male pattern hair loss.

The TGA has reviewed a US Food and Drug Administration (FDA) assessment of two large trials that evaluated the use of finasteride or dutasteride daily versus placebo for the reduction in risk of prostate cancer.

The FDA found that, while the trials demonstrated an overall reduction in prostate cancer diagnoses due to a decreased incidence of lower risk forms of prostate cancer, both trials showed an increased incidence of high-grade prostate cancer.[1]

The TGA has since worked with the sponsors of finasteride and dutasteride to update the Australian Product Information (PI) documents to include a new precaution regarding the risk of patients developing high-grade prostate cancer.

Evidence of risk – dutasteride

The Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial was a four-year study of 8231 men aged 50–75, with a prior negative biopsy for prostate cancer and baseline prostate-specific antigen (PSA) between 2.5 and 10.0 ng/mL. The men received either placebo (n=4126) or dutasteride 0.5 mg (n=4105) once daily for a total of four years.

Prostate biopsies were performed at two years and four years, with 1517 men being diagnosed with prostate cancer. There was a higher incidence of Gleason 8–10 prostate cancer in the dutasteride group (n=29, 0.9%) compared to the placebo group (n=19, 0.6%). There was no increased incidence in Gleason 5–6 or 7–10 prostate cancer.

Evidence of risk – finasteride

The Prostate Cancer Prevention Trial was a seven-year randomised, double-blind, placebo-controlled trial that enrolled 18 882 men aged 55 years or older, with a normal digital rectal examination and a PSA ≤3.0 ng/mL. The men received either finasteride 5 mg or placebo daily. Patients were evaluated annually with PSA and digital rectal exams.

Biopsies were performed for elevated PSA or an abnormal digital rectal exam. The incidence of Gleason 8–10 prostate cancer was higher in men treated with finasteride than in those treated with placebo (1.8% vs 1.1% respectively).

Information for health professionals

5ARIs are not approved for the treatment of prostate cancer and no clinical benefit has yet been demonstrated in patients with prostate cancer treated with 5ARIs.

Before making a decision to prescribe a 5ARI, the known risks should be weighed against the benefits of 5ARI therapy and discussed with the patient.

Evaluations for prostate cancer, including digital rectal examination and serum PSA screening, should be performed on patients with BPH before initiating therapy with a 5ARI and periodically thereafter.

Serum PSA concentration is an important component of the screening process to detect prostate cancer. Use of 5ARIs causes a decrease in serum PSA levels by approximately 50%.

Guidance on how to monitor and interpret PSA levels in patients taking a 5ARI can be found in the PIs.

REFERENCE

1. FDA Drug Safety Communication. 5-alpha reductase inhibitors (5-ARIs) may increase the risk of a more serious form of prostate cancer. US Food and Drug Administration; 2011.

MEDICINES SAFETY UPDATE

Duloxetine and serotonin syndrome

While serotonin syndrome is commonly associated with concomitant use of two or more serotonergic drugs, it can occur with a single drug. The TGA has received 21 reports of serotonin syndrome in which duloxetine (Cymbalta and generics) is the sole suspected drug.

Duloxetine is a serotonin and noradrenaline reuptake inhibitor indicated for the treatment of major depressive disorder, generalised anxiety disorder and diabetic peripheral neuropathic pain.

Serotonin syndrome is a known risk associated with duloxetine therapy and is listed as a precaution in the Product Information (PI).

To reduce the risk of serotonin syndrome, duloxetine should be used with caution with other serotonergic drugs, including selective serotonin reuptake inhibitors, tricyclic antidepressants, opioids, tryptophan and St John's wort.

Serotonin syndrome is characterised by:

- altered mental state, e.g. confusion and agitation
- autonomic dysfunction, e.g. tachycardia and sweating
- neuromuscular excitation, e.g. hyperreflexia, tremor.

The TGA has previously published an article regarding serotonin syndrome, including information about diagnosis and treatment of this potentially life-threatening condition.[1]

Adverse event reports

To 1 September 2013, the TGA has received 31 reports of serotonin syndrome in patients taking duloxetine. Co-suspected drugs were present in 10 reports, including fentanyl (two reports), amitriptyline (two reports), oxycodone, alfentanil, fluoxetine, dexamphetamine, tramadol, mirtazapine and ziprasidone. Duloxetine was the sole suspected drug in the other 21 reports.

The dose of duloxetine used was most commonly 60 mg daily (16 reports), while a dose of 30 mg daily was noted in five reports, and 90 mg or 120 mg daily in two reports each. The time to onset of serotonin syndrome was not generally available, but was within two days of starting duloxetine in five reports.

In one report, a patient with back pain and depression commenced duloxetine 30 mg daily. After three weeks, the dose was increased to 60 mg daily and fentanyl patches were commenced. That same day the patient developed tremor, ataxia and sweating. Serotonin syndrome was diagnosed, requiring hospitalisation for further management.

Information for health professionals

Health professionals are reminded that, while serotonin syndrome most commonly occurs when serotonergic drugs are used in combination, it can be caused by a single drug.

Be cognisant of the risk of serotonin syndrome in patients being treated with duloxetine, even in the absence of a second serotonergic drug.

Duloxetine should be used with caution with other serotonergic drugs, and concomitant treatment with monoamine oxidase inhibitors (MAOIs), including moclobemide, is contraindicated. Duloxetine should not be used within 14 days of discontinuing treatment with an MAOI, and at least five days should be allowed after stopping duloxetine before starting an MAOI.

