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CONTENTS

ARTICLE

Personal electronic health records: the start of a journey

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SUMMARY

Technology is poised to drive dramatic change in the way healthcare is delivered. Many countries are using health information technologies to improve the safety of healthcare and reduce costs.

There is an evolving capability for health information to be accessed and exchanged between healthcare providers in real time.

Shared electronic health records are increasingly seen as having a key role in facilitating access to and exchange of data, promoting engagement with self-management, and supporting continuity of care.

Sharing electronic health records with consumers supports the move to more informed patients becoming active partners in their own health care.

Consumers can access their own health information, contribute to their health record and interact more effectively and efficiently with the health system.

Introduction

In 2009, the National Health and Hospitals Reform Commission recommended the introduction of a person-controlled electronic health record for each Australian as one of the most important systemic opportunities to improve the quality, safety and efficiency of health care.[1] It was proposed that the electronic health record would provide a minimum level of health information that would be available nationally. Access to this information would be controlled by the individual.[1] This recommendation led to the Australian Government funding $467 million in 2010 to begin the development of the personally controlled electronic health record (PCEHR) system.

The start of the PCEHR

The PCEHR was launched in July 2012. From then people could register to participate in the system which is currently viewed through a government-run web-based portal. The key features of the PCEHR are shown in Table 1.

The National e-Health Transition Authority has provided the essential foundations for the PCEHR. These include healthcare identifiers (for individuals, providers and provider organisations), secure messaging, the national security and access framework and national clinical terminologies (for example Australian Medicines Terminology).

The PCEHR is 'opt in' for both consumers and health professionals. With agreement, a shared health summary can be created by a nominated healthcare professional. This will initially include a brief medical history (as a problem list), current medicines, immunisations, allergies and adverse reactions.

Consumers will be able to join or withdraw from the system at any time. If they opt in, they can enter their own information into the consumer area of the portal. This could include details of medicines they are currently taking including prescribed, complementary or over-the-counter medicines, and allergies. Consumers cannot edit information created by others, but they can choose the documents to be shared. This means that people can hide documents which contain sensitive information or healthcare events that they do not want recorded and choose which healthcare organisations access their record.

In contrast to some other systems, the Australian PCEHR is not a shared electronic health record system. Primary records are still maintained and stored locally – general practices, hospitals and other organisations will continue to maintain and

From the Editor

The introduction of paediatric pneumococcal vaccine has seen a dramatic decline in invasive pneumococcal disease. Clayton Chiu and Peter McIntyre update us on this important immunisation for children and the elderly.

Many elderly patients take drugs to lower cholesterol, but they have an increasing risk of adverse effects, according to Sarah Hilmer and Danijela Gnjidic. Some of these adverse effects are due to drug interactions and the article by Catherine Lucas and Jennifer Martin also looks at interactions, specifically those associated with cigarette smoking.

The *Australian Prescriber* article on calcium supplements provoked a lot of interest. The letters section of the journal has therefore been expanded to enable readers to consider the resulting correspondence.

use their own records as the primary data source. The PCEHR is therefore a collection of summary documents and data uploaded from a variety of primary sources at different times (see Table 1). It will not always be clear if the information in the PCEHR is up to date. Reconciling information from different sources may be time-consuming when there are multiple summaries.

Uptake and use

As expected, uptake of the PCEHR has been slow – in the first nine months, approximately 109 000 consumers registered to use it. The original target of 500 000 consumers in the first full year of operation will be difficult to reach. The complexity of the registration process has been a major barrier. There are models being explored to improve consumer registration as it has been recognised that the existing systems are a barrier to uptake. However, there are few drivers for use by either consumers or health professionals when there is little clinical content to see.

Quality use of medicines

Prescribed or ceased medicines will be contained in a variety of documents including the shared health summary, discharge summaries and event summaries. Consumers and providers will also be able to view medicines that have been prescribed and dispensed electronically by participating health practitioners from mid-2013. Bringing this information together into a single, consolidated, current medicines list is desirable but unlikely to be implemented in the short term. It will be important for users to understand that a particular view of medicines information within the PCEHR may be incomplete. Australia's 'Guiding principles to achieve continuity in medication management' are particularly pertinent, outlining a partnership approach in which expertise and responsibility is shared among healthcare providers and consumers, for the consumer's well-being.[2]

International experiences with electronic health record systems

The development and implementation of large scale, shared electronic health records is complex and expensive. It is difficult to find examples where such systems have been delivered on time, on budget and have satisfied the needs of both funders and users. The lessons learned from the implementation of systems in other countries are important as they

Table 1 **Key features of the Australian personally controlled electronic health record (PCEHR)**

Participation model	Opt-in for consumers
	Opt-in for health professionals and healthcare organisations
	Healthcare organisations must register for the PCEHR
	Healthcare organisations need to use compliant software to upload information
	Consumers can register for the system online, by phone, at participating Medicare offices, through participating general practices or by mail
	Consumers can choose the information to be shared, which healthcare events are stored on the system, which healthcare organisations access their record, and can withdraw from the system
	In certain life-threatening situations, where patients are incapable of giving consent, emergency access protocols can be used to search for and then view an ehealth record
Information contributed by healthcare professionals	Shared health summaries containing medical history, allergies and adverse reactions, immunisations and medicines
	Event summaries can be created and uploaded by authorised healthcare professionals and may contain details about the attending healthcare professional or organisation, reasons for the patient's visit, diagnoses, results, treatments and observations
	Discharge summaries are created on a patient's discharge from hospital and may contain details about reasons for the visit, diagnoses, tests ordered and their results, interventions, drugs and recommendations for further treatments
	Specialist letters which will include details about the referring doctor, regular providers, interventions and treatments
	Medicare data including child immunisation data, organ donor register data, benefits claimed and subsidised drugs dispensed
	Until recently, the intention was to have pathology results available from some private laboratories in July 2013. This now appears unlikely. It is not known when pathology and radiology results will be incorporated into the PCEHR.
Information contributed by consumers	Allergies and medicines (this information will be clearly shown as patient-provided information)
	Consumer-entered notes e.g. diet, exercise and potentially results like blood glucose and blood pressure (consumer-entered notes will not be accessible to healthcare professionals)
Incentives for health professionals and organisations to participate	An ehealth practice incentive payment relating to participating in the PCEHR will be introduced from 1 May 2013
	General practitioners can claim under the Medical Benefits Schedule when creating or changing a shared health summary, depending on the length of time it takes

should inform the development of Australia's PCEHR. However, there are marked differences between healthcare systems and the implementation of electronic records in other countries. For example, the Australian healthcare system has a mix of public and private health services, with consumers regularly moving between the different settings, and there is no requirement for consumers to register with one provider.

USA

Kaiser Permanente is a managed care organisation with nine million health plan members. It has developed the largest private shared electronic health record system in the world. The multibillion dollar information technology system connects 533 medical practices and 37 hospitals so that information can be shared between different sites and healthcare providers. The system includes bedside documentation for nursing staff, clinical decision support and bar codes for drug administration. It is used for each patient encounter by all health professionals in the organisation.

Consumers have complete or partial access to their records online or via their smartphones. They can securely email their doctor, book appointments online, refill prescriptions, access information about their condition and view most medical test results. Secure email messaging is an accepted part of healthcare provision and doctors and pharmacists see this as an efficient way of handling many routine issues.[3] It has been associated with a decrease in office visits, an increase in measurable quality outcomes, and excellent patient satisfaction.[4,5]

There is significant uptake of the system by consumers, with 63% of those eligible regularly accessing and using the system. Nine out of ten consumers with chronic conditions agreed the system enables them to more effectively manage their conditions.[6] Consumers also report that the website helps them make informed decisions about their health and makes it more convenient for them to interact with their care teams.[6]

England

The Summary Care Record is an electronic patient record system in England that was developed as part of the National Health Service (NHS) National Programme for IT. In this system, patient information on drugs, allergies and adverse drug reactions is extracted from the general practitioner's computer and added to a centralised database, unless the consumer has 'opted out'.

Consumers can view the Summary Care Record online through a national portal (HealthSpace). They can also amend elements of their personal medical information and add additional information.

An evaluation of the Summary Care Record showed that, when it was accessed, it seemed to support better quality care and increase clinician confidence in some encounters. However, there was no direct evidence of improved safety apart from some rare instances of averted medication errors.[7] HealthSpace, the consumer component, was poorly taken up by consumers in England, most of whom perceived it as neither useful nor easy to use.[8] They were disappointed with the amount and type of data available, the need to enter data themselves, and the limited options for sharing data with their clinician. Policy makers' hopes that HealthSpace would lead to personalised care, lower NHS costs, better data quality, improved health literacy and greater empowerment were not realised. HealthSpace will be closed in 2013.

Scotland

Scotland has implemented a simpler model for use only in after-hours and emergency situations. The Scottish Emergency Care Summary contains current drugs, allergies and adverse reactions. Data are automatically extracted twice daily from all Scottish general practices, which ensures the information is up to date. Patients can opt out of having their information uploaded and even when it is available, the information can only be accessed with the explicit consent of the patient for that episode of care. There is no consumer viewable component to the record at present.

Feedback from users is positive. Over 200 000 records are accessed every month and clinicians have found their decisions can be more timely, accurate, and patient centred.[9]

What can we learn from international experiences?

The purpose and long-term vision for the Australian PCEHR should be clearly communicated to facilitate acceptance by consumers and health professionals. Progress will depend on engaging consumers and clinicians. Providing value for consumers and health professionals is more likely to be achieved by undertaking ongoing evaluation which results in refinement and adaption of the system according to their needs.

Data sharing

There is potential for the PCEHR to offer new ways for health professionals and consumers to share information effectively. Sharing and access to data could be particularly useful for those with chronic

conditions and with multiple healthcare providers or carers. This would also be useful in emergencies and when patients are moving between healthcare settings, especially as medication errors often occur in these situations.

Consent

The current opt-in consent model poses challenges for achieving a critical mass of users to make the system useful. An opt-out model for consumers would lead to more significant uptake, but this could only be achieved once trust in the system has been established.

Establishing trust in the security, accuracy and currency of the data in the system will be critical. Health professionals also have to opt in to the PCEHR. At present there is little perceived benefit in the PCEHR for a patient's usual clinicians who already communicate and share information.

Avoiding problems

Concerns have been raised about the potential for harms and unintended consequences associated with the introduction of the PCEHR and the need for preventive action to avoid these.[10] An evaluation of the English Summary Care Record found instances of incomplete and inaccurate data, such as missing some drugs but including others that the patient was not actually taking.[7] Clinician vigilance prevented harms from occurring in instances where there was incorrect or missing information. Accuracy and currency of data will be a particular challenge for the PCEHR when there are multiple sources of information. For example, medicines information may be contained in multiple documents (for example the shared health summary, specialists' letters and consumer-entered notes). The challenge will be to synchronise this information to build a complete picture of the medicines that are being taken. An electronic system will not replace the need for the patient–clinician interaction to confirm the validity of the information contained in the PCEHR. In addition, as medical care involves more use of, and reliance upon, electronically recorded information, the same robust processes of clinical governance must apply to it as to all other products used in the healthcare sector.[10] Safety governance for clinical information systems is long overdue.[10,11]

Conclusion

Australia has taken the first steps towards a personal electronic health record. Some significant challenges have already been overcome, but there are more ahead. The key to success will be a common understanding of the purpose and potential of the new system – realistic expectations of what the system can achieve now and in future should be developed and communicated to both health professionals and consumers.

This is the start of an e-health evolution and progress will be incremental. It will be some time before benefits emerge. The PCEHR initiative will require long-term commitment and patience from consumers, clinicians and funders. ◅

Conflict of interest: none declared

Acknowledgement: Jonathan Dartnell, Executive Manager, Innovation and Learning, and Michelle Sweidan, e-Health and Decision Support, NPS MedicineWise for their comment.

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FURTHER READING

For more information on the PCEHR see www.ehealth.gov.au

LETTERS

Letters to the Editor

Calcium and cardiovascular risks

Editor, – The recent article on calcium and cardiovascular risks (Aust Prescr 2013;36:5-8) deserves some comment. The largest meta-analysis on the antifracture efficacy of calcium and vitamin D showed that the benefit of this combination in 68 500 participants was very significant.[1] The original Women's Health Initiative study of 36 682 postmenopausal women showed no significant increase in the risk of myocardial infarction or death due to coronary heart disease in those taking calcium and vitamin D compared to those taking the placebo.[2] A recent review by the National Institutes of Health on 388 229 men and women aged 50–71 years concluded that a high intake of supplemental calcium is associated with an excess risk of cardiovascular death in men but not in women.[3] Another relevant paper on the use of vitamin and mineral supplements in 38 772 older women showed that calcium supplementation, unlike other mineral supplements, was associated with decreased mortality.[4]

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Professor BE Christopher Nordin
Emeritus endocrinologist

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Mark Bolland, Andrew Grey and Ian Reid, the authors of the article, comment:

Our discussion of the evidence for fracture efficacy of calcium and/or vitamin D included the DIPART meta-analysis.[1] The claim of very significant antifracture efficacy of co-administered calcium and vitamin D in this meta-analysis is not supported by even superficial scrutiny. There was an 8% relative risk reduction in total fractures with calcium and vitamin D, with a number needed to treat of 213 to prevent one fracture over three years. For hip fractures, the relative risk reduction was 16% and the number needed to treat was 255 to prevent one hip fracture over three years. However, the hip fracture results were heavily dependent on one cluster randomised controlled trial,[2] the results of which are problematic to interpret. When this trial was excluded the relative risk reduction was only 3%.[1] Thus, the DIPART meta-analysis does not provide compelling evidence for the antifracture efficacy of calcium and vitamin D.

