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Editorial

Time for transparency at the TGA

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Key words: drug information, drug regulation.

(Aust Prescr 2008;31:114–5)

Full transparency in pharmaceutical regulation is crucial. There are several reasons why we need access to drug regulatory information about prescription medicines.

First, access to clinical and pharmaceutical data allows health professionals, independent researchers and information providers to review the data to make sure that published findings do not misrepresent the efficacy and safety of medicines. The withdrawal of rofecoxib has shown the importance of scrutinising registration data in order to identify safety problems early. Another example is the recent review of antidepressant trials registered with the US Food and Drug Administration. It showed that antidepressant trials with negative results were much less likely to be published than trials with positive results.[1]

Second, regulatory decisions involve value judgements in balancing multiple data about the benefits and harms of medicines.[2] These value judgements should be disclosed with the reasons for regulatory decisions. This would help people to make their own choices about whether the medicines are suitable for them.

Third, as with many medicines agencies, the Therapeutic Goods Administration (TGA) is now totally financed from fees paid by pharmaceutical companies. Its decisions will be increasingly subject to public scrutiny because of the worry about conflicts of interest. Transparency in pharmaceutical policy making is required to maintain public trust in the TGA.

In this issue …

The Therapeutic Goods Administration (TGA) is a highly regarded organisation. Although it produces detailed evaluations of new drugs, it is prevented from releasing this information. The TGA is currently considering how it could share more of its knowledge. This is a welcome move and Agnes Vitry explains why transparency is important.

Aravind Ravi Kumar talks about transparency of a different kind in his review of positron emission tomography. Specialist imaging is not needed to diagnose attention deficit hyperactivity disorders, but Alasdair Vance says our understanding of the aetiology is increasing.

Three years ago, the Editorial Executive Committee of *Australian Prescriber* published a call for increased transparency in the regulation of prescription medicines.[3] What has happened since then? A recent study compared the provision of information on the websites of national drug regulatory agencies.[4] It found that the TGA ranked among the most 'secret' of the agencies. Assessment reports for new medicines, lists of refused or cancelled marketing authorisations, minutes of advisory meetings, and reports submitted by drug companies are not available publicly in Australia.

Although 'To be as transparent as possible in our processes and decisions' was a key priority announced in the TGA's 2006–2008 strategic plan, a 2006 report commissioned by the TGA made minimalist recommendations in this regard.[5] The main recommendation for increasing the level of transparency involved publishing a short summary of the advice of the Australian Drug Evaluation Committee (ADEC) on the approval of new drugs. The option of publishing full minutes of the ADEC meetings was not supported by the pharmaceutical industry. The option of providing edited evaluation reports on new drugs was also rejected as it was 'inappropriate' and 'would result in increased confusion and anxiety amongst consumers'. However, in 2008 the TGA is considering some regulatory reforms which will include increased transparency.[6]

As regards the provision of product information and consumer medicine information (CMI), the task has been entirely left to other groups with no assurance that this information is comprehensive or regularly updated. Putting the approved product information and CMI on the TGA website (the option that was most favoured by all stakeholders during an extensive public consultation) was initially rejected by the TGA because it was said to be the most expensive option and there was a perceived risk of litigation. However, the recent reforms propose publishing the information on the TGA website.

In the meantime, other international agencies have moved towards greater transparency. In 2004, a European directive required that national regulatory authorities make meeting records, assessment reports of marketing authorisations as well as the underlying reasons for decisions publicly accessible.[7] In the USA, which already has by far the most open regulatory agency, a new law (the Food and Drug Administration Amendments Act) requires that the results of all clinical trials, except phase I drug trials, be posted in a registry from September 2008.

This is not to say that the situation in other countries is optimal; a lot remains to be done. There are also valid exceptions to transparency such as manufacturing information that needs to be protected. However, the current Australian situation, in which the data used to make decisions and the reasons behind these decisions remain secret, is no longer tenable. Full transparency is required at all steps in the marketing of medicines, from publication of the trial protocols to assessment of the data by the TGA. It includes public disclosure of the potential conflicts of interest of all external experts involved in the TGA advisory committees. It concerns not only positive decisions, but also negative decisions, for example when a marketing application for a drug has been refused.

Transparency requires political will and leadership. This is an active process that needs to be adequately resourced. While drug companies spend millions of dollars on promotion of medicines each year, it seems paradoxical that limited funding and cost recovery could prevent the TGA from appropriately informing the Australian public. The TGA urgently needs to take steps to improve its transparency if it wants to retain its credibility not only with the Australian public and health professionals but also on the international scene.

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Conflict of interest: none declared

Letters

Letters, which may not necessarily be published in full, should be restricted to not more than 250 words. When relevant, comment on the letter is sought from the author. Due to production schedules, it is normally not possible to publish letters received in response to material appearing in a particular issue earlier than the second or third subsequent issue.

Varenicline and quitting

Editor, – While Mark Ragg (Aust Prescr 2008;31:60–2) is technically correct in saying that most people quit by themselves[1], he overlooks the more important point that the unaided quit rate is around 5–7%.[2] It is not surprising that quitting is so difficult. Nicotine addiction is a chronic relapsing condition with a relapse curve that resembles that for heroin addiction.[3] Popularity of strategy should not be confused with likelihood of success.

Most smokers find it very difficult to quit and are reluctant to seek help.[4] It is difficult to capture the true natural history of smoking cessation in a study.[1] Studies that have done so show that less than 2% of smokers quit per year.[5] On average, smokers make between five and eight attempts before they are successful despite expressing strong interest in quitting.[6]

In a survey, 92% of smokers used only one strategy to quit.[1] The majority of published evidence recommends the use of a combination of strategies that include some form of pharmacotherapy if nicotine dependent, referral to a proactive callback program like the Quitline, enlisting support, and addressing motivation and confidence.[7,8,9,10] This is reflected in a reduction in the numbers needed to treat as selected strategies are combined. For example, eight smokers need to be treated with varenicline and supportive counselling to get one long-term quitter. Smokers shouldn't have to 'go it alone'. Health professionals should help them to increase their chance of success.

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Therapeutic range for digoxin

Editor, – I read with great interest the target ranges for digoxin interactions in Table 1 of the article on therapeutic drug monitoring (Aust Prescr 2008;31:42–4). The issue of the therapeutic range for digoxin is perhaps a controversial one these days, but the author should certainly be given an opportunity to explain the 'range', particularly because of recent analyses of mortality data in trials of digoxin.

Perhaps a suitable correction as well as clarification would be in order?

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Dr Ghiculescu, author of the article, comments:

The Digitalis Investigation Group found that digoxin reduced hospitalisations, but did not reduce overall mortality in heart failure when the target for the therapeutic range was 0.5–2 nanogram/mL.[1] *Post hoc* analysis of this trial found that mortality and hospitalisations were reduced if the serum digoxin was 0.5–0.9 nanogram/mL. Concentrations greater than 1 nanogram/mL were associated with higher mortality.[2] A concentration less than 1 nanogram/mL equates to less than 1 microgram/L. The currently recommended therapeutic range is therefore 0.5–0.9 nanogram/mL.

It has been suggested that an even lower concentration, less than 1 nanogram/dL, be used in patients with symptomatic systolic left ventricular failure.[3] That equates to 10 nanogram/L which is 0.01 microgram/L. This is significantly lower than the range used in the digoxin trial. However, this low concentration cannot easily be measured.

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Bronchiectasis

Editor, – May I congratulate Amy McLean on her article regarding bronchiectasis (Aust Prescr 2008;31:77–9). She gave a concise and practical approach to strategies often employed in treatment. May I also support the Editor in publishing this article, considering many of the drugs listed and regimens suggested were 'off label' and certainly not supported as subsidised medicines for these indications on the Pharmaceutical Benefits Schedule.

Unfortunately, many such prescriptions are unavailable to doctors who practise outside of major metropolitan teaching hospitals, although the novel approaches with nebulised aminoglycosides and longer term use of macrolides are certainly used by us, the 'respiratory colleagues'. There was also no mention made of colistin, which from experience is expensive to source, and intravenous gammaglobulin used monthly that has proven effective, particularly in those with subclass immunoglobulin deficiency.

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Bipolar disorders

Editor, – There are significant problems with the use of literature to support the statements in the article by Dr Singh and Professor Berk on acute management of bipolar disorders (Aust Prescr 2008;31:73–6). The authors have generalised from bipolar I disorder to bipolar II disorder and from severely ill tertiary-treated bipolar I patients to the broader population of patients with bipolar disorder. They have also misrepresented the risk of suicide and the relationship between medication status and relapse risk.

According to the article, 'sufferers spend 32–50% of follow-up in depressive states and only 1–9% in elevated states'. However, the source cited focused on bipolar I disorder and cautioned that 'Generalization to other samples of BP-I may be limited because the CDS cohort consisted of severely ill, tertiary care, white patients'.[1] Inappropriately generalising biased samples contributes to the clinician's illusion[2], which distorts perceptions of chronicity and severity.

The article claimed that over 90% of patients with bipolar disorders relapse without medications. However, in the source cited the relapse rate applied specifically to bipolar I disorder.[3] The implication that relapse occurs only **without** medication ignores a large body of evidence that it frequently occurs **with** medication.[4,5,6,7] The use of psychotropic drugs between episodes is not associated with time to relapse or recurrence.[8]

The statement that 15% of people with bipolar disorders die by suicide is based on pharmaceutical industry funded grey literature.[9] Australian empirical evidence was lacking in this citation and relied on an article by Goodwin and Jamison.[10] Later, Jamison acknowledged that the quoted risk of 15% may have been too high.[11] The inflated risk was based largely on inpatient samples, inappropriately generalised to the broader population.

The article largely ignored the value of psychological interventions. There is strong evidence that these are effective in the prevention of relapse. Despite emphasising the destabilisation potential of antidepressants, the authors do not mention the potential adverse effects of antipsychotics and other drugs for bipolar episodes. These include obesity, diabetes, metabolic syndrome and dyslipidaemia.[12]

These problems with the article exaggerate both the severity of bipolar disorders and the value of medications, while devaluing psychological treatments.

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Dr Ajeet Singh and Professor Michael Berk, authors of the article, comment:

Several issues are raised by the reader's correspondence. It needs to be stressed that the paper is based on the available, if imperfect, evidence base. Firstly, the validity of suicide risk estimates in bipolar disorders has been raised. A meta-analysis of studies on suicide risk in all psychiatric disorders found that the risk of suicide was about 15-fold for patients with index diagnosis bipolar disorder.[1] In a 1–9 year follow-up study, 6% of bipolar I and 18% of bipolar II patients died by suicide.[2] Based on six independent studies, the rate of suicide attempts is reported as 17% for bipolar I disorder and 24% for bipolar II disorder.[3] Despite varying rates in the literature, the risk of suicide and self-harm in bipolar disorders is the major driver of mortality in the disorder, and needs to be one of the critical foci of treatment.

Secondly, while psychoeducation and cognitive behavioural therapy have an important place in relapse prevention in the maintenance phase, they have not been studied in the acute treatment of either mania or depression, and while we agree that they are of potential value, the absence of an evidence base precludes their inclusion in an evidence-based summary. Clinical trials of psychosocial treatments in the acute phase of the disorder, particularly in depression, are clearly a priority, given the limitations of available treatments.[4,5] While healthy skepticism has an important role in evidence-based medicine, it is still necessary to be guided by the available data.