Similarly, as duloxetine is metabolised by both CYP1A2 and CYP2D6, it should not be used in combination with potent inhibitors of CYP1A2 (such as fluvoxamine).

Treatment with duloxetine should be discontinued if signs or symptoms of serotonin syndrome are identified.

Duloxetine should also not be used in patients with hepatic impairment, and use of a lower dose is recommended in patients with end-stage renal disease (creatinine clearance <30 mL/min).

Refer to the PI for further information regarding contraindications and precautions.

Please report adverse events involving duloxetine and serotonin syndrome to the TGA.

REFERENCE

1. Therapeutic Goods Administration. Serotonin syndrome: a reminder. Med Saf Update 2010;6.

MEDICINES SAFETY UPDATE

Minocycline and intracranial hypertension

A recent report has prompted the TGA to remind health professionals to consider the possibility of benign intracranial hypertension in patients being treated with minocycline if signs and symptoms consistent with that diagnosis are identified. Health professionals should advise patients being treated with minocycline of the signs of benign intracranial hypertension and consider recommending that they read the Consumer Medicine Information.

Minocycline belongs to the tetracycline group of antibiotics and is used to treat acne that is resistant to other antibiotics, as well as various other infections.

While rare, benign intracranial hypertension, also known as pseudotumour cerebri, is a known adverse event associated with tetracyclines, and minocycline treatment in particular.

Benign intracranial hypertension involves a persistent rise in cerebrospinal fluid pressure and is characterised by headache, nausea, vomiting and vision disturbances, including papilloedema with occasional sixth-nerve palsy.

From 1981 to 1 September 2013, the TGA received 43 reports of benign intracranial hypertension in people being treated with minocycline. In 39 of those reports, minocycline was the sole suspected drug. The most recent report was in November 2012. Prior to that, there had been no reports since 2006.

To reduce the risk of benign intracranial hypertension, concomitant treatment with tetracyclines and vitamin A or retinoids, such as isotretinoin, is contraindicated.

Visit the NPS MedicineWise website for further information about the risks associated with treatment of acne with oral antibiotics.[1]

REFERENCE

1. NPS MedicineWise. Oral antibiotics: an option in acne but consider the risks. 2013.

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

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

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

Reports may be submitted:

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

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

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Medicines Safety Update is written by staff from the Office of Product Review

FEATURE

Medicines Australia Code of Conduct: breaches

Key words
Medicines Australia, breaches

Aust Prescr 2013;36:210

The Medicines Australia Code of Conduct guides the promotion of prescription products by pharmaceutical companies.[1] Each year Medicines Australia publishes a report, from its Code of Conduct Committee, which details all the complaints that have been received about advertising and other promotional activities.

There were 18 new complaints and 10 of these were considered and finalised by the Code of Conduct Committee in 2012–13. It could not consider one complaint because it was about a company which was not a member of Medicines Australia.

Only three complaints were made by health professionals. The majority of complaints came from rival pharmaceutical companies.

The Table shows the complaints where at least one breach was identified, and more details can be found in the full report.[2] One complaint was held over from 2011–12. The manufacturer of atorvastatin wanted to inform patients that its brand was still available after the arrival of generic competition. However this 'community service announcement' was ruled to be promoting the product to the general public, resulting in a $50 000 fine.

The largest fine this year also involved a complaint about providing information to the public. An educational booklet about multiple sclerosis provided unbalanced information which could encourage patients to seek a prescription for a specific product.

Another company was questioned about its use of social media to interact with the public. The Code of Conduct Committee recognised that material that is linked by someone else to information provided by a company could be promoting the drug. It agreed that the Code applies to social media. Although the company was not found to have promoted the drug to the public, other elements of its marketing were found to be false or misleading.

The Monitoring Committee of Medicines Australia reviewed over 10 000 educational events organised by 36 companies in 2011–12. None of these were referred to the Code of Conduct Committee.

Table **Breaches of the Code of Conduct July 2012 – June 2013**

Company	Brand (generic) name	Material or activity	Sanction
Abbott Australasia	Lipidil (fenofibrate)	Misleading claims in promotional materials	$100 000 fine Claims not to be used again
Biogen Idec	–	Promotion to the general public Misleading claims in promotional material	$150 000 fine Booklet to be withdrawn and not to be used again
Merck Sharp and Dohme (MSD)	Vytorin (ezetimibe and simvastatin)	Misleading claim in promotional activities	$125 000 fine Claim not to be used again Corrective letter
	Zoely (nomegestrol and oestradiol)	Misleading claims in detailing aids	$75 000 fine Claims not to be used again Corrective letter
Pfizer Australia	Celebrex (celecoxib)	Misleading claims in promotional material	$85 000 fine reduced on appeal to $35 000 Claims not to be used again
	Lipitor (atorvastatin)	Promotion to the general public	$50 000 fine Claim not to be used again
	Prevenar 13 (pneumococcal 13-valent conjugate vaccine)	Misleading claim in promotional material	$10 000 fine Claim not to be used again

REFERENCES

1. Medicines Australia. Code of Conduct. 17th ed. 2012. www.medicinesaustralia.com.au/files/2010/01/20130328-PUB-Edition17-FINAL.pdf [cited 2013 Nov 7]
2. Medicines Australia. Code of Conduct Annual Report 2012–13. www.medicinesaustralia.com.au/files/2010/01/20131021-PUB-CoC-AnnualReport-2012_2013.pdf [cited 2013 Nov 7]

FEATURE

Top 10 drugs

These tables show the top 10 subsidised drugs for the year July 2012 – June 2013.