The Women's Health Initiative study permitted widespread use of non-protocol vitamin D and calcium[3] which obscured both adverse cardiovascular risks and potential benefits on cancer incidence.[4] The Women's Health Initiative investigators have now repeated our analyses on the complete dataset and have produced very similar results to ours.[5] Given this, we do not think it is credible to claim that the original analysis provides reassurance about cardiovascular risks for patients.

Observational studies are hypothesis-generating, not hypothesis-testing. There are numerous examples of discrepant results between observational studies and randomised clinical trials, when positive benefits of drugs observed in observational studies are not observed in clinical trials. Examples include hormone replacement treatment and cardiovascular risk, vitamin D and various outcomes, and folic acid and antioxidants and cardiovascular disease and cancer. It is therefore unwise to emphasise the results of observational studies when there is a large database of randomised controlled trials that shows clear, consistent evidence of modest increases in myocardial infarction and stroke from calcium supplement use.

However, we acknowledge the correspondents' point that the recent very large National Institutes of Health-sponsored observational study from the USA[6] as well as similar large observational studies from Europe[7-9] report increases in cardiovascular effects in association with calcium use.

Finally, our conclusion aligns with the recent recommendation of the US Preventive Services Task Force, whose members are free from both commercial and academic conflicts of interest, that vitamin D and calcium should not be administered for primary prevention of fractures in non-institutionalised postmenopausal women.[10]

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

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Editor, – I find information in the recent article on calcium and cardiovascular risks (Aust Prescr 2013;36:5-8) is opposite to the current recommendation from Osteoporosis Australia,[1] especially the section on implications for practice which says 'recommendations for the widespread use of calcium supplements are no longer appropriate' and 'dietary calcium intake does not require close scrutiny for most people'.

The current Osteoporosis Australia guidelines recommend that calcium intake for adults is 1000 mg/day. This increases to 1300 mg/day for women over 50 and men over 70. For people who do not obtain adequate calcium through their diet, a supplement of 500–600 mg may be required. There is no additional benefit of calcium intake being higher than recommended levels.

Should Osteoporosis Australia, Therapeutic Guidelines and the Australian Medicines Handbook update their recommendations for osteoporosis prevention and treatment?

Tina Nguyen
Accredited consultant pharmacist
Fairfield, NSW

REFERENCE

1. Ebeling PR, Daly RM, Kerr DA, Kimlin MG. An evidence-informed strategy to prevent osteoporosis in Australia. Med J Aust 2013;198:90-1.

Mark Bolland, Andrew Grey and Ian Reid, the authors of the article, comment:

We think that our article accurately summarises evidence from existing randomised controlled trials. In a recent meta-analysis of the effect of calcium supplements on fractures (with or without vitamin D),[1] 15 of the 16 studies with fracture as an endpoint administered at least 750 mg/day of calcium supplement, and the total calcium intake from diet and supplements ranged from 1230 to 2300 mg/day. Thus, the beneficial skeletal effects of calcium have only been demonstrated in trials evaluating the same doses of calcium that also increase risk of myocardial infarction. There is no robust evidence that calcium supplements in doses less than 1000 mg/day prevent fractures.

We agree that the role of calcium in osteoporosis management should be reconsidered by individual healthcare practitioners as well as organisations issuing guidelines on osteoporosis management.

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Editor, – I am writing to you on behalf of the Osteoporosis Australia Medical and Scientific Advisory Committee about the recent *Australian Prescriber* article (Aust Prescr 2013;36:5-8) strongly calling for the use of calcium supplementation to be reconsidered, under the heading 'Implications for practice'. This is one side of a highly debated issue and a view that is predominantly expounded by one New Zealand group of academics. It is certainly not the consensus amongst Australian experts. Furthermore, the publication of such an unbalanced article, with such a strong conclusion, is both misleading and potentially very confusing both to your readers and the general public.

LETTERS

Members of the Osteoporosis Australia Medical and Scientific Advisory Committee have reviewed all of the published literature on this topic, including the studies referred to in the article. While we acknowledge this is an area of ongoing research and debate, we do not believe the evidence is conclusive enough to make such strong recommendations.

Our current position statement on calcium supplementation remains unchanged. This recommends a total daily intake of 1000 mg to 1300 mg of calcium per day (recommended dietary intake or RDI), depending on age and sex. Ideally, the RDI should be achieved by consuming a diet rich in calcium. When the RDI cannot be achieved through diet alone, supplements may be required. In these circumstances, Osteoporosis Australia recommends a supplement of 500–600 mg of calcium.[1]

A recently published extensive evidence-informed review of calcium, vitamin D and exercise to optimise bone health throughout life has similar conclusions.[2]

Instead of adding clarity, printing articles such as this creates confusion. We are disappointed that *Australian Prescriber* elected to publish this story without a broader review of the published literature and without seeking input from expert organisations, including Osteoporosis Australia.

Professor Peter R Ebeling
Medical director
Osteoporosis Australia

Osteoporosis Australia receives limited funding from Pfizer Consumer Healthcare and Swisse, both of which are manufacturers of calcium supplements.

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Mark Bolland, Andrew Grey and Ian Reid, the authors of the article, comment:

The claim that the view that the role of calcium supplementation should be reconsidered is only held by one New Zealand group is incorrect. Several publications in international medical journals written by authors from various countries, including Australia, reached similar conclusions.[1-6] Most recently, the US Preventive Services Task Force, whose members are free from both commercial and academic conflicts of interest, concluded that vitamin D and calcium should not be administered for primary prevention of fractures in non-institutionalised postmenopausal women.[7]

We are surprised that our article is described as unbalanced as we reviewed the best available evidence on the efficacy and safety of calcium supplements. Six large randomised controlled trials with fracture as the primary endpoint have been undertaken. Their results have been incorporated into systematic reviews of the efficacy and safety of calcium supplements that include both trial-level and patient-level meta-analyses. The results of all these analyses were discussed in our article. The evidence is clear – calcium supplements reduce total fractures slightly, do not prevent hip fractures in community-dwelling individuals, and increase cardiovascular events. Within this large clinical trial dataset, the cardiovascular risks of calcium supplements outweigh the skeletal benefits.[8,9]

The position statement of Osteoporosis Australia is not supported by the available evidence. There is substantial overlap in authorship of the position statement and the 'white paper' cited by Professor Ebeling, which explains the similar conclusions.
In a recent meta-analysis of the effect of calcium supplements with or without vitamin D on fractures,[10] 15 of the 16 studies with fracture as an endpoint gave at least 750 mg/day of calcium supplements, and the total calcium intake from diet and supplements ranged from 1230 to 2300 mg/day, well above the levels recommended by Osteoporosis Australia. There is no robust evidence that calcium supplements in doses less than 1000 mg/day or that increasing dietary calcium intake to 1000–1300 mg/day prevents fractures. In fact, observational studies of dietary calcium intake fail to generate a hypothesis of skeletal benefit from achieving dietary calcium intakes at the level recommended by Osteoporosis Australia.[11,12]

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Editor, – I read the article on calcium supplements (Aust Prescr 2013;36:5-8). Nowhere did it mention the form of calcium that was studied. My understanding is that calcium carbonate is the dangerous form with respect to heart attacks and strokes, but that other forms such as calcium citrate are not.

Sylvia Hicks
Clinical manager
Older Persons Mental Health Community Team
ACT Health

Mark Bolland, Andrew Grey and Ian Reid, the authors of the article, comment:

There is no evidence that cardiovascular risks differ substantially between calcium supplement types. In our patient-level meta-analysis of calcium monotherapy, there was no relationship between the risk of myocardial infarction with calcium and supplement type (calcium carbonate: hazard ratio 1.24, calcium citrate:hazard ratio 1.60, p=0.4 for difference in risk between supplement types).[1,2] There was also no relationship between the risk of stroke with calcium and supplement type (p=0.5).[1]

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2. Reid IR, Bolland MJ, Avenell A, Grey A. Cardiovascular effects of calcium supplementation. Osteoporos Int 2011;22:1649-58.

Editor, – I have read the article on calcium and cardiovascular risk (Aust Prescr 2013;36:5-8) and I was puzzled by the paragraph about the re-analysis of data on users and non-users of personal calcium (page 6).

If I am interpreting the statement correctly, there was a cardiovascular protective effect when calcium was being taken before being allocated to add calcium and vitamin D, compared to when they were not taking calcium beforehand.

This seems to contradict the article's conclusion that calcium supplements increase cardiovascular risk, as the opposite might be expected if they were already on calcium.

Robert Gates
Consultant physician
Sydney

Mark Bolland, Andrew Grey and Ian Reid, the authors of the article, comment:

We disagree with this interpretation. In women not using their own calcium supplements, co-administered calcium and vitamin D increased cardiovascular risk. In women already using their own calcium, taking additional calcium supplements did not further increase cardiovascular risk. In this latter subgroup, participants in both treatment groups were taking calcium, thus inferences about whether calcium supplements might alter cardiovascular risk (compared to not taking calcium) cannot be drawn. The findings do suggest that there is no dose-response relationship with calcium supplements and cardiovascular risk at doses used in current practice. Women taking lower doses of calcium supplements thus have a similar cardiovascular risk to those taking higher doses, and this risk is elevated compared to women not taking calcium supplements.

Editor, – What happens to institutionalised elderly women once vitamin D levels are replete? Are they now at increased cardiovascular risk if vitamin D and calcium are continued?

Can this statement be applied to elderly frail men?

Mark Raines
General practitioner
Kangaroo Island Medical Centre
Kingscote, SA

Mark Bolland, Andrew Grey and Ian Reid, the authors of the article, comment:

Current trial data do not suggest there are important differences in cardiovascular risk between the use of co-administered calcium and

LETTERS

vitamin D and the use of calcium monotherapy.[1] Although two trials of frail, institutionalised elderly women prescribed calcium and vitamin D reported reductions in fracture risk,[2,3] cardiovascular event data were not reported. The balance of risk and benefit from calcium and vitamin D in these studies cannot be established. However, a more recent Australian trial in elderly nursing home residents reported that adding calcium to sunlight exposure increased cardiovascular risk,[4,5] suggesting that the balance between risk and benefit may be unfavourable.

We think that elderly frail men and women at high risk of marked vitamin D deficiency should be treated with vitamin D supplements or sunlight exposure to prevent osteomalacia. They should also be assessed for fracture risk. If it is high, appropriate treatment to prevent fractures should be considered.

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Drug treatment of acne

Editor, – In the article on drug treatment of acne (Aust Prescr 2012;35:180-2), Dr Jo-Ann See has omitted the important role of azithromycin in treatment of acne. In cases of severe inflammatory and papulopustular acne, azithromycin pulses (for example three days every week for up to 8–12 weeks) with or without systemic isotretinoin have been found to be safe, well tolerated, effective and promote patient compliance.[1,2] In fact, in a randomised study, pulsed azithromycin treatment for acne vulgaris was as effective and safe as daily doxycycline for two weeks.[3] Tetracyclines (including doxycycline and minocyclin) cannot be combined with isotretinoin because of the risk of the shared adverse effect of raised intracranial tension. This is not the case with macrolides, and early in therapy, when isotretinoin may cause an initial flare in some patients, concomitant azithromycin can be safely used.

Secondly, it should be emphasised that a patient who is taking oral isotretinoin should not donate blood during and for up to one month after completion of therapy, as the blood may be transfused to a female of child-bearing age.

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Jo-Ann See, author of the article, comments:

Many thanks for your interest in the article on drug treatment of acne. The aim was to outline a 'first-line' approach for acne treatment in Australian general practice. Azithromycin is not commonly used for acne in Australia and the intermittent dosing, while effective, may be questioned from an adherence point of view. There have also been recent safety concerns about azithromycin and arrhythmia. The combination of azithromycin with oral isotretinoin was outside the scope of the article. GPs do not prescribe oral isotretinoin, so the discussion of it was aimed at supporting GPs who may have patients they are considering for specialist referral or patients taking isotretinoin who they co-manage with a dermatologist.

As every medicine has potential adverse effects, I have not written about the plethora of potential interactions or concerns that oral isotretinoin may have, including blood donation. It is routine practice for the Australian Red Cross to interview potential blood donors. Donors are also given a questionnaire about medicines taken in the previous 12 months. This would identify any potential risks regarding blood transfusion.

ARTICLE

Statins in older adults

SUMMARY

Statin use in people over 65 years of age is high.

A meta-analysis of older patients included in randomised trials found good evidence that statins reduce vascular events and mortality in people with existing coronary heart disease.

In older adults, exposure to higher doses of statins or higher potency statins does not increase their effectiveness, but does increase the risk of adverse effects such as myopathy and cognitive impairment.

Increasing age is a risk factor for adverse events with statins. Older patients may be less resilient to these effects.

Older patients may have more comorbidities and be taking more concomitant drugs than the study populations in statin trials. Applying the evidence for statins to older individuals therefore requires frequent review and consideration of the therapeutic goals and potential benefits and harms.

Introduction

Statins (hydroxymethylglutaryl coenzyme A reductase inhibitors) are the most commonly used cholesterol-lowering drugs. They are being taken by more than 40% of Australians over 65 years of age.[1] Although the prevalence of statin use increases with age, the balance between evidence of their benefits and the risk of adverse effects such as myopathy or impaired cognition may change. In extreme old age, preserving function and avoiding frailty and injury in the short term may become more important than longer term goals such as preventing future cardiovascular events or even extending life.

