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**Update on medicines for smoking cessation**

**SUMMARY**
Persistent cigarette smokers usually have a nicotine addiction. This addiction has a chronic relapsing and sometimes remitting course and may persist lifelong.

Remission can be facilitated by the use of medication as part of a comprehensive management strategy tailored to the individual patient.

Nicotine replacement therapy is a first-line drug treatment. It is available in many formulations.

Varenicline is also a first-line drug treatment. It should be started before the patient stops smoking.

Bupropion is a second-line therapy. It may be associated with an increased risk of seizures and drug interactions.

While there is some evidence that electronic cigarettes might facilitate smoking cessation, quit rates are not yet comparable with those of the drugs approved on the Pharmaceutical Benefits Scheme.

**Introduction**
Most tobacco smokers are addicted to nicotine. This addiction is a chronic disease state that is prone to relapses and remissions. However nicotine addiction is declining in Australia, indicating that for some smokers remission after quitting may be long lasting. In 2001, 22.4% of the population aged 18 or over smoked, while by 2011–12 this rate had reduced to 16.4%.

Following the decline in smoking prevalence in Australia, the profile of smokers has changed. A higher proportion now have more severe forms of nicotine addiction and comorbidity. Nonetheless, most smokers eventually consider quitting, so few smokers are completely resistant to interventions to stop smoking. Commonly, people who recover from addiction appear to learn how to manage lapses and relapses, largely from their experience of multiple cycles of lapse (‘slip up’) and relapse (reinstatement of dependence). A number of excellent recent reviews on smoking cessation are available.

There is a lot of evidence regarding the efficacy of the drugs used in smoking cessation. There is also emerging evidence about tailoring interventions to individuals in a personalised medicine approach. These drugs are most effective when used in conjunction with behavioural therapies and support (Box 1). Cognitive and behavioural interventions, such as motivational interviewing and relapse prevention, are an essential adjunct to the efficacy of these drugs. Smoking cessation is more likely to succeed when the smoker is motivated to quit, hence skill in motivational interviewing is additionally helpful for the practitioner. Recent evidence suggests some smoking cessation programs that also provide financial incentives for participants can be highly effective.

Obesity is the most important modifiable risk factor for osteoarthritis. Obesity and weight loss in the management of osteoarthritis.

Alcohol can cause pancreatitis, but there are many other possible causes. These drugs are most effective when used in conjunction with behaviour therapies and support (Box 1). Cognitive and behavioural interventions, such as motivational interviewing and relapse prevention, are an essential adjunct to the efficacy of these drugs.

Smoking cessation is more likely to succeed when the smoker is motivated to quit, hence skill in motivational interviewing is additionally helpful for the practitioner. Recent evidence suggests some smoking cessation programs that also provide financial incentives for participants can be highly effective. It is essential that both doctor and patient persevere in managing nicotine addiction regardless of apparently entrenched negative beliefs or the number of previous attempts to quit. The management focus is to help prevent relapse and to continue being supportive when relapse occurs, providing encouragement for further attempts to quit in the future. Common risks for lapse or relapse include...
stressful circumstances, consuming alcohol and being with friends or family who smoke.

**Indications for drug treatment**

Smokers who are not physiologically dependent on nicotine and are ready to quit are more likely to respond to behavioural interventions than dependent patients. Most current smokers are likely to be significantly nicotine dependent (Box 2), so it is appropriate to consider drug therapy to help them quit.

There are three approved drug therapies in Australia – varenicline, bupropion and nicotine replacement therapy. They are available on the Pharmaceutical Benefits Scheme (PBS), as long as they are part of a comprehensive treatment plan for smoking cessation. A Cochrane review has compared the efficacy of drugs that support quitting for six months or longer (Table). Nortriptyline and clonidine are sometimes prescribed 'off-label' for smoking cessation, however their efficacy is not as good as that of the approved drugs.

**Nicotine replacement therapy**

For most patients, nicotine replacement therapy should still be considered first line because of its established evidence base. Multiple formulations are available – gum, lozenges, oral strips, spray, inhaler, patches (16- or 24-hour release) and sublingual tablets. All have comparable efficacy. These different formulations allow for better tailoring to individual requirements including the use of combinations if required. For example, a patient may be prescribed a transdermal nicotine patch and additionally use a nicotine inhaler to supplement blood nicotine concentrations at times of particular craving or risk of relapse. Evidence suggests that combinations of nicotine replacement therapy may be more effective than using a single formulation.

Transdermal patches are a common form of nicotine replacement therapy. It is recommended to start with a higher dose formulation (e.g. 21 mg) and to consider the 16-hour patch for patients who do not usually smoke during the night, to avoid sleep disturbance. Both patch durations are equally efficacious. It is important to provide an adequate dose of nicotine to reduce withdrawal symptoms and risk of relapse, then continue treatment for the appropriate duration (e.g. 12 weeks). Generally, heavier smokers (e.g. more than a packet/day) will require bigger replacement doses of nicotine. Sometimes, two transdermal patches may be required. Advise heavily dependent patients about self-titration of the nicotine dose using additional short-acting formulations like gum, spray or inhaler.

**Box 1  Resources to support smoking cessation**

**QUIT-line**  
Counselling for consumers  
www.quitnow.gov.au or phone 13 7848 (13 QUIT)

**Mental health information**  
www.quitnow.gov.au – Go to the tab ‘I want info on’ and then ‘Mental illness and quitting’ (health professionals and patient information sheets).  

**Pregnancy-related information**  
This site provides access to the ‘Quit for New Life’ program which especially targets Aboriginal mothers.

**Aboriginal and Torres Strait Islander information**  
www.qld.gov.au/atsi/health-staying-active/quit-smoking

**NPS MedicineWise**  
Stop smoking – what works for your patients?  

**Australian Association of Smoking Cessation Professionals**  
http://aascp.org.au

**Royal Australian College of General Practitioners**  
Supporting smoking cessation: a guide for health professionals  
www.racgp.org.au/guidelines/smoking-cessation

**Royal Australasian College of Physicians**  
Smoking cessation training module  
https://elearning.racp.edu.au – Go to the tab ‘Addiction medicine’.

**Cochrane Tobacco Addiction Group**  
http://tobacco.cochrane.org/evidence

**National Cannabis Prevention and Information Centre**  
www.ncpic.org.au

**Box 2  Features of severe nicotine dependence**

Smoking in first five minutes after waking  
Smoking despite illness, such as respiratory tract infections  
Waking during the night to smoke  
Smoking to reduce withdrawal symptoms  
Smoking more than a packet of cigarettes a day

*The more features present, the more severe the dependence*
Discontinuation of nicotine replacement therapy may be abrupt, but if a patient prefers, they can reduce the dose by self-titration using short-acting forms of nicotine replacement therapy. Some patients may choose to keep a supply of lozenges, gum, or an inhaler to use as required for relapse prevention. Persistent dependence on nicotine via nicotine replacement therapy is rare but may occur. While this form of nicotine dependence is less harmful than cigarette smoking, when encouragement to reduce the dose fails, specialist referral should be considered. Certain behavioural aspects of smoking may be more amenable to particular formulations of nicotine replacement therapy. For example, ritual cigarette handling may be substituted by handling a nicotine inhaler. Chewing gum or sucking on a lozenge may reduce anxiety or thoughts about smoking. Nicotine replacement therapy is generally recommended to start when the patient stops smoking. This is to avoid higher than usual nicotine concentrations causing adverse effects, the earliest being nausea.

All forms of nicotine replacement therapy are available over the counter from pharmacies. This means that patients can access it repeatedly. Used nicotine patches should be discarded with care to avoid accidental exposure in children or other inappropriate use. Pharmacists can provide information about safe storage and disposal of medicines.

**Varenicline**

Varenicline has comparable efficacy with combination nicotine replacement therapy but has superior efficacy to nicotine replacement monotherapy (Table). It is therefore recommended as an equal first-line drug for smoking cessation.

Varenicline acts as a partial agonist at central nicotinic receptors, which are important in mediating the reinforcement associated with tobacco smoking.\(^5\)\(^6\) During treatment, drug binding partially activates these receptors thereby reducing withdrawal symptoms and cravings. If the patient lapses and smokes, varenicline reduces the access of nicotine to the receptors. By limiting nicotine binding, its rewarding effect is reduced.

It is recommended that varenicline is started a week or two before the patient stops smoking. This is because a continuous period of dosing is required before sufficient receptors are occupied and optimal drug efficacy is achieved. The dose is gradually increased and treatment continues for 12 weeks. If the patient is not initially successful in quitting within a six-month period, the PBS subsidises an additional 12 weeks supply of varenicline (up to two authority prescriptions per 12 months).\(^5\) Varenicline can be combined safely with nicotine replacement therapy and this may further improve abstinence rates at six months.\(^6\)

Varenicline is principally eliminated by the kidney so reduced doses (or alternative treatments) are recommended for patients with renal impairment. When varenicline was first marketed there were concerns about an apparent increased incidence of neuropsychiatric and cardiovascular adverse effects. After several years of experience with varenicline, these concerns do not appear to have been substantiated.\(^6\)\(^7\)\(^8\) Common adverse effects include nausea, headache and insomnia.

**Bupropion**

Bupropion was originally developed as an antidepressant, but its mode of action in smoking cessation is uncertain. It has equivalent efficacy to nicotine replacement monotherapy but less efficacy than varenicline and is therefore considered a second-line option.

Bupropion is considered when other drugs have been ineffective or contraindicated. Although bupropion can be used in conjunction with nicotine replacement therapy, this combination appears not to offer improved efficacy.\(^9\)

Like varenicline, bupropion is started before the patient stops smoking to allow sufficient time for the drug to mediate its therapeutic effects. A common strategy is for the patient to set a quit date for the second week of therapy.

Bupropion is contraindicated in patients with a history of seizures. Common adverse effects include difficulty concentrating, insomnia and nightmares. Bupropion undergoes significant hepatic cytochrome
P450 2B6 metabolism to an active metabolite (hydroxybupropion) which is later excreted renally. Dose reduction is necessary in patients with hepatic or renal disease. There are potential interactions with other drugs metabolised by this system including selective serotonin reuptake inhibitors and St John’s wort.20

Personalising drug treatment

Among the more common reasons for a poor response to drug treatment are non-adherence, adverse effects, and inadequate dosing particularly with nicotine replacement therapy. Personalising treatment may prevent some of these problems. The choice of drug depends on patient factors and their environment.

Patient factors

Consider any individual preferences, past experiences or medical conditions. For example, nicotine gum usually does not suit patients with dentures, and in Sjogren’s syndrome nicotine lozenges or strips are less likely to be effective due to decreased saliva production. Aphthous ulceration is a recognised adverse consequence related to smoking cessation and not an adverse effect of drugs used to assist quitting.21 The patient might have a generalised dermatological condition that makes transdermal patches less appropriate. Other individual factors to consider include chronic renal or hepatic disease, diabetes (glycaemic control may be unstable during smoking cessation), unstable angina, pregnancy and lactation.

Many smokers have comorbid mental health problems such as anxiety or mood disorder. Identifying these problems can help in determining the need for specific treatments to further facilitate the smoking cessation attempt – for example, engaging the patient in a mental health treatment plan involving a psychologist who can provide assistance with the mental health problem and support smoking cessation. Quitting smoking has been shown to improve the mental health of patients with psychiatric comorbidity and does not exacerbate their symptoms.22-27

Patients with significant depressive symptoms are known to be less likely to respond to smoking cessation interventions. Some may need antidepressant treatment before they will engage in smoking cessation. Although bupropion has antidepressant activity, it has no more efficacy in depressed smokers than other drugs for smoking cessation.24 Encouragingly, evidence supports smoking cessation interventions even in groups previously thought to be resistant, such as patients with chronic psychotic illness, the homeless, the socially disadvantaged and people with other forms of substance abuse.28,29 Caution is needed in patients taking antipsychotic drugs as smoking cessation can lead to rising blood concentrations of drugs such as clozapine and olanzapine.30

Women planning pregnancy should be encouraged to give up smoking. Preconception counselling and antenatal visits are opportunities to reinforce this advice. Patient education and behavioural interventions are recommended as first-line interventions. There are special smoking cessation resources for pregnant women (Box 1). If drugs are considered, neither varenicline nor bupropion is recommended. Although evidence supporting the use of nicotine replacement therapy in pregnancy is limited, it is likely to be much safer than smoking.31,32

Adolescent smokers are less likely to be severely nicotine dependent. A small group may be dependent and there is some evidence supporting the use of nicotine replacement therapy, notably patches and gum.34

Environment

Assessing the patient’s environment involves identifying the factors that positively or negatively affect adherence to the smoking cessation plan.35 For example, the patient may have a partner who continues to smoke at home, or friends or a workplace that exposes them to risks for lapse or relapse. Patients should be helped to develop strategies to better negotiate these situations. Other supports include the QUIT-line providing telephone follow-up, text messaging to enhance adherence,36 and engaging mindfulness therapy.37 Some patients may need specialist referral, for example contacting the Australian Association of Smoking Cessation Professionals or an addiction medicine specialist.