Aust Prescr 2013;36:211

Table 1 **Top 10 drugs by DDD/1000 pop/day** *†

	Constituent drug	PBS/RPBS ‡
1.	atorvastatin	75.06
2.	rosuvastatin	40.97
3.	perindopril	30.94
4.	paracetamol	30.59
5.	irbesartan	28.93
6.	candesartan	26.03
7.	amlodipine	24.49
8.	ramipril	22.86
9.	esomeprazole	22.46
10.	simvastatin	18.52

DDDs in this table include use in combination products

Table 2 **Top 10 drugs by prescription counts** †

	Drug	PBS/RPBS ‡
1.	atorvastatin	9 691 453
2.	rosuvastatin	7 547 176
3.	esomeprazole	6 310 249
4.	paracetamol	5 650 557
5.	pantoprazole	3 853 775
6.	perindopril	3 828 844
7.	metformin hydrochloride	3 402 195
8.	simvastatin	3 155 142
9.	salmeterol and fluticasone	3 082 816
10.	irbesartan	2 987 398

Table 3 **Top 10 drugs by cost to government** †

	Drug	Cost to government (A$)	DDD/1000 pop/day * PBS/RPBS ‡	Prescriptions PBS/RPBS ‡
1.	atorvastatin	416 442 486	75.06	9 691 453
2.	ranibizumab	306 998 667	§	150 641
3.	rosuvastatin	299 200 480	40.97	7 547 176
4.	adalimumab	230 103 495	0.43	129 700
5.	esomeprazole	184 886 525	22.46	6 310 249
6.	salmeterol and fluticasone	174 934 981	#	3 082 816
7.	rituximab	144 051 899	§	42 420
8.	olanzapine	138 378 395	2.97	957 428
9.	etanercept	138 345 090	0.27	78 829
10.	tiotropium bromide	124 515 675	6.67	1 873 047

* The defined daily dose (DDD)/thousand population/day is a more useful measure of drug utilisation than prescription counts. It shows how many people in every thousand Australians are taking the standard dose of a drug every day.

† Based on date of supply. Does not include private prescriptions or prescriptions under PBS co-payment.

‡ PBS Pharmaceutical Benefits Scheme RPBS Repatriation Pharmaceutical Benefits Scheme

§ The World Health Organization has not allocated a DDD for this drug

This combination does not have a DDD allocated

Source: Drug Utilisation Sub-Committee (DUSC) Database, as at 11 September 2013. © Commonwealth of Australia.

Data are based on date of supply with processing date up to the month of August 2013. Data exclude 'Under copayment' and 'Closing the gap' prescriptions processed by the Department of Human Services.

NEW DRUGS

New drugs

Dapoxetine

Priligy (A Menarini)
30 mg tablets
Approved indication: premature ejaculation
Australian Medicines Handbook section 13.3.2

Delayed ejaculation is an adverse effect of selective serotonin reuptake inhibitors (SSRIs) in men. Dapoxetine, a short-acting SSRI, is the first drug to be marketed for premature ejaculation.

After oral administration, peak plasma concentrations of dapoxetine are reached after an hour. Elimination is relatively rapid and the terminal half-life is approximately 19 hours.

There have been several randomised controlled trials of dapoxetine for premature ejaculation.[1-6] The primary outcome for most of the trials was 'intravaginal ejaculatory latency time' measured by the partner using a stopwatch.

An analysis of two trials,[1] in which 2614 men (aged 18–77 years) were randomised to dapoxetine (30 mg or 60 mg) or placebo (all taken 1–3 hours before intercourse), found that dapoxetine increased intravaginal ejaculatory latency time significantly more than placebo. At baseline, men were required to have an intravaginal ejaculatory latency time of 2 minutes or less at least 75% of the time. After 12 weeks, 29% of men taking the 30 mg dose and 34% taking the 60 mg dose had a latency time of 3 minutes or more. This was compared to only 14% of men taking placebo. Men taking dapoxetine perceived that they had better control of ejaculation and were more satisfied with their sexual performance than those taking placebo.

In another trial, dapoxetine (60 mg) was compared to paroxetine (20 mg), another SSRI, in 340 men (aged 22–48 years) with premature ejaculation. Treatments were taken each day divided into two doses. After 12 weeks, intravaginal ejaculatory latency times had increased from 38 to 179 seconds for dapoxetine, from 31 seconds to 370 seconds for paroxetine, and from 34 to 55 seconds for placebo. More men reported sexual satisfaction with dapoxetine and paroxetine than with placebo (66% vs 78% vs 16%). A similar trend in sexual satisfaction was seen with partners who were interviewed independently of their husband. Eleven men dropped out because of lack of efficacy – 3/104 with dapoxetine, 2/105 with paroxetine and 6/100 with placebo. The timing of dosing in relation to sexual intercourse was not described in this trial.[6]

During the trials, nausea (11%), headache (5.6%), diarrhoea (3.5%), somnolence (3.1%) and dizziness (5.8%) were more commonly reported with dapoxetine 30 mg than with placebo. These events were dose-related – all of them were more frequent with the 60 mg dapoxetine dose. Nausea and dizziness were the most common reasons for discontinuation with dapoxetine 30 mg. Because of the increased risk of adverse events, patients should be warned to take no more than one tablet in a 24-hour period.