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Compounding in community pharmacy

Editor, –The editorial 'Compounding in community pharmacy' (Aust Prescr 2008;31:30–1) outlines concerns that regulators have with the activities of some 'compounding' pharmacists. Regulators are concerned with high-volume (bulk) compounding and the promotion of formulations that are not subject to the same regulations as are applied to the pharmaceutical industry. They do not appear to be concerned with single-unit extemporaneous dispensing of low-risk products.

While we agree that compounding practice standards are in need of review, we believe a risk-management approach should be followed. Uniform adoption of standards that may, for example, demand end-product testing would not seem practical, or necessary, for low-risk extemporaneously prepared products such as creams or lotions.

The prescribing of many compounded medicines is regarded as 'off label'. Consequently, prescribers and dispensers should be guided by contemporary standards for evaluating off-label prescribing.[1] We believe the guidance for off-label prescribing should be extended for compounded medicines to include the risk-based evaluation and classification of the factors outlined in Table 1.

We suggest a code of practice in compounding which would include:

- establishing, assuring and maintaining quality through appropriate processes and documentation
- a risk-management approach (Table 1) to the evaluation of compounded medicines
- ensuring that prescribers and consumers have current, evidence-based information to support the quality use of compounded medicines
- complying with therapeutic goods advertising codes and legislation.

These risk-management approaches would support the role of pharmacists in compounding medicines to contemporary standards of quality, safety and efficacy within the spirit of Australia's National Medicines Policy.

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Table 1

A risk-based evaluation of compounded medicines

Factors	Risk criteria
Patient population	Is the medicine to be used in a high-risk population (e.g. children, the frail elderly)?
Site of action	Is the medicine intended to have a local or systemic effect?
Indication	Does the indication require acute or chronic therapy?
Route of administration	Is the medicine intended for topical, enteral or parenteral administration?
Pharmacodynamics	Is there a wide or narrow safety margin (therapeutic index)? Is the dose-response relationship steep or shallow?
Biopharmaceutics	Do formulation factors affect the bioavailability or stability of the medicine? Is the bioavailability highly variable? Is the complexity of the formulation appropriate for a compounded medicine and is dose-uniformity guaranteed (e.g. in sustained release, transdermal or inhaled formulations)? Is quality-assurance testing required and can it be performed?
Regulatory	Are the active and inactive ingredients approved for use in Australia? Have any of the ingredients been withdrawn or rejected from registration because of safety concerns?

How to treat hypercholesterolaemia

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Summary

An elevated low density lipoprotein cholesterol is a major cause of atherosclerosis. Reducing the concentration of this lipoprotein stabilises atherosclerotic plaques, and may lead to regression of the atherosclerosis. A moderate reduction of the plasma concentration of this lipoprotein significantly decreases recurrent coronary events. Therapy is a combination of lifestyle modification, nutraceuticals and drug treatment. The most convenient and effective drugs are the HMGCoA reductase inhibitors or 'statins'. They control hyperlipidaemia and help to prevent myocardial infarction, unstable angina, sudden death and stroke.

Key words: antilipidaemic drugs, cholesterol, coronary disease, diet, dietary supplements.

(Aust Prescr 2008;31:119–22)

Introduction

Hypercholesterolaemia is a major risk factor along with smoking, hypertension and diabetes for developing atherosclerosis. Coronary heart disease is almost entirely due to atherosclerosis in the coronary arteries. Atherosclerosis in the carotid arteries also plays a major role in stroke. Rupture of an atheromatous plaque in the coronary arteries is the pathological event underlying the acute coronary syndromes of sudden death, acute myocardial infarction and unstable angina. Plaques that rupture are generally rich in cholesterol and the risk of coronary events is proportional to the serum cholesterol concentration, specifically low density lipoprotein cholesterol.

Lipoproteins

The serum lipids are cholesterol and triglycerides. They are transported in the blood as large molecules known as lipoproteins. In addition to protein (apoproteins), cholesterol, cholesteryl esters and triglycerides, the lipoproteins also carry antioxidants such as vitamin E, dietary polyphenols and co-enzyme Q10. There are five major classes of lipoprotein (Table 1). Intermediate density lipoprotein and low density lipoprotein (LDL) are the most atherogenic, while high density lipoprotein (HDL) is anti-atherogenic.

When triglycerides are elevated, this is usually associated with an elevation of very low density lipoprotein cholesterol (VLDL cholesterol). This lipoprotein has a triglyceride:cholesterol ratio of 2:1. When fasting triglyceride levels are greater than 1.5 mmol/L, the risk of coronary heart disease and stroke increases significantly. Fasting triglyceride levels greater than 1.9 mmol/L, compared to less than 1.5 mmol/L, increase the risk of coronary heart disease and stroke by more than 30%.

When there is an elevated serum cholesterol it is almost always due to an elevation of the LDL cholesterol. Occasionally an elevated cholesterol is due to a high concentration of HDL cholesterol, but these patients are not at increased risk of cardiovascular disease. As LDL cholesterol accounts for 60–70% of the total cholesterol and is atherogenic, it is the target of treatment in patients with hypercholesterolaemia.

Target concentrations

Patients must be assessed for other risk factors, the presence of cardiovascular disease and other causes of raised cholesterol to determine their absolute risk of a coronary event.[1] An appropriate target can then be set for their LDL cholesterol concentration.

A meta-analysis of randomised trials of statins showed that for each 1 mmol/L reduction of LDL cholesterol (which generally equates to a 20% reduction of LDL cholesterol) there is a 20–30% relative risk reduction of coronary heart disease events.[2] Lowering the LDL a further 30% or so, or an extra 1 mmol/L, reduces coronary heart disease events by a further 20–30%.

The target for an asymptomatic individual who has a low risk of developing coronary heart disease is an LDL cholesterol of

Table 1

Lipoproteins

Chylomicrons	Triglyceride rich	Atherogenic
Very low density lipoprotein		
Intermediate density lipoprotein		
Low density lipoprotein	Cholesterol rich	
High density lipoprotein		Anti-atherogenic

Intermediate and low density lipoprotein contain the highest proportion of cholesterol while chylomicrons contain little cholesterol.

less than 4 mmol/L with triglycerides less than 2 mmol/L, HDL greater than 1 mmol/L and a total cholesterol less than 5.5 mmol/L. For a patient who has already developed coronary heart disease there is the lower target of an LDL cholesterol less than 2.5 mmol/L. Patients with established coronary heart disease and a very high risk of a future cardiovascular event should have a target of less than 2 mmol/L. These targets broadly reflect recommendations by the Australian National Heart Foundation[3] and the American Heart Association guidelines.[4] Reducing LDL cholesterol to below appropriate targets is more important than the method or specific drug used to achieve the reduction.[5]

Diet

Lifestyle factors, particularly a diet rich in saturated fats and low in fibre, play a significant role in the elevation of LDL cholesterol. A key element of the first dietary guidelines to prevent coronary heart disease was to lower foods rich in saturated fat. Subsequent international guidelines have continued to focus on lowering foods rich in saturated fat. Replacing saturated fat with either carbohydrate or foods rich in mono- or polyunsaturated fats and high fibre foods is effective in lowering LDL cholesterol. All of these independently lower LDL cholesterol. Avoid baked foods containing trans fatty acids, such as pies, pastries, cakes and biscuits. An individual patient's response to diet can vary considerably and is usually seen in 4–6 weeks. Some patients are very responsive and can have up to 30% lowering of LDL cholesterol.

Traditional cuisines which are associated with low LDL cholesterol and low rates of heart disease are Mediterranean-type diets, as found in Greece, Italy and Spain, and cuisine low in total fat such as in Japan. It is also clear that a high intake of fish, particularly fish rich in marine omega-3 fatty acids, is associated with a low risk of heart attack and stroke.

After a myocardial infarction, a Mediterranean-type diet compared to a usual low fat diet is associated with a 50% relative reduction in mortality. This is independent of any change in serum cholesterol (see box).[6]

Weight loss

Weight loss can favourably influence lipids irrespective of how it is achieved. For every kilogram decrease in body weight, LDL cholesterol decreases by 0.02 mmol/L, triglycerides decrease by 0.015 mmol/L and HDL cholesterol increases by 0.14 mmol/L.[7] Unfortunately, significant weight loss is difficult to achieve and maintain, but losing 5–10 kg is achievable and can make a difference to the risk profile.

Exercise

Most exercise studies have indicated that regular aerobic exercise improves the lipid profile independent of diet and drugs. Regular exercise decreases LDL cholesterol by 10% and increases HDL cholesterol by 5%.[8] There is a dose response between the amount of exercise and lipoprotein changes. Moderate aerobic exercise is defined usually as moderate effort of half an hour of intentional exercise most days of the week.

Nutraceuticals

The nutraceuticals that can help to lower LDL cholesterol are plant sterols/stanols and soluble fibre. In Australia, the foods which can be enriched with plant sterols are margarine, milk and yoghurt. A dose of 2–4 g of plant sterols is needed, which equates to at least four teaspoons of plant-enriched margarine per day. A 200 g tub of enriched yoghurt only provides the equivalent of one teaspoon so is not that helpful for achieving targets.

On average plant sterols reduce LDL cholesterol by 10%, but this may vary from 0 to 30%. They have an additive effect to drug therapy.

A tablespoon or two of soluble fibre, such as psyllium, lowers LDL cholesterol by approximately 5%. Garlic and policosanol have been found to have negligible effects in most recent studies. Omega-3 fatty acids from fish oil are effective in lowering triglycerides, but have no effect in lowering LDL cholesterol at usual therapeutic doses. Very high doses of fish oil may in fact increase LDL cholesterol.

Drug therapy

If diet and nutraceuticals do not adequately reduce the LDL cholesterol and the patient remains at high risk of a cardiovascular event, drug therapy is indicated. HMGCoA reductase inhibitors, 'statins', are the first drugs to use. They are extremely efficacious and more than 90% of patients can tolerate them with negligible or no adverse effects. All statins have non-lipid lowering properties such as antiplatelet effects. However, most, if not all, the cardiovascular benefit can be accounted for by the improved lipoprotein profile, mainly by lowering LDL cholesterol.

Mediterranean diet after myocardial infarction [6]

The healthy Mediterranean-type diet initially referred to the food traditionally eaten by the people of Naples. It was vegetarian-like, high in nuts and olive oil, vegetables and pasta which was cooked *al dente*. Fruit was eaten frequently along with some cheese, wine and nuts. The Mediterranean diet later extended to include the traditional diets of Crete and Spain.

The Lyon Diet Heart Study involved just over 600 individuals who had survived a myocardial infarction. After 3.5 years the trial was stopped early as there was a clear benefit for patients on the Mediterranean-type diet compared to a low fat diet. The benefit was independent of drug therapy and serum cholesterol.

Efficacy of statins

Statins differ in efficacy, with the earlier statins lowering LDL to a similar extent to bile resins such as cholestyramine and nicotinic acid. The newer statins, atorvastatin and rosuvastatin, are considerably more efficacious in lowering LDL cholesterol, but there is little evidence as yet that this further improves long-term clinical outcomes. High dose simvastatin and controlled-release fluvastatin are of intermediate efficacy. The highest doses of the most efficacious statins can achieve a 2 mmol/L reduction (which is up to a 60% lowering of LDL from baseline). A number of recent trials have compared moderate to vigorous LDL lowering, and there is the expected predictable greater benefit of cardiovascular disease prevention.

Most of the effect of the statins occurs at less than the maximum dose. If the patient's target cholesterol is not reached, adding another drug may therefore have more effect than increasing the statin dose.