Electronic cigarettes

Electronic cigarettes (e-cigarettes) are typically handheld, battery-operated devices that deliver vapourised liquid (‘e-juice’) containing flavourings and sometimes nicotine. The vapour is inhaled by the user in a fashion similar to smoking but without inhaling tobacco tar and carbon monoxide. The process of inhaling these vapours is referred to as ‘vaping’. In Australia nicotine-delivering cartridges are not available over the counter and require individual importation licensing (for personal use only), a medical prescription and are subject to various state legislative sanctions. Some patients source nicotine e-juice over the internet from the USA, Canada and China.

Some recent evidence including a Cochrane review suggests these devices may help some people quit smoking.36,37 However they have not been shown to be more effective than current smoking cessation drugs. Further, there are concerns about safety (e.g. constituents of the vapour may be toxic...
Medicines for smoking cessation

to the lung) and the marketing of e-cigarettes, especially towards young people and current non-smokers. Some advertising suggests to smokers that they use e-cigarettes during times when they are unable to smoke cigarettes rather than as an aid to smoking cessation.40-43

Of concern is the evidence of increasing use of nicotine-containing e-cigarettes by non-smoking adolescents and young adults.44 Further, some evidence suggests that nicotine may function as a gateway drug to future drug addiction by enhancing the brain’s susceptibility to be rewarded by other addictive drugs.45

Cannabis

Most cannabis smokers also smoke tobacco. There is evidence suggesting that tobacco increases cannabis dependence46 and that cannabis use increases difficulty of tobacco cessation.47 Assisting smokers to quit tobacco may also assist with cannabis cessation and vice versa. A recent Cochrane review on cannabis dependence found few good studies and insufficient evidence for most treatments trialled. However, they and others suggest a few drugs that might warrant further investigation.48,49 The National Cannabis Prevention and Information Centre provides good resources and support for cannabis cessation (Box 1).

Conclusion

Current cigarette smokers are likely to be significantly nicotine dependent. To help them quit there are several options for drug therapy, and prescribers, like smokers themselves, need encouragement to persevere despite past unsuccessful attempts. These drugs have good efficacy particularly when used in conjunction with a comprehensive treatment plan. A focus on personalised interventions and relapse prevention is recommended. It is essential to provide support and there are many support services now available including specialist referral. <<

Conflict of interest: none declared

REFERENCES

Letters to the Editor

Antiplatelet drugs and the smokers’ paradox

The review on the new antiplatelet drugs (Aust Prescr 2014;37:182-6) was very useful and timely. However, one important aspect not mentioned was the influence of smoking status on drug efficacy. Smokers have an enhanced response to clopidogrel – the so-called smokers’ paradox.1

A recent meta-analysis concluded that the clinical benefit of clopidogrel in reducing cardiovascular events was seen primarily in smokers (25% risk reduction compared to controls), with little benefit in non-smokers (8% reduction).2 Prasugrel and ticagrelor were 47% and 36% more effective respectively than clopidogrel in smokers. However, in non-smokers the risk reduction was a modest 15% and 18% respectively compared with controls.2

It would be helpful if the authors could comment on the clinical significance of these findings and their implications for drug selection and dosing. For example, is clopidogrel a suitable choice for non-smokers and should they receive larger doses to improve efficacy? Should prasugrel and ticagrelor replace clopidogrel in smokers who quit? Are smokers at higher risk of major bleeds from these antiplatelet drugs?

Colin Mendelsohn
Tobacco treatment specialist
The Sydney Clinic Consulting Rooms
Sydney

Colin Mendelsohn has received payments for consultancy, educational presentations, travel and related expenses from Pfizer Australia, GlaxoSmithKline and Johnson & Johnson Pacific.

REFERENCES

Praveen Indraratna and Christopher Cao, the authors of the article, comment:

The intriguing phenomenon of the smokers’ paradox in relation to P2Y\textsubscript{12} inhibitors refers to their apparent higher efficacy in patients who smoke. It has been proposed that induction of the cytochrome P450 (CYP) 1A2 enzyme may enhance the conversion of the prodrug clopidogrel into its active metabolite.\textsuperscript{1} Also, the P2Y\textsubscript{12} receptor has been found to be upregulated in smokers, which may explain the enhanced effect of P2Y\textsubscript{12} inhibitors in these people.\textsuperscript{2}

Unlike clopidogrel and prasugrel, ticagrelor does not appear to be affected by the smokers’ paradox according to retrospective data from a recent study.\textsuperscript{3} On the other hand, the PARADOX study found that platelet aggregation was inhibited more strongly at a cellular level for both clopidogrel and prasugrel in smokers than in non-smokers, but clinical outcomes were not reported.\textsuperscript{4} Overall, the clinical significance of the smokers’ paradox remains controversial.\textsuperscript{2}

As Dr Mendelsohn pointed out, a meta-analysis noted differing relative risk reductions between smokers and non-smokers (see Table).\textsuperscript{5}

This analysis included patients with both acute coronary syndrome and stable coronary artery disease, whereas our recent systematic review and meta-analysis focused on patients who presented with acute coronary syndrome.\textsuperscript{6}

Another meta-analysis combined the two major trials for prasugrel in acute coronary syndrome (TRILOGY ACS and TRITON TIMI 38).\textsuperscript{7} Post hoc analysis found that prasugrel was superior to clopidogrel in reducing cardiovascular events only in smokers, and that the two drugs were similar in efficacy among non-smokers. A sub-study of the pivotal PLATO study comparing ticagrelor and clopidogrel did not find any significant difference in a reduction of cardiovascular outcomes between smokers and non-smokers. Additionally, the benefits of ticagrelor over clopidogrel were found in both smokers and non-smokers.\textsuperscript{3}

It should be acknowledged that such analyses of smoking status and cardiovascular events do have limitations, and speculative findings should be interpreted with caution. Patients within these trials were not randomised into smoking and non-smoking arms, and the data were analysed retrospectively. Baseline characteristics between the two comparative groups may have differed and cigarette exposure (heavy vs occasional smoking) was often not quantified. It was also unclear whether patients continued to smoke or stopped when they started antiplatelet therapy. Without such data, a clear advantage of one antiplatelet drug over the other is difficult to establish. Furthermore, little is known about the influence of smoking on bleeding risk with antiplatelet drugs, and available data are conflicting.\textsuperscript{3,5}

At this stage, we would not use smoking status as a determinant of drug selection until additional prospective data are available. Premature cessation or non-compliance with antiplatelet therapy is the strongest risk factor for stent thrombosis.\textsuperscript{6} After acute coronary syndrome, in addition to smoking cessation, we would always recommend dual antiplatelet therapy regardless of smoking status in patients who are treated either with percutaneous coronary intervention or medical therapy. This is in line with Australian and New Zealand guidelines (www.csanz.edu.au). The role of P2Y\textsubscript{12} inhibitors following coronary artery bypass grafting remains controversial.

REFERENCES


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<th>Drug</th>
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<td></td>
<td>Relative risk reduction in smokers</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>25% 8%</td>
</tr>
<tr>
<td>Prasugrel</td>
<td>29% 18%</td>
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Preoperative investigations

As an anaesthetist, I read the article ‘Preoperative assessment: a cardiologist’s perspective’ (Aust Prescr 2014;37:188-91) with much interest. The statement that ‘risk assessment before surgery aims to minimise potential perioperative complications’ is likely correct, although there is regrettable little evidence to substantiate this claim. However, I dispute the authors’ view that for emergency surgery ‘preoperative assessment uncommonly alters the course or outcome’. The 2014 American College of Cardiology/American Heart Association guidelines recommend that, even for emergency surgery, clinical risk stratification should be undertaken, and that patients’ morbidity and mortality risk can be estimated with the use of validated tools (www.riskcalculator.facs.org and www.riskprediction.org.uk/pp-index.php). Discussion of morbidity and mortality risk enables shared decision making, including the possibility that patients may decline surgery.

High-risk surgical patients have been described as those with a predicted postoperative mortality of greater than 5%.1 A 2011 report from the UK National Confidential Enquiry into Patient Outcome and Death suggests that high-risk surgical patients should be carefully considered for postoperative high-dependency or intensive care.2 Disturbingly, in Australia (unlike New Zealand) good data on system-wide postoperative mortality are not collected and publicly reported. Clearly, not all postoperative morbidity and mortality is cardiac.

Joanna Sutherland
Conjoint associate professor, UNSW Rural Clinical School
VMO Anaesthetist, Coffs Harbour Health Campus
Coffs Harbour, NSW

REFERENCES


Austin Ng and Leonard Kritharides, the authors of the article, comment:

We stand by our statement that ‘for emergency non-elective surgery, preoperative risk assessment uncommonly alters the course or outcome of the operation as the urgency of the surgery takes precedence’. However, we did not intend for the statement to suggest not conducting preoperative assessments for emergency non-elective surgery. As stated by Dr Sutherland and in our article, ‘identifying high-risk conditions such as class IV congestive heart failure, unstable coronary syndromes, or severe valvular heart disease (by conducting a preoperative assessment) can impact upon perioperative and postoperative management’ from a cardiologist’s perspective. Moreover, we agree that using validated surgical risk assessment tools will identify other non-cardiac high-risk factors. An appropriate risk assessment can then be presented to the patient or relatives for an informed decision. More research is clearly needed as the evidence behind preoperative assessment remains poor.

Data informs debate

The editorial ‘Data informs debate’ (Aust Prescr 2015;38:38-9) describes the uncertainties around the efficacy and safety of new medicines entering the market. It outlines the role that increased access to clinical trial data may have in informing assessments about the appropriate place of new drugs in clinical practice. Just as it is important to consider new drugs, it is also important to consider the use of currently available drugs in new markets, or new populations. Populations vary, for a variety of reasons, in their response to specific drug therapies.1,2 Australia has a unique population in its Aboriginal and Torres Strait Islander people. This population may not have been included in clinical trials, so further analysis of trial data will often not be informative. Substantial uncertainty exists regarding

the safety and efficacy of medicines in Aboriginal and Torres Strait Islander people, despite their need for extensive use of medicines to manage the high burden of disease.

It is important that Australian prescribers are aware of the limitations of drug safety and efficacy data for Aboriginal and Torres Strait Islander people. Clinicians are encouraged to publish their own observations, including reporting adverse drug reactions, to the Therapeutic Goods Administration. These observations are essential to inform robust assessment of medicines for Australia’s indigenous populations.

Genevieve Gabb
Physician
Repatriation General Hospital
Daw Park, SA

Agnes Vitry
Pharmacist
University of South Australia

REFERENCES

Book review

Psychopharmacology and pregnancy

Galbally M, Snellen M, Lewis A
Heidelberg: Springer-Verlag Berlin Heidelberg; 2014. 223 pages

The editors of this book undertook to provide an overview of the current state of knowledge concerning the use of psychotropic medication in pregnancy, with a second stated aim of producing clinical guidelines for practitioners. The historical reluctance to include pregnant women in research, and the need to consider the interests of both mother and baby, makes this a Herculean task. Here, the task is well-accomplished, with noted researchers from the field presenting us with an excellent and concise summary.