Sexual adverse effects including erectile dysfunction, abnormal ejaculation and decreased libido were more common with dapoxetine than placebo. These occurred in 2.9% of patients taking dapoxetine 30 mg and 3.8% taking dapoxetine 60 mg versus 1.5% of patients taking placebo.[1]

Postural hypotension occurred in some patients and caution is urged with concomitant use of vasodilators such as alpha blockers, nitrates and phosphodiesterase 5 inhibitors. Syncope has been reported with dapoxetine and appeared to be dose-related (0.05% with placebo, 0.06% with 30 mg and 0.23% with 60 mg dose). Possible prodromal symptoms such as nausea, dizziness and light-headedness were also more common with dapoxetine than with placebo. Patients should be warned about this risk and advised to maintain adequate hydration and avoid alcohol.

Dapoxetine is metabolised by enzymes in the liver and kidneys, in particular cytochrome P450 (CYP) 2D6 and 3A4. It also moderately inhibits CYP 2D6 and weakly induces CYP 3A4 so numerous interactions are expected. Poor CYP 2D6 metabolisers may be at increased risk of adverse events. Concomitant treatment with potent CYP 3A4 inhibitors such as ketoconazole and ritonavir is contraindicated. Dapoxetine is also contraindicated with antidepressants including monoamine oxidase inhibitors, serotonin reuptake inhibitors, tricyclics and other drugs with serotonergic effects (tramadol, St John's wort and lithium).

Dapoxetine should not be taken in combination with recreational drugs such as ketamine, methylenedioxymethamphetamine (MDMA) and lysergic acid diethylamide (LSD) because of the

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.

potential risk of serious adverse events including arrhythmia, hyperthermia and serotonin syndrome. Concomitant sedatives can increase the risk of somnolence and dizziness.

Dapoxetine is contraindicated in patients with heart problems such as heart failure, conduction abnormalities or significant ischaemic or valvular disease. It is also contraindicated in moderate and severe hepatic impairment. Dapoxetine is not recommended in patients with severe renal impairment or with psychiatric disorders.

Although dapoxetine prolongs intravaginal latency time before ejaculation, improvements seem modest and a placebo effect was apparent in most of the studies. In an analysis of two trials, mean latency time increased from an average of 0.9 minutes at baseline to 1.75 minutes with placebo and 2.78 minutes with dapoxetine (30 mg taken on-demand).[1] In a comparative trial, paroxetine was more effective than dapoxetine, although it was unclear when treatment was taken in relation to sexual intercourse. This may have affected efficacy.[6] The benefits and adverse effects of dapoxetine treatment should be reviewed after four weeks (or six doses).

REFERENCES

1. Pryor JL, Althof SE, Steidle C, Rosen RC, Hellstrom WJ, Shabsigh R, et al. Efficacy and tolerability of dapoxetine in treatment of premature ejaculation: an integrated analysis of two double-blind randomised trials. Lancet 2006;368:929-37.
2. Buvat J, Tesfaye F, Rothman M, Rivas DA, Giuliano F. Dapoxetine for the treatment of premature ejaculation: results from a randomized, double-blind, placebo-controlled phase 3 trial in 22 countries. Eur Urol 2009;55:957-67.
3. McMahon C, Kim SW, Park NC, Chang CP, Rivas D, Tesfaye F, et al. Treatment of premature ejaculation in the Asia-Pacific region: results from a phase III double-blind, parallel-group study of dapoxetine. J Sex Med 2010;7:256-68.
4. Safarinejad MR. Safety and efficacy of dapoxetine in the treatment of premature ejaculation: a double-blind, placebo-controlled, fixed-dose, randomized study. Neuropsychopharmacology 2008;33:1259-65.
5. Kaufman JM, Rosen RC, Mudumbi RV, Tesfaye F, Hashmonay R, Rivas D. Treatment benefit of dapoxetine for premature ejaculation: results from a placebo-controlled phase III trial. BJU Int 2009;103:651-8.
6. Safarinejad MR. Comparison of dapoxetine versus paroxetine in patients with premature ejaculation: a double-blind, placebo-controlled, fixed-dose, randomized study. Clin Neuropharmacol 2006;29:243-52.

First published online 2 October 2013

Dimethyl fumarate

Approved indication: multiple sclerosis
Tecfidera (Biogen Idec)
240 mg modified-release capsules
Australian Medicines Handbook section 16.5

Dimethyl fumarate is a hazardous chemical, but has been studied in Germany as a treatment for psoriasis. It was observed that a few patients who also had multiple sclerosis improved when their psoriasis was treated. This prompted research into dimethyl fumarate as a treatment for multiple sclerosis.

When taken orally, dimethyl fumarate is rapidly hydrolysed to monomethyl fumarate. This active metabolite is further metabolised and has a terminal half-life of only one hour. Most of the dose is exhaled as carbon dioxide. How the chemical works in multiple sclerosis is uncertain.

A phase II trial randomised 257 patients with relapsing-remitting multiple sclerosis to take dimethyl fumarate 120 mg once daily, 120 mg three times daily, 240 mg three times daily, or placebo. After 24 weeks the patients taking 240 mg three times daily had a significantly better response than those taking placebo. They had developed an average of 3.7 new gadolinium-enhancing lesions on MRI of the brain compared with 6.6 lesions in the placebo group. The responses with other doses were not significantly different from placebo, so formulations of 240 mg have been used in phase III trials.[1]

The DEFINE study was a placebo-controlled trial involving 1234 patients with relapsing-remitting multiple sclerosis. This assessed dimethyl fumarate 240 mg two or three times a day. After two years the annual rate of relapse had been reduced by 53% with twice-daily treatment and by 48% with three-times-daily treatment. Compared to placebo, there were fewer new lesions on MRI and less progression of disability (see Table 1).[2]

The CONFIRM study, involving 1417 patients, also compared 240 mg twice or three times daily with placebo, but also included glatiramer acetate as an active control. After two years the reductions in relapse rates, compared with placebo, were 44% with twice-daily and 51% with three-times-daily treatment.