Adverse effects of statins

If adverse effects occur, more than 90% appear within the first three months. Adverse effects tend to be dose related and are similar between statins. If a patient has adverse effects from one statin, the dose can be lowered, given in divided doses or every second day. Alternatively, the patient can be switched to another statin or a controlled-release formulation.

The common adverse effects are musculoskeletal aches. Occasionally there is an associated increase in creatine kinase and rarely (less than 1/1000) a true myositis can occur. There is increased risk of myositis in those with renal failure, diabetes and in the elderly. If the creatine kinase is greater than 300 IU/mL, consider stopping the statin and repeat the test one week later.

A rise in the liver transaminases can occur so liver function tests are recommended before and during treatment. True hepatitis is extremely rare. Measure liver function every six months and if the transaminases are greater than twice the upper limit, stop the statin and repeat the liver function test in 3–4 weeks. Depending on the results, restart at the same dose, for example, if the patient's transaminase levels were only just above the cut-off point and then normalised after stopping the statin. Otherwise, restart the patient on half the dose and retest their liver function in 3–4 weeks. Many patients have a mild transient elevation of liver enzymes which is of no consequence. Persistent elevation of liver enzymes that are in the moderate range (up to 2–3 times above the upper limit of normal) may relate to the presence of fatty liver disease rather than drug therapy.

Long-term follow-up of patients in trials has not shown an increase in the risk of cancer from long-term exposure to statins.

Other drugs

In approximately 75% of the patients who cannot tolerate even half the usual dose of statins, ezetimibe can be effective.

Ezetimibe inhibits the absorption of dietary cholesterol. The dose of ezetimibe is 10 mg per day and there is no value in going higher. Ezetimibe lowers LDL by approximately 15%. Some individuals develop aches and pains on the usual dose of ezetimibe (10 mg/day). Reducing the dose to 10 mg once per week still produces some lowering of LDL cholesterol but without the adverse effects. Ezetimibe can further reduce LDL cholesterol in patients on maximum doses of statins. Adding ezetimibe 10 mg per day can often lead to a synergistic lowering of LDL cholesterol by an extra 20–25%. Patients who are very sensitive to statin adverse effects can be stabilised on ezetimibe, then given a mini dose of a statin, such as rosuvastatin 2.5 mg every second or third day, with significant benefit. However, there is no current evidence that ezetimibe reduces the risk of heart attack or stroke, either alone or in combination with statins.

After statins and ezetimibe, other drugs to consider are bile resins (for example cholestyramine), fenofibrate and nicotinic acid (niacin, vitamin B_3). More than 50% of patients cannot tolerate more than 4 g of cholestyramine per day, and it is best mixed with juice. One sachet per day is expected to lower the LDL cholesterol by around 10% and it has an additive effect with statin therapy. Fenofibrate 145 g per day lowers LDL cholesterol by around 10%, but its major role is to lower triglycerides. Nicotinic acid at a dose of 3 g per day lowers LDL cholesterol by about 20%, but more than 75% of patients cannot tolerate even half this dose due to severe flushing. Gemfibrozil has no effect on lowering LDL cholesterol.

Treatment of hypertriglyceridaemia

First-line treatment for elevated triglycerides (VLDL cholesterol) consists of a diet rich in mono- and polyunsaturated fat and low glycaemic index carbohydrate food, caloric restriction (leading to weight reduction) and exercise. The next step is consideration of marine omega-3 fatty acids (fish oil) and fibrates.

Conclusion

Elevated LDL cholesterol is a major risk factor for coronary heart disease and is the major target of therapy to prevent coronary events. In patients with clinical coronary heart disease, lowering the LDL cholesterol to less than 2.5 mmol/L lowers the relative risk of developing coronary events by approximately 25%, and lowering it to below 2 mmol/L reduces the relative risk by 50%. Therapy involves diet, regular exercise, nutraceuticals and drug treatment along with attention to other risk factors. Statins are the first choice of drug therapy.

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Associate Professor Colquhoun has received honoraria for talks for Merck Sharp & Dohme, Pfizer, AstraZeneca, Solvay and Bristol-Myers Squibb.

Self-test questions

The following statements are either true or false (answers on page 139)

1. Most of the effect of a statin on low density lipoprotein cholesterol occurs below the maximum recommended dose.
2. Fish oil can significantly reduce concentrations of low density lipoprotein cholesterol.

New blue card

The Therapeutic Goods Administration has introduced a new blue card for reporting adverse drug reactions. It can be downloaded from www.tga.gov.au/adr/bluecard.htm

For hard copies of the blue card contact the Adverse Drug Reactions Unit by email (adrac@tga.gov.au) or phone (1800 044 114).

A blue card will be enclosed with the December issue of *Australian Prescriber.*

You can also report an adverse reaction:

- online at www.tga.gov.au/adr/bluecard.htm (click on 'Report electronically')
- by email adrac@tga.gov.au
- by fax 02 6232 8392
- by phone 1800 044 114

Remember, you don't have to be certain, just suspicious!

Diagnostic tests

Current clinical applications of positron emission tomography

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Summary

Positron emission tomography (PET) allows diagnostic imaging of metabolic function using radioisotopes. This technology has undergone significant growth and evolution in recent years with most PET scanners now integrated with CT scanners. The main radiotracer in clinical use is F-18 fluorodeoxyglucose. This was initially used as a research tool and in cardiac and neurological applications, but now has an integral role in oncology. Fluorodeoxyglucose PET has had a major impact on the management of a broad range of malignancies because it is more sensitive than conventional imaging modalities. It is now used for diagnosis, staging and assessing response to therapy in many cancers and in characterising solitary pulmonary nodules. It is important to remember that not all abnormalities on a fluorodeoxyglucose PET scan are due to malignancy, and unexpected findings may need to be evaluated further.

Key words: fluorodeoxyglucose, nuclear medicine, oncology.

(Aust Prescr 2008;31:123–8)

Introduction

Positron emission tomography (PET) scanning allows non-invasive diagnostic imaging of metabolic processes using short-lived radioisotopes. In contrast to computerised tomography (CT) and magnetic resonance imaging (MRI), which provide information on structure, PET can quantify biochemical and physiological function.

PET has been available as a clinical tool in Australia for well over a decade. While initial clinical applications were largely in cardiology and neurology, these have been dwarfed by oncology indications, which now account for over 90% of PET scans worldwide. Facilities have been installed in every mainland state capital city and in Newcastle, New South Wales. At present, only specialists and consultant physicians may refer patients for a PET scan.

A significant recent advance has been hardware integration of CT scanners with PET scanners (PET CT), allowing one to obtain a synergistic combination of anatomical (CT) and functional information (PET) at the same time. Problems of patient and organ motion are also significantly reduced with this approach. Almost all sales of new PET scanners worldwide are now PET CT.

What is a PET scan?

Radiotracers manufactured from positron emitting isotopes can be used to image a variety of biological processes in the body using a PET scanner. A positron is a positively charged electron which is emitted from the nucleus of some low molecular weight radioactive isotopes. These include carbon (C-11), nitrogen (N-13) and oxygen (O-18), which are the 'building blocks' of the body, and fluorine (F-18). These isotopes have very short half-lives (ranging from two minutes for O-18 to 110 minutes for F-18), and have to be manufactured nearby in a medical cyclotron. These isotopes can then be chemically incorporated into trace quantities of biologically relevant molecules. The radiotracers have no pharmacological actions.

A PET scanner does not directly image positrons. Once a positron is emitted from the nucleus, it travels a short distance (several millimetres in soft tissue), and then annihilates with a negatively charged electron. The mass of the two particles is converted to energy in the form of two gamma rays that propagate at 180° to each other. Coincident gamma ray pairs that travel out of the body are detected by a ring of detectors around the patient. Many millions of such 'events' are used to determine the distribution of radiotracers within the body.

PET resolution

In practice, the resolution of a modern PET scanner is 8–10 mm. A negative PET scan in lesions smaller than this cannot reliably exclude serious pathology. Lesions below this size however may still be detected on PET if they are very metabolically active.

F-18 fluorodeoxyglucose (FDG) PET

The most commonly used radiotracer in clinical practice is F-18 fluorodeoxyglucose (FDG), a glucose analogue. Increased glucose metabolism is a characteristic feature of many malignant tissues. FDG-PET scans have been shown to be more accurate than conventional imaging in the evaluation of many (but not all) malignancies.

How does FDG work?

FDG is transported inside cells by the glucose transporter GLUT 1. The FDG molecule is then phosphorylated to FDG-6-phosphate by hexokinase. Further downstream glycolysis is not possible so the tracer is trapped in the cell in virtually all tissues.

No significant adverse reactions have yet been recorded from the intravenous injection of FDG in patients worldwide.

Normal FDG biodistribution

The brain is an obligate glucose user, and there is marked FDG uptake in normal cortex and deep nuclei. Cardiac FDG uptake is very variable as cardiac muscle switches between glucose and fatty acid metabolism depending on the fasting state. The liver demonstrates diffuse moderate levels of FDG uptake. Unlike glucose, there is significant FDG excretion by the kidneys into the bladder (Fig. 1).

What is the standardised FDG uptake value?

A semi-quantitative measure of FDG uptake, the standardised uptake value (SUV), is quoted widely in the literature and is used by some centres in clinical reporting. Higher SUVs are more likely to be associated with malignancy and may be a marker of adverse prognosis. However, there is no 'cutoff' SUV that can distinguish between benign or malignant aetiologies. There may also be variability in SUV measurements and methodology between centres, so using SUV for comparing studies performed at different sites may be problematic.

Patient preparation

A 4–6 hour fast is recommended for a standard FDG-PET oncology study to reduce cardiac and skeletal muscle FDG uptake. Extra preparation for diabetic patients includes avoiding insulin injections for at least four hours before the scan as insulin drives FDG into skeletal muscle. A blood sugar level of over 12 mmol/L can competitively inhibit tumour FDG uptake. In this instance the scan may be rescheduled.

Scan procedure

Following standard preparation, the radiotracer is injected intravenously as a bolus (< 1 mL) and allowed to distribute in the body while the patient is lying comfortably in a quiet room for around 60 minutes. It is important that the patient is relaxed and still during the 'uptake phase' because actions such as talking, chewing gum and jaw clenching all cause FDG uptake in the relevant muscles and may sometimes obscure pathology.

Claustrophobia is rarely a contraindication (unlike MRI), but oral benzodiazepines may be used as an anxiolytic and to reduce FDG uptake in neck muscle during the uptake phase.

The use of oral and intravenous CT contrast agents is controversial as these may cause image artefacts on the PET scan. The PET scan itself takes around 20 minutes and typically ranges from skull base to thighs.

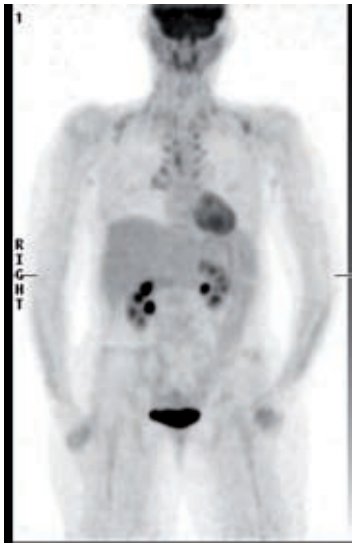
Radiation dose

The radiation dose to the patient from a PET scan is around 8 milliSieverts (mSv). The CT component of the procedure varies, but most centres in Australia use a 'low-dose' non-contrast protocol which adds around 4 mSv. The total dose of 12 mSv is equivalent to around five years of normal background radiation, and is similar to a diagnostic CT scan of the same body region.