The initial chapters set out the unique challenges in perinatal mental health, an understanding of which is essential when counselling a pregnant woman about the options available to her. These include the ethics of informed consent and the difficulties of interpreting a flawed evidence base. They also include explanations of how the interaction of maternal, fetal, genetic and environmental factors may mediate the effects on babies of perinatal exposure to maternal mental illness and associated medicines.

Later chapters consider in turn the major categories of perinatal mental illness, in most cases providing itemised guidelines for clinicians at their conclusion. A minor criticism is that the presentation of these guidelines varies between chapters. This tends to reduce the ease of use of the book as a ‘quick reference guide’.

More difficult topics such as borderline personality disorder, eating disorders and substance abuse have been included. There is a chapter on the impact of popularly used complementary and alternative treatments. Another deals with the use of ECT, a treatment with high efficacy from which pregnant women may find themselves unfairly excluded.

Clinicians unfamiliar with the topic will be able to find some quick, wise pointers by turning immediately to the guideline sections. Those seeking a deeper understanding of the literature will also be rewarded.
Managing osteoarthritis

SUMMARY

Management of osteoarthritis should be based on a combination of non-drug and drug treatments targeted towards prevention, modifying risk and disease progression.

Obesity is the most important modifiable risk factor, so losing weight in addition to land- and water-based exercise and strength training is important.

While paracetamol can be tried, guidelines recommend non-steroidal anti-inflammatory drugs as first-line treatment for osteoarthritis. If there are concerns about the adverse effects of oral treatment, particularly in older patients or those with comorbidities, topical non-steroidal anti-inflammatory drugs can be used.

Glucosamine does not appear to be any better than placebo for pain. Its effect on the structural progression of disease when taken alone or in combination with chondroitin is uncertain. Fish oil has not been found to reduce the structural progression of knee arthritis.

Surgical interventions should be avoided in the first instance, with arthroscopic procedures not showing benefit over sham procedures or optimised physical and medical therapy. Joint replacement surgery should be considered for severe osteoarthritis.

Introduction

Osteoarthritis is a heterogeneous disease characterised by failure of the synovial joint including loss of articular cartilage, osteophyte formation, meniscal damage, ligamentous laxity and subchondral bone changes. It is a chronic condition resulting from the interaction of multiple factors including genetic, metabolic, biochemical and biomechanical. Obesity is the single most important risk factor for knee osteoarthritis over other factors such as joint injury or genetic predisposition.

The management of osteoarthritis has shifted from the traditional approach of pain control to include interventions to improve tolerance for functional activity and quality of life. Optimal management involves non-drug and drug approaches that focus on preventing disease and stopping progression, as opposed to just targeting palliation of disease.

Non-pharmacological management

After managing the pain, core interventions for all patients with osteoarthritis, with or without comorbidities, are land-based exercise, weight management, strength training, water-based exercise, self-management and education.

Exercise is universally recommended by clinical guidelines, and should be individualised after patient assessment. Meta-analyses have shown exercise to have small to moderate effect sizes for improved function and pain relief, similar to those achieved with non-steroidal anti-inflammatory drugs (NSAIDs) and analgesia.

Targeted muscle strengthening and general aerobic exercises are recommended, with water-based exercises suggested for those with functional and mobility limitations. Stretching and flexibility exercises generally form part of an overall exercise program for osteoarthritis, to maintain or increase the range of motion in the joints. Supervised group or individual exercise is superior to independent home exercise for pain reduction.

Mobility aids such as a stick (used in the opposite hand), knee braces and foot orthoses can also diminish pain and improve function.

Obesity is the single most important modifiable risk factor. A meta-analysis found that a 5% decrease in weight within a 20-week period is beneficial for knee osteoarthritis. A more recent trial showed up to a 50% improvement in symptoms with 10% weight reduction through diet and exercise.

NSAIDs

NSAIDs are often considered to be the preferred first-line drug treatment for osteoarthritis. They have shown efficacy similar and superior to paracetamol. Systematic reviews have found that NSAIDs are superior for rest pain and overall pain.

The potential adverse effects of routine NSAID use are well documented. Gastrointestinal toxicity causes over 16 500 deaths and hospital admissions per year in the USA. Associated cardiovascular and...
renal risks are also a concern. These risks pertain to both non-selective and cyclo-oxygenase (COX-2)-selective NSAIDs, even though COX-2 inhibitors have a better safety profile. A meta-analysis of 26 studies comparing the two found that COX-2 inhibitors reduced the relative risk of dyspepsia by 12% and the absolute risk by 3.7%. Other systematic reviews confirm similar findings. The concomitant use of proton pump inhibitors with NSAIDs is generally recommended in patients with associated comorbidity risks. The same meta-analysis found that combining an NSAID with a proton pump inhibitor reduced the relative risk of dyspepsia by 66% and the absolute risk by 9% compared with an NSAID alone.

The optimum duration of NSAID therapy is unclear. A meta-analysis of randomised trials found no clear association between the duration of therapy with selective or non-selective NSAIDs and the risk of cardiovascular events. One small trial found continuous celecoxib use to be slightly more effective than intermittent use on pain and function, with similar rates of withdrawals due to adverse events. No trials have been designed to assess serious gastrointestinal or cardiovascular harms associated with intermittent dosing strategies.

**Paracetamol**

Because of the adverse effect profile of NSAIDs, paracetamol (up to 4 g/day) has been the general analgesic of choice for mild to moderate pain in osteoarthritis for many practitioners. However, it is no longer recommended as first line by osteoarthritis guidelines. A meta-analysis found low-level effects of paracetamol for pain management in osteoarthritis, and a randomised controlled trial found paracetamol 4 g/day was no better than placebo for knee osteoarthritis. In addition, increased safety concerns with paracetamol are arising, especially for patients with comorbidities. A 2012 review found an increased risk of gastrointestinal events and multi-organ failure with supratherapeutic doses, which are often taken for chronic pain. Also, an analysis from the large prospective Nurses’ Health Study found heavy use of paracetamol (>22 days/month) is associated with an increased risk of cardiovascular events (RR* 1.4, 95% CI 1.1–1.6) similar to that with heavy use of NSAIDs (RR 1.4, 95% CI 1.3–1.6).

Furthermore, there are concerns regarding gastrointestinal blood loss with concomitant use of NSAIDs and paracetamol. One study found the risk of gastrointestinal-related hospitalisation was higher with combination treatment (HR† 2.55, 95% CI 1.98–3.28) compared with paracetamol alone (>3 g/day) (HR 1.20, 95% CI 1.03–1.40) and NSAIDs alone (HR 1.63, 95% CI 1.44–1.85).

**Topical therapies**

The benefits of both topical NSAIDs and capsaicin are achieved through regular use, with recommended application of 3–4 times/day. There are associated local adverse effects including rash, burning and itching.

**NSAIDs**

Topical NSAIDs are appropriate for both knee and hand osteoarthritis as local drug delivery reduces gastrointestinal adverse reactions. Efficacy is greater than placebo and comparable to oral NSAIDs. Multiple formulations have been trialled including topical ketoprofen and diclofenac sodium 1.5% topical solution in dimethyl sulfoxide. Safety with diclofenac sodium 1% gel has also been shown in the older population in a 12-month, post hoc analysis of patients with knee osteoarthritis. The overall rates of cardiovascular and gastrointestinal adverse events were similar for people under and over 65 years of age.

To date, most studies have focused on individuals with knee-only osteoarthritis so the benefits of topical NSAIDs on people with multiple-joint osteoarthritis remain uncertain. Despite this, topical NSAIDs are increasingly being considered as a first-line pharmacological option, especially in patients with an increased risk of adverse events.

**Capsaicin**

Topical capsaicin can be used as an alternative or as an adjunct to standard drug treatment. Reviews of randomised controlled trials found that topical capsaicin is superior to placebo for knee osteoarthritis and reduces pain by 50%. In general, a concentration of 0.025% capsaicin was better tolerated than 0.075%. Withdrawal because of an adverse event was more common with capsaicin than with placebo (13% vs 3%).

**Intra-articular injections**

Intra-articular corticosteroid injections provide short-term pain relief (1-2 weeks in randomised controlled trials) and improved function for patients with osteoarthritis. They can be considered in patients who present with acute exacerbations with joint effusions and local inflammation. However, intra-
articul injections given more frequently than once every four months can result in cartilage and joint damage, as well as increased risk of infection. The benefit of intra-articular hyaluronic acid injections is uncertain with inconsistent findings seen in meta-analyses. Trials showing benefit found varying effect sizes. A recent sensitivity analysis assessing blinded trials found only a small beneficial effect on pain. The efficacy of corticosteroids is more significant than intra-articular hyaluronic acid in the short term. However in another comparison, hyaluronic acid provided longer-lasting benefit, extending beyond eight weeks.

Opioids

Opioids are an alternative for patients who cannot tolerate or be prescribed first-line drugs because of contraindications due to comorbidities. Overall, systematic reviews concluded that oral and transdermal opioids were more effective compared to placebo in relieving pain and improving function in patients with hip and knee osteoarthritis. Benefits were small to moderate and adverse events caused many patients to withdraw. The usefulness of opioids in the long term is limited.

Opioids have an increased risk of adverse events when compared with NSAIDs, including fractures (HR 4.47, 95% CI 3.12–6.41), cardiovascular events (HR 1.77, 95% CI 1.39–2.24) and all-cause mortality (HR 1.87, 95% CI 1.39–2.53). When compared with placebo, patients were four times more likely to discontinue opioids due to an adverse event (RR 4.05, 95% CI 3.06–5.38).

Duloxetine

The pain experienced in osteoarthritis is multifactorial. Often coexistent depression and neuropathic pain compound the overall pain syndrome. There is increased interest in centrally acting drugs such as selective noradrenaline and serotonin reuptake inhibitors. In a comparative trial, more people taking duloxetine reported reduced pain (by at least 30%) than those taking placebo (65% vs 44%). Duloxetine can be a potential adjunct to conventional osteoarthritis treatment as additional pain reduction and improvement in function is seen when it is added to oral NSAIDs compared to placebo. Common adverse effects of duloxetine include nausea, constipation, fatigue, dry mouth and decreased appetite.

Surgery

Joint replacement surgery should be considered for severe clinical disease with inadequate response to conservative treatment. Arthroscopic procedures for knee osteoarthritis have not provided additional benefit in people receiving physical and medical therapy.

Complementary medicines

The most commonly used alternative treatment for osteoarthritis is glucosamine. In randomised controlled trials, it has a similar effect to placebo for pain, with independent trials showing smaller effects than commercially funded trials. The Glucosamine/Chondroitin Arthritis Intervention Trial, a US National Institutes of Health-funded study, found that glucosamine was not significantly better than placebo in reducing knee pain (by 20%). Evidence remains controversial regarding a possible structure-modifying effect (slowing or halting the progression of cartilage loss and other structural changes in the joint). Similarly with chondroitin, its effect on symptomatic relief is uncertain – some reviews find an effect while others show no significant benefit over placebo. Its ability to modify disease is also variable. Some studies found a reduction in the rate of decline in joint space width (0.07 mm/year, 95% CI 0.03–0.10).

Another trial found a statistically significant reduction in joint space narrowing after two years for a glucosamine/chondroitin combination compared to placebo. However, no statistical difference was found with individual treatment alone.

Fish oil use is gaining popularity for osteoarthritis. While there are some trials in rheumatoid arthritis, its use in osteoarthritis remains uncertain. The components eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) reduced expression of degradative enzymes and inflammatory cytokines in vitro cartilage models of osteoarthritis. However, in a clinical study fish oil did not retard structural progression of symptomatic knee osteoarthritis at low or high doses.

Newer therapies for osteoarthritis

There are numerous drug treatments for osteoarthritis, however their efficacy and adverse effect profiles often limit their use. At present there is no proven structure-modifying therapy available. The focus in osteoarthritis research is now shifting towards targeted biological therapies used in rheumatoid arthritis. As chronic forms of osteoarthritis are considered to be ‘low’ inflammatory conditions, research is underway into biological therapies targeting angiogenic factors, cytokines and pro-inflammatory mediators.

