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CONTENTS

Pharmaceutical marketing and the internet

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Summary

Pharmaceutical companies are capitalising on the advent of the internet and the development of new media forms to promote their products. Electronic detailing, interactive websites, email prompts and viral marketing campaigns using social networking sites such as YouTube, MySpace and Facebook are among the tools being used. Such campaigns are targeting both health professionals and the general public. The internet is helping to globalise and to change the nature of pharmaceutical marketing, and thus raises some new challenges for regulators.

Key words: advertising, drug industry, drug promotion.

(Aust Prescr 2009;32:2–4)

Introduction

The internet and related technologies have revolutionised many aspects of society. For the pharmaceutical industry, as for other sectors, this has brought new marketing opportunities. The internet can greatly expand a company's reach. For example, a popular video on YouTube may potentially be seen by thousands of people. Perhaps more importantly, internet-based technologies are enabling new styles of communication between the industry and its targets, including more interactive and customer-responsive campaigns. Consultancies have been established and books written[1] to help the pharmaceutical industry develop internet-based marketing.

In this issue…

Each new year brings an increase in prescription charges. However, co-payments are not the only component in prescription pricing. Michael Tatchell explains what else influences the prices patients pay.

While John Sullivan and Veronica Preda tell us about new treatments for psoriasis, Alisa Crouch's review shows there have been few recent advances in the drug treatment of dementia. There have been many advances in electronic communication, but Melissa Sweet warns us that some drug information on the internet is actually marketing material.

Electronic detailing

In the context of drug promotion, detailing has traditionally involved face-to-face contact between a visiting sales representative and a health professional. However, drug companies, especially in North America and Europe, are increasingly turning to electronic detailing or e-detailing for help in marketing their products. E-detailing includes diverse strategies, such as videoconferencing, the provision of electronic education modules, and the use of email and related technologies as prompts and to promote two-way communications. It has been used for disease-awareness campaigns, and for 'customer relationship management'.

Presentations to a pharmaceutical marketing conference in Europe suggest that e-detailing is not popular with all doctors.[2] However, it is cheaper than traditional sales representatives and can result in a significant return on investment through increased sales. Some companies are providing financial incentives for doctors to participate in e-detailing, such as honoraria, product samples, practice tools, and patient education resources.[3] In Poland, for example, Sanofi-Aventis lent physicians internet-connected hand-held devices which were loaded with clinical support information, drug indexes, abstracts of clinical studies, information from key opinion leaders, and advertising and educational materials. In exchange, the doctors participated in a clinical trial of a Sanofi-Aventis drug and entered anonymous patient data into the device. The company aimed to build relationships with the doctors, to use the device as an advertising medium, and to gather feedback. The company also reported that these doctors then prescribed more of its diabetes products.[3]

An important aspect of e-detailing is that it enables 'predictive marketing'. This means that companies can be more effective and timely in eliciting feedback from prescribers in order to tailor marketing strategies to their individual preferences and needs.[4]

Corporate blogs and websites

The global reach of the internet means that Australians now have easy access to overseas blogs and websites promoting prescription medicines and other products, and even selling them. Safety concerns have been raised about the purchase of prescription, non-prescription and complementary medicines over the internet.[5,6]

Companies are also using blogs and websites to develop customer relationships. As GlaxoSmithKline says on its corporate

Understanding the lingo

Blog

A contraction of 'web log', an online journal.

Consumer opinion leaders

Ordinary people who influence what other consumers believe and buy. Often employed in web-based marketing.

E-detailing

Information technology-supported promotional activities which provide customers, whether health professionals or patients, with information.

Podcasts

Repositories of audio and video materials that can be broadcast over the internet, and downloaded to portable media players.

Web 2.0

A second generation of internet-based services, such as social networking sites and wikis, that emphasise online collaboration and sharing among users.

Wikis

Websites that can be edited by anyone who has access to them. The best known example is Wikipedia.

YouTube

A social networking site that lets people watch and share videos over the internet. Other networking sites include MySpace and Facebook.

blog in the USA for a weight loss product (http://alliconnect.com), 'it's a place for you to have a conversation with us about weight loss issues'. Such 'conversations' may enable companies to gather patient stories and feedback for use in positioning their products. The discussions are not only mined for information (http://pharmamkting.blogspot.com), but also ensure the repetition of marketing messages. Sometimes companies use multiple websites to promote their products and issues to different market segments. For example, GlaxoSmithKline also promotes weight loss issues at www.questioneverything.com

Websites are also used for patient support programs and education although it is not always clear from the website name who is behind it. In the USA, Pfizer runs such a program (www.get-quit.com) for varenicline users, providing regular emails and other prompts such as a personalised web page to support their product use. In Australia, the company's advertising and marketing campaign is backed by a consumer website (www.outsmartcigarettes.com.au) that includes prompts for questions to ask doctors. Meanwhile, a Wyeth Consumer Health Care website (www.caltrate.com.au) sounds the alarm on osteoporosis and encourages people to see a doctor if they answer yes to any questions on a 'one minute risk test', including the question 'have either of your parents broken a hip after a minor bump or fall?'.

Company websites can link to other sites that may not meet regulatory requirements. GlaxoSmithKline's Australian website raising consumer awareness of genital herpes and treatment issues (www.thefacts.com.au) links to the Australian Herpes Management Forum but advises that external links such as this 'may not comply with the Australian regulatory environment'. The Forum, whose board comprises prominent physicians, aims 'to improve the awareness, understanding, management and control of herpes virus infections in Australia', and is sponsored primarily by pharmaceutical and diagnostic companies.

Pharmaceutical companies are not alone in using the internet to market products and to conduct awareness-raising campaigns that may affect patients' interactions with doctors. The complementary medicines company Blackmores, for example, has a sophisticated website (www.blackmores.com.au), while Nescafé has launched a website (www.nescafe.com.au/hcp password: Coffee) supported by advertising in the medical press which promotes coffee as an agent that may help lower the risk of developing type 2 diabetes.

Viral marketing and social networking sites

Social networking sites such as YouTube and Facebook have been successfully exploited by many consumer product companies for viral marketing campaigns. These campaigns are so named because the transmission of a marketing message through the networks is seen as analogous to the spread of a viral infection in a population.

It can be extremely difficult to identify who is responsible for content spread through such networks, and it is not clear how widely the pharmaceutical industry is using them. A recent search for 'Champix' on YouTube (accessed 12 November 2008) identified 46 videos, many of which appeared to be of ordinary viewers describing their experiences with varenicline. It was unclear whether any of these videos were commercially generated. However, the first one identified by the search (http://au.youtube.com/watch?v=Vx7baviT1DQ) linked to a website whose name suggests it is an individual's personal site (www.kims-website.info), although it appears in fact to be a commercial site. On the other hand, such networks are also being used for public health purposes, including promoting messages about the quality use of medicines. YouTube also includes, for example, a US Food and Drug Administration (FDA) video discussing potential adverse effects of varenicline.[7]

Even when listings are clearly commercials, as with a bizarre video on YouTube promoting a new medicine for insomnia, ramelteon, it is not necessarily clear who is responsible for posting them. The video features an insomniac chatting with Abraham Lincoln and a talking beaver over a chess board. These characters

also appear in a direct-to-consumer television advertising campaign in the USA. The video was submitted to YouTube in 2006 by 'lewisusauk', who said: 'New Rozerem Ad Campaign. Possibly the best prescription drug ad since the FDA relaxed the rules on drug advertising'. According to a pharmaceutical marketing blog by John Mack (http://pharmamkting.blogspot.com), lewisusauk is a 'sock puppet … a false identity through which a member of an internet community speaks while pretending not to, like a puppeteer manipulating a hand puppet'.

Apart from disseminating company-generated content, social networking sites also offer opportunities for companies to insert themselves anonymously into conversations between site users through postings and comments on blogs. John Mack says some of the postings about the ramelteon video on YouTube smack of this practice, and 'are attempting to hijack the conversation by submitting commercial messages (that is advertisements) disguised as genuine comments from ordinary citizens'.

Meanwhile, in the Netherlands, an industry-driven campaign conducted via Hyves (a Dutch equivalent of Facebook) gathered more than 80 000 signatures in only three weeks for a petition aimed at influencing decisions about funding for human papillomavirus vaccines. According to Dr Ruud Coolen van Brakel, Director of the Dutch Institute for the Proper Use of Medicine, it was 'a very effective way to create public awareness and commitment to a commercial cause disguised as a public health issue'.

Pharmaceutical companies are also seeking to capitalise on medical social networking sites. Pfizer, for example, is reportedly collaborating with Sermo Inc, a web venture based in Cambridge USA, where tens of thousands of doctors discuss diagnostic and treatment issues in anonymous postings. The collaboration allows Pfizer's doctors to ask questions and respond to posts. Members can also rank postings, which will give insights likely to help the company's development of marketing messages. Sermo is said to be in talks with other companies as well. The site earns money by letting clients such as hedge funds monitor doctors' anonymous conversations and thus gain insight into, say, the popularity of certain treatments. Sermo rewards physicians whose input is highly ranked by other members and plans to offer to pay doctors for participating in its clients' surveys.[8,9]

Regulation

The Medicines Australia Code of Conduct attempts to regulate the promotion of prescription medicines on the internet. However, it is difficult to police the anonymous marketing of drugs on blogs and forums, or to regulate consumers' access to information from countries where pharmaceutical marketing may be less regulated than in Australia.

Conclusion

The ongoing development of internet-related technologies is likely to provide pharmaceutical manufacturers with further opportunities to influence consumer expectations of health care and prescribing practices. It is also providing new opportunities for those concerned with the quality use of medicines and evidence-based education.[10] Much can be gained from constructive engagement with the world wide web, and 21st century doctors also need to understand its use as a marketing tool.

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Conflict of interest: none relevant to this article

Note: Websites and links can change quickly. Those cited in this article were accessible at the time the article was accepted for publication.

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.

Severe hyponatraemia due to mirtazapine

Editor, – Dr Cheah and Ms Ladhams highlighted an important interaction between medications prescribed for a 79-year-old woman (Aust Prescr 2008;31:97). A diagnosis of inappropriate antidiuretic hormone secretion (SIADH) can only be made when common causes, such as the use of diuretics, are excluded.[1] Therefore, it is probable that frusemide contributed to the presentation. A serum sodium concentration prior to the initiation of mirtazapine would have been helpful.