Table 1 **Outcomes of the DEFINE trial** [2]

	Treatments (number of patients)		
Outcomes	**Placebo** (408)	**Dimethyl fumarate** 240 mg twice daily (410)	**Dimethyl fumarate** 240 mg three times daily (416)
Proportion who relapsed by two years	46%	27%	26%
Annualised relapse rate	0.36	0.17	0.19
Mean number of new or enlarging hyperintense lesions on MRI	17	2.6	4.4
Proportion with progressive disability	27%	16%	18%

Table 2 **Outcomes of the CONFIRM trial** [3]

Outcomes	Treatments (number of patients)			
	Placebo (363)	**Dimethyl fumarate** 240 mg twice daily (359)	**Dimethyl fumarate** 240 mg three times daily (345)	**Glatiramer acetate** 20 mg daily (350)
Proportion who relapsed by two years	41%	29%	24%	32%
Annualised relapse rate	0.40	0.22	0.20	0.29
Mean number of new or enlarging hyperintense lesions on MRI	17.4	5.1	4.7	8.0
Proportion with progressive disability	17%	13%	13%	16%

Glatiramer reduced the annual rate by 29% relative to placebo. All the active treatments significantly reduced the number of new lesions on MRI, but there was no significant effect on the progression of disability (see Table 2).[3]

In the phase III trials treatment was discontinued by 35–36% of the placebo group, 30–31% of the dimethyl fumarate twice-daily group and 28–31% of the three-times-daily group. Adverse events led to the withdrawal of 10–13% of the placebo group and 12–16% of the dimethyl fumarate groups.[2,3] Adverse reactions to dimethyl fumarate include flushing, abdominal pain, nausea, vomiting and diarrhoea. Taking the capsules with food may reduce the irritant effects of dimethyl fumarate on the gut. An annual measurement of the full blood count is recommended as dimethyl fumarate can cause lymphopenia. This could increase the risk of infection. There have been case reports of progressive multifocal leukoencephalopathy in patients treated with dimethyl fumarate for psoriasis.[4] Some patients develop raised liver enzymes or proteinuria, and annual urinalysis is recommended.

Live vaccines are not recommended during treatment. The safety of dimethyl fumarate in pregnancy and lactation is uncertain.

The relative reductions in relapse rates were significant, but the effect on disability was less clear. For some outcomes, dimethyl fumarate appears to have better efficacy than glatiramer. It also has the advantage that it does not have to be injected like glatiramer and the interferons. A comparison between twice-daily dimethyl fumarate and once-daily oral fingolimod or teriflunomide would be useful.

T manufacturer provided the product information

REFERENCES *

1. Kappos L, Gold R, Miller DH, MacManus DG, Havrdova E, Limmroth V, et al. Efficacy and safety of oral fumarate in patients with relapsing-remitting multiple sclerosis: a multicentre, randomised, double-blind, placebo-controlled phase IIb study. Lancet 2008;372:1463-72.
2. Gold R, Kappos L, Arnold DL, Bar-Or A, Giovannoni G, Selmaj K, et al. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. N Engl J Med 2012;367:1098-107.
3. Fox RJ, Miller DH, Phillips JT, Hutchinson M, Havrdova E, Kita M, et al. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. N Engl J Med 2012;367:1087-97.
4. Mrowietz U, Reich K. Case reports of PML in patients treated for psoriasis [letter]. N Engl J Med 2013;369:1080-1.

First published online 8 October 2013

Lisdexamfetamine

Approved indication: attention deficit hyperactivity disorder

Vyvanse (Shire)

30 mg, 50 mg and 70 mg capsules

Australian Medicines Handbook section 18.5

When attention deficit hyperactivity disorder (ADHD) requires drug therapy as part of its management, dexamphetamine is one of the treatment options.[1] Lisdexamfetamine is a prodrug of dexamphetamine.

After the daily morning dose, lisdexamfetamine is rapidly absorbed from the gut. It is converted to active dexamphetamine by hydrolysis in the blood. Peak concentrations of dexamphetamine occur 3.5 hours after the dose. Only 2% of the dose is excreted as unchanged lisdexamfetamine in the urine. The half-life of the dexamphetamine produced is approximately 10 hours.