Efficacy of statins

Older people have an increased risk of cardiovascular disease. However, epidemiological studies suggest that the relative risk for coronary heart disease associated with high cholesterol decreases with age.[2] In addition, in old age, there is an inverse relationship between high cholesterol and the risk of stroke[3] and there are conflicting data on the relationship between high cholesterol and non-cardiovascular mortality.

Cardiovascular events

Statins are most beneficial for preventing cardiovascular events in patients who already have coronary heart disease. A meta-analysis of patients with existing disease (aged 65–82 years) found that all-cause mortality was significantly lower with statins than with placebo (15.6% vs 18.7%) over five years.[4] This equates to a number needed to treat of 28 over five years to save one life. Approximately 25% of patients in the trials were female. Frail older patients may have been excluded because of comorbidity or organ dysfunction.

The role of statins in primary prevention of cardiovascular disease in older people is unclear. Their effects seem to increase over five years, with only minimal benefits over placebo seen in the first year.[5] It is therefore important to consider the patient's probable lifespan when deciding whether to start or continue a statin.

Studies of secondary prevention in patients with cerebrovascular disease suggest that statins are associated with a decrease in recurrent ischaemic stroke but an increase in haemorrhagic stroke.[5]

Other clinical outcomes

There are very limited data assessing the impact of statins on other outcomes such as frailty, physical and cognitive function and institutionalisation. Epidemiological data suggest that statins are not associated with an increase in the risk of developing frailty.[6] This is a condition of increased vulnerability to external stressors and an independent risk factor for adverse clinical outcomes. Symptoms and signs of frailty include complaints of fatigue, unintentional weight loss and low grip strength. We recently investigated the relationship between statins and institutionalisation and mortality, according to frailty in community-dwelling men aged 70 years and over. There was no association between statin use and institutionalisation or death in older men. Statins did not appear to improve mortality or delay institutionalisation.[7]

Observational studies report conflicting results on the association of statins and muscle mass, strength and function. Results of randomised trials on the effects of statins on cognition are conflicting.[8] In patients with dementia, statins do not significantly affect cognitive decline, global function, behaviour or activities of daily living.[9] A recent pilot study of statin withdrawal showed that statin reduction is associated

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Key words
ageing, deprescribing, HMG CoA reductase inhibitors, myopathy

Aust Prescr 2013;36:79–82

with improvements in cognitive function in patients with Alzheimer's disease. Moreover, rechallenge with statins was associated with a decline in cognition function.[10]

Statin dose

Meta-analyses suggest that 80% of the lipid-lowering effect of statins occurs at half the maximal statin dose.[11] In older patients, the efficacy of statins for secondary prevention of acute myocardial infarction and death appears to be a class effect, with no difference observed between high or low potency statins.[12] Surrogate markers, such as low density lipoprotein cholesterol, should be interpreted with care in older people. Epidemiological data indicate that lowering low density lipoprotein cholesterol has a smaller impact on the relative risk of coronary heart disease as age increases.[11]

Adverse effects of statins

Adverse effects appear to vary between types and doses of statins. The risk of common events such as myopathy and liver enzyme elevations increases with statin potency and exposure. The degree of statin exposure (area under the concentration–time curve) depends on dose, drug interactions and patient factors including genetic polymorphisms. With ageing, there is a decrease in body size, particularly in muscle mass, and in hepatic and renal function, so the same dose will result in a greater degree of exposure in older patients.

Muscle symptoms

The most common adverse effects that limit treatment with statins are muscle symptoms. These include myalgia, myositis and rhabdomyolysis (Table 1). The risks of muscle symptoms are related to the dose of the statin.

The risk of muscle damage with statins increases with age over 70 years, and with age-associated factors such as multiple medicines use, comorbidity and sarcopenia (low skeletal muscle mass and function) (Table 2).

Table 1 rows 1–3 should read creatine kinase, not creatinine kinase
Corrected July 2013

Table 1 **Muscle symptoms associated with statins**

Condition	Clinical presentation	Prevalence
Myalgia	Musculoskeletal pain without creatinine kinase increase	5–10% of patients in clinical trials
Myositis	Muscle symptoms with elevated creatinine kinase	0.1–0.2% of patients in clinical trials
Rhabdomyolysis	Severe muscle symptoms with creatinine kinase greater than 10 times the upper limit of normal, complicated by myoglobinuria and impaired renal function	Rare

Statin myopathy is likely to have a greater impact in older people, with limited musculoskeletal reserve, than in younger people, who generally have more muscle mass and strength and better mobility.

Liver enzyme increases

Elevated hepatic transaminases occur in 0.5–2% of patients treated with statins and are dose-dependent. Their clinical significance is uncertain and progression to liver failure is very rare. The transaminases may normalise if the statin dose is reduced and elevation does not always recur if the patient resumes the statin.[13] The effect of ageing on the risk of hepatic damage with statins is not known. In old age the risk of drug-induced liver injury appears to increase for some drugs, such as non-steroidal anti-inflammatory drugs, and decrease for others such as paracetamol. While drug-induced liver injury is commonly defined as moderate with an increase in liver enzymes over 2.5 times the upper limit of normal and severe at 5 times the upper limit of normal, these thresholds may be lower in older people because of their 30% decrease in liver mass.

Other adverse effects

The commonest adverse effects observed with statins are gastrointestinal, such as abdominal pain, constipation and nausea. A rare but serious adverse event is reversible peripheral neuropathy.

An increased risk of diabetes with statins was recently reported. Diabetes has also been found to be more common in older patients and those taking higher dose and higher potency statins.[14]

Studies have reported reversible cognitive impairment with statin use, both in patients with previously intact cognition and in those with pre-existing cognitive impairment.[15-17] This prompted the US Food and Drug Administration to change the prescribing information for statins* and has been noted by the Australian Therapeutic Goods Administration†.

A recent randomised controlled trial in younger patients suggested that compared to placebo, those prescribed statins were more likely to report a loss of energy and worsening exertional fatigue over six months of treatment.[18] This effect may have considerable impact on older patients with less functional reserve.

* www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm293623.htm [cited 2013 May 3]

† www.tga.gov.au/safety/alerts-medicines-statins-120302.htm [cited 2013 May 3]

Table 2 **Age-associated factors that increase the risk of rhabdomyolysis with statins**

Risk factor	Mechanism	Association with old age
Concomitant medicines	Pharmacokinetic drug–drug interactions increase exposure to statins (vary between statins) Pharmacodynamic interactions with other drugs that cause myopathy	Increased prevalence of polypharmacy
Comorbidity		
Renal and hepatic impairment	Increased exposure to statins	Decreased renal and hepatic function in old age
Hypothyroidism	Also causes myopathy	Increased prevalence and difficult clinical diagnosis in old age
Severe inter-current illness	Impaired metabolism results in increased exposure to statins and may also cause myopathy	Increased prevalence in old age
Low body weight	Increased exposure to statins and lower muscle mass	Weight decreases, particularly muscle mass, in old age and frailty

Adapted from Statins, macrolides and rhabdomyolysis. Medicines Safety Update No 5. Therapeutic Goods Administration; 2010 Oct.

Drug interactions

Gemfibrozil is the drug most commonly associated with statin-induced myopathy. When taken concomitantly it inhibits the hepatic uptake of statins (via the organic anion transporter polypeptide 1B1) and their biotransformation by glucuronidases. There is a smaller increase in the risk of myopathy with co-administration of other fibrates and statins because this pharmacokinetic interaction does not occur. The metabolism of atorvastatin and simvastatin is inhibited by cytochrome P450 3A4 inhibitors (for example macrolide antibiotics, amiodarone), increasing the risk of adverse effects (see Drug interactions: Fatal rhabdomyolysis following voriconazole and simvastatin, Aust Prescr 2012;35:88-9).

When should treatment be stopped?

When healthcare professionals and patients agree that there is no clinical benefit of treatment or the risks are greater than any potential benefit, treatment should be stopped. Withdrawal or deprescribing of statins should be considered when:

- the potential benefits are no longer clinically relevant. In patients with severe physical or cognitive impairments, or those in their last year of life, therapeutic aims often change from preventative to palliative and reducing the risk of vascular events or mortality may not be relevant.
- patients have serious adverse effects such as myositis, rhabdomyolysis or severe hepatic failure
- patients have symptoms or signs consistent with adverse effects in a temporal pattern consistent with statin exposure, such as myalgia, moderate or severe elevation of hepatic enzymes, cognitive impairment or fatigue
- patients need medicines that interact with statins (increasing the risk of toxicity).

Good opportunities to discuss withdrawal of statins include comprehensive health assessments by general practitioners or specialists, assessments on admission to or discharge from hospital or on entry to residential aged-care facilities, and after medication reviews by accredited pharmacists.

Conclusion

Evidence supports statin use for secondary prevention of coronary heart disease in older adults. However, this age group has an increased risk of adverse events from statins, particularly myopathy. The effect of these drugs on frailty, disability and institutionalisation is not well established. They are likely to decrease the risk of these outcomes by preventing vascular events, but to increase the risk by causing myopathy.

Randomised trials in older people (frail and robust) with clinically relevant endpoints are required to inform therapy in this large and growing patient population. Management of older adults relies on extrapolation of the available evidence and frequent reassessment as the patient's physiology, pathology, function and priorities change over time. ◁

Conflict of interest: none declared

Acknowledgement: Danijela Gnjidic is supported by a National Health and Medical Research Council Early Career Fellowship.

Q:

SELF-TEST QUESTIONS

True or false?

1. Statins are associated with a decrease in haemorrhagic stroke in secondary prevention studies of people with cerebrovascular disease.
2. Macrolides increase the risk of adverse effects with atorvastatin and simvastatin.

Answers on page 107

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FURTHER READING

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Your questions to the PBAC

Gabapentin

Readers are invited to write in with their questions about decisions of the Pharmaceutical Benefits Advisory Committee (PBAC). *Australian Prescriber* publishes selected questions from readers, together with answers from the PBAC. Questions may address issues such as regulatory decisions, pharmaceutical benefits listings and withdrawals.

This exclusive arrangement helps *Australian Prescriber* readers understand how the contents of the Pharmaceutical Benefits Scheme (PBS, see www.pbs.gov.au) are determined.

Letters and responses are reviewed by the Editorial Executive Committee and may be edited before publication. It may not be possible to reply to all individual questions.

I noted with interest in the latest edition of NPS RADAR that pregabalin has been approved for neuropathic pain. The stated justification is 'non-inferior in efficacy and safety to amitriptyline and gabapentin (from indirect comparisons)'.[1]

Later it is stated that gabapentin is an effective treatment for neuropathic pain, but is not subsidised on the PBS for that indication. I would add that it has been available for many years and its dosage and adverse effects are well known to prescribers.

Many patients with neuropathic pain have been paying very high prices for their gabapentin for 10 years or more. The recent decision has created the illogical situation in which long-standing users of gabapentin, who are controlled on a well understood drug, will be paying more than patients being started on a much newer drug with less well established efficacy and safety.

Does the PBAC intend to rectify this scenario?

Gillian Shenfield
Clinical pharmacologist
Sydney

REFERENCE

1. Pregabalin (Lyrica) for neuropathic pain. NPS RADAR. 2012 Dec. Updated 2013 Apr.

PBAC response:

Gabapentin is currently available as a pharmaceutical benefit in Australia for the treatment of partial epileptic seizures which are not controlled satisfactorily by other antiepileptic drugs, however it is not listed for neuropathic pain. The PBAC has in the past rejected applications for the subsidy of gabapentin for the treatment of neuropathic pain.

The grounds for rejection were lack of evidence in the proposed population, as the clinical trial data did not reflect the population covered by the proposed PBS restriction, and uncertain cost-effectiveness in this patient group. Any re-submission must address those matters. It may provide new data or modify the previously requested indication.

In order to facilitate the listing of gabapentin for neuropathic pain, Professor Sansom, the former Chair of the PBAC, had held meetings with pain specialists. The Department of Health and Ageing is also in contact with sponsors of gabapentin to try to progress its listing for neuropathic pain. The PBAC would consider any submission proposing the listing of gabapentin as a pharmaceutical benefit for this condition on its merits.

ARTICLE

Opioid treatment of opioid addiction

SUMMARY

Opioid-related problems, including addiction, are increasing in Australia and more medical practitioners are likely to have contact with such patients. Addiction is a chronic disease, but opioid substitution treatment can reduce both mortality and morbidity.

There is a substantial evidence base for opioid substitution treatment. It is of benefit to individual patients and also, if adopted by a greater number of prescribers, to public health.

Opioid substitution is not suitable for all patients. It should also only be used as part of the patient's rehabilitation.

The drugs which are used include methadone, naltrexone and buprenorphine with or without naloxone. Regular assessments are needed, not only to monitor for efficacy and safety, but also to retain the patient in the treatment program.

Introduction

Most medical practitioners will see patients who have become addicted to illegal drugs. In addition, with increasing opioid prescribing in Australia,[1] more patients are developing prescribed opioid addiction.