The risk factors for developing SIADH (previously presented as relating to mirtazapine only) are applicable to most psychotropic medications, including duloxetine, venlafaxine, fluoxetine, paroxetine, citalopram, escitalopram, tricyclic antidepressants, neuroleptics and carbamazepine.[2,3,4] Thus, to rechallenge the patient with mirtazapine would be necessary and acceptable, both to disprove the null hypothesis and because the occurrence of the adverse event cannot be predicted when using another drug.[2,3]

The relevant question is how to treat depression in the elderly, who have a greater probability of developing SIADH. A review suggests that hyponatraemia induced by selective serotonin reuptake inhibitors, in particular, may be a transient effect to which the patient develops tolerance.[2]

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Dr Cheah and Ms Ladhams, authors of the Medicinal mishap, comment:

We agree that the diagnosis of SIADH requires exclusion of other causes, including diuretic therapy. The patient had been treated with frusemide for years prior to presentation with a normal serum sodium. Frusemide was ceased on admission and recommenced at day 10 without a subsequent fall in sodium. We also noted that concomitant use of other drugs which cause hyponatraemia is a risk factor for mirtazapine-induced hyponatraemia. In fact most patients who develop severe hyponatraemia have more than one contributing cause.[1]

While many antidepressant drugs are associated with hyponatraemia,[2] we argue that rechallenge with mirtazapine in this setting is neither safe nor appropriate given the profound and rapid fall in serum sodium precipitating hospital admission. Our purpose was to highlight mirtazapine-induced hyponatraemia which is only rarely described in the literature and not listed in either the product information or MIMS.

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Australian Medicines Handbook 2009

The 2009 edition of the Australian Medicines Handbook is now available. It includes new monographs on medicines marketed during 2008 and updated content, reflecting changed evidence and practice.

Advice from new practice guidelines has been incorporated in areas such as hypertension and rheumatoid arthritis, and safety information has been updated.

The 984-page paperback edition of the handbook, and other formats, can be ordered online at www.amh.net.au or by phoning (08) 8303 6977.

Prescription pricing demystified

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Summary

Patient status, premiums, special contributions and safety nets all affect the cost of prescription medicines. Depending on their status, patients pay different co-payments for subsidised prescription drugs. Extra costs may be added by the manufacturer and the dispensing pharmacist.

Key words: bioequivalence, cost of drugs, Pharmaceutical Benefits Scheme.

(Aust Prescr 2009;32:6–8)

Introduction

Many patients are unsure about the price of their Pharmaceutical Benefits Scheme (PBS) or Repatriation Pharmaceutical Benefits Scheme (RPBS) prescriptions and often ask their doctor 'How much will my prescription cost?'. The final price paid by the patient for these prescription medicines can be broken down into various components and depends on the following (see Fig. 1):

- their status as a patient (general, concessional or repatriation)
- whether a brand price premium, therapeutic group premium or a special patient contribution applies
- the patient's safety net status.

The pricing of 'private' prescriptions that fall outside the PBS and RPBS is not influenced by any Australian government subsidy or pricing restrictions.

Patient co-payments

For the 2009 calendar year, the co-payments payable by patients are as follows:

General patients	up to $32.90
Concessional and repatriation patients	$ 5.30

These amounts are indexed on 1 January each year in accordance with the Consumer Price Index in the previous 12 months. The *National Health Act 1953* precludes pharmacists from discounting the patient co-payment that applies on government-subsidised PBS medicines.

Premiums and special contributions

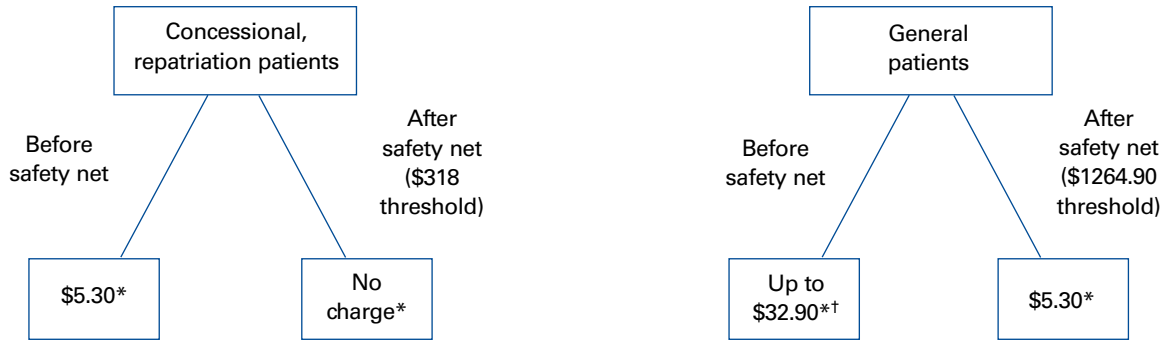
In certain instances the pharmaceutical manufacturer may choose to apply an additional charge for their product which the patient is obliged to pay. These can be a brand price premium, a therapeutic group premium or a special patient contribution. While these extra charges are paid to the pharmacist at the time of dispensing, they are passed on to the manufacturer.

Brand price premiums

Since 1990, manufacturers have been able to set their own prices on PBS medicines in particular circumstances. The policy operates when there are a number of therapeutically equivalent brands available. The government subsidises each of the available brands to the level of the cheapest brand. This means that patients have to pay extra for the more expensive brands – those with a brand price premium.

Fig. 1

Doctor, how much will my prescription cost?



* Plus any premium (brand price premium or therapeutic group premium) or special contribution that may apply
† Actual cost depends on manufacturer price and allowable pharmacist fees and charges

These amounts apply during the 2009 calendar year

Unless the prescribing doctor has specifically indicated otherwise on the prescription, a pharmacist can dispense another bioequivalent brand at the patient's request. In this way, patients can avoid paying the brand price premium. However, when the brand price premium applies, it cannot be discounted by the pharmacist and the patient must pay it in full.

In August 2008, 334 of the approximately 3000 brands listed on the PBS attracted a brand price premium. The average brand price premium was $2.69 and ranged from $0.08 to $75.30. The majority of brand price premiums were in the range of $1.00–$4.00.

Therapeutic group premiums

Since 1998, a therapeutic group premium policy has applied to specifically defined groups of drugs which have similar safety and health outcomes. Within these groups, the drugs can only be interchanged by the prescriber. The government subsidises all drugs within a group to the level of the lowest priced drug. The difference in price between the lowest priced drug and the highest priced drugs within the group is called a therapeutic group premium. This is paid by the patient and goes to the manufacturer, not to the pharmacy or the government.

The principle is that there is always at least one drug within each therapeutic group of drugs that does not have the therapeutic group premium. In addition, when a patient is only able to take a drug with a therapeutic group premium for medical reasons, the prescribing doctor can request an exemption from the therapeutic group premium from Medicare Australia. Where there is no exemption, the patient has to pay the therapeutic group premium in full.

In August 2008, there were four groups of drugs affected by the therapeutic group premium policy. These were angiotensin converting enzyme (ACE) inhibitors, calcium channel blockers, proton pump inhibitors, and the H_2 receptor antagonists. Of the many items within these therapeutic groups, only eight attracted therapeutic group premiums ranging from $1.52 to $4.02. The prices of items in these groups are reviewed by the Pharmaceutical Benefits Pricing Authority each year, as are all drugs listed on the PBS.

Special patient contributions

For certain expensive medicines where the government and the manufacturer cannot negotiate a mutually acceptable price, the government makes a part contribution towards the manufacturer's price. In these instances the patient pays their normal co-payment plus a special patient contribution. This is the difference between the government's part contribution and the actual cost of the supplied medicine.

The special patient contribution cannot count towards the safety net, nor does it apply to RPBS prescriptions, so veterans only pay their normal co-payment contribution and the Department of Veterans' Affairs pays the rest.

In August 2008, there were 11 items on the PBS attracting a special patient contribution, which ranged from 61 cents to $437.01 (bleomycin sulfate).

Other charges for the patient

A significant number of PBS items are priced below the maximum co-payment for general patients of $32.90. As no government subsidy applies to these items, the patient pays the full cost for these medicines.

The amount the patient pays for these items will depend not only on the manufacturer's price for the item, but also on the fees and charges the pharmacist is entitled to apply. The online version of the PBS Schedule (accessible at www.pbs.gov.au) includes a 'price to consumer' column which lists the price the consumer can expect to pay, including the allowable fees and charges. There is also a column showing the 'maximum recordable value for safety net' – this is the maximum amount that can be recorded on the patient's 'prescription record form' to count towards the safety net for that patient. It does not necessarily equate to the amount the patient pays which could well be higher due to the additional fees and charges that do not count for safety net purposes.

The allowable extra fees and charges the pharmacist can apply to items priced under the maximum co-payment of $32.90 include the following:

Additional fee for safety net recording	$1.03
Allowable additional patient charge	up to $3.79

The additional fee ($1.03) can be charged for the extra work involved in recording the prescription details on the prescription record form. It may take the form of a part charge to take the cost up to $32.90. It is not compulsory for the pharmacist to charge the patient, but if the fee is charged it should be added to the PBS dispensed price recorded on the patient's prescription record form. Only one fee is payable per medicine, even if there are multiple quantities dispensed. It does not apply to prescriptions dispensed for concessional and repatriation patients.

The allowable additional patient charge (up to $3.79) applies where the PBS dispensed price is below the general patient contribution of $32.90. It is added to the PBS dispensed price in lieu of charging private prescription rates. The charge is agreed between the Pharmacy Guild and the government and has been in place since 1991 (when it stood at $2). This charge is optional and it can be discounted by the pharmacist. It may only be added to general patients' prescriptions and cannot be entered on the prescription record form as part of the cost of the medicine.

Some pharmacies discount below the base price of the medicine. Such pricing practice is usually associated with pharmacies offering a low-overhead, low-service model of care which may not be geographically convenient for some patients.

The maximum amount that may be charged to a general patient is $32.90 so this charge cannot be applied if the total cost (including the additional fee and this allowable extra charge) takes the amount over $32.90. However, this allowable additional patient charge may take the form of a part charge to take the cost up to $32.90.

The PBS reforms that took effect on 1 August 2008 lowered the prices patients pay for many items priced below the maximum patient co-payment – the prices of more than 1000 medicines have fallen by between 20 cents and $4.65. There is a $1.50 government incentive payment to pharmacists for dispensing substitutable, premium free prescriptions. This only applies to subsidised items and is not paid by the patient.

Patient safety nets

Since the late 1980s, a PBS safety net has been in place to protect patients and their families (particularly those who may be using large quantities of medicines) from the high cumulative cost of prescription medicines.

Two safety nets apply – one for pensioner, concessional and repatriation patients, and the other for general patients. The thresholds for each safety net are adjusted each year in line with the Consumer Price Index. For the 2009 calendar year the respective safety net thresholds are as follows:

General	$1264.90
Concessional and repatriation	$318 (equivalent to 60 prescriptions at $5.30)

The thresholds do not take into account brand price premium, therapeutic group premium or special patient contribution charges, or the allowable additional patient charge.