Different drugs targeting bone remodelling, including bisphosphonates and strontium ranelate, are also under investigation. Strontium ranelate reduced pain
Managing osteoarthritis and radiological progression in randomised controlled trials.\textsuperscript{50,51} However, in light of emerging data on cardiovascular risks, the potential benefits may not be justifiable.\textsuperscript{52}

Commercial stem cell therapies have recently emerged for knee osteoarthritis. To date, there is no supportive evidence to advocate these treatments. Both the International Society for Stem Cell Research and Australian Rheumatology Association are against their current use for osteoarthritis.

Developing novel therapies for osteoarthritis is not without its challenges. Newer analgesics such as tanezumab, a nerve growth factor inhibitor, showed promise for improving pain and function in hip and knee osteoarthritis. However, the trials were halted after a small number of patients developed rapid joint destruction.\textsuperscript{53}

\textbf{Conclusion}

There is a need for better therapeutic interventions for osteoarthritis. In the meantime, the management of osteoarthritis should be multifaceted, including non-drug interventions aiming at preventing disease and slowing its progression. If required, choosing optimal analgesia for an individual requires careful consideration and discussion regarding the relevant trade-offs.\textsuperscript{54}

\textbf{References}


FURTHER READING

Arthritis Australia aims to support people with all forms of arthritis including osteoarthritis, rheumatoid arthritis and gout. It publishes information in several languages on the types of disease, treatments, blood tests, surgery, complementary therapies and supplements, diet, exercise and lifestyle advice.

An interactive website www.myjointpain.org.au supports people who are self-managing their osteoarthritis.

Arthritis Australia runs educational events and webinars for health professionals on arthritis topics.

The state and territory branches provide support, information and lifestyle management advice on topics such as diet, managing pain, and local exercise classes including land- and water-based activities.

There is an online community forum where users can post comments and questions. It also provides videos, useful links and expert tips (http://livingwitharthritis.com.au).

Website www.arthritisaustralia.com.au
Arthritis information line 1800 011 041 (free call)
Email info@arthritisaustralia.com.au

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Managing obsessive compulsive disorder

SUMMARY

Unlike obsessive compulsive personality traits or occasional repetitive habits, obsessive compulsive disorder can be highly distressing and associated with significant disability. Treatment should always be offered.

Psychological interventions and selective serotonin reuptake inhibitors are first-line treatments for obsessive compulsive disorder.

Patients with obsessive compulsive disorder respond to selective serotonin reuptake inhibitors at a slower rate than those with depression.

The dose of a selective serotonin reuptake inhibitor can be increased at two-week intervals depending on the patient’s response. Aim for doses in the higher therapeutic range.

Improvements from treatment usually plateau at 12 weeks.

Successful treatment should continue for at least 12 months. There is a significant risk of relapse when treatment is stopped.

Introduction

Obsessive compulsive disorder (OCD) is a common and disabling condition. It occurs in approximately 2% of the population and 6–8% of people have subclinical symptoms. OCD is characterised by recurrent and intrusive thoughts, images or impulses (obsessions) that are distressing, accompanied by repetitive behaviours or compulsions. In most cases, patients see their symptoms as senseless or unreasonable, but they have difficulty resisting them. The repetitive behaviours, distress and indecisiveness can lead to obsessional slowness and avoidance. It is ranked as one of the top 10 most disabling medical conditions.

Patients tend to disclose their symptoms to their GP after many years of suffering in silence. They are often embarrassed by their symptoms and may fear that their symptoms will be seen as trivial. They might also believe there is no effective treatment.

OCD is difficult to screen for as it can present with a variety of symptoms, including:

- doubt and checking
- contamination fears and cleaning
- the need to have objects symmetrical or in order
- unacceptable aggressive, sexual or religious intrusive thoughts.

It is often confused with obsessive compulsive personality disorder (anankastic personality disorder) in which perfectionism, orderliness and rigidity is an ego-syntonic or non-distressing aspect of personality. The personality disorder does not always accompany OCD.

Psychological interventions

Patients often fear adverse effects associated with drug treatment, or the risk of drug dependency. They will therefore often request psychological strategies to assist them to resist and cope with their symptoms. Of the many psychological treatments that are available, exposure and response prevention has the most evidence for its effectiveness.

Exposure and response prevention therapy involves exposing patients to their fears and preventing their response (or their compulsion). For example, a person with contamination obsessions is asked to touch something that they deem contaminated (exposure) and would normally avoid. The patient is then taught to manage their anxiety without using washing or cleaning compulsions (response prevention). Exposure should be conducted in a graded manner with exposure to less anxiety-provoking stimuli in the initial stages.

Internet-based treatment programs based on cognitive behavioural therapy can also be beneficial. In clinical trials, both therapist-guided and self-guided programs were effective. This may be particularly useful for those in rural and remote areas.

Drug treatments

Pharmacological interventions are recommended when patients are unable to face the prospect of...
heightening their anxiety in exposure and response prevention, when they have severe symptoms and when they are unable to access an appropriately trained psychologist. It may be difficult to find a psychologist with adequate experience of OCD or waiting lists may be long. The cost of psychological counselling is also a commonly reported problem.

The evidence for drug treatment is robust (see Table). Most patients will have some alleviation of their symptoms. Some studies indicate that 50% of people will achieve remission when treated with a selective serotonin reuptake inhibitor (SSRI).

Treatment usually commences with an SSRI (see Table). Response rates are similar between drugs so the choice of which one to prescribe is usually determined by the doctor’s familiarity with an SSRI or by the need to reduce the risk of drug interactions. Trials have not convincingly proven the superiority of clomipramine over SSRIs. Although clomipramine can be effective for some patients, it is usually used after two failed trials of an SSRI due to problems with the tolerability of clomipramine. Unlike other anxiety disorders, OCD tends not to respond to benzodiazepines.

Some patients respond to standard doses of SSRIs, however most will need higher doses. Doses used in trials are listed in the Table. Patients prescribed higher doses should be informed of this and monitored carefully in consultation with a psychiatrist. They should also be warned that response to treatment may be slow and the full effect of their medication may only become evident after 12 weeks. It is usually recommended that SSRIs are increased every two weeks depending on the individual’s response and how they tolerate the medication. Based on response rates in multiple studies, an SSRI should be trialled at its maximum dose for at least 12 weeks before concluding it is ineffective.

It is generally recommended that successful treatment with an SSRI should be continued for at least 12 months. Several studies have shown that patients continue to benefit during this period. A decision to cease successful treatment should be considered carefully as most studies report relapse rates of over 50% within 12 weeks. A patient’s life circumstances will need to be evaluated to gauge the risk of relapse and the effect it may have on them. Withdrawing an SSRI should occur slowly, over several months, and preferably with guidance from a psychiatrist when symptoms have been severe.

Combining exposure and response prevention therapy with an SSRI has been shown to be more effective than either alone. When a patient does not respond to pharmacotherapy, adding exposure and response prevention therapy is usually recommended. Treatment-resistant patients should be referred to a psychiatrist. Deep brain stimulation is used as a treatment of last resort in Australia but is prohibited under the NSW Mental Health Act (2007).

**Adverse effects and drug interactions**

Prescribers should be aware of the risks associated with prescribing high-dose SSRIs. Patients should be monitored for signs of serotonin syndrome and warned that concomitant St John’s wort or tramadol frequently cause it and should be avoided. High-dose SSRIs and clomipramine can cause prolonged QT and arrhythmias and so regular ECGs are recommended following a dose escalation. Fluoxetine and paroxetine are both potent inhibitors of cytochrome P450 2D6 and clomipramine inhibits several cytochrome P450 enzymes.

**Table** Drug treatments for OCD

<table>
<thead>
<tr>
<th>Drug</th>
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<tr>
<td>Citalopram†</td>
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<td>Escitalopram</td>
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<td>Fluoxetine</td>
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<td>Fluvoxamine</td>
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<td>Paroxetine</td>
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<td>Sertraline</td>
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<tr>
<td>Clomipramine</td>
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† only recommended up to 40 mg/day

**Conclusion**

OCD can be treated with exposure and response prevention, SSRIs or both. Treatment requires some patience (and perseverance in the case of exposure and response prevention), but significant improvements can be achieved. <

Conflict of interest: none declared
REFERENCES


FURTHER READING

Minor burn management: potions and lotions

SUMMARY

The first aid for burns is to run cold water over the burn for 20 minutes. This is effective for up to three hours after the injury.

Assess the affected body surface area using the rule of nines. Consult a burn unit if more than 5% of the total body surface area is burnt in a child or if more than 10% in an adult.

Extensive or deep burns and burns to special areas, such as the hands, should be referred. Chemical or electrical burns should also be assessed by a burn unit.

For minor burns, antimicrobial dressings are recommended, but oral antibiotics should be avoided unless there are signs of infection. As burns are tetanus prone, check the patient’s immunisation status.

Burns that become infected or are slow to heal should be discussed with a burn unit. The burn unit can also provide advice if there are uncertainties about how to manage a patient.

Introduction

Burns affect at least 1% of Australians each year, although the number is probably higher due to the under-reporting of minor burn injuries. Pharmacists and GPs may be asked about managing minor burns. The majority of injuries are caused by scalds from hot liquids, contact with hot objects and fire. However, mechanisms such as friction burns, for example from treadmills, are becoming more prevalent.

Determining the severity of a burn injury

The significance of a burn injury depends on its depth and the percentage of total body surface area affected. The depth of the injury is determined by the temperature of the heat source and the duration of contact with that source.

The rule of nines is a practical method to quantify the area affected by the burn. For a person at least 10 years old, the head is equal to 9%, each upper limb 9%, the anterior trunk 18%, the posterior trunk 18% and each lower limb 18% (see Fig.). In children under 10 years old, the rule varies slightly, as the head represents a larger proportion of their body surface area. In addition, the palm and fingers of the patient of all ages can be used to estimate 1% total body surface area, which is useful when calculating scattered burn injuries.

Capillary refill is a good indicator of the depth of the burn. Any burn that is only erythematous and does not have blisters or a break in the skin is superficial. Any burn with brisk capillary refill is also likely to be superficial. Burns with slow capillary refill, or that are white, mottled or cherry red in appearance, are likely to be deep.

Fig. The rule of nines, for burns in people at least 10 years old

Percentages represent proportions of total body surface area.
**When to refer**

In general terms, if more than 10% of the total body surface area is burnt in children, and more than 20% in adults, the injuries are severe and must be referred to a specialist burn unit, as emergency management and fluid resuscitation are required (see Box). This is due to the release of inflammatory mediators which leads to a systemic inflammatory response and potential shock. 

Burns of 5–10% total body surface area in children and 10–20% in adults still require referral as the patients may require admission for management of problems such as pain.

Patients should also be referred to a burn unit if the injury involves the airway, face or neck, or affects the hands, feet or perineum. Patients with significant medical comorbidities such as diabetes, those who are immunocompromised, very young or very old patients, and those with associated trauma should also be referred.

All patients with burn injuries from chemical or electrical sources should be referred to a burn unit. Chemical burns often cause very deep injuries and may require specific decontamination or urgent debridement. Electrical injuries, while potentially appearing innocuous, may require cardiac monitoring due to the risk of cardiac arrhythmia.

Any burn that crosses a joint should be referred as it may lead to significant scar contracture irrespective of size. Circumferential burns and burns with the potential to compromise circulation or respiratory effort should be referred immediately for consideration of escharotomy.

Small burns and those localised to specialised areas can be significant. For example friction burns from treadmills to the fingers of a toddler often require skin grafting, leave permanent scarring and have a risk of lifelong morbidity due to scar contracture.

Some burns that do not initially meet the criteria for referral to a tertiary hospital may still need consultation with a burn unit if the wound takes longer than 10 days to heal. Burns that take longer than 14 days to heal may scar and any burn that takes longer than 21 days will very likely scar. Burn units not only look after acute burn injuries but also provide management of scarring if required.

When a burn is more than the size of a 20 cent piece, or deep burns that are smaller, need to be reviewed by a medical practitioner for advice and potential referral.