Opioid addiction or dependence syndrome are synonymous terms which refer to a state of compulsive drug use despite related harm. This is exemplified by continued opioid injecting despite sustaining overdoses or infections. In other opioid dependent patients (for example with prescribed opioid dependence) excessive or unsanctioned use may be correlated with drug-related impairment (such as sedation or overdose) and accidents. Addiction can be considered as a chronic disease, with a relapsing and remitting pattern, significant long-term morbidity and an increased risk of death.[2,3]

One approach to managing addiction is the use of opioid substitution therapy with drugs such as methadone. This therapy has a substantial evidence base for improving physical and social health outcomes (reducing drug crimes, blood-borne viral spread and overall mortality).[4-8]

The provision of opioid substitution therapy is not simply maintaining addiction, because it also significantly reduces harm. It is therefore appropriate that methadone is included in the World Health Organization's Essential Medicines List for treating opioid addiction.[9]

The decision to use opioid substitution therapy

Identifying addiction involves applying diagnostic criteria based on history, examination and urine drug testing.[4-8] Australian states and territories maintain information about patients who have been notified as drug dependent and those who have previously received opioid substitution therapy. These details can be accessed via confidential communication with the local health department. When there is diagnostic uncertainty or case complexity, referral to a specialist in addiction medicine is recommended.

Not every patient with opioid addiction is suitable for opioid substitution therapy (Box 1). Consideration of alternative therapies is therefore necessary. These include abstinence-focused programs, behavioural interventions – particularly contingency management approaches[10] – and self-directed interventions such as Narcotics Anonymous. If these strategies are unsuccessful or deemed inappropriate, opioid substitution therapy is considered.

Box 1 **Assessing suitability for opioid substitution therapy**

Requirements

Addiction to opioids

Ongoing risk of opioid-related harms

Other treatment options ineffective or unsuitable

Capacity for informed consent

Circumstances appropriate (e.g. able to access pharmacy and take opioid substitution therapy)

Contraindications

Proven or likely sensitivity (or allergy) to some form of opioid substitution therapy

Pregnancy generally excludes treatment with buprenorphine with naloxone, and naltrexone

Active current alcohol dependence (e.g. daily drinking)

QTc prolongation syndrome with methadone – especially when combined with conditions or other drugs which prolong the QTc interval

Travel to some countries where opioid substitution therapy is not sanctioned

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Key words
buprenorphine, methadone, naloxone, naltrexone, opioid substitution treatment

Aust Prescr 2013;36:83–7

There are two indications for opioid substitution therapy – brief treatment of opioid withdrawal and prolonged maintenance therapy. While the former is used in crisis intervention, only the latter has good correlation with long-term outcomes like remission and recovery.

Management of withdrawal

Short-term prescribing of an opioid substitute (such as buprenorphine) in reducing doses, supervised daily (or in an inpatient 'detox unit') for about a week, is used to manage acute opioid withdrawal symptoms (Table). Supervised dosing reduces the risk of intoxication, for example if the patient continues using other drugs.

Later, the patient should be offered a general health review and relapse prevention counselling provided by local drug rehabilitation agencies. Importantly, the patient's risk of overdose is increased following any prolonged period of abstinence (for example after hospitalisation, release from prison), therefore medical counselling about overdose prevention is essential.[11-13]

Maintenance

Opioid substitution therapy is mainly used for long-term drug rehabilitation, as in the methadone maintenance program. Such programs have proven efficacy, but have barriers including low numbers of prescribers[14] and patient costs.

Potential problems

The risks of opioid substitution therapy include the drug's potential for adverse effects.[15] There is an increased risk of toxicity during methadone's induction period, but there are guidelines to help minimise this problem.[5] There is a risk of drug interactions especially if the patient continues using illicit drugs. Prescription drugs such as phenytoin, rifampicin and the HIV protease inhibitors also interact.[16-18]

The risk of diversion (that is, diverting take-away supplies to 'other people' for financial or other gain) needs to be appraised. This is especially important if the patient is living in a group household with other illicit drug users. Also consider if there are young children in the house (accidental exposure risk).

Some occupations, such as the airline and mining industries, do not permit any use of opioids. Opioid substitution therapy poses risks for driving, mostly during induction and dose adjustment. When combined with other sedating drugs (alcohol, benzodiazepines, antihistamines) this risk is increased. However, once a patient is on a stable, long-term dose and there are no signs suggesting opioid impairment (miosis with sedation, unsteady gait), they may be able to drive.[19,20]

Opioid substitution therapy in special circumstances (for example in inpatients, pain management and pregnancy) and travel, particularly overseas, poses problems for patients.[5,21]

Choice of therapy

All forms of opioid substitution therapy are more effective when used as part of a comprehensive approach to drug rehabilitation (Box 2). Opioid substitution therapy includes methadone (a full agonist), buprenorphine (a partial agonist) and naloxone and naltrexone (antagonists). All have different formulations and Pharmaceutical Benefits Scheme (PBS) indications.

Methadone

Methadone syrup 5 mg/mL is available with or without added ethanol and sorbitol (some patients have preferences). It is a full agonist at the mu opioid receptor which is possibly why it is preferred by many patients. The syrup formulation is useful for dispensing under direct supervision, because liquid cannot be concealed under the tongue like tablets. Methadone is approved for use in pregnancy. Its metabolism does not produce active metabolites so it can be cautiously used in patients with liver or renal impairment.

Methadone has slightly more drug interaction risks than buprenorphine. Many patients taking methadone also smoke and there is the potential for toxicity if they suddenly stop smoking. There is a risk of QTc prolongation at higher doses (for example more than 100 mg daily) and in those with other risk factors for QTc prolongation.[22,23]

Methadone in its oral formulation has approximately 70% bioavailability compared with the parenteral

Table **Options for managing acute opioid withdrawal**

Drug	Dose
Buprenorphine*	Start at 4 mg (test dose) then up to a total of 8 mg on day one, thereafter reduce by 2 mg daily
Methadone syrup*	Start at 25 mg on day one, thereafter reduce by 2–5 mg daily
Metoclopramide	10 mg tablets (or intramuscularly if inpatient or in clinic) 6-hourly as needed for about three days
Loperamide	2 mg tablets for problematic diarrhoea in opioid withdrawal, as needed for about three days

Benzodiazepines are generally avoided when specific symptomatic care with opioid substitution therapy is provided

Although an off-label use, clonidine is sometimes used to treat acute opioid withdrawal in situations where avoiding opioids is preferred

While not specific to opioid withdrawal treatment, metoclopramide and loperamide are commonly used in providing symptom relief

* begin after opioid withdrawal signs appear

Box 2 **Elements of comprehensive drug rehabilitation**

Targeted counselling and education regarding blood-borne viruses, injecting and overdose

Primary health care including contraception, viral screening, vaccination – consider hepatitis B, tetanus and pneumococcal vaccines

Assessment and management of any concurrent substance use like benzodiazepines, smoking

Assessment and management (and/or shared care) of any concurrent comorbidities (e.g. hepatitis C related liver disease, diabetes, chronic obstructive pulmonary disease, dental disease)

Assessment and management of concurrent mental health problems (e.g. depression, anxiety)

Psychosocial support including assistance with family, housing, legal, work and other related problems

Relapse prevention counselling – cognitive behavioural therapy

formulation. When 'nil orally' restrictions apply a 30% (of usual) dose reduction is recommended. Patients on methadone who have acute pain will usually require higher than usual doses of opioid analgesics (because of tolerance) while having their regular daily methadone dose maintained.[21,24]

Buprenorphine and naloxone

Buprenorphine is formulated alone or in combination with naloxone. In the combination the buprenorphine to naloxone ratio is 4:1, for example 8 mg buprenorphine with 2 mg naloxone. In addition to sublingual tablets, the combination is formulated as a film that dissolves rapidly under the tongue. In comparison with methadone, buprenorphine is a partial agonist and antagonist at the mu opioid receptor so it is often recommended as first line in cases where the degree of opioid tolerance is lower (as estimated by considering daily dose, potency, route of administration and the observed severity of opioid withdrawal).

The combination of naloxone with buprenorphine generally reduces the risk of diversion or self-injection, because the predominant effect following intravenous use is naloxone-induced withdrawal (aversive). There are comparatively few deaths associated with buprenorphine opioid substitution therapy in contrast with methadone.[25] The combination has therefore been approved in some states for prescription by any medical practitioner, with some caseload limitations.

Naloxone has not been proven safe in pregnancy and therefore the combination formulation is not approved for use by pregnant women or those contemplating pregnancy. Evidence supporting the safety of buprenorphine alone is emerging. It may possibly be associated with less neonatal abstinence syndrome than methadone.[26] Buprenorphine alone is usually only recommended with informed consent in pregnancy or when naloxone allergy exists. In the vast majority of instances, the combination formulation is preferred.

Naltrexone

Naltrexone is listed on the PBS only for alcohol dependence, however it has been used for opioid addiction as it may facilitate the maintenance of opioid abstinence. While naltrexone has efficacy in treating alcohol dependence,[27] the evidence for naltrexone's efficacy in treating opioid addiction is less impressive.[5,8] Naltrexone is not recommended for facilitating rapid opioid detoxification.[4] As it is not listed on the PBS, naltrexone costs patients up to approximately $180 per month.[5,8]

Naltrexone is formulated as a 50 mg tablet. Implant formulations are available, but these are not approved by the Therapeutic Goods Administration, and the National Health and Medical Research Council (along with some medical defence insurers) has issued cautions regarding the lack of safety and efficacy data. In the USA, a depot naltrexone formulation is available for the treatment of alcohol dependence and can be used for treating opioid addiction.

A minority of patients seek this 'antagonist' treatment, but if naltrexone is used, it is recommended to be prescribed with an adherence strategy that involves the patient's spouse or other reminders. Opioid substitution therapy with an agonist has primary (rewarding) and secondary (avoidance of withdrawal) reinforcing efficacy and so patients are more likely to remember to take their treatment.[5,8]

Considering dose and duration of therapy

The starting dose is always low (for example methadone 20 mg, buprenorphine 4 mg, naltrexone 25 mg). Apart from methadone the dose is mostly increased to the effective maintenance dose within days. To reduce the risk of toxicity, not increasing the methadone dose more than 10 mg per week during induction (later, 10–20 mg per week) is recommended and no take-away doses are approved. As methadone has a long half-life, accumulation will occur slowly and steady-state concentrations are not achieved for, on average, 5–7 days. The efficacy of any increased dose of methadone is therefore evaluated after a week. Treatment is titrated to effect which can be assessed by reduced use of other opioids

(for example illicit heroin injecting) and reduction of withdrawal and craving symptoms. An average target dose range of 60–80 mg methadone or approximately 16 mg buprenorphine daily has been correlated with better outcomes.[4-7,28] Take-away doses of opioid substitution therapy are only approved when the prescriber is satisfied that the patient is stable and the risk for diversion is reduced.[5] Divided daily doses of methadone (and buprenorphine) are sometimes used for inpatients with acute pain (analgesic efficacy being of shorter duration than other opioid effects),[21,24] or in situations of enhanced metabolism (for example pregnancy and interactions with enzyme-inducing drugs such as rifampicin) to avoid very high peak concentrations and extend the duration of effects.

Addiction is a chronic disease so prolonged treatment (for example more than a year) has the best outcomes, but many patients will want to discontinue opioid substitution therapy after relatively brief periods of improvement. Retaining a patient in therapy is therefore an ongoing challenge for the prescriber. While many Australian opioid substitution programs retain patients for less than 12 months, treatment outcomes are better when longer retention is achieved. Measuring treatment retention rates provides a good method of evaluating opioid substitution therapy programs.[4-7,28,29]

Evaluating safety and efficacy

Monitoring opioid substitution therapy is part of the management plan. This includes regular assessment for any adverse events and the patient's progress.

Box 3 **Monitoring the efficacy and safety of opioid substitution therapy**

- Pay particular attention to methadone dose during induction – first two weeks (e.g. methadone 20 mg to 40 mg maximum)
- Regular review of treatment progress and any new drug therapy – assess risk of interaction or diversion
- Engage family or significant others in treatment monitoring (e.g. occasional family inclusive consultations)
- Educate family or significant others in drug risk management (e.g. recognising possible toxicity)
- Regular communication with the pharmacist who frequently sees the patient
- Regular physical examination includes looking for any injection sites and any signs of drug-related impairment (e.g. is patient fit to drive?). Always document these findings.
- Random urine drug screening
- Consider use of breathalyser and selected blood tests where appropriate (e.g. gamma-glutamyl transferase)
- Careful consideration of risk before approving any take-away, unsupervised, doses
- Compliance with treatment guidelines

There are many long-term problems and other complications of opioid therapy including gut motility disturbances, hypogonadism, hyperalgesia, osteoporosis, tooth decay, hyperhydrosis, sleep disorder and driving hazards.[15-20] Monitoring safety includes ensuring safe storage and transport of the medicine by the patient. Buprenorphine film may melt in temperatures above 25° C. Using a lockable box to store take-away doses is essential when children are at home.

As patients see their pharmacist frequently, the pharmacist can give the prescriber further information about the patient's treatment adherence and daily functioning. Because addiction is associated with significant mental and physical risks and adversely impacts on families, opioid substitution therapy is recommended to be provided in a family inclusive context. This also helps the prescriber obtain further important information about the patient's functioning. In most states, prescribers and pharmacists need accreditation to provide opioid substitution therapy and there is some state variability in regulations, hence familiarity with state guidelines is necessary. National treatment guidelines are in press[5] and Box 3 summarises recommended monitoring.

Access to treatment

Opioid substitution therapy was originally restricted to accredited prescribers, however recently a number of states have allowed any medical practitioner to prescribe the buprenorphine with naloxone formulation. During any temporary absence of an accredited prescriber (for example in a group practice), state regulations generally permit another prescriber from the same practice, who has access to the treatment plan, to cover the continuation of a regular prescription for opioid substitution therapy.