After reaching the threshold of $1264.90, general patients are issued with a safety net concession card that entitles them to pay the concessional co-payment ($5.30 per prescription) for the rest of that calendar year. These patients are still required to pay any relevant brand price premium, therapeutic group premium or special patient contribution charges.

After concessional patients have reached the threshold of $318, they are issued with a safety net entitlement card that allows them to receive their prescriptions free of charge for the remainder of that calendar year. However, these patients are still required to pay any relevant brand price premium, therapeutic group premium or special patient contribution charges.

Patients can keep a record of their accumulating expenditure on PBS/RPBS medicines on a prescription record form. This form is available from community pharmacies and can either be kept by the patient or the pharmacist. If kept by the patient, the form needs to be handed to the pharmacist on every occasion a PBS prescription is dispensed. Many patients (particularly those who use only one pharmacy) leave it to the pharmacist to keep their accumulating prescription usage on the dispensary computer.

Conclusion

There are many variables that need to be considered before a definitive answer can be given to patients about their prescription costs, including the patient's entitlement status (concessional, repatriation, general, safety net), whether a premium or special contribution applies and whether (for general patients) the amount falls below the maximum patient co-payment. In simple terms, Fig. 1 provides a useful summary of the likely cost, taking into account these variables.

Conflict of interest: none declared

Australian Prescriber's 250th meeting

The Editorial Executive Committee celebrates *Australian Prescriber's* 250th meeting in October 2008

From left to right: Dr FG Mackinnon – Deputy Editor; Ms M Ryan – Editorial Assistant; Dr S Twaddell – Clinical Pharmacology Registrar, 2008; Dr J Randall – Chair, National Prescribing Service Board; Prof T Usherwood – General Practitioner; Dr JS Dowden – Editor-in-Chief; Prof JWG Tiller – Psychiatrist and Chair, Editorial Executive Committee; Dr L Weekes – Pharmacist and Chief Executive Officer, National Prescribing Service; Dr S Kanagarajah – Geriatrician; Dr A Knight – General Physician; (absent: Dr P Kubler – Clinical Pharmacologist)

Treating dementia

***Alisa M Crouch**, Advanced Trainee in Geriatric Medicine, Princess Alexandra Hospital, Brisbane*

Summary

With increasing numbers of elderly patients, general practitioners are uniquely placed to investigate and treat dementia. Screening tests can be used, but a thorough history and physical examination are usually needed to make the diagnosis. Other conditions such as delirium and depression should be excluded. Both pharmacological and non-pharmacological treatments are important, depending on the particular problems facing the patient and their carer. The treatment of concurrent chronic disease may need to be modified as dementia progresses.

Key words: Alzheimer's disease, cholinesterase inhibitors, memory.

(Aust Prescr 2009;32:9–12)

Introduction

The prevalence of dementia approximately doubles with every five years of age beyond the age of 65. By 2050, the estimated number of new diagnoses in Australia will reach 175 000 annually compared with 45 700 in 2001.[1]

General practitioners are often the first point of contact for patients or families who have concerns about memory and cognitive function. They are also in a unique position to suspect the diagnosis of dementia when a patient presents with other problems.

The variation in presentation can make diagnosis of cognitive impairment or early dementia difficult. However, early diagnosis may enable planning for the future, decrease anxiety with appropriate education and allow consideration of treatment.

A multinational survey of carers for people with Alzheimer's disease showed a delay of 12 months from first symptoms to diagnosis, including a delay of four months in making an appointment. In the Australian component of this survey, 30% of patients were diagnosed by their general practitioners. In 93% of the Australian cases, general practitioners were the first point of contact.[2]

Diagnosis

The diagnosis of dementia is made on clinical assessment using formal criteria.[3] These include a history of the gradual onset of impairments in two or more cognitive domains, which cause difficulty in everyday function. These impairments should not be attributable to another cause, such as a drug effect or depression. Cognitive domains which are commonly impaired include memory, language and decision-making ability.

A detailed history with a collateral history from family and friends is essential in making the diagnosis, determining a pattern of progression and assessing any impact on daily living. As this is a time-consuming process, a screening test is often used to determine whether this is necessary.

The most commonly used screening test is the Folstein Mini-Mental State Examination (MMSE). Its validity has been demonstrated in many populations, however in patients of non-English speaking background the Rowland Universal Dementia Assessment Scale (RUDAS) may be more appropriate. The Mini-cog and General Practitioner Assessment of Cognition tests also have reasonable sensitivity and specificity and may take less time to administer.[4]

Differential diagnoses

It is worth deliberately excluding other conditions that may appear to cause cognitive impairment such as delirium, depression and the adverse effects of some drugs such as antipsychotics. The clinical features of these conditions are usually different from those of dementia when considered closely (see Table 1). Blood tests to help exclude illnesses mimicking dementia would include measurement of full blood count, biochemistry, thyroid stimulating hormone, vitamin B_{12} and

Table 1

Alternative causes of cognitive impairment

Condition	Clinical features
Delirium	Disorder of attention Fluctuation of symptoms over hours Recent onset (usually days to a few weeks)
Depression	Low mood is predominant feature May have biological features of mood disturbance May be motivated to improve performance on testing for a short time Often coexists with dementia May have history of depression
Drug effects	Common offenders are: • anticholinergics • sedatives and hypnotics • antipsychotics • analgesics Usually cause features of delirium, but the duration of symptoms may be very long

Table 2

Subtypes and features of dementia

Dementia subtype	Important features
Alzheimer's dementia	Clinical diagnosis requires memory impairment and impairment of language, executive function, motor function (dyspraxia) or agnosia
Vascular dementia	Stepwise progression, associated with physical signs of stroke or history of transient ischaemic attack
Mixed dementia	Most commonly mixed Alzheimer's disease and vascular dementia
Dementia with Lewy bodies	Progressive dementia with at least two of the three features of fluctuating cognition, visual hallucinations, and Parkinsonism Falls common Severely intolerant of the adverse effects of antipsychotic drugs Some evidence for benefit from cholinesterase inhibitors
Parkinson's disease with dementia	Ability to function can also be related to adequacy of dopa replacement and is often worse in 'off' periods May be part of a spectrum of disease with dementia with Lewy bodies
Frontotemporal dementia	Younger patients (less than 65 years of age) Family history of frontotemporal dementia often found 'Dysexecutive syndrome' with change in behaviour and personality common Delusions common Also includes progressive fluent and nonfluent aphasia types Memory relatively spared Mini-Mental State Examination unreliable Deteriorates with use of antipsychotics
Post-traumatic	History of injury with consistent imaging Not progressive Appears to increase the risk of later developing Alzheimer's type dementia
Toxic encephalopathy (e.g. alcohol)	History of toxin exposure

folate. A CT scan of the brain is useful in excluding conditions that may be amenable to treatment, such as subdural haemorrhage and normal pressure hydrocephalus. Although there may be reversible elements for many with abnormal tests, reversible causes of dementia are extremely rare (less than 1.5%).[5]

Identify the type of dementia

There is no 'cure' for most dementias. However, if the diagnosis includes information about the subtype of dementia (see Table 2) it allows a patient and their family to:

- access information that may help them deal with functional difficulties
- benefit from specific treatments (for example cholinergic therapies)
- avoid drugs known to aggravate problems (for example, anticholinergics, and antipsychotics in dementia with Lewy bodies)
- make plans for the future.

There is a good correlation between the clinical diagnosis of Alzheimer's disease and the neuropathology at autopsy. This association is less certain with other subtypes of dementia, but even a putative diagnosis may allow a patient and carer to make sense of the patient's symptoms. An example is the severe fluent aphasia seen in a younger patient with frontotemporal dementia.

Assessment and planning

Assess how the patient and their carer are coping and what formal and informal supports and help are available. This assessment can be time consuming and a home visit (perhaps by associated nursing or allied health staff) may be an efficient way of getting this information. Reimbursement for gaining collateral information may be included in a comprehensive health assessment which may be reimbursed under Medicare*. If there are areas of need identified, an Aged Care Assessment Team (ACAT) evaluation may enable access to a range of services.

People with dementia may be irritable and aggressive. They can experience delusions and hallucinations. Look for challenging behaviours as they are common and burdensome. They warrant a specific assessment and management approach.[6]

* Medicare Benefits Schedule – Items 700 and 702 www9.health.gov.au/mbs Search for 700 and 702 [cited 2009 Jan 13]

Ask about the making of wills, enduring powers of attorney and advance health directives. If these arrangements are not in place and the patient is competent to make these decisions they should be encouraged to do so. If capacity to perform these actions has been lost, the carer may have to apply for these powers through guardianship legislation.

Give the patient information about managing their disease and consider referring them to a local patient support organisation. Education of the carer can be invaluable.

Ask if the patient is still driving. The ability to drive safely is affected by many factors including visuospatial attention, switching of attention between tasks, and judgement. These are difficult to assess in a routine medical assessment. A specialist off-road and on-road assessment may be required. There may be state-funded access to these assessments, but the waiting lists can be very long and legal requirements vary from state to state.

Incontinence, increased nocturnal activity, impaired mobility[7] and aggressive behaviour increase the burden on carers. These problems are also predictors of nursing home placement within one year, independent of the level of cognitive impairment.

Referral

Sending the patient to a memory clinic or specialist (geriatrician, psychiatrist or neurologist) may be required to access some treatments or to confirm the diagnosis. Offer referral if the diagnosis is in doubt, if the patient is young, the presentation is unusual or if requested by the patient or the family.

Non-drug therapy

Monitor the patient's general health and other chronic conditions, especially vascular risk factors, to optimise health and independence. Should there be unexpected changes in cognition or behaviour, reconsider the possibility of incident delirium or depression. Other problems that can cause aggravated behaviours or distress in patients with dementia include pain, constipation, reduced vision and hearing loss.

Psychosocial interventions for carers, such as teaching them specific problem-solving skills, are more effective if the patient is also involved. Other factors that appear to be important include structured individual counselling, involvement of the extended family and consistent professional long-term support. These interventions can help to reduce the psychological burden and can reduce the need for institutional care of the patient. However, there is little impact on the carer's overall burden.[8] Interventions that do not improve outcomes include single interviews and interventions not associated with long-term contact such as short educational programs and support groups alone.

There is some evidence for the cost-effectiveness of community-based occupational therapy aimed at improving the patient's daily function.[9] Cochrane reviews have found no supportive evidence for the use of aromatherapy, music therapy, transcutaneous electrical nerve stimulation (TENS) or bright light therapy.

In practice, maintaining cognitive, physical and social activity appears to help in improving quality of life for the patient and reducing the burden of care. This burden is also improved by education about symptom progression, burden management and enabling appropriate access to services including respite care. Local patient support organisations can be useful resources for this. It is also important that carers maintain a relationship with their own general practitioner so that their own needs are addressed.