### Box Burn unit referral criteria

- Burns >10% total body surface area
- Full thickness burns >5% total body surface area
- Paediatric burns >5% total body surface area
- Burns to the face, hands, feet, genitalia, perineum and major joints
- Chemical burns
- Electrical burns including lightning injuries
- Burns with associated trauma
- Burns with inhalation injury
- Circumferential burns of the limbs or chest
- Burns in patients with pre-existing medical conditions
- Burns with suspected non-accidental injury, assault or self-inflicted
- Burns during pregnancy
- Burns in the extremes of age – infants and elderly
- Infected burns (although not an Australian and New Zealand Burn Association criterion, we recommend that infected burns be referred to a burn unit)

**First aid**

If someone is on fire, it is important for them to stop, drop, cover their face and roll. Clothing, nappies and jewellery must be removed, as they can continue to burn and store heat. If, however, the clothing is firmly stuck to the skin, cut around the area leaving adherent cloth in place. This will require removal in hospital.

For all thermal burns, 20 minutes of cold running water (2–15° C) has been proven to reduce the area and depth of the burn. Consequently, this reduces the area requiring skin grafting. Cold running water should ideally be applied within an hour of the injury, but is useful up to three hours post injury. It may also have an analgesic effect. Copious cold running water should be used to decontaminate chemical burns. Ice is never appropriate first aid for burns, as it can deepen these injuries and cause hypothermia.

Care must be taken with cooling to avoid hypothermia. This is particularly important in people with large surface area burns, young children and older people. These patients must be kept warm by covering unaffected areas as much as possible. Hydrogels containing tea tree oil have also been shown to have an analgesic effect, and sheet hydrogels may be useful as a temporary wound dressing.
Minor burn management

cover. They do not, however, replace the need for 20 minutes of cold running water, and hypothermia is also a risk.

Wound management for minor burns

Following the application of cold running water, wound management depends on the integrity of the skin. If the skin is intact and not blistered, wound coverage is not necessary and the application of a simple moisturiser is recommended. If the skin is blistered or broken, an assessment of wound size and depth should be undertaken. Consultation with a burn unit should be considered.

Burns are tetanus prone. Tetanus immunisation status and subsequent immunisation or provision of tetanus immunoglobulins should be considered.

Dressings

A large range of dressings can be applied to burns. The most important principles are to keep the wound clean and moist during healing. If blisters are present, or have been broken, use a protective dressing. An antimicrobial dressing is generally recommended. Silver dressings, which come in many forms (e.g. nanocrystalline silver sheets, silver impregnated foam, hydrofibre) or products such as chlorhexidine-impregnated tulle gras can be useful for their antimicrobial properties. If any signs of infection develop, patients should be referred to a burn unit.

Dressings should be applied according to the manufacturers’ recommendations. The frequency of dressing changes can vary from daily to weekly, and is determined by the product used and the amount of wound exudate. While health practitioners may favour a less expensive dressing, they should be aware that less frequent dressing changes and a lower chance of infection may make some relatively expensive antimicrobial dressings more cost-effective. As burns are very painful, fewer dressing changes, and therefore less associated procedural pain and distress, are highly desirable and may expedite healing.

The length of treatment depends on the time to healing. This is generally indicated by a pink, fully epithelialised wound surface.

Silver sulfadiazine cream

In the recent past, creams containing silver sulfadiazine were commonly used for burn injuries. While an effective antimicrobial, silver sulfadiazine requires daily dressing changes, which can be labour intensive and distressing for patients. Silver sulfadiazine produces a pseudo-eschar, which makes burns assessment difficult and may be implicated in reduced rates of wound re-epithelialisation. With the advent of new dressing technologies, the role of silver sulfadiazine should be limited to treating infected burns.

If it is used on an infected burn, silver sulfadiazine cream should be applied onto a sterile cloth or tulle gras. This ensures that it remains in contact with the wound bed. Infected burns should be referred to a burn unit as soon as possible as early debridement and intravenous antibiotics may be indicated.

Moisturising creams

Burn injuries often lead to dry skin and pruritus so moisturisers are commonly recommended. There are many moisturising products available, but a simple water-based sorbolene cream is very efficacious and cost-effective. In patients with intact, non-blistered skin, a moisturising cream can be used for primary wound management. Dry skin and pruritus can sometimes persist for many months after the burn has healed. Regular application of a water-based moisturising cream is recommended. However, moisturising products containing sodium lauryl sulphate, such as aqueous cream, are not recommended as they have been shown in some instances to worsen dryness. There is little evidence that adding vitamin E to sorbolene cream results in scar reduction but such creams are commonly used.

Soaps

Generally, soaps should be avoided due to their drying nature, sometimes for up to 12 months post injury. Washing with a moisturising cream or a non-soap-based product is recommended.

Oils

Oils are generally discouraged in the initial months after a burn, especially in children, as they are not readily absorbed into the skin. They may interfere with the integrity of pressure garments which are prescribed for scar management in some patients. In the longer term, bath oils may be of benefit to some individuals. Some bath oils are infused with colloidal oatmeal which may relieve itch. Products such as Bio-Oil or vitamin E oil can be used for scar management, however evidence of their effectiveness is limited and conflicting.

Sun protection

Sun protection is essential. Sun exposure in the initial 12 months after injury is anecdotally known to increase the risk of skin pigmentation. In the longer term, burned skin is at higher risk of malignancy than unburned skin. When choosing a product, those for sensitive skin are preferred. In the initial post-burn period, creams may be too irritating or too oily. Other measures such as protective clothing should therefore be strongly recommended.
Antipruritics

Pruritus is commonly experienced after a burn, particularly with patients having larger injuries. Itching and consequent scratching can be extremely detrimental to wound healing. In many instances antihistamines may be required. Topical preparations such as moisturising cream or colloidal oatmeal may also have a role. In patients with larger burn injuries, and pruritus resistant to first-line treatments, drugs such as gabapentin may be considered by burn or pain specialists.

Oral antibiotics

The prescribing of prophylactic oral antibiotics within the community setting is an area of increasing concern. The inappropriate use of antibiotics leads to high incidences of multi-resistant organisms. Multi-resistant Staphylococcus aureus and multi-resistant Pseudomonas aeruginosa are becoming increasingly prevalent and difficult to treat. Usually, antimicrobial dressings can keep wound colonisation to a minimum.

Wounds should only be treated with antibiotics if they are clinically infected or a wound swab shows moderate to heavy colonisation despite antimicrobial dressing management, or there is clinical evidence of systemic infection. Prescribing of oral antibiotics should align with microbiology results where possible. Any infected burn should be referred to a burn unit for ongoing advice and management.

Conclusion

While some burns require specialist management, vast numbers of injuries present to pharmacists and GPs. Burn units and some plastic surgery units are useful resources if advice regarding management is required. The nearest burn unit should be contacted if the patient meets referral criteria.

Conflict of interest: none declared

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Blood tests for acute pancreatitis

SUMMARY

The diagnosis of acute pancreatitis requires the presence of at least two of the three diagnostic criteria – characteristic abdominal pain, elevated serum amylase or lipase, and radiological evidence of pancreatitis.

Serum concentrations of amylase and lipase rise within hours of the pancreatic injury. A threshold concentration 2–4 times the upper limit of normal is recommended for diagnosis.

Serum lipase is now the preferred test due to its improved sensitivity, particularly in alcohol-induced pancreatitis. Its prolonged elevation creates a wider diagnostic window than amylase.

Neither enzyme is useful in monitoring or predicting the severity of an episode of pancreatitis in adults.

New biomarkers including trypsinogen and elastase have no significant advantage over amylase or lipase.

Diagnostic criteria

The diagnosis of acute pancreatitis usually requires a combination of clinical, laboratory and radiological findings. A number of international guidelines have suggested two of the following three features are required for the diagnosis:

- abdominal pain consistent with acute pancreatitis (acute onset of persistent severe epigastric pain often radiating to the back)
- serum lipase activity (or amylase activity) at least three times greater than the upper limit of normal
- characteristic findings of acute pancreatitis on abdominal ultrasound (a CT scan or MRI is considered if the diagnosis is uncertain).

Pathophysiology

Pancreatitis is thought to occur as a consequence of premature, intra-pancreatic activation of pancreatic proenzymes. These include chymotrypsinogen, procolipase, prophospholipase A2 and proelastase. The proenzymes are synthesised by the acinar cells and stored in vesicles known aszymogens. They are released into the pancreatic duct and activated at the brush border of the duodenal enterocytes.

The specific mechanisms by which the various aetiologies of pancreatitis cause this premature activation of proenzymes are not well understood. It appears that ‘autodigestion’ starts a local inflammatory response. The release of proinflammatory and chemotactic mediators, the activation of macrophages and the influx of other inflammatory cells damage the pancreas. Systemic complications such as bacteraemia, acute respiratory distress syndrome and a systemic inflammatory response syndrome may also occur if the various mediators enter the systemic circulation.1,2

Serum amylase

Serum amylase is secreted in specific isoforms by the salivary glands (s-amylase) and pancreas (p-isoamylase). It predominantly acts to digest starch, glycogen and related polysaccharides. Almost all laboratories currently measure total serum amylase so the result includes both isoenzymes. The reference range is typically 20–300 U/L, but does vary with age and gender. It also varies between laboratories despite attempts to adopt standardised reference methods. In studies using radiological evidence as the ‘gold standard’ for acute pancreatitis, serum amylase has a sensitivity of 81–95%. However, this does depend...
on the definition of ‘abnormal’ and the cut-off values chosen. Most guidelines now suggest an amylase concentration 2–4 times the upper limit of normal is optimal for diagnostic accuracy, but this may reduce the sensitivity of the test to as low as 60%. The sensitivity is also influenced by other factors, including the timing of the test and the cause of the pancreatitis.

Timing

In acute pancreatitis, amylase can rise rapidly within 3–6 hours of the onset of symptoms, and may remain elevated for up to five days. However, it has a short half-life of 12 hours so the concentration can normalise within 24 hours. This significantly reduces its value as a diagnostic test relatively early in the clinical course.

Cause of pancreatitis

In pancreatitis due to hypertriglyceridaemia, the serum amylase can be normal in up to 50% of cases. This is due to interference with the assay by either a circulating inhibitor or the hyperlipidaemia itself. A number of studies have also suggested that amylase may be less elevated in alcohol-induced pancreatitis compared to other causes.

Many conditions (see Table) can increase serum amylase so it is not specific for pancreatitis. These conditions include various intra- and extra-abdominal illnesses and drugs. Macroamylasaemia is an uncommon condition in which amylase rises because its clearance is reduced.

Given that up to 60% of the total serum amylase originates from non-pancreatic sources, measuring the pancreatic isoenzyme may improve the diagnostic accuracy in acute pancreatitis. However, this isoenzyme also rises in many of the other non-pancreatic causes of hyperamylasaemia. There are few studies on whether measuring the isoenzyme significantly improves the diagnostic accuracy of acute pancreatitis. Consequently, pancreatic amylase is not routinely measured in most laboratories.

Serum lipase

Lipase has now replaced amylase as the biochemical test of choice in acute pancreatitis. With an important role in fat digestion, the tissue concentration of lipase in the pancreas is 100-fold higher than in other tissues such as the duodenum, stomach, adipose tissue and lung.

Serum lipase typically increases 3–6 hours after the onset of acute pancreatitis and usually peaks at 24 hours. Unlike amylase, there is significant reabsorption of lipase in the renal tubules so the serum concentrations remain elevated for 8–14 days. This means it is far more useful than amylase when the clinical presentation or testing has been delayed by more than 24 hours. Serum lipase also has a greater sensitivity than amylase in patients with alcoholic pancreatitis. A number of studies suggest its sensitivity is 85–100%.

There are a number of other conditions that can elevate lipase including pancreatic disease, cholecystitis, intestinal ischaemia, renal impairment and malignancy (Table). However, the test’s specificity has been shown to be higher than amylase testing in several studies. Depending on the cut-offs, specificity may be higher than 95%.