Unfortunately, many doctors who undertake accreditation for opioid substitution therapy do not prescribe for various reasons. If more general practitioners prescribed opioid substitution therapy, additional general healthcare advantages would be likely, for example disease screening, immunisation, contraception and more comprehensive care. The low number of prescribers diminishes public access to this essential treatment and is a public health problem.[14] There are also concerns about prescribing other opioids to patients undergoing opioid substitution therapy because of the risk of toxicity and breaching the sanctions of the patient's rehabilitation program.[30]

Although methadone and buprenorphine formulated for opioid substitution therapy are fully funded under the PBS, the pharmacist-supervised daily dispensing

requirement is not. That costs, on average, $6 per day, which is not insignificant for many patients. Some hospital pharmacies or public-funded clinics may, for a time, waive the dispensing fee. As resources are limited, usually such access to free treatment is restricted to special cases.

Conclusion

Opioid substitution therapy is a highly effective component of comprehensive drug rehabilitation for opioid addiction. It reduces mortality and morbidity. All states and territories provide services to support opioid substitution therapy, including detailed treatment guidelines. However, the numbers of patients seeking treatment are increasing, while the numbers of prescribers are decreasing.

Different opioid substitution therapy formulations allow treatment selections better suited to the individual patient.

It is important to try and keep the patient in therapy. Regular follow-up is advised to monitor the patient's progress. ⋖

Dr McDonough was a medical adviser to Reckitt-Benckiser regarding buprenorphine until 2011.

Q:

SELF-TEST QUESTIONS

True or false?

3. The effect of a change in the dose of methadone cannot be evaluated for 5–7 days.

4. Methadone is contraindicated in pregnancy.

Answers on page 107

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ARTICLE

Pneumococcal vaccines: past, present and future

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SUMMARY

Universal vaccination of Australian children with the 7-valent pneumococcal conjugate since 2005 has substantially reduced invasive pneumococcal disease. Herd immunity has also been observed in adults.

Conjugate vaccines of higher valency, which provide additional serotype coverage, became available in 2009. The 13-valent vaccine replaced the 7-valent vaccine in the National Immunisation Program in July 2011.

The 23-valent polysaccharide vaccine is recommended for all adults aged 65 years or over and for Aboriginal and Torres Strait Islander adults aged 50 years or over. It is also indicated in younger people with risk factors for invasive disease.

Additional pneumococcal vaccine doses are recommended for children and adults at increased risk of invasive disease.

The Australian Immunisation Handbook 10th edition contains detailed recommendations.

Introduction

Pneumococcal vaccines are designed to prevent diseases caused by *Streptococcus pneumoniae* (pneumococci), broadly referred to as pneumococcal disease. There are two different types – the conjugate vaccines and a polysaccharide vaccine (Table 1). The conjugate vaccines can induce an immune memory response, and are immunogenic in young infants. In contrast, the polysaccharide vaccine is poorly immunogenic in children under two years and those with impaired immunity. Although it contains more serotypes, it is not conjugated to a protein and does not induce a memory immune response.

Among the pneumococcal conjugate vaccines, formulations vary in the number of pneumococcal serotypes included (valency) and the conjugating proteins used. Table 1 shows the serotypes contained in the pneumococcal vaccines registered in Australia. The original 7-valent conjugate vaccine has now been superseded in the National Immunisation Program by the 13-valent conjugate vaccine.

Pneumococcal disease

S. pneumoniae is a Gram-positive bacterium with a polysaccharide capsule, which is a virulence factor. More than 90 polysaccharide serotypes have been identified, with each serotype eliciting serotype-specific immune responses. Different serotypes vary in their propensity for nasopharyngeal colonisation and for causing disease. In Australia in 2002–04, before the universal infant pneumococcal conjugate vaccination program, 85% of invasive pneumococcal disease in children under two years was caused by the serotypes contained in the 7-valent conjugate vaccine (Table 1).[1] Serotype distribution of pneumococcal disease is more diverse among Aboriginal and Torres Strait Islander people, including children, and among adults in general compared to children.

Transmission and carriage

Transmission of pneumococci occurs via respiratory droplets from individuals with nasopharyngeal colonisation.[2] Carriage of pneumococci in the nasopharynx varies with age and environmental factors. The duration of carriage is generally longer in children. All pneumococcal disease presumably begins with nasopharyngeal colonisation.

Invasive disease and its risk factors

For disease surveillance purposes, detection of *S. pneumoniae* in a normally sterile site, such as blood, cerebrospinal fluid or pleural fluid, by culture or polymerase chain reaction, is classified as invasive pneumococcal disease. The highest incidence of invasive pneumococcal disease is seen among young children, especially those under two years, and in the elderly.[3,4] The major categories of invasive pneumococcal disease are:

1. meningitis, which is associated with the highest case-fatality rate and possible neurological sequelae among survivors
2. bacteraemic pneumonia
3. bacteraemia without focus, the commonest clinical category in young children.

Various medical, environmental and lifestyle factors are associated with an increased risk of developing invasive disease (see Box).[5,6] Aboriginal and Torres Strait Islander children and adults have a higher rate of invasive pneumococcal disease compared with other Australians.[7,8]

Table 1 **Pneumococcal vaccines and their serotypes**

Vaccine type	Valency (brand name)	Conjugating protein	Shared serotypes	Additional serotypes
Conjugate vaccines	7-valent (Prevenar)	non-toxic *Corynebacterium diphtheriae* CRM_{197} protein	4, 6B, 9V, 14, 18C, 19F, 23F	–
	10-valent (Synflorix)	protein D from non-typeable *Haemophilus influenzae,* tetanus toxoid, and diphtheria toxoid	4, 6B, 9V, 14, 18C, 19F, 23F	1, 5, 7F
	13-valent (Prevenar 13)	non-toxic *Corynebacterium diphtheriae* CRM_{197} protein	4, 6B, 9V, 14, 18C, 19F, 23F	1, 5, 7F, 3, 19A, 6A
Polysaccharide vaccine	23-valent (Pneumovax 23)	none	4, 6B, 9V, 14, 18C, 19F, 23F	1, 5, 7F, 3, 19A, 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, 33F

Box **Risk factors for invasive pneumococcal disease** [6]

Category A: Conditions associated with the highest increased risk of invasive disease

Functional or anatomical asplenia:

- sickle cell disease or other haemoglobinopathies
- congenital or acquired asplenia (e.g. splenectomy), splenic dysfunction

Immunocompromising conditions:

- congenital or acquired immune deficiency, including symptomatic IgG subclass or isolated IgA deficiency (Note: children who require monthly immunoglobulin infusion are unlikely to benefit from vaccination)
- immunosuppressive therapy (including high-dose corticosteroids for more than one week) or radiation therapy, where there is sufficient immune reconstitution for vaccine response to be expected
- haematological and other malignancies
- solid organ transplant
- haematopoietic stem cell transplant*
- HIV (including AIDS)
- chronic renal failure, or relapsing or persistent nephrotic syndrome

Proven or presumptive cerebrospinal fluid leak

Cochlear implants

Intracranial shunts

Category B: Conditions associated with an increased risk of invasive disease

Chronic cardiac disease:

- particularly cyanotic heart disease or cardiac failure in children
- excluding hypertension only (in adults)

Chronic lung disease:

- chronic lung disease in preterm infants
- cystic fibrosis
- severe asthma in adults (requiring frequent hospital visits and use of multiple medications)

Diabetes

Down syndrome

Alcoholism

Chronic liver disease

Preterm birth at <28 weeks gestation†

Tobacco smoking

* Recommendations vary for haematopoietic stem cell transplant recipients[6]

† All infants born at <28 weeks gestation should receive the recommended vaccine doses as for those with an increased risk of invasive disease, up to age 5 years. After that, they only require further vaccine doses if they have chronic lung disease or another chronic medical condition that increases their risk.

Non-invasive disease

Otitis media and pneumonia (without bacteraemia) are classified as non-invasive disease for surveillance purposes. Pneumococcus is estimated to account for over a third of all community-acquired pneumonia in adults.[2]

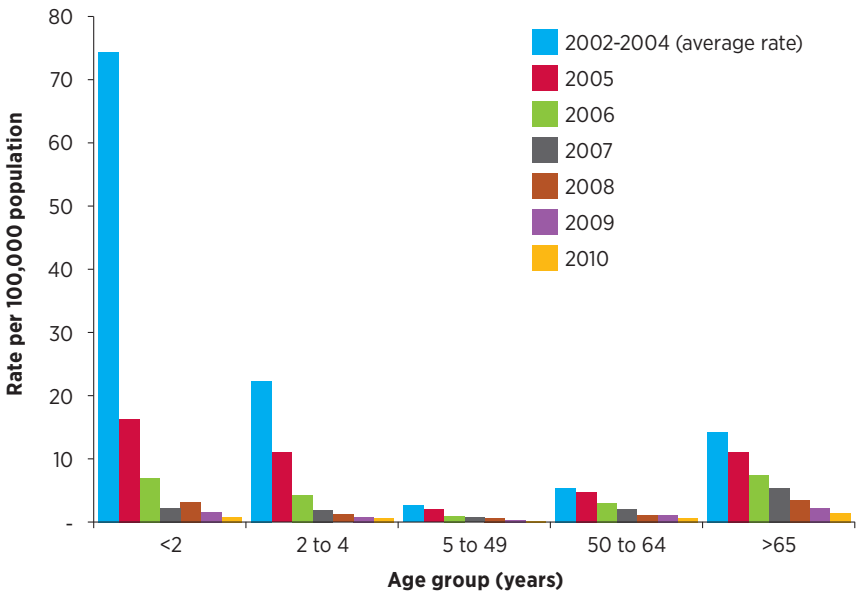
The impact of pneumococcal vaccination in Australia

In January 2005, Australia implemented universal vaccination of all young children with the 7-valent conjugate vaccine, and of adults aged 65 years and over with the 23-valent polysaccharide vaccine. Before then, there were publicly-funded pneumococcal vaccination programs for Australians with increased risks of pneumococcal disease[3] (www.ncirs.edu.au/immunisation/history/Pneumococcal-history-June-2012.pdf).

Following universal vaccination, the overall incidence rate of invasive pneumococcal disease decreased by 75% among non-indigenous children under two – from 78 per 100 000 in 2002–04 to 19.5 per 100 000 in 2007. Invasive disease caused by the seven vaccine serotypes declined by 97%, from 60.9 per 100 000 to 2.1 per 100 000.[3,9] Rates of hospitalisation due to pneumonia have decreased by 38% in children under two years.[10] Substantial reductions in invasive disease were also observed in older children and adults, the age groups who did not receive the vaccine. The decline was mostly due to a decrease in invasive disease caused by the seven vaccine serotypes (see Fig. 1).[3,4] This suggests a strong benefit of herd immunity, additional to any direct effect arising from the adult 23-valent vaccine program.

Increasing rates of invasive pneumococcal disease caused by serotypes not contained in the 7-valent vaccine ('serotype replacement') have been observed since 2005. Serotype 19A has emerged to become the dominant serotype causing invasive pneumococcal disease,[8] constituting 44% of all invasive disease among non-indigenous children under two years of age in 2007.[9] The number of cases due to serotype 19A among non-indigenous Australians increased by more than four-fold between 2002 and 2008 in most age groups.[8] However, this was not seen among indigenous Australians.[9,11]

Fig. 1 **Notification rate for invasive pneumococcal disease caused by serotypes contained in the 7-valent pneumococcal conjugate vaccine, Australia, 2002 to 2010, by age group** *



* Figure modified with permission from reference 4

Current vaccination schedules and recommendations

In Australia, recommendations on the specific pneumococcal vaccines vary according to age, indigenous status, jurisdiction and risk of invasive disease. For more detail about the risk categories and vaccine recommendations, consult the Australian Immunisation Handbook 10th edition.[6]

Children

Table 2 summarises the current recommended childhood pneumococcal vaccinations. For the 13-valent conjugate vaccine, a three-dose primary vaccination schedule, at two, four and six months of age without a booster dose, is recommended. Based on efficacy data from the pivotal randomised controlled trial of the 7-valent conjugate vaccine,[12] the potential additional benefits are not considered sufficient to justify a routine booster (fourth) dose for healthy non-indigenous children. For those with a higher risk of invasive disease or indigenous children living in states and territories where there is a high incidence of invasive disease (WA, NT, SA and Qld), a fourth dose of the 13-valent conjugate vaccine is now recommended (see immunise.health.gov.au).

Guidance on catch-up vaccination schedules for children who are delayed in presenting for pneumococcal vaccination or who have an increased risk of invasive disease, including those diagnosed after completion of the age-based recommended course, can be found in the Australian Immunisation Handbook 10th edition.[6]

Adults

Table 3 summarises the current recommended adult pneumococcal vaccinations in Australia. A single dose of the 23-valent polysaccharide vaccine is recommended for healthy non-indigenous adults

Table 2 **Australian recommendations for pneumococcal vaccinations in children under 5 years**

Conjugate vaccine	Indigenous status, risk and jurisdiction	Age of child			
		2, 4 and 6 months*	12 months	12–18 months	4–5 years
13-valent	All healthy children in ACT, NSW, Tas or Vic Non-indigenous healthy children in NT, Qld, SA or WA	13-valent vaccine	–	–	–
	Indigenous healthy children in NT, Qld, SA or WA	13-valent vaccine	–	13-valent vaccine	–
	All children with increased risk of invasive disease	13-valent vaccine	13-valent vaccine	–	23-valent polysaccharide vaccine
If 10-valent is used	All healthy children	10-valent vaccine	–	10-valent vaccine	–

Table modified from the Australian Immunisation Handbook 10th edition [6]
* The first dose can be given as early as six weeks of age. The next scheduled doses should still be given at 4 and 6 months of age.