Although FDG is not excreted in breast milk, it is prudent to advise suspension of breastfeeding for six hours. No other special precautions need to be taken for the patient's relatives or carers due to the rapid decay of PET radiotracers.

Fig. 1

Brown fat uptake on an otherwise normal FDG-PET scan



Maximum intensity projection of the typical pattern of thermogenic brown fat uptake, an easily recognisable normal variant on FDG-PET scans. This typically occurs symmetrically in the neck, supraclavicular fossae and paravertebral regions. It is more common in colder climates, in young women, children and people with low body weight. Brown fat uptake can be reduced pharmacologically (for example beta blockers) or by warming the patient before tracer injection. There is otherwise normal FDG distribution – note the renal excretion, high uptake in the BRain, variable cardiac uptake (high in this case), and diffuse mild uptake in the liver and salivary glands.

FDG-PET F-18 fluorodeoxyglucose positron emission tomography

FDG-PET in clinical practice

Medicare Australia-approved indications for FDG-PET are summarised in Table 1. It is important to emphasise that FDG-PET is not a 'cancer scan'. It shows areas of abnormal glucose metabolism. Non-malignant causes of FDG uptake are relatively common and should always be considered in the differential diagnosis (Fig. 1). Clinically implausible or unexpected abnormalities may require further confirmatory investigation. There are innumerable causes of FDG uptake that are not due to malignancy. Many of these can be recognised on correlation with patient history/physical examination or typical imaging patterns. Common causes are infection (including tuberculosis – see Fig. 2), inflammation (sarcoidosis and granulomatous diseases), trauma, enthesopathies and fractures.

FDG-PET (and PET CT) has been shown to be more accurate than conventional imaging in a variety of malignancies in many clinical settings (for example staging, restaging, detection of occult primary site, rising tumour markers, assessment of residual mass, detecting radionecrosis from viable tumour). It is also cost-effective as PET often leads to upstaging of disease, thus reducing futile attempts at curative therapies, and helping allocation of finite resources to patients most likely to actually benefit from aggressive intervention.

Malignancies that typically have very high levels of FDG uptake include squamous cell carcinomas of the head and neck, oesophagus, most lung cancers, melanoma, most types of lymphoma, high-grade sarcoma and metastatic colon carcinoma. Gastric, uterine, cervical, breast, testicular and thyroid malignancies may also be usefully evaluated, but not all are reimbursed by Medicare (see Table 1).

Primary liver tumours generally have low FDG uptake (due to intracellular dephosphorylation of FDG) and may not be distinguishable from normal background liver, but liver metastases are sensitive to imaging. Other malignancies where FDG-PET is not useful (high false negative rate) include bronchoalveolar cell carcinoma of the lung, carcinoid tumours, mucinous adenocarcinomas and some low-grade sarcomas.

Malignancies of the urinary tract (such as renal cell, transitional cell and prostate carcinomas) are not well imaged due to variable FDG uptake in the tumours and high background levels of FDG in urine.

FDG-PET is not sensitive in detecting cerebral metastases because there is a high background uptake and the brain is not routinely included in the imaging field. However, FDG-PET may be indicated in the evaluation of primary brain tumours.

Bony metastases that cause densely sclerotic reaction (typically prostate cancer) are best imaged with bone scans as these lesions may be poorly FDG-avid. FDG-PET is much more sensitive for lytic, soft tissue or marrow lesions.

Staging of non-small cell lung cancer

Historically, the five-year survival rate after surgery of even clinical stage I lung cancer is only 50%, with much of the mortality being accounted for by undetected metastatic disease.

FDG-PET has an important role in staging and treatment planning in non-small cell lung cancer. Studies have shown that a staging PET scan predicts patient prognosis and mortality much more accurately than conventional imaging techniques.

Table 1

Medicare-approved indications for FDG-PET *

Oncology	
Diagnosis	Solitary pulmonary nodule that cannot be pathologically characterised or biopsied, and metastatic squamous cell carcinoma in cervical nodes with unknown primary
Staging	Non-small cell lung cancer, cervical, oesophageal, gastric, head and neck carcinomas and lymphoma
Restaging for suspected recurrence	Epithelial ovarian carcinoma, lymphoma and head and neck carcinoma
Biopsy guidance	Primary brain tumours and bone/soft tissue sarcomas
Evaluation of residual structural lesions	Primary brain tumours, colorectal carcinoma, sarcoma and lymphoma
Assessment before definitive oncology surgery	Apparently isolated liver or lung metastasis in colorectal carcinoma, apparently limited metastatic disease in melanoma
Other conditions	
Epilepsy	Evaluation of refractory epilepsy being evaluated for surgery where location of epileptogenic focus is not clear
Myocardial viability	Prior to revascularisation in the presence of impaired left ventricular function when standard viability testing is negative or inconclusive

* only some facilities are eligible under Medicare
FDG-PET F-18 fluorodeoxyglucose positron emission tomography

FDG-PET detects unsuspected metastatic disease in 10–20% of patients, with a higher yield in patients with more clinically advanced disease. Confirmation of metastatic disease leads to decreased iatrogenic morbidity from fewer futile thoracotomies.

FDG-PET is the most accurate non-invasive means of mediastinal nodal staging, with a pooled sensitivity and specificity of 74% and 85%.[1] Its particular strengths are identifying benign (hyperplastic) but enlarged lymph nodes and to a lesser extent detection of metastatic disease in small sub-centimetre nodes. However, biopsy is still considered the gold standard. FDG-PET positive nodes should be confirmed by biopsy as they may be due to inflammation. Micrometastatic disease cannot be detected by any current non-invasive imaging technique.

External beam radiation therapy is also commonly used in the management of lung cancer. There is increasing interest in incorporating metabolic data from PET scans into radiotherapy planning systems, leading to PET-guided changes in radiotherapy fields. Clinical trial results of patient outcomes with this approach are currently sparse.

Diagnosis of solitary pulmonary nodule

Pulmonary nodules are becoming an increasingly common diagnostic problem with more widespread use of CT scanning. No evaluation is complete without clinical risk factor assessment. Many pulmonary nodules cannot be characterised on CT, and may be difficult to biopsy. For lesions greater than 8–10 mm in size, FDG-PET has been shown to differentiate between benign and malignant nodules (sensitivity 87%, specificity 83%)[2] and decreases the biopsy rate of benign lesions.

Lesions that are hypermetabolic should be considered malignant until proven otherwise. Granulomatous disease and infections are also hypermetabolic conditions and may be considered 'false positive' for malignancy, although they require specific diagnosis and treatment in their own right.

While complete absence of FDG uptake indicates a benign lesion, low levels of FDG uptake can be seen in carcinoid, bronchoalveolar and well differentiated adenocarcinomas. Stability on serial anatomical imaging over a two-year period is also considered an indicator that a lesion is benign.

Lymphoma

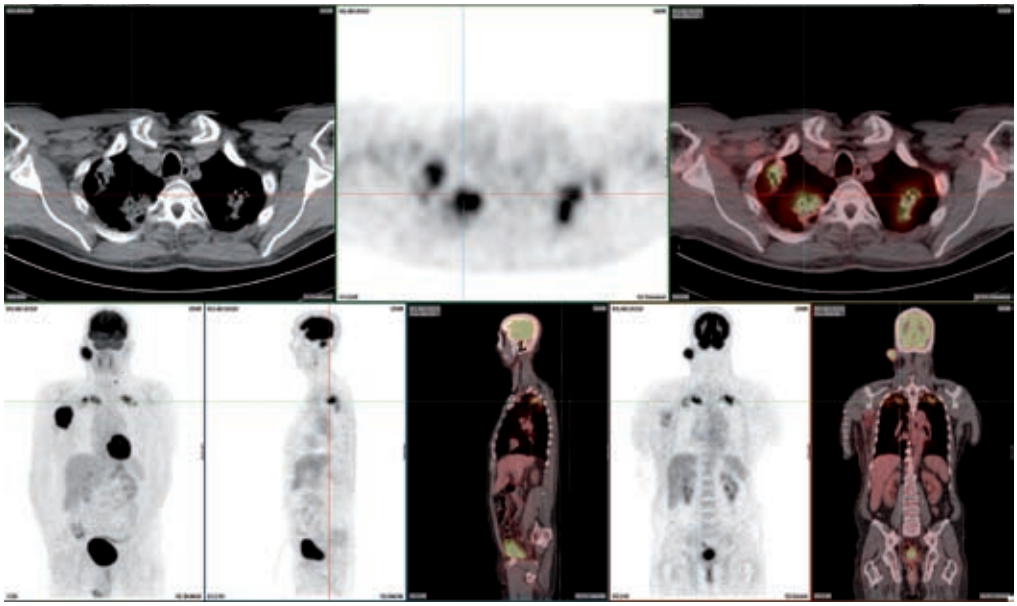
Staging

Accurate staging is integral to the development of a management plan for most types of lymphoma. FDG-PET has superseded gallium scans in functional evaluation of both Hodgkin's and non-Hodgkin's lymphoma, and is considered the most accurate imaging test for this condition.

Overall, FDG-PET is more sensitive than CT scan in detecting extranodal (particularly marrow, liver and spleen – see Fig. 3) and small volume nodal involvement, and changes management during initial staging in a median of 10.5% of cases.[3] There is often variation between studies and pooled statistical data due to the many different histological subtypes, therapies and grades of biological behaviour of Hodgkin's and in particular non-Hodgkin's lymphoma.

Fig. 2

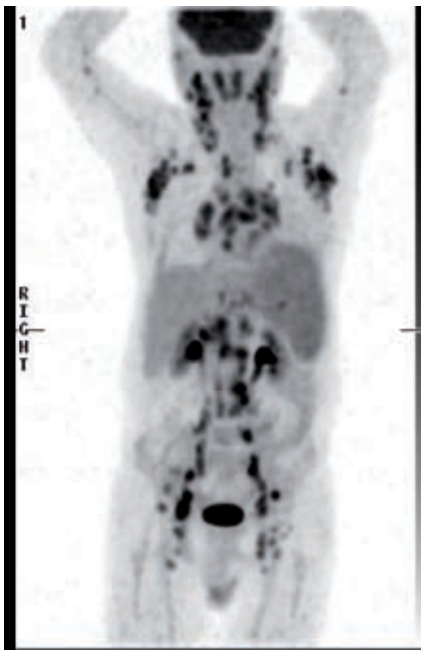
Diagnostic FDG-PET scan



FDG-PET CT scan of a patient with cutaneous squamous cell carcinoma (primary site of malignancy not shown) metastatic to right cervical and axillary nodes. The unexpected additional PET scan findings of marked FDG uptake in both lung apices led to a diagnosis of intercurrent active tuberculosis.

FDG-PET F-18 fluorodeoxyglucose positron emission tomography

Fig. 3
Staging of Hodgkin's lymphoma using FDG-PET



Maximum intensity projection image of a staging FDG-PET scan of a 68-year-old man with newly diagnosed Hodgkin's lymphoma. There are markedly FDG-avid lymph nodes in a symmetrical pattern above and below the diaphragm. Note the pathological diffusely increased uptake in the spleen (more than liver uptake). FDG-PET is a more sensitive indicator of diffuse splenic involvement, which is not possible to diagnose in the absence of splenomegaly on CT.