Drug therapy

Dementia is a progressive disease. Drug treatment at best only slows the decline in cognitive function.

Cholinesterase inhibitors

The drugs available in Australia are donepezil, galantamine and rivastigmine (also now available in a topical formulation). Patients must meet specific criteria to be eligible for subsidised treatment under the Pharmaceutical Benefits Scheme (PBS).

There is a statistical benefit of cholinesterase inhibitors in mild to moderate Alzheimer's disease, however the clinical benefit remains uncertain and all the studies are short term.[10] There is no evidence that one drug has a benefit over another. Many specialists switch to another cholinesterase inhibitor if there is no efficacy or tolerance of the first. If required, a trial of memantine may then be appropriate.

A study of patients taking one of several cholinesterase inhibitors (donepezil, tacrine and rivastigmine) showed improvement in cognition and function at one year and delay in nursing home placement.[11] However, some randomised controlled trials have shown the drugs do not delay placement.

There is also some evidence for the efficacy of cholinesterase inhibitors in vascular dementia and dementia with Lewy bodies.[12,13] The drugs have not been approved for these indications.

Common adverse effects include nausea, vomiting and diarrhoea. These are less troublesome with dose titration. Other adverse effects include bronchoconstriction (particularly in patients with asthma), bradycardia, cramps and vivid dreams.

Memantine

Memantine is a non-competitive antagonist of the N-methyl D-aspartate (NMDA) receptor. It is available on the PBS and may be an alternative for those patients unable to tolerate cholinesterase inhibitors.

Placebo-controlled trials have shown benefit in patients with moderate to severe Alzheimer's disease. Memantine has

been used in combination with cholinesterase inhibitors in clinical trials. As with the cholinesterase inhibitor studies, the outcomes measured do not translate easily into clinical practice. Memantine requires dose titration over a month to minimise the adverse effects of agitation, hallucination and headache. It may also increase the risk of seizure activity. Memantine is excreted in the urine and is probably not suitable for use in those with renal impairment.

Other drugs for dementia

Hundreds of different drugs are currently in various stages of clinical testing including vaccines and monoclonal antibodies against amyloid protein. There is no consistent evidence of efficacy or safety for drugs such as vitamin E, selegiline, vitamin B_{12} or ginkgo biloba.

Disease progression

While the patient's functional state is still intact, treatment of chronic conditions can improve symptoms and life expectancy. As dementia progresses the benefits are reduced and the need for investigations or therapy should be discussed with the carer. A previously completed advance health directive can be very valuable to guide therapy.

Timing of cessation of drug therapy for dementia is controversial, but should be considered if the patient is completely dependent in their care needs. Cessation should be discussed with the patient's family, particularly as they may notice some deterioration in the patient's functional abilities.

Conclusion

Most cases of dementia are diagnosed on clinical assessment. Excluding treatable causes of cognitive impairment is vital. Management of the patient and their care needs should be individualised. Consider the needs of the carers as well as the patient themselves. Early education and planning for future events can assist both the patient and their support network.

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Alzheimer's Australia: see www.alzheimers.org.au

Conflict of interest: none declared

Medicinal mishap

Monitor morphine

*Prepared by **John S Dowden**, Editor-in-Chief, Australian Prescriber*

Case

A 29-year-old woman presented to her general practitioner, having become unwell overnight with a sore throat. She was shivering, had muscle aches and a headache. Her past medical history included tonsillitis and migraine.

The general practitioner found exudate or pus on the woman's tonsils and her cervical lymph nodes were enlarged. Bacterial tonsillitis was diagnosed and the doctor took a throat swab. He gave the patient intramuscular procaine penicillin and a prescription for phenoxymethylpenicillin. Ibuprofen was recommended for symptomatic treatment.

Next morning, the patient was still unwell and contacted her general practitioner several times. He made a house call around 6.30 pm, by which time the patient was complaining of headache, nausea and vomiting. On examination her tonsils were still swollen, but a 'thick tonsillar membrane' made the doctor think the diagnosis could be glandular fever. He thought this may have brought on a migraine.

The general practitioner decided to give intramuscular morphine and metoclopramide. After estimating the patient's weight he gave a dose of 30 mg morphine from his doctor's bag supplies.

By midnight the patient's headache had returned and she was vomiting, so her husband called the doctor again. The general practitioner, who had been working since 5 am, had only got home a short time before the call. He decided not to see the patient again, but to admit her to the local hospital.

This was a small country hospital which only had two nurses on duty at night. The doctor spoke to one of the nurses and gave an order for intramuscular morphine and prochlorperazine. At a quarter to one in the morning, 30 mg morphine was given. The nurses decided to make observations of the patient's pulse, blood pressure, temperature and respiration every four hours.

One nurse then went to attend to a mother and newborn baby, while the other went into another room for a couple of hours. Each nurse assumed the other would do the regular round of all patients at 2 am.

At 3.15 am the nurse who had attended the new mother checked the patient. The woman was lying prone with her face in the pillow. She was not breathing. Resuscitation started and the doctor was called. He arrived quickly and intubated the patient, but she could not be revived.

A post-mortem examination found enlarged tonsils with narrowing of the upper airway. The diagnosis of glandular fever was confirmed. The blood concentration of morphine was found to be 0.16 mg/L. Death was attributed to respiratory depression caused by morphine intoxication on a background of upper airways narrowing which was a consequence of infectious mononucleosis.

Comment

Morphine is an appropriate drug for severe acute pain, but it is not usually recommended for migraine. The dose to use is determined by the patient's age, not their weight. For a 29-year-old woman, the recommended intramuscular dose is 7.5–12.5 mg which can be repeated after two hours, depending on the response. The dose is adjusted according to the response, so patients need to be observed more frequently than four-hourly.

There is an overlap between the therapeutic and toxic concentrations of morphine. Although 0.16 mg/L is within the therapeutic range, this concentration was too high for someone who had not been taking morphine regularly.

Therapeutic doses of morphine cause respiratory depression. The effect increases with the dose and respiratory arrest is a frequent cause of death in overdose. Metoclopramide and prochlorperazine would have added to the sedative effects of the 60 mg morphine the patient received over five hours.

In many hospitals it is mandatory for nursing staff to monitor a patient's pain score and sedation score after giving an opioid. If the patient is being observed, respiratory depression should be detected. It can be managed by giving naloxone, an opioid antagonist. There is a rapid response to an injection of naloxone, although its effect may wear off faster than the effect of morphine.

Conclusion

Patients who have not previously been taking opioids should start with a low dose of morphine. If the subcutaneous or intramuscular route is used, the first dose should be determined by the patient's age.

Hospitals should have protocols for observing patients who have been given opioid analgesics. This is to assess the response and to monitor for adverse effects, particularly respiratory depression.

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Prepared with the assistance of the general practitioner and clinical pharmacologist involved in the case.

Treatments for severe psoriasis

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Summary

Methotrexate, cyclosporin, acitretin and narrow-band ultraviolet B phototherapy help most patients with severe psoriasis. However, toxicity tends to limit the dose and duration of therapy, so other treatments are being developed. Biological therapies of proven benefit in severe psoriasis include etanercept, adalimumab and infliximab, which target tumour necrosis factor. Lymphocytes are the target of other therapies including efalizumab and alefacept. Biological therapies have a range of safety concerns which differ from, but overlap with, those of other systemic treatments for psoriasis. In Australia, the Pharmaceutical Benefits Scheme subsidises a therapeutic trial of approved biological therapies in severe psoriasis if traditional therapies are insufficiently effective or are contraindicated by intercurrent disease or adverse effects. Ongoing therapy is only subsidised for patients whose psoriasis significantly improves. Care must be taken when withdrawing efalizumab or cyclosporin in case of rebound disease.

Key words: adalimumab, efalizumab, etanercept, infliximab, ustekinumab.

(Aust Prescr 2009;32:14–18)

Introduction

Psoriasis is a chronic disorder characterised by erythematous plaques, patches and papules which may be pruritic and classically have silver scale. Morphologically there are varying forms, with 80–90% being of the plaque variety. Other less common psoriasis forms include inverse psoriasis (involving the skin folds), erythrodermic (from chronic plaque psoriasis or acute), pustular and guttate (with 'dewdrop' lesions).[1]

The peak onset of psoriasis occurs during the teenage and early adult years which means that most patients will be affected for the majority of their lives. This necessitates careful consideration as to the short-, medium- and long-term risks of psoriasis, its comorbidities and its treatments. The consequences of severe psoriasis are more than just skin deep. It may be associated with conditions such as arthritis, liver disease, cardiovascular disease and the metabolic syndrome. Severe psoriasis involves large areas of the skin's surface. Due to the chronic and very visual nature of this disease, there can be profound psychosocial consequences.[2]

The autoimmune lesions of psoriasis are hyperproliferative, hyperaemic, abnormally thick and shed increased amounts of highly visible scales. Psoriasis plaques are packed with enormous numbers of activated T cells which drive the inflammatory process, cause dysmaturation of epidermal cells and impair skin function. This results, for example, in the increased loss of water through the epidermis and makes psoriatic skin more susceptible to physical and chemical irritation, contributing to itching and irritation. The plaques are also prone to develop painful fissures and cracks.

Psoriasis involving sensitive skin areas such as genitals, groin and face or the glabrous skin of the hands and feet is often symptomatic. Involvement of these areas is particularly likely to adversely impact on activities of daily living, personal interactions, especially those involving skin contact, and the ability to work.

The aims and frustrations of therapy

Patients want a safe, convenient therapy that will rapidly clear their disease and keep it in remission. Surveys of patient support groups have found most patients were not satisfied with the control obtained with standard therapies. Around a third felt that their medical treatment was insufficiently aggressive. To add to their frustration, patients often trial a therapy for several months before their treatment is altered because of an inadequate response. Following a switch, the mean time to treatment failure is another 3–6 months.[3]

Untreated severe psoriasis tends to follow a fluctuating but persistent course. In contrast, the course of disease in mild to moderate psoriasis is generally one of relapse and remission.