Table 3 **Australian recommendations for pneumococcal vaccinations in adults**

Risk of invasive disease (see Box)	Indigenous status	Age (years)	13-valent conjugate vaccine*	23-valent polysaccharide vaccine†
Normal (healthy)	non-indigenous	≥65	–	single dose
	indigenous	≥50	–	two doses‡
Increased risk (category B)	non-indigenous	18–64 ≥65	– –	three doses# two doses‡§
	indigenous	18–49 ≥50	– –	three doses# two doses‡
Highest risk (category A)	non-indigenous	18–64 ≥65	single dose single dose	three doses# three doses‡
	indigenous	18–49 ≥50	single dose single dose	three doses# three doses‡∞

Table modified from the Pneumococcal vaccines for Australians factsheet of the National Centre for Immunisation Research and Surveillance, based on the 10th edition of the Australian Immunisation Handbook [6]
* Recommended for those with risk factors for invasive disease who have never received the 13-valent conjugate vaccine. This dose should precede the first dose of the recommended 23-valent polysaccharide vaccine by 2 months. For those who have had the polysaccharide vaccine, the 13-valent vaccine dose should be given at least 12 months later.
† The minimum interval between any 2 doses of 23-valent polysaccharide vaccine should be 5 years, with a maximum of 3 lifetime adult doses
‡ The second dose should be given 5 years after the first dose
# The second dose should be given 5–10 years after the first dose. The third dose should be given at 65 years for non-indigenous people and 50 years for indigenous people or 5 years after the second dose, whichever is later.
§ Those diagnosed as being at increased risk after receiving the 23-valent vaccine at age 65 should receive a second dose at time of diagnosis or 5 years after the previous dose, whichever is later
∞ The third dose should be given at 65 years or 5 years after the second dose, whichever is later

at age 65. A routine second dose is no longer recommended, based on a harm–benefit re-evaluation in 2011.[13]

Younger adults with an increased risk of invasive disease, including smoking (see Box), should also be vaccinated. More doses of the 23-valent vaccine are recommended for Aboriginal and Torres Strait Islander people or those with risk factors for invasive disease. The minimum interval for a repeat dose of the 23-valent polysaccharide vaccine is five years. The maximum number of lifetime doses in adulthood is three, based on concerns regarding adverse events and limited effectiveness, and uncertainty about immune hyporesponsiveness following multiple revaccinations.

Adults with a medical condition associated with the **highest** increased risk of invasive disease (category A conditions in the Box) are also recommended to have a single dose of 13-valent conjugate vaccine.

7-valent conjugate vaccine

A pivotal US trial in a setting similar to the Australian general population found that the vaccine reduced the risk of invasive pneumococcal disease due to the seven vaccine serotypes by about 95% among infants and toddlers.[12] Some cross-protection against serotype 6A invasive pneumococcal disease was also shown.[14]

A Cochrane review of conjugate pneumococcal vaccines reported that the pooled vaccine efficacy was 80% (95% CI 58–90%) against vaccine-type disease and 58% (95% CI 29–75%) against all-serotype invasive disease in children under two years. Effectiveness against X-ray defined pneumonia was lower at 27% (95% CI 15–36%).[15]

Another Cochrane review on young children concluded that while the efficacy against clinically defined otitis media due to serotypes in the vaccine was about 60%, the overall preventive benefit against acute otitis media due to any cause was only 6–7%.[16] This is due to the cancelling out of the preventive benefits of 7-valent vaccine against disease due to vaccine serotypes by non-vaccine serotypes and other organisms. However, studies from several countries, including Australia, have shown a decrease in the likelihood of tympanostomy tube insertion among vaccinated children.

The 7-valent vaccine is safe. However, it is more commonly associated with local adverse events and fever than comparator vaccines such as hepatitis B or meningococcal C conjugate.[17] There is no pattern of increasing local reactogenicity with subsequent doses.[12]

Higher valency conjugate vaccines

The 10-valent and 13-valent conjugate vaccines were registered for young children based on non-inferiority of immunogenicity compared with the 7-valent vaccine. There are no definitive serological correlates of clinical protection against the whole spectrum of pneumococcal disease, especially where specific serotypes are concerned. Currently, clinical efficacy data are not available for either of these two vaccines.

10-valent vaccine (Synflorix)

This vaccine was approved in 2009 for children. While its clinical efficacy is yet to be published, a study of a prototype vaccine containing 11 pneumococcal serotypes (the 10 serotypes in the 10-valent plus serotype 3), also conjugated to *H. influenzae* protein D, showed significant protective efficacy against acute otitis media caused by vaccine serotypes (57.6%; 95% CI 41.4–69.3%) as well as by *H. influenzae* (35.6%; 95% CI 3.8–57.0%).[18]

The safety profile of the 10-valent vaccine is similar to that of the 7-valent vaccine, with no clinically relevant difference when co-administered with routine childhood vaccines.[19]

There are no specific data available that address the immunogenicity and safety around the interchangeability of the 10-valent vaccine and other CRM_{197}-conjugated vaccines (see Table 1). However, a mixed schedule consisting of different conjugate vaccines necessitated by changes in vaccination programs is considered acceptable.

13-valent vaccine (Prevenar 13)

Children

This vaccine was approved in 2010 for children. Because of the extensive postmarketing data on the 7-valent vaccine, and established immunologic correlates of protection against invasive pneumococcal disease in children, efficacy trials have not been conducted.[20] Licensing in Australia has been based on non-inferiority of immunogenicity for the 7-valent conjugate vaccine serotypes and comparable antibody responses to the additional serotypes. This includes serotype 19A, which has emerged as the dominant serotype in Australia. Field effectiveness against invasive pneumococcal disease caused by the additional serotypes contained in 13-valent vaccine has been shown.[21]

The safety profile of the 13-valent vaccine is similar to that of the 7-valent vaccine.[22] However, post-licensure surveillance in the USA has suggested that there is a slightly higher risk of febrile seizures in young children within a day of concurrent administration with inactivated trivalent influenza vaccine compared with the vaccines given alone on separate days (especially in children aged 12–23 months).[23] Concurrent administration of these two vaccines is considered acceptable. However, if relevant, parents should be given the option of having the vaccines separately at least three days apart.[6]

Adults

In 2011, the 13-valent vaccine was registered in Australia for adults aged 50 years and over, based on immunogenicity data showing comparable or better antibody responses compared to the 23-valent polysaccharide vaccine for the shared vaccine serotypes.

There is only limited safety information on the 13-valent conjugate vaccine in adults. Pain, redness

and swelling at the injection site is observed in about half of vaccine recipients. Concurrent administration of trivalent inactivated seasonal influenza vaccine with the 13-valent vaccine may increase the frequency of systemic but not local reactions.[24]

23-valent polysaccharide vaccine (Pneumovax 23)

This vaccine is available for adults and children two years and over. The majority of serotypes found in invasive pneumococcal disease isolates of Australian adults are contained in this vaccine.[25,26]

A Cochrane review in 2013 estimated that pneumococcal polysaccharide vaccines have an overall protective efficacy of 74% (95% CI 55–86%) against invasive disease in adults.[27] Recent observational data from England and Wales have shown moderate effectiveness (48%) of the 23-valent vaccine against invasive disease within two years of vaccination in adults aged 65 years or over. However, effectiveness waned after two years and became insignificant after five years. In the subgroup of adults aged 65–74 years who had no clinical risk factors for pneumococcal disease, effectiveness was higher (65%) and was maintained for longer.[28] There are no specific studies on the clinical effectiveness of a second dose of the polysaccharide vaccine.

Boosting of antibody responses to the 7-valent vaccine serotypes after vaccination with the polysaccharide vaccine has been shown in small studies of children and adults with underlying medical conditions. Some antibody response to a few additional polysaccharide vaccine serotypes was also observed.

The frequency of adverse reactions varies among study populations (and possibly with age), and is higher with repeat doses. At least half of the recipients will experience some soreness at the injection site after the first dose. Swelling and redness are also very common (approximately 20%). More severe injection site reactions occur in up to 5% of first dose recipients and may occur in up to 20% of people after a second dose.[29-31] In these studies, repeat doses were given at least five years after the previous dose. Cellulitis-like reactions can also occur. Local adverse events occurred more often after subcutaneous administration than after intramuscular administration.[32] Systemic reactions like myalgia, fatigue and chills are also very common.

Conclusion

The universal childhood pneumococcal conjugate vaccination program has substantially reduced pneumococcal disease, especially invasive disease in the target age group. Herd immunity has been observed in other age groups. Introduction of the 13-valent vaccine is likely to lead to further reduction in invasive pneumococcal disease caused by emergent serotypes, particularly 19A.

The 23-valent polysaccharide vaccine is modestly effective against invasive pneumococcal disease in adults, including older adults, especially those without underlying chronic medical conditions. However, due to an increase in local reactions after repeat doses, revaccination should be limited to those with higher risks of invasive pneumococcal disease.

Conflict of interest: none declared

SELF-TEST QUESTIONS

True or false?

5. A fourth booster dose of the 13-valent conjugate pneumococcal vaccine is not recommended for non-indigenous healthy children.

6. The 23-valent polysaccharide vaccine is recommended for all Aboriginal and Torres Strait Islander people aged 50 or older.

Answers on page 107

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Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Medicines Safety Update

Volume 4, Number 3, June 2013

In this issue

Anticholinergics and cognitive impairment

Health professionals should be aware that anticholinergic drugs may cause cognitive impairment in older patients when used long term.

Anticholinergics are a class of drug that blocks muscarinic actions of acetylcholine and has a wide range of effects. Drugs with definite anticholinergic properties include antiemetics (promethazine), anti-Parkinson agents (benztropine), gastrointestinal spasmolytics (propantheline), bladder spasmolytics (oxybutinin, tolterodine) and antidepressants (imipramine).[1]

Precautions for anticholinergics include using with caution in elderly patients, who are more sensitive to adverse events associated with these drugs. In particular, confusion can be precipitated or worsened. When used in elderly patients, anticholinergics should be initiated at a low dose and increased slowly to the lowest effective dose.

Evidence in the literature

Two recent long-term studies examined cognitive impairment in older patients.

One of those studies followed 13 004 patients aged 65 and older for two years. At the commencement of the study, 4% of patients were using a drug with definite anticholinergic properties.[2] These patients experienced a 0.33 point greater decline in mini-mental state examination (MMSE) compared to patients not taking anticholinergics.

The other study followed 1652 African American subjects over 70 years of age, for six years. At the commencement of this study, 11% of patients were using a drug with definite anticholinergic properties.[3] These patients experienced a 1.43 times increased risk of developing cognitive impairment compared to patients not taking a drug with definite anticholinergic properties. Also, the risk increased with the number of anticholinergics being used.

Information for health professionals

Health professionals are advised that anticholinergics should be used with caution in elderly patients due to a risk of cognitive impairment.

Consideration should be given to routine measurement of cognitive function in older patients taking drugs with anticholinergic properties for any indication, including non-nervous system indications.

It may be possible to lower the anticholinergic burden by replacing such drugs with alternatives that do not have anticholinergic properties.

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

TGA Health Safety Regulation

System for Australian Recall Actions

The TGA recently launched the System for Australian Recall Actions (SARA) – an online, searchable database of recall actions for therapeutic goods undertaken in Australia.

Health professionals are encouraged to use SARA, along with other resources on the TGA website, such as the Database of Adverse Event Notifications and the alerts webpage, to access valuable information on medicine safety.

A recall action is a regulatory action taken for a therapeutic good supplied in Australia to resolve issues or deficiencies relating to safety, quality, efficacy or performance. Recall actions can be recalls, recalls for product correction or hazard alerts. Not all recall actions result in a product being removed from the market, for example hazard alerts may be issued in cases involving implantable devices, and corrections may be undertaken for products that have software issues.

SARA includes recall actions for a range of therapeutic goods including prescription medicines, over-the-counter medicines, complementary medicines, medical devices including in vitro diagnostic medical devices, and biologicals.

The database holds information on all recall actions that have been undertaken in Australia since 1 July 2012.

SARA has been launched as part of the TGA's commitment to improve transparency, as well as trust and confidence in the safety and quality of therapeutic goods and regulatory processes.

Changes to cough and cold medicines for use in children

With the arrival of winter, health professionals are reminded that cough and cold medicines should not be given to children under 6 years of age and only to children aged 6 to 11 years on the advice of a doctor, pharmacist or nurse practitioner.

These changes – and others relating to labelling and packaging – were made in 2012 as a result of a review of safety and efficacy for over-the-counter cough and cold medicines used in children (for further details visit www.tga.gov.au/industry/otc-notices-cough-cold-review-outcomes.htm).

The review found there was evidence that these medicines may cause harm to children, while the benefits of using them in children had not been proven. No changes were made to the scheduling of these medicines. Use of these medicines for a child under 6 years of age constitutes off-label use.

See also: Cranswick N. Cough and cold remedies for children. Aust Prescr 2013;36:e1.

Update - Progressive multifocal leukoencephalopathy (PML)

Following the publication of the article titled 'Progressive multifocal leukoencephalopathy – a rare but serious disease' (Medicines Safety Update Vol 4; No 1, 2013), the cases of PML in the TGA's database have been updated with new information which changes the final diagnosis for multiple cases. This update has occurred as part of the TGA's routine pharmacovigilance processes. The number of Australian reports of PML associated with immunomodulatory medicines, to 1 March 2013, is now:

- Rituximab – 12
- Natalizumab – 7
- Leflunomide – 1
- Alemtuzumab – 1.