In a phase II study 52 children with ADHD took lisdexamfetamine, extended-release amphetamine or placebo. For part of the study they took each treatment for a week then swapped over so that they all had a week of each treatment. The children's symptoms were judged to be significantly better with the active treatments than with placebo on a rating scale of classroom behaviour.[2]

A phase III study randomised 290 children aged 6–12 years to take a placebo or lisdexamfetamine 30 mg, 50 mg or 70 mg. Although the trial was for

four weeks, the dose had to be titrated so the children taking 50 mg or 70 mg had a shorter duration of treatment at those doses. All three doses had a significantly greater effect than placebo on a scale which rated the symptoms of ADHD. At least 70% of the children were judged to be much, or very much, improved by lisdexamfetamine compared with 18% of the placebo group.[3]

Lisdexamfetamine has also been studied in 314 adolescents with ADHD. These 13–17 year olds were randomised to take lisdexamfetamine 30 mg, 50 mg, 70 mg or a placebo for four weeks. Again dose titration meant that the adolescents randomised to receive 50 mg or 70 mg took those doses for less than four weeks. Active treatment had a significantly greater effect than placebo on rating scales of inattention, and of impulsivity and hyperactivity.[4]

Another placebo-controlled trial studied 336 children and adolescents (6–17 years old). Those randomised to take lisdexamfetamine started at 30 mg daily and increased the dose weekly up to 70 mg according to their response. After optimising the dose over four weeks there was a three-week maintenance phase. In another arm of the trial the patients were given an osmotic-release formulation of methylphenidate. After seven weeks both lisdexamfetamine and methylphenidate had improved the patients' symptoms significantly more than placebo. The investigators judged that 78% of the lisdexamfetamine group and 61% of the methylphenidate group were much, or very much, improved compared with 14% of the placebo group.[5]

The longer-term effectiveness of lisdexamfetamine was studied in an open-label trial involving 272 children aged 6–12 years. These children took lisdexamfetamine 30 mg, 50 mg or 70 mg for an average of 8.6 months. Compared to their scores on a rating scale at the start of the study, there was a significant improvement in the symptoms of ADHD. Almost 96% of the 139 children who persisted with treatment for 12 months were judged to have improved.[6]

Lisdexamfetamine has also been approved as part of a comprehensive treatment program for adults with ADHD. Similar to the trials in younger patients, a group of 420 adults (mean age approximately 35 years) was randomised to take lisdexamfetamine 30 mg, 50 mg or 70 mg, or placebo for four weeks. All three doses had a significantly greater effect than placebo on an adult ADHD rating scale.[7] A total of 349 patients from this study joined an open-label extension study. This showed that improvements were sustained for up to 12 months in most patients.[8]

Another trial looked at the maintenance of efficacy in 116 adults who had been taking lisdexamfetamine for at least six months. They were randomised, in a double-blind phase of the trial, to continue treatment or switch to a placebo. After six weeks 75% of the patients who took placebo had experienced a relapse of their symptoms compared with 9% of those who continued treatment.[9]

The adverse effects of lisdexamfetamine are similar to those of other stimulant drugs. These include decreased appetite and insomnia. Patients may also develop headaches, dry mouth and nausea. Children may complain of abdominal pain. It is important to check each person's cardiovascular, neurological and psychiatric history before prescribing any stimulant drug. A study of 281 children aged 6–13 years, who took lisdexamfetamine for an average of 8.8 months, reported reduced growth. Height and weight did not increase as expected.[10]

Lisdexamfetamine should not be taken during pregnancy. As amphetamines are found in breast milk, it should not be used during lactation.

Although the main trials of lisdexamfetamine were relatively short, there is a lot of clinical experience with dexamphetamine. A once-daily dose will be useful for schoolchildren with ADHD, so lisdexamfetamine should be compared with controlled-release methylphenidate. Many children with ADHD also have other mental health problems,[1] however some trials of lisdexamfetamine excluded patients with certain psychiatric comorbidities.

T T T manufacturer provided clinical evaluation

REFERENCES *

1. Tonge B. Principles for managing attention deficit hyperactivity disorder. Aust Prescr 2013;36:162-5.
2. Biederman J, Boellner SW, Childress A, Lopez FA, Krishnan S, Zhang Y. Lisdexamfetamine dimesylate and mixed amphetamine salts extended-release in children with ADHD: a double-blind, placebo-controlled, crossover analog classroom study. Biol Psychiatry 2007;62:970-6.
3. Biederman J, Krishnan S, Zhang Y, McGough JJ, Findling RL. Efficacy and tolerability of lisdexamfetamine dimesylate (NRP-104) in children with attention-deficit/hyperactivity disorder: a phase III, multicenter, randomized, double-blind, forced-dose, parallel-group study. Clin Ther 2007;29:450-63.
4. Findling RL, Childress AC, Cutler AJ, Gasior M, Hamdani M, Ferreira-Cornwell MC, et al. Efficacy and safety of lisdexamfetamine dimesylate in adolescents with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 2011;50:395-405.
5. Coghill D, Banaschewski T, Lecendreux M, Soutullo C, Johnson M, Zuddas A, et al. European, randomized, phase 3 study of lisdexamfetamine dimesylate in children and adolescents with attention-deficit/hyperactivity disorder. Eur Neuropsychopharmacol 2013 Jan 14. doi: 10.1016/j.euroneuro. 2012.11.012.
6. Findling RL, Childress AC, Krishnan S, McGough JJ. Long-term effectiveness and safety of lisdexamfetamine dimesylate in school-aged children with attention-deficit/hyperactivity disorder. CNS Spectr 2008;13:614-20.
7. Adler LA, Goodman DW, Kollins SH, Weisler RH, Krishnan S, Zhang Y, et al. Double-blind, placebo-controlled study of the efficacy and safety of lisdexamfetamine dimesylate in adults with attention-deficit/hyperactivity disorder. J Clin Psychiatry 2008;69:1364-73.