FDG-PET F-18 fluorodeoxyglucose positron emission tomography

Some lymphoma subtypes have variable or low FDG uptake including mucosa-associated lymphoid tissue (MALT)-type, small lymphocytic and marginal-zone lymphoma.

Restaging and assessing response to therapy

There is great interest in early prediction of response to chemotherapy. Identification of poor responders would lead to early change to second-line therapies, and there is potential to truncate therapy in good responders. The latter is particularly relevant in young patients with Hodgkin's disease where there are significant delayed toxicities from curative therapy. Prospective trials, particularly those in which truncation of therapy is guided by PET scan response, are still lacking.[4]

Studies also suggest that persistently positive PET scans several cycles into therapy implies the presence of chemotherapy resistant clones and therefore a worse prognosis.

Post-therapy FDG-PET scans can show a variety of features including diffuse skeletal uptake from bone marrow hyperplasia (particularly in the setting of colony stimulating factor use), thymic hyperplasia in younger patients, and inflammatory FDG uptake in recently irradiated tissues. The scan should therefore ideally be scheduled just prior to commencing the next cycle of therapy, or at least eight weeks after the completion of radiotherapy.

Residual masses

Assessment of remission status with CT is often uncertain due to the presence of residual masses after therapy, which may represent inactive scar tissue or residual active malignancy. PET (and PET CT) is considered the most accurate method of assessing this, with radiotherapy or further chemotherapy being considered for patients with active disease. Persistent FDG uptake in a residual mass is also an adverse prognostic marker.

Colorectal cancer

Metastatic disease confined to liver or lung is now treated with surgical resection as a potentially curative procedure. FDG-PET aids greatly in patient selection by identifying sites of occult disease that would preclude surgery.

Analogous to lymphoma, FDG-PET is accurate in determining the aetiology of residual pelvic masses after therapy, and also has a role in the setting of rising carcinoembryonic antigen (CEA) with normal CT or MRI.

FDG-PET is not useful in the detection or primary staging of colon cancer due to the extremely variable physiological colonic uptake patterns. The exception to this is rectal cancer, where detection of nodal disease may influence neoadjuvant radiation or chemotherapy before definitive surgery.

Other indications

The site of an otherwise occult primary malignancy can be identified on PET in 25% of cases of metastatic head and neck squamous carcinoma (Fig. 4). FDG-PET is also used in post-therapy evaluation of head and neck cancer, where residual disease and sequelae of treatment may be difficult to distinguish on CT scan. A negative PET scan in this setting has a high negative predictive value but should only be performed at least 8–12 weeks after completion of therapy to avoid false positive results from residual inflammation.[5]

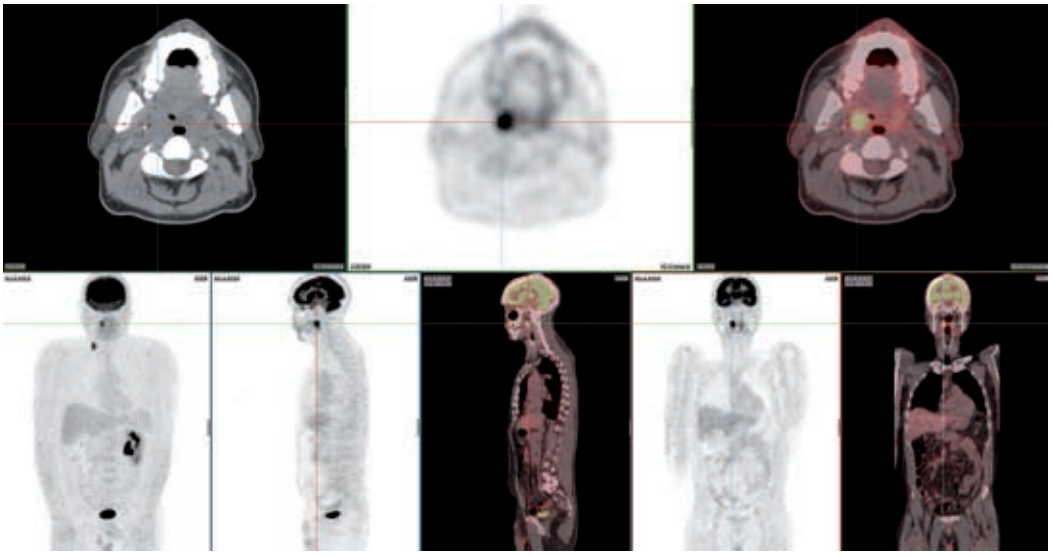
FDG-PET is useful for biopsy guidance in a variety of conditions, particularly soft tissue sarcomas which may have histological heterogeneity, and in larger necrotic masses to identify sites of viable tumour. Other indications for which PET is used include distinguishing radionecrosis from residual tumour in brain malignancies, and planning radiation therapy fields.

Incidental findings

Significant incidental findings are noted in up to 3% of scans, and often are an indicator of occult synchronous malignancies. Many malignancies also share common risk factors, particularly

Fig. 4

Diagnosing occult primary malignancy using FDG-PET



FDG-PET CT scan of a 55-year-old man with metastatic squamous cell carcinoma to right cervical lymph nodes from an unknown primary site. Abnormal FDG uptake in the right tonsil was subsequently proven to be the primary site. A repeat FDG-PET scan (not shown here) six months after therapy was normal.

FDG-PET F-18 fluorodeoxyglucose positron emission tomography

in head and neck, lung and upper gastrointestinal tract tumours in smokers. Other 'incidental' findings of particular significance that should not be ignored are FDG-avid thyroid nodules and focal uptake in the large bowel, which are associated with around a 25% risk of malignancy.

Future clinical applications

Future applications of PET are likely to come from tracers other than FDG. Non-oncology applications are also emerging, particularly in the fields of dementia, movement disorders and detection of infection.

A variety of tracers are under development and have undergone clinical trials. They include oncology applications as diverse as the imaging of tumour hypoxia, cellular proliferation, lipid membrane synthesis, receptor expression (for example, oestrogen receptor expression) and angiogenesis. These emerging 'molecular imaging' techniques may lead to new insights into disease biology, and play a central role in selection and monitoring of therapy.

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 139)

3. Liver metastases cannot usually be distinguished from normal background liver on an FDG-PET scan.
4. Abnormal FDG uptake can be caused by inflammation.

A current treatment approach for attention deficit hyperactivity disorder

Alasdair Vance, Professor and Head, Academic Child Psychiatry, Department of Paediatrics, University of Melbourne, Royal Children's Hospital, Murdoch Children's Research Institute, Melbourne

Summary

Attention deficit hyperactivity disorder is a common neurodevelopmental disorder mainly affecting primary school aged children. There are usually one or more comorbid conditions that add to the child's functional impairment and affect their response to medication and psychosocial treatments. There is emerging evidence that children do better when medicines are given in conjunction with comprehensive behavioural interventions. The psychostimulants dexamphetamine and methylphenidate are the primary drug treatments for attention deficit hyperactivity disorder.

Key words: atomoxetine, dexamphetamine, methylphenidate, psychotropic drugs.

(Aust Prescr 2008;31:129–32)

Introduction

Attention deficit hyperactivity disorder (ADHD) is characterised by developmentally inappropriate levels of inattention and hyperactivity/impulsiveness. It is associated with academic underachievement, social marginalisation, early school-leaving and occupational underachievement. ADHD can have deleterious effects on adult personality formation and is a risk factor for a range of adult psychiatric disorders, alcohol and substance abuse and dependence disorders.[1]

The two most common subtypes of ADHD are the combined type, where impairment is due to inattention and hyperactivity/impulsiveness (also known as hyperkinetic disorder), and the inattentive type, where impairment is caused by inattention alone. About 3–5% of primary school aged children have ADHD at any one time, with approximately 1.5% having the combined type. The prevalence of ADHD reduces by approximately 50% every five years from childhood through adolescence into adulthood. Hence, there are a small group of adult ADHD patients who require ongoing comprehensive treatment.

Aetiology

The precise cause of ADHD remains unknown although there appear to be numerous risk factors that contribute to its onset.

Biological factors remain pivotal and include high familial heritability. Genes involved in the regulation of neurotransmitter catabolism and release have been implicated in ADHD.

Dysfunction of the dopamine and noradrenaline neurotransmitter systems are crucial for the onset, progression and treatment responsiveness of children with ADHD. Key regions of the human brain rich in these two neurotransmitters are structurally altered and functionally different in ADHD. These brain regions promote verbal and visuospatial attention, memory, working memory and impulse control. These abilities are known to be deficient in affected children.

Key psychosocial risk factors, such as the quality of relationships in the family unit, school classroom and playground, are now considered to be non-specific maintaining (risk) or protective (resilience) factors, depending on their nature.[2] Dietary factors such as artificial food colourings and additives are now known to be non-specific risk factors of small effect in primary school aged children. Similarly, other environmental factors such as maternal smoking, exposure to toxic levels of lead, reduced iodine levels and early physical abuse or neglect exert non-specific effects that have remained hard to define.

Comorbid disorders

ADHD is rarely encountered as a 'pure', discrete disorder. The majority of children present with one or more comorbid disorders that can make ADHD symptoms worse or affect treatment responsiveness. Up to 75% of children with tic disorders manifest ADHD. Oppositional defiant disorder (such as impairment due to excessive arguing back, wanting your own way, being negative) affects between a third and a half of children with ADHD, with 2–3% of these children then developing conduct disorder (impairment due to rule-breaking behaviour such as lying, thieving, destruction of property, cruelty). Anxiety disorders such as separation anxiety, social anxiety and obsessive compulsive disorder affect 20–30% of children with ADHD. Similar rates of comorbid depressive disorders such as dysthymic disorder (the most common depressive disorder in children) and major depressive disorder are reported in ADHD sufferers. Language learning disorders (reading, spelling, arithmetic and writing disorders) are present in 20–30% of children with ADHD. Developmental coordination disorder and speech and language disorders make up the list of key comorbid disorders most often associated with ADHD.

However, recent clinical research interest in comorbid autistic spectrum disorders and an early onset form of bipolar disorder may well extend this list.

Diagnosis

A comprehensive specialist clinical assessment is required to identify ADHD. This should include a patient history provided by multiple informants (parents, children, teachers and other responsible adults, siblings, peers with parental permission) and patient examination. Comorbid conditions such as learning disorders, hearing impairment, speech and language developmental delay and developmental coordination disorder need to be identified so they can be treated appropriately.

Treatment strategies

There is insufficient evidence to identify which child with ADHD will respond to psychosocial or drug treatments. All cases of ADHD should be initially treated with psychosocial interventions alone. This is usually sufficient for milder cases, while moderate to severe cases of ADHD need medication in conjunction with psychosocial interventions. Often psychiatric referral is indicated to optimise the complex mix of medication, targeted psychosocial and specific specialist services that are needed to maximise learning and development.[3,4] These services include speech therapy for speech and language disorders, educational remediation for learning disorders, and occupational therapy for developmental coordination disorder.

At present, there is insufficient evidence to support targeted dietary adjustments or free fatty acid supplementation (for example, fish oils).[2,4]

Psychosocial interventions

Appropriate psychosocial interventions include positive reinforcement of desired behaviours (including token systems), penalties for undesired behaviours, and contingency contracts for older children and adolescents. Learning techniques to self-manage stress and group social skills training have also proven helpful. In contrast, other psychosocial treatment approaches such as psychodynamic therapies are ineffective, aside from improving a given child's or parents' level of satisfaction that something is being done.[2]

Dexamphetamine and methylphenidate

The psychostimulants dexamphetamine and methylphenidate remain the primary effective drug treatments for ADHD.[2,4] They do not differ in effectiveness or adverse effects, although individual patients may appear to respond better to one than to the other.