Phototherapy and standard systemic drugs in severe psoriasis

Our standard therapies can control psoriasis in the majority of patients with severe psoriasis (Table 1), however potential therapy-related toxicities limit the dose and duration of

Table 1

Treatments for severe psoriasis

	Administration	Dosing	Induction therapy	Maintenance therapy
Standard				
Acitretin	Oral	10–50 mg daily	Low initial dose followed by dose escalation often used	May be daily, alternate days or less, used long-term, often years
Cyclosporin	Oral	2–5 mg/kg daily in two doses	3.5–5 mg/kg daily	2–4 mg/kg daily, 6–24 months
Methotrexate	Oral or intramuscular	5–25 mg weekly	Close clinical and blood monitoring needed	Long-term, often years
Phototherapy	In cabinet	3 times a week	Dosing tailored depending on skin type and response	6–12 week course, intermittent therapy
Biological				
Adalimumab	Subcutaneous	Fortnightly	80 mg followed by 40 mg one week later	40 mg fortnightly
Alefacept	Intravenous	Weekly	7.5 mg for 12 weeks	If the course is repeated there must be a gap of at least 12 weeks between courses
	Intramuscular	Weekly	15 mg for 12 weeks	
Efalizumab	Subcutaneous	1 mg/kg weekly	0.7 mg/kg first dose	Long-term, potentially years
Etanercept	Subcutaneous	Weekly or twice-weekly	50–100 mg weekly for up to 12 weeks*	50 mg weekly either continuously or 12 weeks on/12 weeks off, potentially years
Infliximab	Intravenous	5 mg/kg	Weeks 0, 2, 6, 12	6–8 weekly maintenance, potentially years

* Australian Medicines Handbook and product information give 50 mg twice weekly as an option for initial treatment

therapy. This has led to intermittent, sequential, rotation and combination therapies which aim to maintain reasonable disease control while reducing the risk of treatment-specific cumulative toxicities. Other than acitretin (an oral retinoid) all systemic treatments, including biological therapies, are immunosuppressive and are contraindicated in patients with cancer or infections. Only around a third of patients with chronic plaque psoriasis achieve and maintain good disease control when acitretin is used as monotherapy although its efficacy in pustular and erythrodermic psoriasis is higher.

Narrow-band phototherapy is generally administered three times a week. Moderate psoriasis can usually be cleared with around six weeks of phototherapy and will normally result in around 3–6 months of improved disease control. Onset of significant change usually occurs within 20–25 treatments (at approximately three weeks into therapy). Phototherapy can be combined with topical therapy. Concurrent acitretin can speed up and increase the response to phototherapy. Once adequate clearance has been achieved, phototherapy is normally stopped. Phototherapy can cause erythema, pruritus and nausea. High cumulative doses increase the risk of skin cancer.[4]

Cyclosporin usually works quickly to clear psoriasis (6–12 weeks) and is generally very effective in maintaining disease remission. Depending on the dose required for maintaining control, hypertension, nephrotoxicity, malignancy and metabolic concerns usually limit the total duration of cyclosporin therapy to 12–24 months.

Methotrexate is generally slower at clearing psoriasis than cyclosporin partly because of cautious initial dosing. It often takes three or more months to induce remission, but if tolerated and there is no haematological or hepatic toxicity methotrexate can often be continued for many years to maintain good disease control. The dose is titrated to the lowest dose that balances safety concerns and disease control. Monthly or more frequent monitoring is needed for the first six months when starting or increasing the dose of methotrexate. Second monthly monitoring of full blood count, liver function tests, urea and electrolytes needs to be continued long-term to help avoid preventable toxicities. Taking folate supplements daily (5 mg folic acid) may help prevent a number of potential toxicities such as gastrointestinal adverse effects and bone marrow toxicity and is the standard of care in Australia.[5]

Biological therapies

Biological therapies for severe psoriasis either target T cells or block pro-inflammatory cytokines. Efalizumab is a recombinant humanised monoclonal antibody against cells with the CD11a marker. Binding interferes with T cell activation in lymph nodes and T cell trafficking to skin and interferes with their activation and reactivation in the skin. Alefacept binds to the CD2 receptor

on lymphocytes. It reduces the number of T lymphocytes and interferes with their activation. Etanercept, infliximab and adalimumab bind with tumour necrosis factor (TNF), a key pro-inflammatory cytokine in psoriasis. Ustekinumab is a human monoclonal antibody against interleukin-12 and interleukin-23. It is thought to rebalance the T cell response away from the psoriatic diathesis.

Biological therapies appear to work in severe psoriasis irrespective of the response to standard therapies. However, there must have been an inadequate response or significant intolerance to at least three treatments before patients can use a biological therapy subsidised by the Pharmaceutical Benefits Scheme (PBS). There are no markers, other than a trial of therapy, to help us identify responders to biological therapies.

Most patients start to improve by four weeks and achieve good reductions in disease severity by 12 weeks. Infliximab is associated with the best response rates as 80% of patients achieve a 75% improvement in their psoriasis area and severity index which equates closely to disease clearance. The greatest improvements in quality of life are with infliximab followed by etanercept.[6]

To date the literature on combination therapy involving biologicals is extremely limited. This area needs to be further explored to improve patient outcomes and important drug safety issues such as skin cancer.

Safety

The efficacy and safety of the biological therapies requires long-term disease-specific data. The effects associated with psoriasis and the toxicities of previous therapies are likely to influence the frequency and severity of the harm associated with long-term treatment, particularly when using an immunosuppressive drug.

The safety data from a cohort of patients treated with efalizumab continuously for longer than 2.5 years is a reassuring beginning and suggests that efficacy is well maintained.[7] However, this cohort differs significantly in their disease severity and previous treatments from those currently qualifying for therapy subsidised by the PBS. Serious adverse events with efalizumab include infections and severe arthritis.

Long-term efficacy and safety data are more limited for the therapies which act on TNF. When TNF inhibitors are used to treat rheumatoid arthritis the patients' already elevated risk of lymphoma may increase. There is also a risk of serious infections including tuberculosis reactivation. These therapies can also worsen congestive cardiac failure. New neurological symptoms such as visual disturbance and paraesthesia warrant stopping treatment if a demyelinating cause is suspected. There are rare reports of demyelinating disease, such as optic neuritis, and exacerbations of multiple sclerosis occurring in patients taking TNF inhibitors.

Risk of disease rebound

A rebound in psoriasis can occur after stopping a drug or therapy. In a rebound episode the disease becomes unstable and rapidly more severe than before therapy. It may also affect previously uninvolved body regions or change its form, for example becoming erythrodermic or pustular. The risk of rebound varies with the treatment.

Ceasing efalizumab appears to have a significant risk of causing severe and unstable disease that can result in prolonged hospitalisation. Efalizumab should only be stopped under the guidance of a dermatologist familiar with its use. To minimise risks of a disease rebound when switching therapy, these patients need to be closely monitored. Combination therapy may be needed during the transition period. Pharmacogenetics show promise for helping to predict and prevent this adverse effect in subpopulations of patients.

Renal and cardiovascular problems

Patients with severe psoriasis have several factors that place them at increased risk of clinically significant renal and cardiovascular disease. They are more likely to smoke, with the number of cigarettes smoked per day correlating with disease severity. They are also more likely to have hypertension, hyperuricaemia, nephrocalcinosis and hyperlipidaemia. Although most of the evidence is from transplantation medicine, calcium antagonists are nephroprotective when used for small increases in blood pressure occurring during the first 1–2 months of cyclosporin therapy. An increase in blood pressure after this time warns of cyclosporin nephrotoxicity, especially if associated with an elevated creatinine or an increase in the patient's creatinine of more than 30% above baseline. If this fails to settle with dose reduction, cyclosporin should be stopped before significant permanent renal damage can occur.

The liver and obesity

Patients with severe psoriasis have an increased risk of liver disease including non-alcoholic steatohepatitis and cirrhosis due to associated comorbidities. Methotrexate and acitretin therapy can contribute to these liver problems.

Lifestyle interventions can reduce the risk of medically significant liver-associated comorbidities. Health professionals should regularly counsel all patients, but particularly those with severe psoriasis, about the importance of maintaining a healthy weight, regularly exercising, having a diet with a low glycaemic index and low fat plus moderation of their often excessive alcohol consumption. Patients with psoriasis should be offered vaccination for hepatitis A and B.

Malignancy

Patients with severe psoriasis are at increased risk of skin cancer and this increases further if phototherapy is followed

or combined with cyclosporin or methotrexate. Education about the importance of sun protection, sun avoidance, skin monitoring and lifelong regular (at least annual) full skin examinations is warranted.

It is unclear if immunosuppressive therapies further increase the risk of skin cancer. They are likely to increase the risk of oncogenic virus-related malignancies including human papillomavirus-related cervical, vulval and penile cancer, warranting regular check-ups. Patients with psoriasis should be regularly counselled regarding lifestyle modification and interventions to reduce the impact of associated comorbidities and exposures known to increase malignancy including smoking, obesity and diet.

Good long-term control of the inflammation due to severe psoriasis could theoretically reduce the background risk of malignancy such as lymphoma. However, this is likely to be counterbalanced by the immunosuppressive actions of therapies for severe psoriasis. All appropriate recommendations for cancer screening should be followed.

Periodontal disease

Good dental hygiene and regular dental review are important for everyone on immunosuppressive therapy. Cyclosporin carries the greatest risks for causing as well as worsening periodontal disease, including acute and chronic gingivitis and gingival hypertrophy.

Infections and vaccination

Patients with severe psoriasis should keep their immunisations up to date. In general, vaccinations are recommended before commencing biological therapy. The standard of care that is appropriate to follow may be similar to that of organ transplantation where pneumococcal, hepatitis A and B, influenza and tetanus-diphtheria vaccines are recommended before starting immunosuppressive therapy.[1] Live vaccines should not be given without specialist advice if the patient is taking immunosuppressive therapy. All patients should be screened for tuberculosis before immunosuppressive therapy especially when starting a TNF inhibitor.[8]

When a patient with psoriasis presents with sepsis while on systemic therapy, always consider atypical infections. Careful consideration is also required regarding ongoing therapy for their psoriasis. In contrast to efalizumab, a TNF inhibitor can be stopped, given the absence of the risk of rebound on cessation. Thought needs to be given to the possible ongoing immunosuppressive effect of the biological therapies; etanercept has a short half-life of days, but the half-life of adalimumab and infliximab is considerably longer, up to weeks in duration.

When taking a medication history for a patient presenting with potential sepsis, remember to ask about injectable drugs, including the biological therapies.

Pregnancy and lactation

Effective pregnancy prevention advice and precautions need to be regularly provided and checked when women of childbearing age are taking systemic psoriasis therapies. Should pregnancy occur, all systemic psoriasis drugs should be stopped immediately and specialist advice sought. The risk of disease rebound with efalizumab has to be balanced against the uncertain risk to the fetus. Acitretin and methotrexate have significant proven adverse effects on the fetus. The long half-life of acitretin means that a planned pregnancy must be postponed for several years after stopping treatment. Cyclosporin has been used in pregnancy when severe psoriasis has not responded to other therapies. The safety of biological therapies in pregnancy and breastfeeding is unknown.

Psoriatic arthritis

Approximately 10% of patients with psoriasis also have psoriatic arthropathy. Drugs which improve the skin may have less effect on the arthritis.

The treatment of psoriatic arthritis is similar to that of other joint diseases and may involve disease-modifying drugs. If there is no response to drugs such as sulfasalazine and methotrexate, biological therapies may be considered. Adalimumab, etanercept, infliximab and ustekinumab can be used to treat severe active psoriatic arthritis.