8. Ginsberg L, Katic A, Adeyi B, Dirks B, Babcock T, Lasser R, et al. Long-term treatment outcomes with lisdexamfetamine dimesylate for adults with attention-deficit/hyperactivity disorder stratified by baseline severity. Curr Med Res Opin 2011;27:1097-107.
9. Brams M, Weisler R, Findling RL, Gasior M, Hamdani M, Ferreira-Cornwell MC, et al. Maintenance of efficacy of lisdexamfetamine dimesylate in adults with attention-deficit/hyperactivity disorder: randomized withdrawal design. J Clin Psychiatry 2012;73:977-83.
10. Faraone SV, Spencer TJ, Kollins SH, Glatt SJ. Effects of lisdexamfetamine dimesylate treatment for ADHD on growth. J Am Acad Child Adolesc Psychiatry 2010;49:24-32.

First published online 1 October 2013
Updated version published 22 October 2013

Romidepsin

Approved indication: peripheral T cell lymphoma
Istodax (Celgene)
vials containing 10 mg powder for reconstitution
Australian Medicines Handbook section 14.2

Peripheral T cell lymphomas are a rare group of cancers that result from clonal proliferation of mature T cells. They account for up to 5–10% of all non-Hodgkin's lymphomas and multiple sites are usually involved including blood, bone marrow, lymph nodes, spleen and skin. These T cell neoplasms are generally aggressive. They do not respond well to chemotherapy and are associated with a poor prognosis.

Romidepsin, which is isolated from *Chromobacterium violaceum*, is a new drug for peripheral T cell lymphomas in patients who have already had previous systemic treatment. The drug is thought to reduce the growth and division of cancer cells by inhibiting histone deacetylases involved in gene regulation.

Romidepsin has been studied in a phase II trial involving 130 pre-treated patients.[1] They had had 1–8 previous therapies and some had had autologous stem cell transplants. There was no comparator in the study so all participants received romidepsin 14 mg/m^2 as a four-hour infusion on days 1, 8 and 15 of a 28-day cycle. Six cycles were planned but treatment was stopped if disease progressed or toxicity occurred. The median duration of treatment was 1.4 months. According to an independent review committee, 25% of patients responded to romidepsin but 49% progressed despite treatment. The overall median progression-free survival was 4 months. However, this was longer for responders (see Table).

Adverse events in the trial were common. Over half of the patients had nausea (59%), infections (55%) or fatigue (55%). Other common events included vomiting (39%), diarrhoea (36%), fever (35%), constipation (30%), reduced appetite (28%) and dysgeusia (21%). Thrombocytopenia (41% of patients), neutropenia (30%) and anaemia (24%) were frequently observed and were serious (grade 3 or more) in many cases. Blood monitoring is therefore recommended during treatment and the dose may need to be reduced or stopped if abnormalities occur.

Four patients had a prolonged QTc interval but no other concurrent cardiac problems. An ECG should be performed at baseline and during treatment in patients taking other medicines that prolong the QT interval. Serum potassium and magnesium should be within the normal range before treatment is started.

Just under half of the patients required a dose interruption. Thrombocytopenia, infections and neutropenia were the most common reasons for this. Treatment was discontinued in 19% of patients because of an adverse reaction – events included thrombocytopenia, pneumonia, fatigue, dyspnoea and sepsis. Eight patients died within 30 days of receiving treatment – three deaths were due to progressive disease and five were related to an infection.

Following intravenous administration for four hours, romidepsin is metabolised by cytochrome (CYP) P450 enzymes – mainly CYP3A4. Strong inhibitors or inducers of CYP3A4 are best avoided as they may alter romidepsin concentrations. This drug is a substrate of P-glycoprotein so care should be taken

Table **Efficacy of romidepsin in a single-arm phase II trial in patients with peripheral T cell lymphoma** [1]

	Proportion of patients	Median progression-free survival
Overall objective response	25% (33/130)	4 months (overall)
Complete response	15% (19‡/130)	18 months
Partial response	11% (14/130)	7 months
Stable disease	25% (33/130)	6 months
Progressive disease or not evaluable	49% (64/130)	<2 months

‡ six of these were unconfirmed

if the patient is taking inhibitors of this transporter. Prolonged prothrombin time and INR have been observed in patients taking concomitant warfarin so increased monitoring is recommended.

A quarter of patients with peripheral T cell lymphoma responded to romidepsin. However because there was no control arm in the trial, it is not possible to quantify how much of the clinical benefit was due to romidepsin and how much was due to the patients' underlying condition. It is also difficult to assess whether the benefits of treatment outweigh the risks. Because of these reasons, the application for licensing romidepsin in Europe was rejected.

T T manufacturer provided additional useful information

REFERENCE *†

1. Coiffier B, Pro B, Prince HM, Foss F, Sokol L, Greenwood M, et al. Results from a pivotal, open-label, phase II study of romidepsin in relapsed or refractory peripheral T cell lymphoma after prior systemic therapy. J Clin Oncol 2012;30:631-6.

First published online 3 October 2013

Ruxolitinib

Approved indication: myelofibrosis
Jakavi (Novartis)
5 mg, 15 mg and 20 mg tablets
Australian Medicines Handbook section 14.2.3

Myelofibrosis can present as a primary disease or develop from polycythaemia vera or essential thrombocythaemia. It is characterised by fibrosis of the bone marrow, progressive anaemia and hepatosplenomegaly from overproduction of abnormal, immature blood cells. Survival of patients after diagnosis ranges from 2 to 11 years. Apart from stem cell transplant, current treatment is usually supportive and directed at symptoms.