Like serum amylase, there is some variability in the reference ranges for lipase, and debate about the

<table>
<thead>
<tr>
<th>Causes</th>
<th>Amylase</th>
<th>Lipase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal conditions</td>
<td>acute pancreatitis, pancreatic trauma, perforated viscus, intestinal infarction and obstruction, peritonitis, acute cholecystitis, appendicitis, hepatitis, abdominal aortic aneurysm, ruptured ectopic pregnancy, fallopian and ovarian cysts</td>
<td>acute pancreatitis, pancreatic trauma, perforated viscus, intestinal infarction and obstruction, peritonitis, acute cholecystitis, appendicitis, hepatitis, abdominal aortic aneurysm, malignancy (especially oesophagus, stomach, duodenum, pancreas)</td>
</tr>
<tr>
<td>Extra-abdominal conditions</td>
<td>salivary disease, renal failure, ketoacidosis, pneumonia, cerebral trauma, burns, anorexia nervosa and bulimia</td>
<td>renal failure, ketoacidosis, fat embolism, bony fractures</td>
</tr>
<tr>
<td>Others</td>
<td>macroamylasaemia, idiopathic hyperamylasaemia</td>
<td>mumps, hyperlipoproteinaemia</td>
</tr>
</tbody>
</table>

* These drugs can cause acute pancreatitis, but can also elevate pancreatic enzymes without pancreatitis.
optimal cut-off value that should be used to diagnose acute pancreatitis. Most guidelines now recommend 2–3 times the upper limit of normal as the most appropriate cut-off.\(^2,3\)

### Combined testing

In clinical practice it is not uncommon to see a combination of amylase and lipase being measured. Most guidelines do not advocate this approach as the increase in sensitivity achieved over a single test is only marginal and not cost-effective.

The ratio of the two enzymes may sometimes be useful in establishing the cause of the pancreatitis. Some studies suggest that a lipase–amylase ratio of more than 2–3 is more indicative of alcoholic pancreatitis, while a ratio of less than 1:2 is more likely to be related to gallstones.\(^4,5\) In an acute exacerbation of chronic pancreatitis neither enzyme may be elevated.

The magnitude of the elevation of amylase and lipase does not predict disease severity in adults. Ongoing daily measurements should not be used as a guide of disease activity or resolution. A serum C-reactive protein (CRP) greater than 150 mg/L measured 48 hours after the onset of symptoms is the best single laboratory predictor of disease severity,\(^6\) while a number of scoring systems that are a composite of clinical and laboratory criteria (Ranson’s,\(^7\) BISAP,\(^8\) APACHE,\(^9\) Glasgow\(^10\)) have also been devised for this purpose.

In children, lipase may be related to severity. One Australian paediatric study found that a lipase more than seven times the upper limit of normal in the first 24 hours could predict severe acute pancreatitis.\(^11\)

### Other markers

A number of other pancreatic enzymes and inflammatory biomarkers have been evaluated for their diagnostic value in acute pancreatitis. These include trypsinogens, phospholipase A2, pancreatic elastase, urine trypsinogen activated protein and carboxypeptidase B.

Trypsinogen is the best studied, with concentrations rising in the serum and urine within a few hours of the onset of pancreatitis. The sensitivity is estimated to be over 90% and the specificity is over 83%. However, this test along with most of the other new biomarkers appears to offer little advantage over lipase and amylase in terms of diagnostic accuracy.\(^2,5\)

### Conclusion

Serum concentrations of amylase and lipase rise within hours of an episode of acute pancreatitis. They are key components of the diagnostic criteria along with abdominal pain and radiological findings.

Lipase is now preferred over amylase due to a higher sensitivity, particularly in cases of pancreatitis due to alcohol and hypertriglyceridaemia. It also tends to remain elevated for longer than amylase, making it more useful when the presentation has been delayed by more than 24 hours.

Both enzymes may be elevated in various conditions other than pancreatitis. Neither is useful in monitoring the disease course or predicting severity in adults.\(^<\)

**Conflict of interest:** none declared

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**REFERENCES**

Medical management of chronic stable angina

SUMMARY
Stable angina pectoris is characterised by typical exertional chest pain that is relieved by rest or nitrates.

Risk stratification of patients is important to define prognosis, to guide medical management and to select patients suitable for revascularisation.

Medical treatment aims to relieve angina and prevent cardiovascular events. Beta blockers and calcium channel antagonists are first-line options for treatment. Short-acting nitrates can be used for symptom relief.

Low-dose aspirin and statins are prescribed to prevent cardiovascular events.

Introduction
Cardiovascular disease is the leading cause of death in Australia. Angina pectoris affects more than 353 000 Australians and accounts for approximately 72 000 hospital admissions annually. Angina is caused by myocardial ischaemia. Chronic stable angina has a consistent duration and severity, and is provoked by a predictable level of exertion. It can also be provoked by emotional stress. The pain is relieved by rest or short-acting nitrates. The aim of medical therapy is to minimise symptoms and retard disease progression. This requires lifestyle modification as well as drug treatment.

Diagnosis
The diagnosis of angina is usually suspected from a thorough history and examination. Patients should have an ECG and undergo assessment for cardiovascular risk factors such as diabetes and hyperlipidaemia. An echocardiograph can help with the assessment of left ventricular function. Once the clinical diagnosis of stable coronary artery disease is established, the patient’s risk of future cardiovascular events is evaluated.

Risk stratification
In patients with stable coronary artery disease the risk of cardiovascular mortality may be predicted by clinical and demographic variables. These include gender, left ventricular function, the provocation of myocardial ischaemia with stress testing, and the severity of coronary artery disease seen on angiography. Patients at high risk of cardiovascular events may need revascularisation as well as medical therapy.

Clinical evaluation
The history, examination, ECG and laboratory tests provide important prognostic information. Increasing age, chronic kidney disease, diabetes, hypertension, current smoking, previous myocardial infarction, hypercholesterolaemia and heart failure are predictive of adverse outcomes.

Echocardiography
Echocardiography provides information about left ventricular function, and regional wall motion abnormalities that may be related to infarction or ischaemia. In patients with stable coronary artery disease, left ventricular ejection fraction is the strongest predictor of long-term survival. The 12-year survival of medically treated patients with ejection fractions greater than 50% is 73%, and 54% if the ejection fraction is between 35% and 49%. Survival is only 21% if the ejection fraction is less than 35%.

Stress testing
Stress testing on a treadmill or bicycle is recommended for patients with normal resting ECGs who can exercise. Symptoms such as chest discomfort and dyspnoea, exercise workload, blood pressure response and ECG changes consistent with ischaemia are recorded as the patient exercises. Abnormalities present at rest such as atrial fibrillation, left ventricular hypertrophy, intraventricular conduction abnormalities and ECG changes related to electrolyte imbalance or digoxin will result in more frequent false-positive results. Stress testing is also used to evaluate the efficacy of revascularisation and medical treatment, and to direct the prescription of exercise.

Key words
beta blockers, calcium channel antagonists, glyceryl trinitrate, stable angina

Aust Prescr 2015;38:131–6
Exercise or pharmacological stress echocardiography may be necessary to demonstrate ischaemic changes in left ventricular systolic function in patients whose resting ECGs are abnormal or unable to be interpreted (because of left bundle branch block, paced rhythm). Exercise echocardiography provides information about cardiac structure and function, exercise workload, heart rate and rhythm and blood pressure response. Pharmacological testing may be necessary in patients who cannot exercise. Myocardial perfusion scintigraphy is an alternative for those with uninterpretable ECGs or inability to exercise.

Imaging of coronary arteries
Computed tomography (CT) of the coronary arteries without contrast injection can show coronary calcification, although correlation with the degree of luminal narrowing is poor. Intravenous injection of a contrast agent allows visualisation of the vessel lumen. The severity and extent of the lesions determine the risk of a cardiovascular event (Table 1). CT angiography exposes patients to radiation. It should be reserved for those who are not overweight, without excessive coronary calcium (Agatston score <400) and who are in sinus rhythm with resting heart rates of 65 beats/minute or less, with or without medication. If patients have a high risk of cardiovascular events or if their symptoms are not adequately controlled, invasive coronary angiography may be indicated. It helps define prognosis and options for revascularisation. The 12-year survival rate in medically treated patients is 74% for single-vessel disease, 59% for two-vessel disease and 50% for three-vessel coronary disease. Severe stenosis of the left main coronary artery or proximal left anterior descending artery has a poor prognosis if not revascularised. Conversely, the exclusion of significant obstructive disease on angiography is reassuring.

Lifestyle modification
The management of cardiovascular risk factors plays an important role in the overall care of patients with chronic stable angina (Fig.). Modifiable cardiovascular risk factors include hypertension, hypercholesterolaemia, smoking, diabetes, obesity and sedentary lifestyle. Regular exercise, a healthy diet and maintenance of ideal weight reduce the risk of adverse cardiovascular events. Smoking is a strong and independent risk factor for coronary artery disease so efforts to quit should be encouraged and supported. Control of blood pressure and diabetes is paramount to reducing cardiovascular morbidity and mortality. Patients should be screened for sleep apnoea. Annual influenza vaccination is recommended.

Prevention of cardiovascular events
Low-dose aspirin reduces major cardiac events by up to 30% and should be prescribed to patients with coronary artery disease. Clopidogrel is an alternative option for patients intolerant of aspirin. Patients with established coronary artery disease should be prescribed statin therapy irrespective of their lipid profile to slow the progression or even promote regression of coronary atherosclerosis. Angiotensin converting enzyme (ACE) inhibitors should be prescribed for patients with stable angina, particularly those who have hypertension, left ventricular dysfunction, diabetes or chronic kidney disease. Adverse effects include a persistent cough, hyperkalaemia and, rarely, angioedema. Angiotensin receptor antagonists may be used for those who do not tolerate ACE inhibitors.

Drug therapy
The aim of drug therapy is to minimise symptoms and prevent progression of coronary artery disease. Short-acting nitrates are prescribed to relieve acute symptoms or anticipated angina. Drug therapy aims to reduce myocardial oxygen demand or increase coronary blood supply. The choice of drugs is influenced by factors such as comorbidities, tolerance and adverse effects.

Beta blockers
Beta blockers are first-line therapy to reduce angina and improve exercise tolerance by limiting the heart rate response to exercise. Although they reduce the risk of cardiovascular death and myocardial infarction by 30% in post-infarct patients, their benefits in those with stable coronary artery disease are less certain.

<table>
<thead>
<tr>
<th>Table 1 Risk stratification by CT coronary angiography</th>
<th>12,16,18-20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of cardiovascular event</td>
<td>Angiographic findings</td>
</tr>
<tr>
<td>High</td>
<td>Disease of left main or left anterior descending coronary artery, three-vessel disease with proximal stenoses</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Significant lesion in large and proximal coronary artery, but no high-risk features</td>
</tr>
<tr>
<td>Low</td>
<td>Normal coronary artery or non-obstructive plaques</td>
</tr>
</tbody>
</table>
However, verapamil should be avoided in patients taking beta blockers owing to the risk of heart block, and in those with heart failure because of its negative inotropic effect. Diltiazem has a low adverse effect profile with a modest negative inotropic effect. Care should be taken when prescribing in combination with a beta blocker and in patients with left ventricular dysfunction.

The dihydropyridines such as amlodipine, felodipine and lercanidipine have greater vascular selectivity and minimal negative inotropic properties. They are therefore safer in patients with left ventricular dysfunction. Amlodipine is an effective once-daily antianginal drug that can be used in combination with a beta blocker. Long-acting nifedipine is a proven antianginal drug and is most effective when used in conjunction with a beta blocker.25

Contraindications to nifedipine use include severe aortic stenosis, obstructive cardiomyopathy and heart failure. Short-acting nifedipine is rarely used as monotherapy due to reflex tachycardia, which can worsen ischaemia and has been associated with a dose-related increase in mortality. It should therefore be avoided.

**Calcium channel antagonists**

Calcium channel antagonists improve symptoms of angina via coronary and peripheral vasodilation. They are indicated for those who cannot tolerate or have insufficient control of ischaemic symptoms on beta blockers alone.

Non-dihydropyridine drugs such as verapamil and diltiazem also reduce heart rate and contractility. Verapamil has comparable antianginal activity to metoprolol and can be useful for treatment of supraventricular arrhythmias and hypertension. However, verapamil should be avoided in patients taking beta blockers owing to the risk of heart block, and in those with heart failure because of its negative inotropic effect. Diltiazem has a low adverse effect profile with a modest negative inotropic effect. Care should be taken when prescribing in combination with a beta blocker and in patients with left ventricular dysfunction.