These drugs decrease ADHD symptoms, improve cognitive deficits (for example, attention, memory and working memory), decrease academic and social impairments due to ADHD, improve quality of life for children and their families, and increase adherence and learning from psychosocial interventions. These effects were evident in short-term (4–6 weeks) and long-term (1–2 years) controlled trials.

Psychostimulant medications are thought to work by increasing the functional activity of dopamine and noradrenaline through inhibiting their presynaptic uptake. These actions appear to facilitate compensatory brain neural networks that promote more situation-appropriate cognitions, emotions and behaviour in a child with ADHD.[5] The effects are dose-dependent for hyperactivity/impulsiveness, while, in a subgroup of children, attention and working memory improve at low doses but can become impaired at high doses.

The clinical effects of dexamphetamine and methylphenidate last for 3–4 hours on average, necessitating 2–3 times daily dosing. Modified-release formulations of methylphenidate are available in Australia with the primary advantage of once-daily dosing which aids adherence. The medication can be taken every day during the week with a break on weekends. This is an option that some families may prefer because of mild adverse effects (for example mild initial insomnia) or for ideological reasons (they want their child to use the least amount of medication possible).

Initiating and monitoring drug therapy

Paediatricians, psychiatrists and neurologists are approved prescribers of psychostimulant medication in Australia and should initiate and optimise the dosage in children with ADHD. General practitioners can be approved (through their state drug regulatory authority) to provide maintenance doses when working with a paediatrician or child psychiatrist. They can monitor for specific beneficial and adverse effects of psychostimulant medication and seek a second opinion if unsure of either.

Before starting psychostimulant drug therapy, children with pre-existing heart disease, a strong family history of heart disease or current symptoms and signs suggesting heart disease, require ECG monitoring.[6]

To assess for therapeutic and adverse effects in the early phase of treatment, children should be carefully monitored by their parent(s) for the first five days with weekly consultations by phone or in person. Dosing is usually optimised after 1–2 weeks, and then weekly to monthly face-to-face monitoring is recommended. Each child should be thoroughly reassessed every six months and their requirement for psychostimulant medication re-evaluated. This involves a comprehensive diagnostic reassessment (including risk and resilience factors) and re-targeting of medication or psychosocial treatments to minimise impairment and maximise adaptation. Withdrawal of psychostimulant medication should be considered to evaluate whether ADHD symptoms re-emerge.

Stopping treatment

Psychostimulant treatment should be ceased if there is no beneficial effect at home or at school, unacceptable adverse effects emerge in the short- or long-term, or the legal guardian of the child requests a trial of an alternative treatment.

If psychostimulant medication is ceased, it should be withdrawn gradually decreasing by one tablet per day until finished for short-acting preparations, and by switching from a long-acting to an equivalent short-acting form and then decreasing gradually until finished. Children should be monitored carefully over the following 1–2 weeks for re-emerging ADHD symptoms.

Adult use

Occasionally, psychostimulant medication will need to be continued into adult life. The abuse potential of such drugs has been repeatedly noted in the media. Interestingly, the pharmacodynamic and pharmacokinetic properties of psychostimulant medication and methamphetamine (the illegal form of amphetamine) differ to the extent that psychostimulant medication has a much lower potential for abuse.

Adverse effects

Key adverse effects are all dose-dependent and can be managed through subtle dose reduction. Appetite suppression and initial insomnia are the most common adverse effects, along with nervousness, dysphoria, nausea and headache early in treatment. Motor or vocal tics and growth retardation (of small effect) can occur. Rarer adverse effects are vomiting, rash, dizziness, weight loss and irritability.

Other medications

When psychostimulant medication is ineffective, has adverse effects such as emotional disturbance or worsening of tics, or is not a treatment option that a patient will use, alternative options can be considered.[2,4] These involve additional types of medication or specific psychosocial interventions known to ameliorate ADHD symptoms when mastered and put into practice by children with ADHD and their families.

Atomoxetine

Atomoxetine is the current second-line treatment for ADHD. It is a potent reuptake inhibitor of noradrenaline at the presynaptic terminal and is of some benefit for children with ADHD in the short and long terms. It has a longer duration of action than psychostimulant medication and can be helpful during the evening and sleep as well as during the day. Its adverse effects profile is similar to psychostimulant medication. Initial insomnia, appetite suppression, irritability and nervousness are the most common adverse effects along with nausea and headache. There is a precaution in the product information that atomoxetine may increase the risk of suicidal ideation.

Imipramine

Imipramine, a tricyclic antidepressant, is a current third-line treatment for ADHD, although it is being virtually phased out of routine clinical practice. It is similar to atomoxetine although it has significant potential for cardiac adverse effects, mainly cardiac arrhythmias and/or conduction defects.

Clonidine

Clonidine, a central adrenergic agonist that reduces the presynaptic release of noradrenaline, is an alternative to imipramine. It can be used when other options are ineffective or contraindicated. Clonidine decreases the hyperactivity/impulsiveness symptoms more than inattention at low doses, while there is some evidence of improved attention at higher doses.

Neuroleptic drugs

Atypical antipsychotics (for example, risperidone) and the sedative antipsychotics (for example, pericyazine) have limited benefit on core ADHD symptoms and unreliably improve cognition. However, they can be of benefit when there is severe co-occurring aggression or irritability/affective instability. Specialist assessment is required before these medications are prescribed, given the potential for drug interactions and effects on the psychosocial treatments being applied.

Drug combinations

Every attempt should be made to use a single medication that maximises benefits and minimises adverse effects. However, combinations of medication are frequently required that target specific key symptoms associated with impairment, for example psychostimulants and clonidine to aid initial insomnia. Specialist advice is always recommended when drug combinations are used.

Conclusion

Developing an effective treatment plan for a child with ADHD involves careful and comprehensive assessment of information from the parents, child and teacher (with permission). Key comorbid conditions need to be identified and specific approved treatments applied for them. These treatments may require the management of ADHD to be modified.

The general practitioner has a central role in reviewing an agreed treatment plan and liaising with the paediatrician or psychiatrist to ensure adjustments are being made as each child with ADHD develops through adolescence into adulthood.

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Further reading

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false
(answers on page 139)

5. Atomoxetine is the most effective drug for children with ADHD.
6. Psychosocial therapy is the initial intervention in ADHD.

Subsidised palliative care medicines

The Pharmaceutical Benefits Scheme (PBS) website contains a new consolidated list of palliative care medications (see www.pbs.gov.au/html/healthpro/browseby/palliative-care). This list is for use in conjunction with the general PBS listings section, which also contains many drugs used in palliative care.

For the purposes of prescribing these medicines, a patient receiving palliative care is defined as 'a patient with an active, progressive, far-advanced disease for whom the prognosis is limited and the focus of care is the quality of life'.

All of the drugs on this list (see box) are 'Authority required'. Prescribers can request an **initial** authority for up to four months of treatment. When **continuing** treatment is required, the prescriber must confirm that a palliative care physician or palliative care service has been consulted about the care of the patient.

Authority approvals can be obtained by phoning 1800 888 333 for general benefits and 1800 552 580 for repatriation benefits.

Prescribers must heed state and territory laws when prescribing narcotic drugs and must notify, or receive approval from, the appropriate health authority.

When a palliative care authority application is for a drug of addiction, the following guidelines apply:

- the maximum quantity authorised is generally for 1 month
- where supply for a longer period is warranted, quantities are for up to 3 months
- telephone approvals are limited to 1 month's therapy.

Doctors should also state (on the prescription) the interval of repeat where repeats are called for, and ensure state and territory health authorities are notified about ongoing treatment.

PBS listings as at 1 September 2008

Analgesics
- morphine sulfate tablets (10 mg, 20 mg, 200 mg)
- fentanyl lozenges (200, 400, 600, 800, 1200, 1600 microgram)
- methadone hydrochloride oral liquid (25 mg/5 mL)
- paracetamol suppositories (500 mg) and tablets (665 mg)

Antiemetics and antinauseants
- promethazine hydrochloride oral liquid (5 mg/5 mL) and tablets (10 mg and 25 mg)

Antiepileptics
- clonazepam oral liquid (2.5 mg/mL) and tablets (500 microgram, 2 mg)

Anti-inflammatory and antirheumatic products
- diclofenac sodium suppositories (100 mg) and tablets (25 mg, 50 mg)
- indomethacin suppositories (100 mg) and capsules (25 mg)
- sulindac tablets (100 mg, 200 mg)
- ibuprofen tablets (200 mg, 400 mg)
- naproxen tablets (250 mg, 500 mg, 750 mg, 1 g)
- naproxen oral suspension (125 mg/5 mL)
- naproxen sodium tablets (550 mg)

Drugs for functional gastrointestinal disorders
- hyoscine butylbromide injection (20 mg/mL)

Laxatives
- bisacodyl suppositories (10 mg) and tablets (5 mg)
- sterculia with frangula bark granules (62% / 8%)
- lactulose mixture (3.34 g/5 mL)
- macrogol 3350 powder (13.125 g sachets)
- bisacodyl enemas (10 mg/5 mL)
- sorbitol with sodium citrate and sodium lauryl sulfoacetate enemas (3.125 g/450 mg/45 mg in 5 mL)
- glycerol suppositories (700 mg, 1.4 g, 2.8 g)

Psycholeptics
- diazepam tablets (2 mg, 5 mg)
- oxazepam tablets (15 mg, 30 mg)
- nitrazepam tablets (5 mg)
- temazepam tablets (10 mg)

Stomatological preparations
- benzydamine hydrochloride mouth and throat rinse (22.5 mg/15 mL)
- carmellose sodium mouth spray (10 mg/mL)

Managing acute pain in patients with an opioid abuse or dependence disorder

Lindy J Roberts, Anaesthetist and Pain Specialist, Director of Acute Pain Service, Departments of Anaesthesia and Pain Management, Sir Charles Gairdner Hospital, Perth

Summary

Assessing and managing patients with acute pain who are addicted to opioids is often challenging. Treatment may be complicated by pharmacological therapies, including methadone, buprenorphine and naltrexone. There is limited evidence to guide the management of acute pain in these patients as they are usually excluded from analgesic studies. Principles of management include thorough assessment of both the pain and the addictive disorder, consultation and referral as appropriate, maximisation of non-opioid analgesics and non-pharmacological therapies, and use of opioids when indicated.

Key words: opioids, substance-related disorders.

(Aust Prescr 2008;31:133–5)

Introduction

In Australia, the lifetime prevalence of heroin use is 1.6%. Within the previous 12 months, 0.2% of the population will have used heroin and 15.3% will have illicitly used any drug (including cannabis and prescription drugs).[1] Those with a substance abuse disorder commonly use more than one drug, usually both legal and illicit substances. Other psychiatric diagnoses, such as personality disorders of the antisocial or borderline type, frequently coexist. There may be significant concomitant psychological, behavioural and social dysfunction.

People with a drug dependence, particularly those with high-risk behaviours such as intravenous drug use, are predisposed to certain types of acutely painful conditions such as infections, traumatic injury and pancreatitis. Acute pain is often undertreated.[2] This is more likely in those with a history of addiction where the knowledge, attitudes and behaviours of both patient and staff may create barriers to effective management.