Conclusion

Biological therapies for psoriasis are proving valuable for achieving and maintaining disease control in patients with severe psoriasis. They complement rather than replace our standard therapies. They also provide alternatives in resistant disease and greater therapeutic choice should allow better tailoring of treatment to the patient's needs. Treatment choice should take into consideration the order in which drugs are prescribed, a person's stage in life, associated comorbidities and variation in disease severity. The best use of biological therapies will be guided by the ongoing collection of data on their long-term safety.

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Conflict of interest: Dr Sullivan has served on advisory committees for Schering and Wyeth, and has received (unconditional) educational grants from Merck Serono. Dr Preda: none declared.

Self-test questions

The following statements are either true or false (answers on page 27)

1. Patients with severe psoriasis may experience a flare-up of the disease when treatment with efalizumab is ceased.
2. Women taking acitretin should not plan to become pregnant until at least two years after stopping treatment.

Patient support organisation

Psoriasis Australia

Psoriasis Australia provides information about psoriasis, and support to people with psoriasis, to enable informed decisions on treatment choices and lifestyle. It provides pamphlets and other material for health professionals and the public. Although based in Victoria it is a national organisation.

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Dental notes

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Treatments for severe psoriasis

Dentists have become increasingly aware of the effects that systemic medications can have on the oral cavity. Cyclosporin has long been known to be associated with gingival enlargement, and the degree of enlargement appears to be associated with both the daily dose and length of time the drug is taken. This was first observed in patients with renal transplants and these patients remain the group most commonly affected by cyclosporin-induced gingival hyperplasia.[1] However, cyclosporin and other immunomodulatory drugs are commonly used for patients with severe psoriasis. Cyclosporin-induced gingival enlargement resolves following cessation of the drug and, in some patients, it will also resolve following a reduction in drug dosage.[2]

A recent study has shown that isotretinoin (a retinoid used for severe acne) has significant oral adverse effects with a decrease in salivary flow and a concomitant increase in the number of decayed, missing or filled teeth.[3] It is possible that acitretin (a retinoid used for severe psoriasis) could have a similar effect. Acitretin is known to cause dry mouth and gingivitis. Patients taking methotrexate also have a decrease in salivary function, although this has not been studied in patients with severe psoriasis. People taking medication for severe psoriasis require very high levels of oral hygiene and regular professional cleaning to prevent or minimise deterioration of their periodontal structures. It would be advisable for these measures to start at the same time they begin their treatment for psoriasis.

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Drug treatment of pituitary tumours

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Summary

The primary therapeutic aims in the management of pituitary tumours are to correct the excess hormone secretion and to reduce tumour size to prevent damage to normal pituitary tissue and adjacent structures such as the optic chiasma. Treatment of pituitary tumours has been improved by advances in transphenoidal surgery and radiotherapy and by the development of effective drug therapy for prolactinoma and acromegaly. Dopamine agonists are first-line treatment in prolactinomas, and somatostatin analogues are often used in the management of acromegaly.

Key words: acromegaly, dopamine agonists, prolactinoma, somatostatin analogues.

(Aust Prescr 2009;32:19–21)

Introduction

Pituitary tumours are almost always benign adenomas classified by size and cell of origin. Lesions smaller than 1 cm are classified as microadenomas, and larger lesions are macroadenomas. Prolactin, adrenocorticotrophic hormone, thyroid-stimulating hormone, luteinising hormone, follicle stimulating hormone and growth hormone are all secreted by cells in the anterior pituitary and the tumour may arise from any of these cell types. Patients with pituitary tumours may therefore present with:

- hormonal hypersecretion (for example prolactinoma, Cushing's disease, acromegaly)
- symptoms of mass effect due to tumour compression of adjacent structures (for example visual field defects)
- hormone deficiencies caused by the tumour damaging other cell types in the pituitary.

Tumours may also be an incidental finding on radiological imaging.

Investigations

The diagnosis of pituitary tumours rests on biochemical assessment and magnetic resonance imaging (MRI). Specific tests can be organised to assess secretory abnormalities or hormonal deficiencies.

Management

The management options for pituitary tumours include neurosurgery, medical therapy or irradiation, depending on the clinical presentation and type of pituitary tumours. Drug treatments can be used as first-line therapy for prolactinomas and acromegaly.

Prolactinoma

Stress, renal failure and drugs can cause mild to moderate hyperprolactinaemia, but a greatly increased concentration is usually caused by a pituitary adenoma. Prolactinomas are the most common hormone-secreting pituitary adenomas, accounting for approximately 60% of functioning tumours. Over 90% of prolactinomas are small, benign intrasellar tumours that rarely increase in size.[1]

Dopamine agonists

Dopamine agonists are usually the first therapy for patients with either prolactin-secreting microadenomas or macroadenomas. The aim of treatment is to normalise prolactin concentrations, restore gonadal function and shrink the tumour. Not all patients with prolactin-secreting microadenomas require treatment with dopamine agonists. Premenopausal women with normal menstrual cycles or postmenopausal women with tolerable galactorrhoea can be monitored with 6–12 monthly measurements of serum prolactin. Women treated with dopamine agonists who do not desire pregnancy but require contraception may take an oral contraceptive provided that there is tight control and monitoring of serum prolactin because oestrogen may stimulate lactotroph growth.

Patients with prolactin-secreting macroadenomas, including those with associated visual field defects, can be safely treated with dopamine agonists. Tumour shrinkage often occurs within 1–2 weeks of commencing therapy, and may continue for many months to years.

The dopamine agonists currently available in Australia are bromocriptine, cabergoline and quinagolide. If the patient cannot tolerate the first dopamine agonist prescribed, or serum prolactin does not normalise, it is reasonable to switch to another dopamine agonist. Transphenoidal surgery is reserved

for patients who are either resistant or intolerant to medical therapy.

Cabergoline

Cabergoline is an ergot derivative with a very prolonged duration of action. It is preferred to bromocriptine as it is more potent and effective in achieving normoprolactinaemia. Cabergoline is given once or twice weekly and the usual maintenance dose is 0.5–2 mg weekly. It is better tolerated than bromocriptine and may be effective in patients resistant to bromocriptine.

There is an increased risk of cardiac valve regurgitation with the use of cabergoline in patients with Parkinson's disease.[2] The doses used to treat prolactinomas are much smaller, but it may be reasonable to offer echocardiograms to patients who have been on prolonged treatment with cabergoline.

Bromocriptine

Bromocriptine is an ergot alkaloid and suppresses prolactin secretion by directly binding to D_2 dopamine receptors within the anterior pituitary. Therapy should be started at 0.625 to 1.25 mg at night to minimise the adverse effects of nausea, vomiting, dizziness and postural hypotension with the initial dose. The dose can be gradually increased to a maintenance dose of 2.5 mg twice or three times daily. Bromocriptine normalises prolactin and reduces tumour mass in 80–90% of patients with microadenomas and in 70% of patients with macroadenomas.[1]

Quinagolide

Quinagolide is a non-ergot, well-tolerated, oral dopamine agonist. If patients cannot tolerate bromocriptine or cabergoline, it is best to switch them over to quinagolide as it may be better tolerated given its specificity for the D_2 dopamine receptor. Quinagolide is given once daily and a starter pack is used to gradually increase the dose over seven days to a maintenance dose of 75 microgram daily. The dose can be increased further to 150–300 microgram daily if required.

Monitoring patients with prolactinoma

Serum prolactin should be checked one month after starting a dopamine agonist and then 3–6 monthly as clinically indicated. Once hyperprolactinaemia is normalised, serum prolactin can be monitored annually. When prolactin has been normal for more than two years and the reduction in tumour size is more than 50%, the dose of dopamine agonists can be gradually decreased to the lowest maintenance dose.[1] However, cessation of treatment may lead to tumour regrowth and recurrence of hyperprolactinaemia. Follow-up of these patients is important with regular (3–6 monthly) monitoring of serum prolactin.

Patients with microadenomas whose serum prolactin concentrations have been suppressed for more than 1–2 years by dopamine agonist therapy may be able to stop their medication. It is also reasonable to withdraw treatment in those patients with macroadenomas and no evidence of residual tumour on MRI, but the dopamine agonists should be gradually tapered before cessation. Serum prolactin should be monitored every three months during the first year of drug withdrawal.[3] Therapy should be continued in patients with any tumour mass on MRI.

Pregnancy

Once pregnancy is confirmed, bromocriptine or cabergoline are often withdrawn in patients with microadenomas, but dopamine agonists may be continued in patients with macroadenomas. Patients are asked to report headaches and visual disturbances during pregnancy as prolactinomas, especially macroadenomas, may grow during pregnancy under continued oestrogen stimulation.

Bromocriptine has an extensive safety record in pregnancy and emerging experience suggests cabergoline may also be safe in early pregnancy. Insufficient safety data on quinagolide preclude its use during pregnancy.

Acromegaly

Growth hormone secreting adenomas account for 20% of functional pituitary tumours. The aims of treatment in acromegaly are to:

- remove the tumour and resolve symptoms due to tumour mass
- normalise growth hormone and insulin-like growth factor (IGF-1) secretion
- prevent progressive disfigurement, bone expansion and osteoarthritis
- improve cardiovascular and metabolic abnormalities.

Transphenoidal surgery is the mainstay of treatment, with surgical cure achieved in more than 80% of patients with microadenomas.[4] However, only 50% of patients with macrodenomas can be cured surgically and this rate is significantly reduced in patients with invasive macroadenomas. Cure is defined biochemically as normalisation of IGF-1 within the age-related reference interval or a random growth hormone concentration less than 2.5 microgram/L (5 mU/L) or adequate suppression of growth hormone secretion during an oral glucose tolerance test.

Medical treatment with somatostatin analogues has assumed a prominent role in the management of acromegaly and is successful in the control of hormone excess in about 60% of patients.[4] It has often been used as adjuvant therapy after unsuccessful surgery, but more recently somatostatin analogues have been proposed as first-line therapy. Studies have shown that biochemical control of acromegaly and tumour shrinkage can be achieved when somatostatin analogues are used as first-line therapy, especially when surgical cure is not possible for invasive macroadenomas.[5] Somatostatin analogues may also be used in preoperative treatment of patients with significant

obstructive sleep apnoea or cardiovascular disease, to attempt to rapidly lower growth hormone concentrations and possibly reduce perioperative complications.

The availability of long-acting depot preparations of somatostatin analogues has improved the ease of administration and patients' compliance. Octreotide and lanreotide are currently available in Australia. Patients resistant to medical therapy are often referred for radiotherapy.