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### Table 2  Drugs for angina 2,3,5,23

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indications</th>
<th>Mechanism</th>
<th>Adverse effects</th>
<th>Precautions</th>
</tr>
</thead>
</table>
| Nitrates (short- and long-acting) | Relief of acute or anticipated pain (short-acting)  
Prevention of angina (long-acting) | Systemic and coronary vasodilation | Headache  
Hypotension  
Syncope  
Reflex tachycardia | Avoid sildenafil and similar drugs  
Tolerance with long-acting nitrates |
| Beta blockers | First-line therapy for exertional angina and after myocardial infarction | Reduce blood pressure, heart rate and contractility  
Prolongs diastolic filling time | Fatigue  
Altered glucose  
Bradycardia  
Heart block  
Impotence  
Bronchospasm  
Peripheral vasocostriction  
Hypotension  
Insomnia or nightmares | Avoid with verapamil because of risk of bradycardia  
Avoid in asthma, 2nd and 3rd degree heart block and acute heart failure |
| Dihydropyridine calcium channel antagonists (e.g. amlodipine, felodipine, nifedipine) | Alternative, or in addition, to a beta blocker  
Coronary spasm | Systemic and coronary vasodilator | Hypotension  
Peripheral oedema  
Headache  
Palpitations  
Flushing | Avoid short-acting nifedipine because of reflex tachycardia and increased mortality in ischaemia |
| Non-dihydropyridine calcium channel antagonists (e.g. verapamil, diltiazem) | Alternative, or in addition, to a beta blocker | Arteriolar vasodilator  
Centrally acting drugs reduce heart rate, blood pressure, contractility, and prolong diastole | Negative inotropic effect  
Bradycardia  
Heart block  
Constipation  
Hypotension  
Headache | Avoid verapamil in heart failure and in combination with a beta blocker |
| Nicorandil | Angina | Systemic and coronary vasodilator | Headache  
Dizziness  
Nausea  
Hypotension  
Gastrointestinal ulceration | Avoid sildenafil and similar drugs  
Metformin may reduce efficacy |
| Ivabradine | Angina  
Chronic heart failure | Reduces heart rate | Visual disturbances  
Headache  
Dizziness  
Bradycardia  
Atrial fibrillation  
Heart block | Caution with drugs that induce or inhibit cytochrome P450 3A4  
Avoid in renal or hepatic failure |
| Perhexiline | Refractory angina | Favours anaerobic metabolism in active myocytes | Headache  
Dizziness  
Nausea, vomiting  
Visual change  
Peripheral neuropathy | Narrow therapeutic range  
Need to monitor adverse effects and drug concentrations |
Nitrates

Sublingual glyceryl trinitrate tablets or nitroglycerin spray remain the treatment of choice for rapid relief of acute symptoms and anticipated angina. Sublingual glyceryl trinitrate tablets are absorbed in the sublingual mucosa and take effect within a couple of minutes. The tablet can be discarded with resolution of chest pain to minimise adverse effects such as headache. Glyceryl trinitrate spray is equally effective and, due to its longer shelf-life, is more convenient for those with infrequent symptoms of angina. Isosorbide dinitrate undergoes hepatic conversion to mononitrate, resulting in an onset of action of 3–4 minutes. It can provide an antianginal effect for up to one hour. Less commonly it is used as a chronic antianginal drug but requires multiple dosing, and tolerance limits its usefulness. It is often used up to three times per day with a nitrate-free period of up to 14 hours to minimise tolerance. Long-acting nitrates such as oral isosorbide mononitrate or transdermal patches are effective in relieving angina and can improve exercise tolerance. Chronic nitrate therapy is limited by the development of nitrate tolerance. A nitrate-free period of at least eight hours may reduce this problem. The mechanism of nitrate tolerance is not well established but involves attenuation of the vascular effect of the drug rather than altered pharmacokinetics. A nitrate-free period restores the vascular reactivity of the vessel. Transdermal patches are generally used for 12 consecutive hours with a 12-hour nitrate-free period. There is no evidence that nitrates improve survival. Common adverse effects include headache, hypotension and light-headedness. Nitrates should not be prescribed for patients taking phosphodiesterase-5 inhibitors such as sildenafil due to the risk of profound hypotension. Other contraindications include severe aortic stenosis and hypertrophic cardiomyopathy.

Nicorandil

Nicorandil is a potassium channel activator that improves coronary flow as a result of both arterial and venous dilation. It may be added in use to beta blockers and calcium channel antagonists to control angina in patients who are intolerant of nitrates. Nicorandil has been shown to reduce cardiovascular events by 14% in patients with chronic stable angina. Its use has been associated with headaches, hypotension, painful ulcers and genital and gastrointestinal fistulae.

Ivabradine

Ivabradine can be considered for patients intolerant of, or insufficiently responsive to, other drugs. It acts on If channels in the sinus node to lower the heart rate of patients in sinus rhythm without affecting blood pressure, conduction or myocardial contractility. Ivabradine has been shown to reduce a composite primary end point of cardiovascular death and hospitalisation with myocardial infarction or heart failure. However, a recent placebo-controlled trial involving 19 102 patients with stable coronary artery disease found that adding ivabradine to standard therapy did not improve a composite outcome of death from cardiovascular causes, or non-fatal myocardial infarction. Ivabradine has been used in combination with beta blockers.

Perhexiline

Perhexiline promotes anaerobic metabolism of glucose in active myocytes. Its use is limited by a narrow therapeutic window and high pharmacokinetic variability. Given its potential for toxic effects such as peripheral neuropathy and hepatic damage, it is usually reserved for patients whose angina is refractory to other therapies. It may be used safely with conscientious monitoring of clinical effects and regular measurement of plasma drug concentrations.

Conclusion

Stable angina is typically provoked by exertion and relieved by rest or nitrate therapy. Risk stratification should be done to define prognosis, guide management and select appropriate patients for revascularisation. The aims of medical therapy are to control symptoms, improve quality of life and prevent cardiovascular events. Beta blockers and calcium channel antagonists remain first-line options for treatment. Short-acting nitrates can be used for symptoms.

Conflict of interest: none declared

REFERENCES

Medical management of chronic stable angina


Book review

**Therapeutic Guidelines: Antibiotic. Version 15.**

Melbourne: Therapeutic Guidelines Limited; 2014. 636 pages
Also available online www.tg.org.au

Therapeutic Guidelines: Antibiotic is a concise and convenient guide and useful in both clinic and inpatient settings. The new version has many helpful features that make it a must-have.

The guidelines begin with brief chapters on appropriate prescribing, optimising therapy, and commonly prescribed classes of antibiotics. The book provides guidance on prophylaxis for surgical, medical, obstetric and immunocompromised patients. The presence of highlighted important information and comprehensive tables makes information easy to find and process. The footnotes are useful and include drug precautions, interactions and further reading.

Chapters are allocated by system, making it easy to locate pathology of interest and differential diagnoses. The guidelines give an up-to-date and useful outline of indications for antibiotic use, pathogens, investigations and non-antibiotic therapy. The occasional management flow diagrams also help to show key management steps. Special populations such as aged-care residents, immunocompromised patients and children are covered.

There are chapters on malaria, tuberculosis, typhoid, schistosomiasis and other less commonly seen conditions in Australia. Perhaps having a chapter dedicated to infections in the returned traveller would make this information easier to locate.

The final chapters on outpatient parenteral antimicrobial therapy, aminoglycoside use and monitoring, and antibiotic desensitisation protocols are probably more useful to infectious disease specialists than to GPs. The concise reference tables with the Therapeutic Goods Administration categorisation in pregnancy and compatibility with breastfeeding are handy. The section on renal impairment gives a guide on dosage adjustment based on the estimated glomerular filtration rate and doses for the different modes of dialysis.

In short the book is an up-to-date and easy-to-read guide that has transitioned many a junior medical officer to independent practice. It provides resources for generalist and specialist audiences and is well worth the read.

**Mehrulnisa Alam**
Associate lecturers
Department of General Practice
University of Sydney

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**And there’s more on the RADAR...**

In October this year there will be a special issue of RADAR devoted to a review of the evidence supporting changes to the National Cervical Screening Program.

**And remember...**

To help you stay abreast of the latest independent, evidence-based information about medicines, medical devices and current health topics, visit our Health News & Evidence page at www.nps.org.au/publications/health-professional/health-news-evidence. While there, subscribe to NPS Direct, a monthly email service providing links to our most recent articles.
New drugs

Dienogest

Approved indication: endometriosis
Visanne (Bayer)
2 mg tablets

Australian Medicines Handbook section 17.4

Endometriosis is a common condition, affecting up to 10% of women. It occurs when endometrial cells proliferate outside the uterus, for example on the ovaries or in the peritoneum. It is associated with symptoms such as chronic pelvic pain, and pain during menstruation and sexual intercourse.

Drug treatments for endometriosis aim to suppress ovarian function and include androgens (e.g. danazol), gonadotropin-releasing hormone agonists (e.g. goserelin) and progestogens.

Dienogest is a progestogen-only hormone preparation for the treatment of endometriosis. It works by suppressing oestradiol production and preventing the growth of the endometrium. Dienogest is already available in Australia in combination with an oestradiol in some oral contraceptive pills (Aust Prescr 2007;30:50-5, Aust Prescr 2015;38:6-11).

In an open-label, dose-finding trial of 68 women, daily dienogest 2 mg or 4 mg significantly reduced the severity of endometriosis, scored by laparoscopic examination at baseline and 24 weeks later. It also decreased rates of pain during sexual intercourse from 52% to around 6%. Rates of premenstrual pain, dysmenorrhoea and diffuse pelvic pain were also reduced. The trial concluded that dienogest 2 mg once a day was the lowest effective dose.1 (A 1 mg dose of dienogest was also included in the trial, but randomisation was stopped prematurely due to irregular bleeding in all four patients receiving this dose.)

In a 12-week placebo-controlled trial involving 198 women, daily dienogest 2 mg significantly reduced pelvic pain compared with placebo on a 100-mm visual analogue scale (by 27.4 mm vs 15.1 mm).2 The clinical significance of this difference was unclear. In a 52-week open-label extension of this study, 87 women continued dienogest and 81 who had taken placebo started the drug. Treatment continued for up to 52 weeks. The mean pain score declined from 27.89 mm to 9.72 mm in previously treated patients, and from 40.73 mm to 13.49 mm in those who switched from placebo. At the end of treatment the mean score for all patients was 11.52 mm.3 However, approximately a quarter of the women still used analgesia for their symptoms. A group of 34 women were followed up for 24 weeks after treatment finished. Their mean pain score increased slightly to 14.56 mm.3

Dienogest has been compared to the gonadotropin-releasing hormone agonist leuprolide (leuprolide) in an open-label non-inferiority study of 252 women. After 24 weeks of treatment, pelvic pain – assessed by a 100-mm visual analogue score – had reduced from 60.2 mm to 12.7 mm with daily dienogest 2 mg and from 57.9 mm to 11.9 mm with leuprolide (3.75 mg by depot intramuscular injection every four weeks). The trial concluded that dienogest was non-inferior to leuprolide.4 (A non-inferiority margin of 15 mm was pre-specified on a 100-mm visual analogue scale.)

Similarly dienogest was found to be as effective as buserelin (given intranasally), another gonadotropin-releasing hormone agonist. However, dienogest was associated with more vaginal bleeding than the comparator.5

In a safety cohort of 727 women, the most frequently reported adverse effects with dienogest were headache (9%), acne (5.1%), nausea (4.2%), weight gain (3.6%), breast tenderness (3.3%), depressed mood (3.0%) and flatulence (3.0%). As severe depression has been reported with dienogest,4 patients with a history of depression should be monitored closely.

Changes in menstrual bleeding patterns were common in the trials, but did not usually lead to discontinuation. After 9–12 months, bleeding was normal in 22.8% of women but had stopped (28.2%), become infrequent (24.2%), frequent (2.7%), irregular (21.5%) or prolonged (4%) in others.

Dienogest is contraindicated in undiagnosed vaginal bleeding and during pregnancy and lactation. Although ovulation is inhibited in most patients, dienogest is not a contraceptive and use of a non-hormonal method is recommended while taking dienogest. The menstrual cycle resumes within two months of stopping the drug.