Assessment

Due to the subjective nature of pain, with self-reporting as the gold standard, assessment of the patient with substance abuse disorder and pain may be challenging (see Box 1). For a variety of reasons including stigma and past experiences of pain management, the patient may not disclose drug use, either current or historical.

It is important to take a thorough drug history including details of all drugs used, how often they are taken and when they were last used. Patients in remission may be concerned that treatment with opioids will result in relapse.[3] This is a complex area and undertreatment of pain may increase the risk of relapse.

Drug-seeking behaviour

The treating doctor may be faced with the dilemma of potential drug-seeking behaviour in a patient who presents with a painful condition such as 'renal colic'. Clearly, careful clinical judgement is required. It may be preferable to err on the side of treating

Box 1

Assessing acute pain in opioid addiction

- Remain open and non-judgemental, promote realistic expectations and set clear limits
- Take a history of the pain, identify aetiology of pain with relevant examination and investigation
- Exclude serious pathology such as epidural abscess or discitis presenting as back pain
- Identify the addictive disorder where possible, maintain high index of suspicion, consider drug use screening
- Look for signs of drug use (intoxication, withdrawal, 'track marks', conduct a urine drug screen)
- If drug use is identified, take a thorough drug history (record substances and doses, treatment providers, comorbid pathologies such as blood-borne viruses, persistent pain, other psychiatric diagnoses)
- Assess degree of distress and contribution of psychological and social factors to the presentation
- Gather additional information from:
  - family and friends
  - usual prescriber or dispenser (to confirm current drugs and doses, among other things)
  - regulatory authorities such as state-based drug and alcohol advisory services, the Medicare Prescription Shopping Program (www.medicareaustralia.gov.au/provider/pbs/prescription-shopping/index.shtml, telephone 1800 631 181)

the occasional drug-seeker rather than undertreating those with legitimate acute pain. Developing practice or departmental policies for situations where drug seeking is suspected may help.[4,5,6]

Management

After assessing the patient, consultation, referral and treatment may be required (Box 2). Patients with a previous addiction who are in remission should be treated as any other patient presenting with pain. However, they may need to be reassured that relapse to opioid addiction is unlikely after taking analgesia.

Patients currently using illicit opioids

One goal of managing acute pain in these patients is to optimise non-opioid analgesia, noting that complete relief may not be realistic. For moderate pain unresponsive to non-opioid analgesia and other measures, adding tramadol may be appropriate since it has a lower potential for abuse than other opioids. However, it may not be sufficiently potent for severe pain, particularly in those who are opioid-tolerant. If using another opioid, select a drug and an administration route with lower reinforcing properties, for example morphine in preference to pethidine, oral rather than parenteral. In some circumstances intravenous administration will be required for initial or ongoing management.

Box 2

Managing acute pain in opioid addiction

- Consult and collaborate with registered methadone or buprenorphine prescriber or dispenser, drug and alcohol service, pain specialist or psychiatrist
- Communicate with the patient's usual general practitioner or drug and alcohol service
- Consider early referral for interdisciplinary assessment and management
- Treat the painful condition (e.g. immobilise fracture, give antibiotics for infection, drain abscess)
- Use best practice guidelines where available (e.g. for migraine, acute low back pain). These emphasise non-opioid therapy and pain prevention strategies.[2]
- Maximise non-opioid analgesia (regular paracetamol, non-steroidal anti-inflammatory drugs)
- Use non-pharmacological therapies such as physiotherapy, gentle-paced exercise program, hot or cold packs and transcutaneous electrical nerve stimulation
- Tramadol
- Opioids
- Consider adjuvants such as ketamine, clonidine, anxiolytics, antidepressants and anticonvulsants

Adjuvant drugs, including ketamine, clonidine (also useful for opioid withdrawal), anxiolytics, antidepressants and anticonvulsants, may also be useful, particularly if the pain has a neuropathic element.[2]

Another goal in the management of these patients is to prevent withdrawal syndromes, particularly in an inpatient setting. Psychiatric and behavioural disorders may also need to be treated.[2]

Patients in drug treatment programs

Many patients with an opioid addiction are given drugs to treat the dependence, which can further complicate the management of pain.

Methadone

Taking methadone will invariably result in opioid tolerance. Additionally, those receiving methadone have lower pain thresholds on experimental pain testing than do those with substance dependence not being treated with methadone.[2] In patients receiving methadone, ensure that the usual dose is continued or replaced parenterally to prevent withdrawal, especially if the patient is vomiting. Contact the prescriber or dispensing pharmacist to check the correct dose. If indicated, give additional opioid to treat the acute pain.[7] As a general guide, opioid-tolerant patients with acute postoperative pain require on average two to three times more opioid than opioid-naive patients. Commence with a dose 50–100% greater than usual (e.g. 1.5–2 mg morphine intravenously every 10–15 minutes instead of 1 mg, 15–20 mg intramuscularly instead of 10 mg) and titrate to effect.

Buprenorphine

Buprenorphine binds avidly to the mu-opioid receptor but has only partial activity compared with morphine, and dissociates from the receptor very slowly. This reduces access of drugs like morphine to the receptor, and may oppose analgesia for up to 72 hours after the last dose. This does not appear to occur with the low doses of buprenorphine administered by transdermal 'patch' for persistent pain.

When treating patients who are taking buprenorphine, seek advice from their usual prescriber, a drug and alcohol service or a pain specialist. Maximise the use of non-opioid analgesia including paracetamol and non-steroidal anti-inflammatory drugs. Tramadol, local anaesthesia infiltration/block and non-pharmacological therapies may also be used. Mild to moderate pain can be managed by an increased dose of buprenorphine, although this must be supervised by a registered prescriber.[8] For moderate to severe pain, hospital admission for specialist management may be required.

Naltrexone

The long-acting opioid-receptor antagonist naltrexone is administered as a once-daily tablet or as a subcutaneous

implant for opioid or alcohol abuse, although it is only licensed for the latter. An oral dose will block the activity of morphine-like drugs for 24–72 hours, whereas the implant is usually active for between three and six months. Receptor blockade may be overcome by giving high doses of opioids, but this is most safely done in a monitored environment.

Non-opioid analgesia and non-pharmacological strategies should be maximised and may be sufficient for mild pain. Those with more severe pain may require hospital admission. Analgesic approaches include titration of opioid to effect (very high doses are often required), use of regional blocks where feasible, use of systemic adjuvant drugs such as ketamine, and possibly stopping naltrexone treatment to restore opioid efficacy.

There are particular concerns when naltrexone is ceased. Up-regulation of opioid receptors initially results in increased opioid sensitivity. This may cause an exaggerated response, in particular life-threatening respiratory depression. In this situation, opioid administration must be undertaken with extreme caution, starting with low doses, monitoring closely and titrating to effect.

Patients abusing other drugs

As there is no cross-tolerance between opioids and most other drugs of abuse (such as alcohol, benzodiazepines, cannabis, cocaine, amphetamines[2]), patients using these drugs will usually only require conventional opioid doses. A thorough drug history is required to identify all substances used, in particular to prevent withdrawal syndromes. Withdrawal protocols are of great value in this situation providing staff have been trained in their use.

Acute exacerbations of persistent pain

There is a significant overlap between persistent non-cancer pain and substance abuse disorder. Up to one-third of patients prescribed opioids for non-malignant pain will exhibit aberrant drug-taking behaviour. Of those attending drug treatment programs, a significant proportion report a history of persistent non-cancer pain, sometimes with pain identified as the precipitating cause for the addictive disorder.

Ideally, such patients will be managed by a single general practitioner in consultation with relevant specialist services including a pain centre. When pain is relatively stable, it is helpful to develop a plan for management of exacerbations. This should focus on prevention and non-pharmacological and non-opioid therapies. If opioids are to be used, avoid parenteral administration and instead prescribe slow-release formulations for a limited period, perhaps with controls such as daily pharmacy pick-up.

Surgery

It is important that patients with opioid dependency present for preoperative assessment at least a week before elective surgery. Management should be planned in consultation with the patient, the usual prescriber or general practitioner, the hospital drug and alcohol service, and the anaesthetist or acute pain service managing the patient perioperatively.

Continue methadone up to the time of surgery and postoperatively if feasible, or replace the dose parenterally. Planned naltrexone cessation may be required. There is currently no consensus as to whether buprenorphine should be ceased (in which case conversion to another opioid would be required) or continued, although there is an emerging trend to continue it.[8] Patient-controlled analgesia is the technique of choice in the early postoperative period.

Conclusion

Patients who are addicted to opioids provide substantial challenges for acute pain management. It is important to ensure they are thoroughly assessed, incorporating interdisciplinary communication and collaboration. Treatment with non-pharmacological therapy and non-opioid analgesia as well as carefully titrated opioid analgesia may be required to relieve pain.

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For a glossary of terms used in this article, see the online article at www.australianprescriber.com in Vol. 31 No. 5.

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Dental notes

Managing acute pain in patients with an opioid abuse or dependence disorder

Prepared by Dr M McCullough of the Australian Dental Association

The use of illicit drugs, in particular heroin, can have profound effects on the dentition, causing rampant caries, advanced periodontal disease and exacerbation of mucosal diseases. In surveys of injecting drug users, up to 70%, reporting concern about the state of their mouths, described problems such as 'teeth snapping off', 'teeth falling apart', gum disease and trauma. Methadone and methamphetamines are perceived by some injecting drug users to 'eat away their teeth'.[1] This may be partly related to the effect these drugs have on salivary flow, dietary changes and the concomitant long-term lack of oral hygiene.

Dentists can therefore be confronted with patients presenting with acute dental pain who are either currently dependent or are recovering from their dependency. It is essential that our attitudes, and those of our staff, do not become barriers to effective management of these patients' pain. Self-reporting of the degree of dental pain must be accepted on face value, as the experience of pain is totally subjective in nature and these patients' pain thresholds may have been significantly affected by long-term drug use. This can result in diagnostic dilemmas with the reported pain appearing out of proportion to the clinical signs.

Most dental pain can be treated clinically with effective local anaesthesia, interventional dental treatment and in the immediate post-treatment phase, by maximising the use of non-opioid analgesia such as paracetamol and non-steroidal anti-inflammatory drugs. If a patient has extreme pain which does not respond appropriately to dental treatment and short-term, non-opioid analgesia, it would be wise to consult with the patient's medical practitioner.

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New drugs

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

Anti-thymocyte globulin

Thymoglobuline (Genzyme)

vials containing 25 mg freeze-dried powder

Approved indication: renal transplant rejection and aplastic anaemia

Australian Medicines Handbook section 14.5.3

Anti-thymocyte globulin is indicated for the prophylaxis of renal graft rejection as well as the treatment of steroid-resistant renal transplant rejection. Kidney transplantation is the treatment of choice for most patients with end-stage renal disease. However, 15–35% of transplant recipients will experience one episode of acute rejection in the first year. Giving antibody to deplete thymocytes (T cells) is one way to suppress the immune system to prevent or reverse graft rejection.

Anti-thymocyte globulin is a polyclonal antibody against human T cells. It is a gamma immunoglobulin produced by immunising rabbits. As well as depleting T cells in the circulation, anti-thymocyte globulin is also thought to reduce T cell proliferation, homing and cytotoxic effects within the body. Depletion of T cells occurs within a day of starting intravenous treatment.