Octreotide

Octreotide is an eight-amino acid synthetic somatostatin analogue. The short-acting form is available as subcutaneous injections, given as 100–200 microgram three times daily. The modified-release, long-acting formulation of octreotide is given as a monthly intramuscular injection. Gastrointestinal adverse effects, due to drug-induced suppression of gastrointestinal motility and secretion, occur in one-third of patients. These effects include nausea, abdominal discomfort, fat malabsorption, diarrhoea and flatulence, but are often short-lived. The most significant adverse effect involves the formation of gallstones and in symptomatic patients cholecystectomy may be required. Mild glucose intolerance may develop due to transient suppression of insulin secretion.

Lanreotide

Lanreotide is a cyclic octapeptide analogue of somatostatin. Lanreotide acetate is given as fortnightly intramuscular injections. The availability of lanreotide as a gel in a pre-filled syringe (60, 90, 120 mg) has further improved the ease of administration. This is given as a deep subcutaneous injection every four weeks. Extended dosing with 120 mg every 6–8 weeks may be as effective for patients established on 60–90 mg every 4 weeks. The adverse effect profile is similar to that of octreotide.

Dopamine agonists

Dopamine agonists may suppress growth hormone secretion in patients with acromegaly and some growth hormone-secreting adenomas may co-secrete prolactin. These drugs are often used in conjunction with somatostatin analogues for an additive suppressive effect when biochemical cure is not achieved with somatostatin analogues alone. Dopamine agonists alone are rarely effective in the treatment of acromegaly.

Pegvisomant

Pegvisomant is a pegylated recombinant analogue of human growth hormone which acts as a growth hormone receptor antagonist. It normalises IGF-1 in over 90% of patients with acromegaly. Pegvisomant is given as subcutaneous injections. This drug can be used in patients with active acromegaly not cured by surgery and resistant to somatostatin analogues. Pegvisomant, as a growth hormone antagonist, does not act on the tumour and is unlikely to influence tumour growth and secretion. It is well tolerated and long-term safety data are gradually accumulating, but it may cause elevated transaminases on liver function tests. This treatment is not readily available in Australia.

Future directions

The development of new therapies and the availability of long-acting depot formulations have provided improved therapeutic options in the management of growth hormone- and prolactin-secreting pituitary tumours. Further drug development for the management of pituitary tumours should enable more patients with hormone-secreting adenomas to be successfully treated medically.

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 27)

3. Dopamine agonists are first-line therapy for prolactin-secreting microadenomas.
4. Gallstones are an adverse effect of octreotide.

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.

Desvenlafaxine succinate

Pristiq (Wyeth)

50 mg and 100 mg extended release tablets

Approved indication: depression

Australian Medicines Handbook section 18.1.4

Venlafaxine is a serotonin reuptake inhibitor which, at higher doses, also inhibits reuptake of noradrenaline. It is metabolised in the liver to desvenlafaxine which also has antidepressant actions. The decision to market the active metabolite might be related to the expiry of the patent on the controlled release formulation of venlafaxine.

Desvenlafaxine is well absorbed and only needs to be taken once a day. Although it is mainly metabolised by conjugation, desvenlafaxine is partly metabolised by cytochrome P450 3A4. Inhibitors of this enzyme, such as ketoconazole, may increase plasma concentrations of desvenlafaxine. The half-life of desvenlafaxine is 11 hours, but this may be increased by hepatic impairment. As almost half the dose is excreted unchanged in the urine, less frequent dosing is recommended for people with renal impairment.

Desvenlafaxine was compared to placebo in 234 patients with major depressive disorder. The mean score on the Hamilton Rating Scale for Depression was 23.7. The 120 patients randomised to use desvenlafaxine took 100 mg for two weeks then increased to 200 mg. After eight weeks the mean depression score had fallen to 14.1 with desvenlafaxine and 15.1 with placebo. This difference was not significant.[1]

A larger randomised trial evaluated the efficacy of daily desvenlafaxine in 114 patients who took 100 mg, 116 who took 200 mg, 113 who took 400 mg and in 118 who took a placebo. At the start of the study the mean score on the Hamilton Rating Scale for Depression was approximately 23. After eight weeks the mean reduction in the score was 10.6 with 100 mg, 9.6 with 200 mg, 10.7 with 400 mg and 7.7 with placebo. Only the reductions in the 100 mg and 400 mg groups were significantly better than the placebo response.[2]

Another eight-week study compared desvenlafaxine 200 mg and 400 mg to placebo. The scores on the Hamilton Rating Scale were reduced by 12.6 with 200 mg, 12.1 with 400 mg and by 9.3 with placebo.[3]

In the clinical trials the most common adverse effects of desvenlafaxine were nausea, dry mouth, somnolence, anorexia, constipation and nervousness.[1,2] Other adverse effects include vomiting, dizziness, blurred vision, sexual dysfunction, hypertension, increased cholesterol and triglycerides and altered liver function. Approximately 12% of patients who took desvenlafaxine withdrew from trials because of adverse events. Ideally, the dose should be tapered off as stopping the drug abruptly can cause discontinuation reactions.

Venlafaxine is metabolised to desvenlafaxine by cytochrome P450 2D6. Giving the metabolite as a drug bypasses this step so there could be less potential for drug interactions, but there is little evidence that desvenlafaxine has any advantage over venlafaxine. The precautions for prescribing the two drugs are similar. Overseas, the manufacturer applied to have desvenlafaxine approved for the treatment of menopausal hot flushes, but the US Food and Drug Administration has asked for more data and in Europe the application has been withdrawn.

The recommended dose in depression is 50 mg daily, but until recently there was little published information about this dose. Two trials have compared desvenlafaxine 50 mg and 100 mg to placebo. After eight weeks, both doses had reduced the scores on the Hamilton Rating Scale, but only the 50 mg dose was significantly better than placebo in both trials.[4,5] It appears that higher doses may have more adverse effects, but no additional benefit. For patients who are being satisfactorily managed with venlafaxine there seems little reason to change to desvenlafaxine.

T T manufacturer provided additional useful information

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Methylnaltrexone bromide

Relistor (Wyeth)

vials containing 12 mg/0.6 mL solution

Approved indication: opioid-induced constipation

Australian Medicines Handbook section 12.4.4

Constipation is one of the common adverse effects of opioid analgesics. This constipation is caused by several mechanisms such as altered smooth muscle tone in the gut.

Methylnaltrexone is related to the opioid antagonist naltrexone. Whereas naltrexone is particularly used to block the effects of opioids on the central nervous system, methylnaltrexone is more selective for peripheral opioid receptors. This is because adding a methyl group reduces lipid solubility which limits the molecule's ability to cross the blood-brain barrier. Blocking opioid receptors in the gut should relieve constipation without counteracting the analgesic effects of opioids.

While naltrexone is taken by mouth, methylnaltrexone has to be given by subcutaneous injection. It has a half-life of approximately eight hours and most of the dose is excreted unchanged, mainly in the urine. The dose is adjusted according to the patient's weight and is usually given on alternate days as needed.

A dose-ranging study was carried out in 33 patients receiving opioids for palliative care. For patients receiving a minimum dose of at least 5 mg the median time until a bowel movement was 1.26 hours. Almost half of these patients responded within four hours. Higher doses did not improve the response.[1]

A double-blind placebo-controlled trial was carried out in 133 terminally ill patients taking opioids and laxatives. They were given injections every other day for two weeks. A bowel motion occurred within four hours of the first injection in 48% of the methylnaltrexone group and in 15% of the placebo group. The median time between the injection and a bowel movement was 6.3 hours with methylnaltrexone, but more than 48 hours with placebo. After two weeks the response rate was 38% with methylnaltrexone and 8% with placebo. Pain scores were largely unchanged during the study.[2]

Patients given methylnaltrexone are more likely than those given placebo to complain of nausea, dizziness, flatulence, abdominal pain and increased temperature.[2] Diarrhoea can occur and if it is persistent, treatment should be discontinued. The drug should not be used if the patient is suspected of having an obstruction of the bowel.

The longer-term efficacy of methylnaltrexone is uncertain because the patients in the trials had a limited life expectancy. At present methylnaltrexone is reserved for palliative care patients with opioid-induced constipation whose response to laxatives has been insufficient.

T T T manufacturer provided clinical evaluation

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Rivaroxaban

Xarelto (Bayer Schering)

10 mg film-coated tablets

Approved indication: prevention of postoperative venous thrombosis

Australian Medicines Handbook section 7.1.3

The search for alternatives to heparin and warfarin has looked at different sections of the coagulation cascade. One approach is to inhibit activated factor X (Xa) which is responsible for the conversion of prothrombin to thrombin. Fondaparinux is an indirect inhibitor of factor Xa, but has to be given by injection. Rivaroxaban offers an oral alternative and has a more direct action.

Rivaroxaban is well absorbed from the gut and maximum inhibition of factor Xa occurs three hours after a dose. The effect lasts 8–12 hours, but factor Xa activity does not return to normal within 24 hours so once-daily dosing is possible. Rivaroxaban is eliminated in the urine and by metabolism. It is contraindicated in patients with significant renal or hepatic disease. As the hepatic metabolism involves cytochrome P450 3A4 there is a potential for interactions with drugs such as rifampicin and the azole antifungals. There are also theoretical interactions with inhibitors of the P-glycoprotein transporter, such as verapamil and diltiazem.

Anticoagulation after orthopaedic surgery on the lower limb can reduce the incidence of deep vein thrombosis. A dose-ranging study of rivaroxaban was therefore carried out in 873 patients having total hip replacements. These patients were randomised to one of five doses of rivaroxaban or a daily injection of enoxaparin. After 5–9 days of treatment the patients had venography. Deep vein thrombosis was less frequent in the patients taking rivaroxaban. There was no significant relationship between dose and efficacy, but the risk of major bleeding increased with dose.[1] A dose of 10 mg rivaroxaban was then selected for the Phase III trials called the RECORD studies.

RECORD1 randomised 2275 patients to daily injections of 40 mg enoxaparin and 2266 to take rivaroxaban after total hip replacement. Efficacy was assessed by venography after 35 days of prophylaxis. The primary outcome measure was a composite of death, pulmonary embolism and deep vein thrombosis. This outcome occurred in 3.7% of the enoxaparin group and 1.1% of the rivaroxaban group. There were four deaths in each group so the difference between the groups was accounted for by a significantly lower incidence of deep vein thrombosis with rivaroxaban.[2]

RECORD2 also studied patients having a total hip replacement and had the same primary efficacy outcome as RECORD1. A total of 2509 patients were randomised to daily injections of 40 mg enoxaparin for 10–14 days or rivaroxaban for 31–39 days. The enoxaparin group took placebo tablets and the rivaroxaban group had injections of placebo. After 32–40 days the patients had venography. The primary outcome occurred in 9.3% of the enoxaparin group and 2% of the rivaroxaban group. There were significantly fewer thromboses with rivaroxaban.[3]

RECORD3 had a similar primary efficacy outcome to the other trials, but enrolled patients having total knee replacements. A group of 1277 was randomised to receive 40 mg enoxaparin daily while a group of 1254 took rivaroxaban for 10–14 days. Venography after treatment found deep vein thrombosis in 18.2% of the enoxaparin group and 9.6% of the rivaroxaban group. The primary outcome occurred in 18.9% of the enoxaparin group and 9.6% of the rivaroxaban group.[4]

RECORD4 also studied patients who had knee replacement surgery, but compared rivaroxaban with an American regimen of enoxaparin (30 mg twice daily). The 3148 patients were treated for 10–14 days and had venography after 40 days. The primary outcome occurred in 10.1% of the enoxaparin group and 6.9% of the rivaroxaban group.