Dienogest should not be given to patients with an active thromboembolic disorder or a history of cardiovascular disease. The risk of cardiovascular events is associated with older age, hypertension and smoking. Diabetes and severe hepatic disease, a history of liver tumours or sex-hormone dependent malignancies are contraindications to dienogest. If cholestatic jaundice or pruritis develops, dienogest should be stopped.
It was not clear from the trials if dienogest affects bone mineral density. If treatment is continued for longer than six months, consider monitoring bone mineral density.

After oral administration, dienogest is rapidly absorbed with peak serum concentrations being reached after approximately 1.5 hours. It is completely metabolised, mainly by cytochrome P450 (CYP) 3A4, and metabolites are rapidly excreted in the urine and faeces.

Inducers of CYP3A4, such as rifampicin or St John’s wort, may decrease plasma concentrations of dienogest, whereas CYP3A4 inhibitors, such as fluoxetine, ketoconazole or erythromycin, may increase dienogest concentrations.

Dienogest can be started on any day of the menstrual cycle. It should be taken every day without interruption. If a tablet is missed, the next one should be taken as soon as possible and dosing continued as normal the next day. As with the contraceptive pill, vomiting and diarrhoea can reduce the efficacy of dienogest.

Dienogest reduces the pain associated with endometriosis and is comparable to gonadotropin-releasing hormone agonists. However, some women may still need analgesia for their pelvic pain.

**REFERENCES**


**Febuxostat**

**Approved indication: hyperuricaemia**

**Adenuric (A Menarini)**

**80 mg tablets**

**Australian Medicines Handbook Appendix A**

Some patients with gout, such as those with tophi, require treatment to reduce their plasma urate concentration. Allopurinol achieves this by inhibiting xanthine oxidase, an enzyme involved in the production of uric acid.

Febuxostat is also an inhibitor of xanthine oxidase and, like allopurinol, it is taken once a day. It is well absorbed. Most of the dose is metabolised with approximately half the dose being eliminated in the urine. No dose adjustment is recommended if the creatinine clearance is at least 30 mL/min or in patients with mild or moderate liver impairment.

Inhibition of xanthine oxidase creates a risk of serious interactions with azathioprine and mercaptopurine. The Australian approval of febuxostat is based on two main trials (see Table).\(^1\)\(^2\) In the largest trial, 1072 patients with hyperuricaemia were randomised to

| Trial and duration | Number of randomised patients | Treatment | Proportion of patients with serum urate below 0.36 mmol/L at final visit
<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>APEX(^1) 28 weeks</td>
<td>134</td>
<td>placebo</td>
<td>1%</td>
</tr>
<tr>
<td></td>
<td>267</td>
<td>febuxostat 80 mg</td>
<td>72%</td>
</tr>
<tr>
<td></td>
<td>268</td>
<td>allopurin 300 mg(^4)</td>
<td>39%</td>
</tr>
<tr>
<td>FACT(^2) 52 weeks</td>
<td>257</td>
<td>febuxostat 80 mg</td>
<td>74%</td>
</tr>
<tr>
<td></td>
<td>254</td>
<td>allopurin 300 mg</td>
<td>36%</td>
</tr>
<tr>
<td>CONFIRMS(^3) 28 weeks</td>
<td>757</td>
<td>febuxostat 40 mg</td>
<td>45%</td>
</tr>
<tr>
<td></td>
<td>756</td>
<td>febuxostat 80 mg</td>
<td>67%</td>
</tr>
<tr>
<td></td>
<td>755</td>
<td>allopurin 300 mg(^4)</td>
<td>42%</td>
</tr>
</tbody>
</table>

\(^1\) Primary outcome in CONFIRMS, secondary outcome in APEX and FACT.

\(^4\) Lower doses of allopurinol were used in patients with renal impairment.
NEW DRUGS

The incidence of rash with febuxostat is not significantly different from the incidence with allopurinol. There have been rare reports of serious hypersensitivity reactions including anaphylaxis. In the pivotal trials there were more cardiovascular events with febuxostat than with allopurinol. An open-label extension of these studies, involving 1086 patients followed for up to 40 months, reported serious adverse cardiac events in 4% of patients taking febuxostat 80 mg and in 3% of the allopurinol group.

The product information states that febuxostat is not recommended in patients with ischaemic heart disease or congestive heart failure.

More common adverse effects of febuxostat include diarrhoea, nausea and headache. In general, these symptoms had a similar frequency in patients taking allopurinol.

In the extension study more than 80% of the patients taking febuxostat continued to have urate concentrations below 6 mg/dL (0.36 mmol/L). There was also a decrease in the number and size of tophi.

Although the efficacy of febuxostat 80 mg was significantly greater than the efficacy of allopurinol in the pivotal trials, the allopurinol dose was fixed. In practice the dose of allopurinol can be adjusted according to the response. The Australian Medicines Handbook also advises on how to prescribe allopurinol in renal impairment. While the trials included higher doses, the recommended starting dose for febuxostat in Australia is 40 mg, only increasing to 80 mg if the serum urate is greater than 0.36 mmol/L after 2–4 weeks.

Febuxostat is indicated for patients who have chronic gout who cannot be managed with allopurinol. For hyperuricaemia due to causes other than gout, the most likely role of febuxostat will be in patients with chronic disease or congestive heart failure.

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Febuxostat is indicated for patients who have chronic gout who cannot be managed with allopurinol.

REFERENCES


First published online 6 May 2015
**Ofatumumab**

**Approved indication: B cell chronic lymphocytic leukaemia**

**Arzerra (GlaxoSmithKline)**

100 mg/5 mL and 1000 mg/50 mL concentrate for infusion

**Australian Medicines Handbook section 14.2.1**

Chronic lymphocytic leukaemia is the most common adult leukaemia and is characterised by an accumulation of abnormal B lymphocytes. Ofatumumab adds to the growing number of treatments for this disease, including bendamustine (Aust Prescr 2014;37:214-21), chlorambucil, fludarabine (Aust Prescr 1995;18:86-7), rituximab (Aust Prescr 1999;22:20-3) and alemtuzumab (Aust Prescr 2006;29:167-71).

Ofatumumab is a human monoclonal antibody. Like rituximab, it binds to an epitope of CD20, which is expressed on B lymphocytes and B cell tumours. Binding to CD20 is thought to cause cell death mainly through complement-dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity. Ofatumumab is approved for two indications in chronic lymphocytic leukaemia:

- first line in combination with chlorambucil or bendamustine for people who cannot have fludarabine
- as monotherapy for refractory disease.

**First-line treatment when fludarabine cannot be given**

In an open-label trial, ofatumumab added to chlorambucil was compared with chlorambucil alone in 447 previously untreated patients in whom fludarabine was contraindicated (e.g. due to age or comorbidities). They received treatment for a maximum of twelve 28-day cycles or for a minimum of three months. Ofatumumab was given intravenously (300 mg on day 1 and 1000 mg on day 8 for the first cycle, followed by 1000 mg on day 1 of subsequent cycles) and chlorambucil was given orally (10 mg/m² on days 1-7 of each cycle). Progression-free survival was statistically longer with ofatumumab and chlorambucil compared to chlorambucil alone (22.4 months vs 13.1 months). The overall response rate was also higher with combination treatment than with chlorambucil alone (82% vs 69%). This trial is currently unpublished.

In a single-arm trial, the same dose of ofatumumab was combined with bendamustine (90 mg/m² intravenously on days 1–2 of each 28-day cycle) in 44 previously untreated people who could not have fludarabine. After a median of six cycles, almost all patients had responded with 43% of them having a complete response. This trial has also not yet been published.

**Refractory disease**

Ofatumumab monotherapy is also approved for patients whose disease is refractory to fludarabine and alemtuzumab. Survival of these patients is often less than a year. In an open-label dose-escalation study, 33 patients were given weekly intravenous infusions for four weeks. There were three different ofatumumab regimens – one 100 mg dose followed by three 500 mg doses (3 patients), one 300 mg dose followed by three 1000 mg doses (3 patients), or one 500 mg dose followed by three 2000 mg doses (27 patients).1 After 19 weeks, one patient in the lowest dose group and 13 patients in the highest dose group had a partial remission. Although two patients maintained their response until week 27, the others had progressive disease. Overall, the median progression-free survival was approximately 3.5 months.

By the end of treatment, malignant B cells in peripheral blood had decreased by a median of 97% (15–100%) in patients given the highest ofatumumab dose. Normal B cells were also depleted and this was sustained until week 24, after which cell numbers started to increase.1 In another trial, the efficacy of ofatumumab was assessed in a subset of 59 patients with disease refractory to fludarabine and alemtuzumab. Participants were given eight weekly infusions then monthly infusions for four months (first dose of 300 mg followed by 2000 mg doses). After 24 weeks, 58% of these patients had responded to treatment – all were partial responses. Median progression-free survival was 5.7 months (4.5–8 months) and median overall survival was 13.7 months.2

**Safety and precautions**

In 138 people who received monotherapy for refractory disease, almost two-thirds had an infusion-related reaction to ofatumumab. These were mostly mild to moderate and occurred during the first and second infusion. Other common adverse events included infection (67% of patients), cough (18%), diarrhoea (16%), anaemia (16%), fatigue (15%), fever (15%), neutropenia (15%), dyspnoea (13%), nausea (11%) and rash (10%). Overall, 37 of the infections were serious and 13 that started during treatment led to death. Six deaths were due to sepsis, five to pneumonia, one to Fusarium infection and one to progressive multifocal leukoencephalopathy.2 In 261 people who received ofatumumab with chlorambucil or bendamustine, neutropenia was...
the most common event (31%) and was serious in most cases. Nausea (25%), rash (25%), fever (22%), diarrhoea (17%), fatigue (16%), cough (15%), pruritus (13%), vomiting (12%), dyspnoea (11%), headache (10%) and urticaria (10%) were also frequently reported.

As with monotherapy, infusion-related reactions were very common during the first cycle of combination therapy and were the reason for stopping treatment in 3% of patients. Because of this risk, which can include serious effects such as respiratory and cardiac problems, premedication with an analgesic, an antihistamine and a corticosteroid is recommended, particularly at the beginning of therapy. The first and second infusions should be given more slowly, starting at 12 mL/hour. The rate can be increased later if reactions do not occur.

As cytopenias are common, blood counts (including platelets) should be monitored regularly. Because ofatumumab reduces the number of B lymphocytes, there is an increased risk of infection. Neurological symptoms such as confusion, dizziness, loss of balance, difficulty with walking or talking could be a sign of progressive multifocal leukoencephalopathy and should be investigated further. There is also a risk of hepatitis B reactivation, so people with evidence of previous infection should be monitored during and for 6–12 months after treatment. Live vaccines are not recommended.

Conclusion

Ofatumumab as monotherapy for refractory disease, or in combination with chlorambucil or bendamustine when fludarabine cannot be given, seems to prolong progression-free survival in people with chronic lymphocytic leukaemia. Premedication is recommended to reduce infusion-related reactions, particularly at the beginning of treatment. Prescribers should be aware that progressive multifocal leukoencephalopathy can occur with this drug.

**REFERENCES**


First published online 20 April 2015

The Transparency score (†) is explained in ‘New drugs: T-score for transparency’, Aust Prescr 2014;37:27.

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

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

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

**Safe disposal of prescribed medicines**  
*(Aust Prescr 2015;38:90-2)*  
The citation details (year and volume) for this article in the printed issue were incorrect.

**Concerns about quetiapine**  
*(Aust Prescr 2015;38:95-7)*  
A study of coronial data found that 20% (not a third) of deaths associated with quetiapine did not include a psychiatric diagnosis, raising concerns that off-label use or misuse contributed to the deaths. This was an author’s error which only appeared in the printed version.

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**EDITORIAL OFFICE**

For general correspondence such as Letters to the Editor, contact the Editor.

**Postal**  
The Editor  
**Australian Prescriber**  
PO Box 104  
DEAKIN WEST 2600

**Telephone**  
(02) 6202 3100

**Fax**  
(02) 6282 6855

**Email**  
info@australianprescriber.com

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**ANSWERS TO SELF-TEST QUESTIONS**

1 False  2 False  3 False  4 True  5 False  6 True