Note: in many of these cases the patient had a history of chemotherapy and/or co-suspected immunosuppressant medicines such as nucleoside analogues, fingolimod, prednisolone and methotrexate.

The TGA's Database of Adverse Event Notifications has been updated to reflect the new diagnoses.

MEDICINES SAFETY UPDATE

Mitigating risks of dabigatran: right patient, right dose and careful clinical monitoring

A recent TGA safety review has found that careful patient and dose selection, along with careful clinical monitoring, are the keys to the safe use of dabigatran (Pradaxa).

Dabigatran is a direct thrombin inhibitor, indicated for the prevention of stroke in patients with non-valvular atrial fibrillation, and for the prevention of venous thromboembolism in patients undergoing total hip or knee arthroplasty.

Patient selection

As with all anticoagulants, bleeding is the major concern when using dabigatran. Age, renal function, comorbidities and concomitant drugs are the main determinants of bleeding risk. These risk factors are outlined in more detail in the table below. Health professionals should take these risk factors into consideration when selecting dabigatran for their patients.

Health professionals should carefully consider the risks and benefits of dabigatran compared with warfarin before switching patients who are well-controlled on warfarin. Additional information regarding patient selection and risk:benefit considerations for dabigatran can be found at www.nps.org.au.

Table
Factors known to increase haemorrhagic risk when taking dabigatran

Age	Being aged 75 years or over
Factors increasing dabigatran plasma levels	Moderate renal impairment (30–50 mL/min CrCL) Selected P-glycoprotein-inhibitor co-medication
Pharmacodynamic interactions	Acetylsalicylic acid (ASA; aspirin) Non-steroidal anti-inflammatory drugs (NSAIDs) Clopidogrel
Diseases/procedures with special haemorrhagic risks*	Congenital or acquired coagulation disorders Thrombocytopenia or functional platelet defects Active ulcerative gastrointestinal disease Recent gastrointestinal bleeding Recent biopsy or major trauma Recent intracranial haemorrhage Brain, spinal or ophthalmic surgery Bacterial endocarditis

* Prescribers should note that these are contraindications

Clinical studies have demonstrated a trend towards increased risk of myocardial infarction in patients taking dabigatran compared with warfarin, but the significance of this is uncertain. Health professionals should bear this in mind when making a decision to prescribe dabigatran.

Dose selection

Renal function testing should occur before commencement of dabigatran. Creatinine clearance should be estimated using the Cockcroft-Gault calculation.

The Cockcroft-Gault formula is:

$$\frac{1.23 \times (140 - \text{age[years]}) \times \text{weight[kg]} \ (\times 0.85 \text{ if female})}{\text{serum creatinine [micromol/L]}}$$

Health professionals are reminded that patients with a creatinine clearance of less than 30 mL/min should not be prescribed dabigatran. Patients with a creatinine clearance of 30–50 mL/min requiring dabigatran for stroke prevention should receive the reduced dose of 110 mg twice daily.

For patients with an increased haemorrhagic risk (see Table) the 110 mg twice-daily dose should be considered when prescribing dabigatran for the prevention of stroke in patients with non-valvular atrial fibrillation.

Clinical monitoring

- Clinical monitoring for early signs of bleeding is important in the management of patients taking dabigatran. Patients need to be informed of signs and symptoms to be aware of, and when to seek medical help.
- Renal function testing should be repeated at least annually, but more frequently in clinical situations where a decline in renal function may be expected, for example dehydration, shock or change in medications.
- Coagulation testing may be helpful in certain circumstances, such as in the event of bleeding, in emergency situations or a suspected overdose and in the perioperative setting. Refer to the Product Information (PI) for further information about coagulation testing. The clinical usefulness of routine testing as a risk stratification measure for dabigatran is unknown.

- There is currently no commercially available antidote. Surgical haemostasis and supportive therapies including the use of non-specific reversal agents are suggested when managing the bleeding patient. Clinical guidelines are available to assist health professionals manage the actively bleeding patient – see www.health.qld.gov.au/qhcss/mapsu/documents/dabigatran_info.pdf

New information about drug–drug interactions added to PI

The use of dronedarone has been added to the list of contraindications with dabigatran after a pharmacokinetic study showed a 2.4 fold increase in exposure to dabigatran when it is taken with dronedarone. More details regarding this interaction can be found in the Precautions section of the PI.

'Real world' experience

The 'real world experience' published to date indicates that dabigatran and warfarin share a similar overall bleeding risk.

The TGA continues to monitor reported adverse events for dabigatran and evaluate new information as it comes to hand.

New dabigatran contraindication

Dabigatran (Pradaxa) is now contraindicated in patients with prosthetic heart valves.

An interim analysis of the RE-ALIGN study – of dabigatran versus warfarin for thromboprophylaxis in patients with mechanical heart valves – found more frequent thromboembolic events and major bleeding in those patients taking dabigatran. Further information can be found in a US Food and Drug Administration safety announcement published on its website on 19 December 2012.

Patients with prosthetic valves taking dabigatran should be transitioned to warfarin. Suddenly stopping dabigatran is not recommended because of the risk of stroke. See the Product Information for guidance.

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

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

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

Reports may be submitted:

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

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

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

ABNORMAL LABORATORY RESULTS

Anti-Xa assays

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anticoagulation, low molecular weight heparins, thromboembolism

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SUMMARY

The plasma anti-Xa assay is a laboratory test that indirectly measures the activity of heparins. It is predominantly used for monitoring patients treated with low molecular weight heparins, particularly when dosing at the extremes of weight and in patients who are pregnant, critically ill or have renal impairment.

This monitoring is controversial as there is a poorly defined therapeutic range in different clinical settings and with different dosing regimens. Consequently, the timing of blood tests and their interpretation is problematic, often resulting in empirical dosing strategies.

Limitations to the assay include its lack of availability. The assay is not available in many hospitals. Its use is also restricted by the lack of Australian consensus guidelines that assist clinicians to adjust doses in response to the result of the assay.

The monitoring of prophylactic doses of low molecular weight heparins is seldom indicated.

Introduction

Heparins are commonly used anticoagulants. Treatment may be with an unfractionated heparin or a low molecular weight heparin.

Unfractionated heparin is routinely monitored by measuring the activated partial thromboplastin time. When low molecular weight heparins were first marketed regular monitoring was not recommended. While this is generally the case for prophylactic use, some patients require their treatment to be monitored.

As low molecular weight heparins are a mixture of molecules of varying length, their concentration is difficult to measure. Instead a pharmacodynamic observation, the anti-Xa activity, is used as a surrogate.

Mechanism of action of heparins

The anticoagulant properties of low molecular weight heparins and unfractionated heparin are derived from their interaction with antithrombin, a naturally occurring anticoagulant protein. Antithrombin suppresses coagulation by inactivating proteins involved in the coagulation cascade, primarily thrombin and clotting factor Xa. Heparins bind to antithrombin, inducing a change in the molecule that results in a many-fold increase in its anticoagulant activity.

The specific binding of any size heparin molecule to antithrombin is sufficient for inactivation of factor Xa. Unfractionated heparin also inactivates thrombin (coagulation factor IIa) as larger molecules are necessary for this process.

Dosing

The low molecular weight heparins have a purported predictable dose–response relationship and a half-life that permits once- or twice-daily dosing.[1,2] These properties help facilitate simple fixed or weight-based (mg/kg) dosing and enable outpatient treatment without the need for routine monitoring. This is reflected in the product information of enoxaparin and dalteparin.

The need for monitoring low molecular weight heparins

Patients with renal disease and obesity were predominantly excluded from the drug development studies. There is little evidence to guide the management of patients with extreme values of renal function or body weight. Data are also limited in newborns, children, pregnant women and the critically ill.

Many clinicians recognise the limitations of the fixed or weight-based dosing strategies. They reduce the recommended doses in an effort to minimise the likelihood of an adverse event or opt for monitoring to guide their choice of dose.[3]

Measuring anti-Xa activity

Low molecular weight heparins predominantly affect the activity of factor Xa, so it is appropriate to monitor them with an anti-Xa assay. The measured anti-Xa activity is considered to be directly proportional to the plasma concentration. Fondaparinux and danaparoid are two other drugs that inhibit factor Xa and their activity can also be measured using an anti-Xa assay.

The recommended method is the chromogenic procedure.[1] The patient's plasma is added to a known amount of excess factor Xa. If a heparin is present in the plasma, it will bind to antithrombin and form a

complex with factor Xa. The amount of residual factor Xa is inversely proportional to the amount of heparin in the plasma. The residual factor Xa is detected by adding a substrate that mimics the natural substrate of factor Xa. This is cleaved by the residual factor Xa, releasing a coloured compound (chromophore) that can be detected by a spectrophotometer. The quantity of chromophore released is inversely proportional to the activity of the heparin present. Each chromogenic substrate release is measured against a calibration curve that is specific to each heparin (or heparinoid). Recently multicalibration kits have become commercially available. Results are expressed as units/mL or units/L of anti-Xa activity.

The assay is not widely available and is reported to be poorly standardised between laboratories. There can be wide variations in the results obtained from the same plasma sample.[4] Antithrombin deficiency affects the assay, however this is rare.

Sampling

If the monitoring of anti-Xa activity is deemed necessary, sampling should occur as soon as possible after starting or adjusting treatment. The low molecular weight heparins have a half-life of four to six hours in average adults and a steady state will occur within one day. The half-life will be prolonged in renal impairment, but this should not detract from an assessment of these patients who are at risk of bleeding.

A maximum plasma activity or concentration above the target range increases the risk of bleeding. To estimate this peak concentration (C_{max}), the recommended sampling time is four hours after the dose. This time will often misrepresent the true C_{max} due to inter-individual variation in pharmacokinetic parameters. In some patients the peak concentration can be reached in one hour, however a reasonable representation can be gained between three and five hours after the dose. Sampling outside this time window will affect the ability to interpret the results. Often blood cannot be collected at the preferred time, so the result needs to be extrapolated to the 'true' C_{max}. This can be difficult and when in doubt the clinician should take another sample after the next dose.

Trough monitoring has been suggested. If trough monitoring is indicated the sample should be taken 12 hours after the dose, immediately before the next dose.

Therapeutic range

As with all anticoagulation, clinicians seek a therapeutic range that minimises the risk of bleeding and embolic events. The most robust data for enoxaparin come from the Thrombolysis in Myocardial Infarction 11A trial where peak anti-Xa concentrations greater than 1.0 IU/mL increased the incidence of bleeding.[5] A later study found that patients with a peak concentration less than 0.5 IU/mL had a three-fold increase in re-infarction and mortality when compared to patients with a concentration between 0.5 and 1.2 IU/mL.[6] When using enoxaparin at a twice-daily dose, the clinician should therefore aim for a peak concentration between 0.5 and 1.0 IU/mL although some guidelines recommend 0.5–1.2 IU/mL or 0.6–1.0 IU/mL.[1] A recent study suggested that a 50% reduction in adverse events would occur if the trough (C_{min}) is less than 0.5 IU/mL provided that the peak (C_{max}) is above 0.5 IU/mL.[7]

The suggested peak activity range for once-daily treatment is 1.0–2.0 IU/mL and 0.2–0.4 IU/mL for prophylactic use, albeit without supporting evidence.[2,8] As evidence supports the link between bleeding and a peak concentration greater than 1.0 IU/mL, the higher range for once-daily treatment is fraught with danger if a patient has severe renal impairment with reduced ability to eliminate the drug.

The target anti-Xa range for a peak concentration for dalteparin is listed in the product information as 0.5–1.5 IU/mL. Although clinical studies are lacking to support this range, it is assumed the concentrations above this range are linked to bleeding. For treatment doses, the reported therapeutic range for anti-Xa activity of danaparoid is 0.5–0.8 IU/mL.

The evidence for all therapeutic ranges originates from studies in arterial disease. Few data exist that define a separate range for venous disease.

When are anti-Xa assays indicated?

There is a developing consensus that monitoring is advisable in patients who have renal impairment, are pregnant or obese.[2] In these patients the pharmacokinetics of the drugs are altered when compared to otherwise healthy adults.

Pregnancy changes renal function and the distribution of fluid, which affects the clearance and distribution of the drugs, and makes predicting a therapeutic dose more difficult.[9] As warfarin is commonly contraindicated during early pregnancy, low molecular weight heparins with accompanying anti-Xa monitoring are recommended for indications such as recurrent deep vein thrombosis and in pregnant women with mechanical heart valves. In high-risk patients, trough anti-Xa monitoring is often used to ensure constant anticoagulation although there is no consensus on the target concentration.

Monitoring is also indicated in patients who receive extended therapy or do not have the expected

response, for example, those who thrombose or bleed during therapy. Anti-Xa monitoring should be considered in patients at high risk of bleeding as, unlike unfractionated heparin, the anticoagulant effects of low molecular weight heparins are not so readily reversible.

Renal impairment

Low molecular weight heparins are polar, hydrophilic drugs that are approximately 80% renally eliminated. In patients with renal impairment, accumulation could potentially occur with standard doses.[1,10] This increases the risk of bleeding.[10,11] Numerous studies of enoxaparin have shown higher peak and trough anti-Xa activity in patients with renal impairment.[8] However, the size of the risk has never been quantified in suitably powered studies, leaving a range of 0.5–1.0 IU/mL as the best dosing guide. According to the product information for dalteparin, monitoring only needs to occur after the patient has received three to four doses. However, drug accumulation will occur if the patient has severe renal impairment so it would be prudent to monitor before this time.