Although rivaroxaban prevents more thromboses than enoxaparin, the frequency of bleeding is slightly higher. In RECORD1 major bleeding occurred in 0.3% of the rivaroxaban group and 0.1% of the enoxaparin group.[2] In RECORD3 the corresponding figures were 0.6% and 0.5%.[4] Less serious, but clinically relevant, bleeding is also more frequent with rivaroxaban. The incidence of other adverse effects is similar for rivaroxaban and enoxaparin. Special precautions are needed if the patient has had spinal or epidural anaesthesia. Although rivaroxaban can increase the concentrations of liver enzymes it has not yet shown the toxicity which was associated with ximelagatran, another oral anticoagulant. More safety data will emerge from longer-term study of the drug in conditions such as atrial fibrillation. When used for short-term prevention of thrombosis, routine monitoring of the anticoagulant effect is not required.

If overdose occurs there is no specific antidote to rivaroxaban.

The currently available data suggest that rivaroxaban will be as effective as low molecular weight heparin for prophylaxis after surgery to the lower limb. Patients will probably prefer a daily tablet to a daily injection.

T manufacturer provided some information

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Triptorelin embonate

Diphereline (Ipsen)

6 mL vials containing 3.75 mg or 11.25 mg as powder for reconstitution

Approved indication: prostate cancer

Australian Medicines Handbook section 14.3.3

Locally advanced or metastatic prostate cancer can be managed by androgen ablation. This can be achieved by orchidectomy or hormonal treatment. Several agonists of luteinising hormone releasing hormone, such as goserelin and leuprorelin, are approved for this indication. Like other agonists, triptorelin initially causes a surge in luteinising hormone concentrations, but continued use reduces pituitary secretion. This leads to reduced androgen production with testosterone concentrations falling to levels similar to those seen after orchidectomy. Patients can be given a monthly intramuscular injection (3.75 mg) or an injection of the long-acting formulation (11.25 mg) every three months. As the molecule is a synthetic peptide it is probably degraded like a protein. Clearance is reduced by hepatic or renal impairment.

A South African trial randomised 172 men with advanced prostate cancer to have monthly injections and 174 to receive the long-acting formulation. After 29 days 93% of the patients on the monthly regimen and 98% of those on the three-monthly regimen had reached the target testosterone concentration. Both regimens maintained these concentrations in most patients during the 36 weeks of the study.

Another South African trial randomised 140 men to receive monthly triptorelin and 144 to receive monthly leuprorelin. After 29 days the proportion of men with target testosterone concentrations was significantly higher with leuprorelin (99% vs 91%). By 57 days there was no significant difference.[1]

The hormonal surge at the start of treatment may exacerbate symptoms, such as bone pain and bladder outflow obstruction. As treatment continues patients may complain of decreased libido, impotence, breast pain and hot flushes. Other adverse events include skeletal pain, hypertension, oedema, weight gain and pain at the injection site.

Although triptorelin has been available overseas for a few years there is little published information about its impact on survival. Although survival was not the primary end point of the comparative study, the nine-month survival rate was 97% with monthly triptorelin and 91% with leuprorelin.[1]

☒ manufacturer declined to supply data

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Valsartan

Diovan (Novartis)

80 mg and 160 mg film-coated tablets

Approved indications: hypertension, heart failure

Australian Medicines Handbook section 6.3.5

Valsartan/hydrochlorothiazide

Co-Diovan (Novartis)

80 mg/12.5 mg, 160 mg/12.5 mg, 160 mg/25 mg film-coated tablets

Approved indication: hypertension

Australian Medicines Handbook section 6.3.5

Amlodipine/valsartan

Exforge (Novartis)

5 mg/80 mg, 5 mg/160 mg and 10 mg/160 mg film-coated tablets

Approved indication: hypertension

Australian Medicines Handbook section 6.3.5

Valsartan

Valsartan is an angiotensin II antagonist which was launched overseas more than 10 years ago, but was not marketed in Australia. Like other members of the class, such as candesartan and losartan, valsartan lowers blood pressure by acting at the angiotensin type I receptor.

The antihypertensive effect of valsartan reaches a maximum after four weeks. Although raising the dose can increase the antihypertensive effect, doubling the dose from 160 mg to 320 mg may only reduce blood pressure by an extra 1–2 mmHg, while increasing adverse effects such as dizziness.[1]

Patients take the tablets once a day for hypertension and twice a day for heart failure. Most of the dose is excreted unchanged in bile, but it is recommended that the maximum dose should be limited in patients with severe renal impairment as well as in those with mild to moderate hepatic impairment. It is contraindicated in pregnancy.

A large trial has compared valsartan with amlodipine in more than 15 000 hypertensive patients. After a mean follow-up of 4.2 years the reduction in mean blood pressure was greater in patients taking amlodipine than in those taking valsartan. Systolic pressure fell by 17 mmHg with amlodipine and by 15 mmHg with valsartan, while the diastolic pressures fell by 10 mmHg and 8 mmHg. Although the composite end point of cardiovascular morbidity and mortality was not significantly different, there were more myocardial infarctions in the patients taking valsartan. The incidence of infarction per 1000 patient years was 11.4 with valsartan and 9.6 with amlodipine.[2]

Valsartan has been studied in patients with acute myocardial infarction. They were enrolled if they had signs of heart failure or left ventricular systolic dysfunction. More than 14 000 patients were randomised to receive valsartan, captopril or both drugs. After a median follow-up of 24.7 months, 19–20% of the patients in each group had died. Valsartan was not inferior to captopril, but their combination had no advantage and resulted in more patients stopping treatment because of adverse effects.[3]

Valsartan has also been used to treat chronic heart failure. In a controlled trial valsartan, or a placebo, was added to the treatment of 5010 patients with heart failure (New York Heart Association class II, III or IV). After a mean follow-up of 23 months, 19–20% of the patients in each group had died, however a combined end point of mortality and morbidity showed an advantage for valsartan. This was mainly because fewer patients, than in the placebo group, were admitted to hospital because of worsening heart failure (13.8% vs 18.2%). Valsartan should not be used in patients who are already taking an ACE inhibitor and a beta blocker. In the trial, adding valsartan to this combination significantly increased mortality.[4]

Valsartan with hydrochlorothiazide

In the comparison with amlodipine, more of the patients taking valsartan needed to take additional drugs, such as hydrochlorothiazide, to control their blood pressure.[2] These patients can now be considered for management with a combination tablet containing valsartan and hydrochlorothiazide.

There is an interaction between the drugs. Hydrochlorothiazide reduces the concentrations of valsartan and valsartan reduces the availability of hydrochlorothiazide. These changes do not negate the antihypertensive effect.

The combination of valsartan and hydrochlorothiazide was compared with valsartan in a placebo-controlled trial involving 871 patients with essential hypertension. These patients were randomised to one of nine groups using different doses of the combination, or monotherapy. After eight weeks all the active treatments had reduced the mean sitting blood pressure significantly more than placebo. Any combination of valsartan and hydrochlorothiazide reduced blood pressure more than either drug alone. For example, valsartan 80 mg with 12.5 mg of hydrochlorothiazide will reduce the diastolic pressure by 3.2 mmHg more than 80 mg valsartan and by 4.7 mmHg more than 12.5 mg hydrochlorothiazide.[5]

Another trial compared two combinations of valsartan and hydrochlorothiazide with valsartan alone in 774 patients with systolic hypertension. After eight weeks the mean sitting systolic blood pressure had been reduced by 20.7 mmHg with valsartan 160 mg. In combination with hydrochlorothiazide 12.5 mg the reduction was 27.9 mmHg and with hydrochlorothiazide 25 mg it was 28.3 mmHg.[6]

The combination of valsartan and hydrochlorothiazide has also been compared with amlodipine. In addition to hypertension, the 1088 patients in this study all had at least one other cardiovascular risk factor. After 24 weeks amlodipine 10 mg had reduced the mean systolic sitting blood pressure by 27.6 mmHg. Valsartan reduced the pressure by 27.1 mmHg when combined with hydrochlorothiazide 12.5 mg and by 29.7 mmHg with hydrochlorothiazide 25 mg.[7]

The main adverse effects of the combinations are dizziness, headache and fatigue.[5] Approximately 4% of patients will have a greater than 20% decrease in serum potassium.

Amlodipine with valsartan

Valsartan has also been combined with a calcium channel blocker to treat hypertension. The combination of amlodipine and valsartan is taken once daily. The bioavailability of the tablet is equivalent to that of its components when they are given separately. There is no significant interaction between the drugs, so their pharmacokinetic parameters are expected to be the same when they are given in a combined formulation.

Two placebo-controlled studies involving more than 3000 patients have compared the antihypertensive effects of amlodipine and valsartan alone with different strengths of the combination. Over eight weeks, most of the combined formulations produced significantly larger reductions in blood pressure than either drug alone or placebo.[8]

Another study compared the combined tablets (amlodipine 5 mg or 10 mg with valsartan 160 mg) with a combination of lisinopril and hydrochlorothiazide in 130 patients who had diastolic blood pressures of 110–119 mmHg. After six weeks both combinations had controlled the diastolic blood pressure in 77–80% of patients. The mean reduction in diastolic pressure with amlodipine and valsartan was 29 mmHg and with lisinopril and hydrochlorothiazide it was 28 mmHg.[9]

Combination products expose patients to the adverse effects of both components, but in some cases one drug may ameliorate the effects of the other. Peripheral oedema occurs in approximately 5% of those taking amlodipine and valsartan. This is significantly less than with amlodipine alone (9%), but more than with valsartan alone (2%).[8] Less frequent reactions are headache and dizziness.

Most patients will need more than one drug to control their blood pressure, but the treatment of hypertension should not begin with a combination product. Ideally, the doses of the individual drugs should be titrated to an optimum dose. If these doses correspond to those of a combination product, the patient can be switched to the combination. The problem with fixed dose combinations is that the ability to titrate the dose is limited.[10]

T manufacturer provided only the product information

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* 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.eu).

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2. True
3. True
4. True

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