Myelofibrosis is associated with overactivation of the Janus kinase pathway. In many patients, this is associated with a mutation in the Janus kinase 2 gene (V617F mutation). Overactivity of the pathway results in increased signalling of a number of cytokines and growth factors involved in haematopoiesis and immune functions.

Ruxolitinib is a selective inhibitor of Janus kinase 1 and 2. Its safety and efficacy has been assessed in two phase III trials – COMFORT-I and COMFORT-II.[1,2] COMFORT-I compared ruxolitinib to placebo for 24 weeks whereas COMFORT-II compared it to best available therapy (usually hydroxyurea or glucocorticoids) for 48 weeks. Approximately half of the patients in the trials had primary myelofibrosis, a third had post-polycythaemia vera myelofibrosis and the rest had post-essential thrombocythaemia myelofibrosis.

In both studies, more patients receiving ruxolitinib (15–25 mg twice daily) had at least a 35% reduction in spleen size compared to patients receiving the control treatments (see Table). Spleen size increased in patients who did not receive ruxolitinib. In COMFORT-I, more patients taking ruxolitinib reported a 50% or more improvement in disease-associated symptoms (such as night sweats, itching and abdominal discomfort) than those taking placebo (45.9% vs 5.3%). Similarly in COMFORT-II, more patients taking ruxolitinib reported an improved quality of life and better functioning than those taking best available treatment. In both trials, patients with the V617F mutation seemed to have a better response to ruxolitinib than those without the mutation.

After a median follow-up of 12–14 months, there appeared to be a survival advantage for ruxolitinib over placebo in COMFORT-I (8.4% vs 15.6% of patients had died). However, this was not the case for ruxolitinib over best available treatment in COMFORT-II (7.6% vs 5.6% of patients had died).

Haematological effects with ruxolitinib are common. Anaemia (81.7%), thrombocytopenia (67.4%) and neutropenia (15.3%) were the most frequently reported in the trials. These were generally managed by dose interruption or adjustment but some patients required a blood or platelet transfusion. Three cases of bleeding were fatal in patients receiving ruxolitinib,

Table **The efficacy of ruxolitinib for myelofibrosis in the COMFORT trials** [1,2]

Proportion of patients with 35% reduction in spleen volume	COMFORT-I		COMFORT-II	
	ruxolitinib	placebo	ruxolitinib	best available therapy
at 24 weeks	41.9% (65/155)	0.7% (1/154)	32% (46/144)	0% (0/72)
at 48 weeks	–	–	28% (41/144)	0% (0/72)

but only one was attributed to the treatment. The dose should be reduced if platelets fall below 100 x 10^9/L and interrupted if they fall below 50 x 10^9/L.

Overall, infections were common with ruxolitinib and control treatments (38.1% vs 41.7% in COMFORT-I and 63.7% vs 42.5% in COMFORT-II) and were fatal in some cases. Urinary tract infections, herpes zoster, tuberculosis and progressive multifocal leukoencephalopathy[3] have been reported. Ruxolitinib should not be started until serious infections have resolved and patients should be monitored for signs and symptoms of infection.

Diarrhoea[1,2], headache, dizziness, fever and bruising frequently occurred with ruxolitinib, as did hypercholesterolaemia. Elevations in alanine aminotransferase and aspartate aminotransferase were very common during treatment so monitoring of liver function should be considered.

Ruxolitinib is a pregnancy category C drug and is not recommended in pregnancy or lactation. Animal studies found that it crosses the placenta and is excreted in breast milk.

Following oral administration, ruxolitinib is rapidly absorbed with maximum plasma concentrations reached after an hour. The drug is mainly metabolised by cytochrome P450 (CYP) 3A4 and metabolites are excreted in the urine (74%) and faeces (22%). Its elimination half-life is approximately three hours.

Blood counts should be measured before starting ruxolitinib as the initial dose is determined by the patient's platelet count. Blood monitoring every 2–4 weeks is required to initially titrate the dose (maximum is 25 mg twice daily). A lower starting dose should be used in hepatic impairment, moderate to severe renal impairment (creatinine clearance <60 mL/minute) and in people taking concomitant strong CYP3A4 inhibitors (such as boceprevir, clarithromycin and ketoconazole).

After stopping treatment, myelofibrosis symptoms return to baseline after seven days. Serious withdrawal symptoms have been reported and tapering the dose has been recommended.[4]

Ruxolitinib reduces spleen volume and disease-associated symptoms in patients with myelofibrosis and offers another option for symptom control. However, its long-term efficacy and tolerability are still to be determined.

[X] manufacturer did not supply data

REFERENCES *†

1. Vertovsek S, Mesa RA, Gotlib J, Levy RS, Gupta V, DiPersio JF, et al. A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis. N Engl J Med 2012;366:799-807.
2. Harrison C, Kiladjian JJ, Al-Ali HK, Gisslinger H, Waltzman R, Stalbovskaya V, et al. JAK inhibition with ruxolitinib versus best available therapy for myelofibrosis. N Engl J Med 2012;366:787-98.
3. Wathes R, Moule S, Milojkovic D. Progressive multifocal leukoencephalopathy associated with ruxolitinib [letter]. N Engl J Med 2013;369:197-8.
4. Tefferi A, Pardanani A. Serious adverse events during ruxolitinib treatment discontinuation in patients with myelofibrosis. Mayo Clin Proc 2011;86:1188-91.

First published online 4 October 2013

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).

Correction

New drugs: axitinib

Aust Prescr 2012;35:208-9

The manufacturer of axitinib is Pfizer, not Shire.

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