This immunoglobulin has been compared to other treatments in renal transplant patients who are also receiving other immunosuppressant drugs. In a randomised trial of 72 patients, anti-thymocyte globulin was more effective at preventing acute rejection during the first year after transplantation than a similar polyclonal antibody derived from horses (4% vs 25% patients had acute rejection).[1] Five years after surgery, patient survival was similar for both treatments, but graft survival was significantly better in patients treated with anti-thymocyte globulin (77%) compared to those treated with the horse antibody (54%).[2]

The rabbit polyclonal has also been compared to basiliximab (an antibody directed towards the interleukin-2 receptor) for the prevention of acute rejection in 278 renal transplant patients.

Although there was a lower incidence of biopsy-proven acute rejection with anti-thymocyte globulin compared to basiliximab (16% vs 26% of patients), approximately half of the patients in both groups had acute rejection, delayed graft function, graft loss or had died after one year.[3]

In another trial, the rabbit antibody was found to be as effective as a horse antibody at reversing acute rejection episodes (return of serum creatinine to baseline levels). After one year, there was no significant difference in overall graft survival between the two treatments (83% vs 75% of patients). Response to treatment depended on the severity of the initial rejection episode.[4]

Anti-thymocyte globulin is also indicated for refractory or relapsing aplastic anaemia. This is an autoimmune disease resulting from the destruction of pluripotent stem cells in the bone marrow. Depletion of these stem cells reduces the number of red and white blood cells and platelets. Anti-thymocyte globulin is thought to benefit these patients by preventing activation and clonal expansion of cytotoxic T cells which are involved in mediating the disease.

The approval of anti-thymocyte globulin for the treatment of aplastic anaemia is based on an uncontrolled trial of 30 adults and children who had not responded to a course of immunosuppressive therapy (which included a horse anti-lymphocyte antibody). These patients were given a second course of treatment consisting of rabbit anti-thymocyte globulin for 1–5 days plus cyclosporin for 1–180 days and in addition most received granulocyte colony stimulating factor for 1–90 days. After a median of 95 days, 23 of the 30 patients had responded to treatment, which was defined as transfusion not required for at least one month. (Women were less likely to respond than men.) After two and a half years, 93% of the patients were still alive. One patient had died early during treatment from sepsis.[5]

Following intravenous administration of this drug, fever, chills, dyspnoea, nausea, diarrhoea, changes in blood pressure, malaise, rash and headache consistent with cytokine release syndrome have been reported. Anaphylaxis has also occurred. Reducing the infusion rate may help to reduce the incidence and severity of these adverse events. Premedication with paracetamol, corticosteroids and/or antihistamines is also recommended. This antibody is contraindicated in patients with hypersensitivity to rabbit proteins.

Leucopenia and thrombocytopenia are common with anti-thymocyte globulin treatment but can be reversed by decreasing the dose. White blood cell and platelet counts should be monitored. Not surprisingly, infections or reactivation of infections (such as cytomegalovirus) are very common so careful patient monitoring and appropriate prophylaxis are recommended. Immunisation with live vaccines should be avoided. In one of the trials, 19% of patients developed acne.[1]

Some patients have developed cancer, in particular lymphoma and post-transplant lymphoproliferative disease, after receiving anti-thymocyte globulin as part of their immunosuppression therapy.

Around two-thirds of renal transplant patients developed anti-rabbit antibodies to the anti-thymocyte globulin. It is not clear if these antibodies would affect the efficacy of this drug if it is used again. Monitoring the patient's T cell count to ensure depletion is recommended for all patients receiving treatment.

This polyclonal antibody seems to be effective in preventing or reversing rejection in renal transplant patients when given with other drugs to induce immunosuppression. Patients with aplastic anaemia may also benefit from this drug. However, because of the profound depletion in T cells, patients must be monitored closely for serious adverse events.

T T T manufacturer provided clinical evaluation

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Galsulfase

Naglazyme (Cedarglen Investments)

glass vials containing 5 mg/5 mL

Approved indication: mucopolysaccharidosis VI

Australian Medicines Handbook Appendix A

Mucopolysaccharidosis VI is one of the lysosomal storage diseases. It is also known as Maroteaux-Lamy syndrome. As there is an inherited deficiency of the enzyme acetylgalactosamine sulfatase, the degradation of dermatan sulfate is reduced. This substrate accumulates in the lysosomes resulting in deformities, organ damage and growth retardation. Hydrocephalus can develop, but mental development is usually normal. The condition may progress slowly or rapidly. Bone marrow transplant helps a few patients, but has a high mortality and morbidity.

Galsulfase is a recombinant form of acetylgalactosamine sulfatase, produced using Chinese hamster ovarian cells. The solution has to be infused intravenously over at least four hours. Although the half-life of galsulfase is less than 30 minutes, it only needs to be infused once a week.

As mucopolysaccharidosis VI is a very rare disease the main trial of galsulfase only included 39 patients. They were given a weekly infusion of the enzyme or a placebo for 24 weeks. Although the patients were randomised, there was a significant baseline difference between the groups. Before treatment the mean distance patients in the galsulfase group could walk in 12 minutes was 227 metres, whereas the placebo group could cover 381 metres. At the end of the trial the patients given galsulfase could walk 336 metres, while those in the placebo group could walk 399 metres. The mean change in the enzyme group (109 metres) was significantly greater than in the placebo group (26 metres). The mean number of stairs patients could climb in three minutes increased from 19 to 27 with galsulfase and from 31 to 33 with placebo.[1]

Common adverse events during treatment with galsulfase are fever, headache, arthralgia, abdominal pain, ear pain, diarrhoea and vomiting. There can be severe adverse reactions to the infusion, with urticaria, bronchospasm, respiratory distress and apnoea. Although patients should be given antihistamines before each treatment, this will not prevent all the infusion reactions. These reactions can occur for the first time after many weeks of infusions, so resuscitation equipment must always be available during treatment. Nearly all patients develop antibodies to galsulfase, but these do not predict the severity of the infusion reactions.

The assessment of galsulfase was complicated by the imbalance between the groups in the clinical trial.[1] Re-analysis of the data by regulatory authorities was needed to confirm the efficacy of the enzyme. There is also evidence, from a 24-week extension of the trial, that patients who switch to galsulfase from placebo will increase the distance they can walk in 12 minutes (mean increase 66 metres). This extension was 'open label' so there is some uncertainty about the benefit. Galsulfase had no significant effect on joint pain and stiffness, but the trial was not powered to show a difference.[1] In view of these uncertainties and the unknown long-term effect of anti-galsulfase antibodies on clinical outcomes, patients given galsulfase should be in a clinical surveillance program.

T manufacturer provided only the product information

Reference *†

1. Harmatz P, Giugliani R, Schwartz I, Guffon N, Teles EL, Sa Miranda MC, et al; the MPS VI Phase 3 Study Group. Enzyme replacement therapy for mucopolysaccharidosis VI: a phase 3, randomized, double-blind, placebo-controlled, multinational study of recombinant human N-acetylgalactosamine 4-sulfatase (recombinant human arylsulfatase B or rhASB) and follow-on, open-label extension study. J Pediatr 2006;148:533-9.

Panitumumab

Vectibix (Amgen)

vials containing 20 mg/mL in 5 mL, 10 mL or 20 mL volume

Approved indication: metastatic colorectal carcinoma

Australian Medicines Handbook section 14.2.1

Panitumumab is a humanised monoclonal antibody for the treatment of metastatic colorectal carcinomas expressing the epidermal growth factor receptor. It is indicated for patients whose tumours have progressed after fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy.

This antibody prevents the growth of tumour cells and causes cell death by binding to the epidermal growth factor receptor and competitively inhibiting autophosphorylation induced by various ligands such as epidermal growth factor and transforming growth factor-alpha. Antibody binding also decreases the production of interleukin-8 and vascular endothelial growth factor.

Panitumumab is given as an intravenous infusion. The pharmacokinetics of this drug vary depending on the dose, with clearance decreasing at higher doses. Steady state is reached after three doses of 6 mg/kg once a fortnight. The mean half-life during this dosing interval is approximately 7.5 days.

In an open-label phase III trial of 463 patients with progressive metastatic colorectal cancer, panitumumab with best supportive care was compared to best supportive care alone. Patients were given panitumumab until their disease progressed or they died. Although the median progression-free survival time with panitumumab was similar to the control (8 vs 7.3 weeks), the mean progression-free survival for panitumumab was 5 weeks longer (13.8 vs 8.5 weeks). There was no difference in overall survival between the groups.[1]

The efficacy of panitumumab seems to be confined to a subset of patients with tumours expressing the wild-type (non-mutated) KRAS gene (Kirsten rat sarcoma-2 virus oncogene). Following further analysis of the phase III trial, the median progression-free survival was 12.3 weeks in patients with wild-type KRAS and 7.4 weeks in those with mutant KRAS, after receiving panitumumab. There was no difference in overall survival between the groups.[2] In total, 43% of patients in the trial were found to have KRAS mutations so this is an important factor to consider when selecting patients for panitumumab therapy.

Although panitumumab benefits some patients, it causes considerably more adverse events than supportive care alone. Skin-related toxicity is the most common adverse effect, affecting over 90% of patients. Erythema, acneiform dermatitis, pruritus, skin exfoliation, paronychia, rash and skin fissures have been reported.[1] (The likely cause of these reactions is inhibition of epidermal growth factor receptor in the basal layers of the skin.) Eye-related toxicities and stomatitis have also been observed with this drug. Patients should be monitored for inflammatory and infectious conditions associated with skin

toxicity. Sunlight can exacerbate skin reactions so protection from the sun is recommended.

Health professionals should be aware that panitumumab has been associated with an increased risk of venous thromboembolic events. In the phase III trial, 12 of 231 patients had a thromboembolic event.[1] One case of pulmonary embolism with panitumumab was fatal and two were life-threatening.

Almost 40% of patients who received panitumumab developed hypomagnesaemia, 5% of which were serious, so patients should be regularly monitored during and for eight weeks after completion of therapy. Gastrointestinal problems were more common with panitumumab than with the control treatment.[1]

So far, adding panitumumab to chemotherapy does not appear to give clear benefits. Severe diarrhoea was reported by 58% of patients who received panitumumab in combination with fluorouracil, leucovorin and irinotecan. As diarrhoea can exacerbate electrolyte depletion, this combination of drugs should be avoided. In another trial, adding panitumumab to oxaliplatin- and irinotecan-based chemotherapy and bevacizumab resulted in increased toxicity without improving efficacy.

Although the benefits seem marginal, panitumumab does offer another option for patients who have not responded to standard chemotherapy. It is not known how panitumumab compares with cetuximab, another inhibitor of the epidermal growth factor receptor, for the treatment of colorectal cancer.

Before starting treatment it is important to first ascertain that the patient's tumour is expressing epidermal growth factor receptor. Expression of the wild-type KRAS gene may improve a patient's response to panitumumab. However, these findings are still preliminary and need to be confirmed in further studies.

T manufacturer provided only the product information

References *†

1. Van Cutsem E, Peeters M, Siena S, Humblet Y, Hendlisz A, Neyns B, et al. Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. J Clin Oncol 2007;25:1658-64.
2. Amado RG, Wolf M, Peeters M, Van Cutsem E, Siena S, Freeman DJ, et al. Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. J Clin Oncol 2008;26:1626-34.

The T-score (T) is explained in 'New drugs: transparency', Aust Prescr 2007;30:26–7.

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

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

Answers to self-test questions

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

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