The table shows a summary of US monitoring guidelines.[2,8]

Obesity

The dosing and monitoring of low molecular weight heparins in obese patients is contentious. As the drugs are hydrophilic they are predominantly distributed in plasma and lean tissue and do not easily partition into adipose tissue. The clearance of low molecular weight heparins correlates with lean body mass, therefore the addition of adipose weight into the weight-based dose calculation is difficult to justify.[12]

Dosing based on total body weight may result in excessive concentrations so physicians often introduce an arbitrary dose adjustment that has never been formally evaluated. One method is to 'cap' the dose (for example 100 mg for enoxaparin), regardless of the patient's total body weight, however capping is likely to result in sub-therapeutic concentrations. Despite suggestions that anti-Xa monitoring should only be considered in the morbidly obese,[8] monitoring peak activity in adults with a total body weight more than 100 kg is justifiably common practice.

Table **Anti-Xa monitoring according to renal function**[2,8]

Renal function (mL/min) *	Anti-Xa monitoring
Severe impairment (<30)	Always
Moderate impairment (30–60)	For extended therapy (more than 48 hours)
Normal (>60)	Not required †

* Calculated using the Cockcroft-Gault equation
† Factors such as obesity need to be considered

Does anti-Xa activity change with different heparins?

Heparins have different molecular weights and consequently differing anti-IIa and anti-Xa activity. Unfractionated heparin molecules have approximately equivalent anti-Xa and anti-IIa activity. Low molecular weight heparins are approximately one-third the molecular weight of unfractionated heparin. This decreases their ability to bind to thrombin, giving an anti-Xa:anti-IIa ratio between 2:1 and 4:1.[1] It is this reduced anti-IIa activity which makes the activated partial thromboplastin time less reliable for monitoring low molecular weight heparins. At present there is no evidence to show that the differences in anti-Xa activity among the low molecular weight heparins influence clinical outcomes.[1]

Dose modification

No strategies have been evaluated in large, randomised studies to assist in dose modification once anti-Xa activity is known. A small Australian study demonstrated that the risk of bleeding is reduced when doses are individualised using anti-Xa concentrations.[13] Other dose reduction strategies for obesity and renal impairment have been proposed, but are yet to be tested against clinical outcomes.[8] Drug monitoring principles suggest that a linear dose adjustment could be used if the clearance of the low molecular weight heparins is stable, or an extension in dosing frequency if clearance is significantly reduced.

Conclusion

The anti-Xa assay is being increasingly used when treating patients with low molecular weight heparins, but a clear correlation between anti-Xa concentrations and clinical outcome is yet to be shown. The best evidence points towards a peak concentration between 0.5 and 1.0 IU/mL taken four hours after a dose. While clinical studies are pending, it is prudent to monitor anti-Xa activity in at-risk patients such as those with renal impairment, in the obese, and in pregnant women.

Measurement of anti-Xa activity assesses the activation of only a single component of the clotting system. There is a need for an alternative, simple, stable, diagnostic clotting time-based test to monitor treatment with low molecular weight heparins. New tests are promising, but require evaluation.[14]

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SELF-TEST QUESTIONS

True or false?

7. The activity of low molecular weight heparins is monitored by measuring the activated partial thromboplastin time.

8. A fall in anti-Xa activity, in a patient treated with low molecular weight heparins, is associated with an increased risk of bleeding.

Answers on page 107

ARTICLE

Smoking and drug interactions

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Key words
clozapine, cytochrome P450, nicotine

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SUMMARY

When patients enter hospital they may have to stop smoking abruptly if the hospital has a 'no smoking' policy. Abrupt smoking cessation can affect the metabolism of drugs.

Cigarette smoking induces the activity of human cytochromes P450 (CYP) 1A2 and 2B6. These enzymes metabolise several clinically important drugs, including clozapine, olanzapine and methadone.

Decreased CYP1A2 activity after smoking cessation increases the risk of adverse drug reactions, with reports of increased toxicity from clozapine and olanzapine. Predicting the required dose reduction of drugs metabolised by CYP1A2 after smoking cessation is challenging. Therapeutic drug monitoring should be used when possible.

Nicotine replacement therapy does not influence CYP1A2 activity.

Introduction

Despite anti-smoking campaigns, there are about 1.3 billion cigarette smokers worldwide and this number is still increasing.[1] Both smoking prevalence and daily tobacco consumption are very high in patients with psychiatric disorders.[2] Over two-thirds of Australians with psychosis smoke cigarettes, compared with one quarter of the general population.[3]

Smoking restriction or cessation is now commonly imposed on patients by 'no smoking' policies in Australian hospitals. Stopping smoking is particularly important in patients with mental health problems as they often have an adverse cardiovascular risk profile (from factors including obesity, dyslipidaemia, insulin resistance and hypertension). This is associated with high rates of premature mortality from cardiovascular disease.[4]

Even with nicotine replacement therapy as a cessation aid, patients with psychiatric illness appear to have more difficulty maintaining long-term abstinence than other smokers.[5] Most resume smoking within five weeks of hospital discharge.[6] These patients should be regularly asked about their smoking status, as an additional risk of resuming or abruptly ceasing cigarette smoking has the potential for drug interactions.[7]

Drug interactions

The chemicals in smoke may interact with antipsychotics, antidepressants, benzodiazepines,[8] oral contraceptives, inhaled corticosteroids and beta blockers via pharmacokinetic and pharmacodynamic (often nicotine-mediated) mechanisms.[9]

Pharmacokinetic interactions

Cigarette smoking induces the activity of cytochrome P450 (CYP) 1A2 (via chemicals in cigarette smoke such as polycyclic aromatic hydrocarbons)[10] and also CYP2B6.[11] These enzymes metabolise several clinically important drugs (such as antidepressants and antipsychotics) (Box) and a number of procarcinogens (such as those in cigarettes).[10,12]

The effect of smoking on hepatic enzymes is not related to the nicotine component of tobacco. Nicotine replacement therapy does not influence CYP1A2 activity.[13]

Genetic polymorphisms of the CYP1A2 gene contribute to extensive inter-individual variability in drug metabolism[14,15] and are associated with altered inducibility of gene expression in smokers.[7,16] There are also marked ethnic differences in the distribution of CYP1A2 mutations,[10,17] meaning that different ethnic groups respond differently when the patient stops smoking.

CYP1A2 activity is significantly higher in heavy smokers (more than 20 cigarettes/day) than in non-smokers.[18] This is likely to be clinically relevant for some drugs which have a narrow therapeutic index and are metabolised by CYP1A2, such as clozapine. The induction varies depending on the bioavailability of the components of cigarette smoke and the extent of inhalation.[8] It is not known how the number of cigarettes smoked daily or inter-individual variation affects CYP1A2 induction,[9] but heavier smokers appear to have a greater increase in the clearance of drugs.[19]

This enzyme induction is rapidly reversed when patients abruptly stop smoking, with a new steady state of CYP1A2 activity reached after approximately one week.[20] This reduction in enzyme activity reduces clearance and increases the risk of adverse drug reactions for patients taking drugs metabolised by CYP1A2.[20,21] These patients should be regularly asked about their smoking and the extent of their cigarette consumption.[16]

Clozapine and olanzapine

Cigarette smoking induces the metabolism of

clozapine and olanzapine,[22] resulting in lower plasma concentrations.[7,16,21] The daily consumption of 7–12 cigarettes is probably sufficient to cause the maximum induction of clozapine and olanzapine metabolism.[22] A 50% difference in the mean daily dose of clozapine needed by smokers and non-smokers to reach a given blood concentration has been reported.[23]

Irrespective of smoking status, the mean oral bioavailability of clozapine is 27–47% and clozapine plasma concentrations have more than a 45-fold variability amongst individuals during chronic treatment.[24] There are also large inter-patient differences in olanzapine exposure, with gender and genetic factors contributing.[25]

Non-smokers are at higher risk of adverse effects if treated with standard doses, suggesting that there is an interaction between smoking, olanzapine and clozapine.[20,22] In one case report, a patient receiving olanzapine experienced extrapyramidal symptoms (including akathisia, akinesia and bradyphrenia) within days of significantly reducing tobacco consumption.[21] Case reports on smoking discontinuation by patients taking clozapine outline effects including confusion,[21] tonic–clonic seizures, stupor, coma[26] or aspiration pneumonia.[27]

Clearance of clozapine has been shown to decrease when smoking is ceased, with a mean increase of 72% in plasma clozapine concentrations.[27] It is suggested that daily dose reductions (of approximately 10% until the fourth day after smoking cessation) should be made whenever patients cease smoking during treatment with clozapine.[20] Patients who resume smoking after leaving hospital may need their drugs and doses reviewed to account for this change.[28] Therapeutic drug monitoring of clozapine is useful.

Antidepressants

As fluvoxamine is metabolised by CYP1A2, smokers might require higher doses than those recommended from clinical trial data.[8] Smoking is not anticipated to alter the pharmacokinetics of other selective serotonin reuptake inhibitors as they are not substrates of CYP450 isoenzymes induced by smoking.[8]

Smokers might require higher than normal doses of the tricyclic antidepressant imipramine. They do not appear to require dose adjustments of amitriptyline, nortriptyline or clomipramine.[8]

Warfarin

Warfarin's less active R isomer is eliminated to a minor extent by CYP1A2.[29] Smoking may therefore potentially interact with warfarin by increasing its clearance and reducing its effect. A recent meta-analysis showed that smoking appeared to increase the warfarin dose requirement by 12%, resulting in an extra 2.26 mg per week compared with non-smoking.[30] Consequently, INR should be closely monitored when there is a change in patients' smoking status.

Box **Substrates of some cytochrome P450 enzymes induced by smoking**

CYP1A2

amitriptyline, caffeine, clozapine, duloxetine, fluvoxamine, haloperidol, imipramine, olanzapine, ondansetron, paracetamol, propranolol, theophylline, warfarin (R-isomer)

CYP2B6

bupropion, clopidogrel, cyclophosphamide, efavirenz, ifosfamide, methadone, nevirapine

More comprehensive lists are available[8,17]
Adapted from Australian Medicines Handbook 2013

Clopidogrel and prasugrel

CYP isoenzymes (including CYP2C19, 3A4/5, 1A2, 2B6 and 2C9) convert clopidogrel and prasugrel into their active metabolites, which bind irreversibly to the receptors on platelets. As smoking is known to enhance CYP1A2 activity, theoretically it could increase the antiplatelet efficacy of these thienopyridine drugs.[31]

An enhanced response to clopidogrel has been seen in smokers who are CYP1A2 (163CA) A-allele carriers.[32] Two retrospective analyses of large randomised clinical trials of clopidogrel showed that clopidogrel might be more effective in active smokers.[33,34] However, a systematic review concluded that smoking is not associated with reduced platelet reactivity in patients on clopidogrel.[31] Genetic polymorphisms seem not to impact on the activity of prasugrel.[31]

Caffeine

Caffeine is highly dependent on CYP1A2 for its metabolism. Smokers require up to four times as much caffeine as non-smokers to achieve the same plasma caffeine concentration. Caffeine can increase the concentration of clozapine and olanzapine.[35]

Pharmacodynamic drug interactions

Pharmacodynamic drug interactions with tobacco smoke are largely due to nicotine.[9]

Methadone

The vast majority of patients using methadone maintenance therapy also smoke tobacco.[36] Methadone doses have been found to be higher in heavy smokers[37] and methadone has been shown to increase both smoking rates and smoking satisfaction.[38] Patients report less methadone-induced

sedation when they smoke around the time of their methadone dose.[39]

Although methadone is a CYP2B6 substrate (Box), nicotine affects the endogenous opioid system. Cigarette smoking enhances the effect of methadone on opioid withdrawal symptoms.[40]

Methadone attenuates nicotine withdrawal. Reducing methadone doses when the patient is trying to stop smoking could be detrimental.[40]

Benzodiazepines

Nicotine activates the central nervous system[9] and this may explain the attenuated sedation observed in smokers compared to non-smokers taking benzodiazepines.[41] Prescribers should be aware that when patients taking benzodiazepines stop smoking, there is a risk of central nervous system depression.

Oral contraception

Smoking increases the adverse effects of the combined oral contraceptive pill (specifically thromboembolism, ischaemic stroke and myocardial infarction). The combined oral contraceptive pill is contraindicated in women aged 35 years or older who smoke 15 or more cigarettes a day.[9] For smokers who use combined low-dose oral contraceptives, the attributable risk of death from cardiovascular disease is 19.4 per 100 000 women aged 35–44 years (vs 3.03 per 100 000 for non-smoking women of the same age).[42] This risk is also presumed to be associated with other contraceptives containing oestrogen.[9]

Limited data suggest no convincing association between cardiovascular disease and progestogen-only pill use.[43] If smoking cessation is unsuccessful, non-hormonal or progestogen-only contraceptives are preferred from a cardiovascular perspective.[9]

Other drugs

The efficacy of inhaled corticosteroids may be reduced in asthmatic patients who smoke,[9] so these patients might require higher doses of inhaled corticosteroids to attain asthma control.[44]

Proposed mechanisms of corticosteroid insensitivity include suppression of histone deacetylase expression and activity by cigarette smoking, causing inflammatory gene expression and a reduction in glucocorticoid function.[45] Clearance of corticosteroids from the lungs may be altered by increased mucus secretion or airway permeability.[46]

Smokers may require higher doses of beta blockers. Although propranolol is a CYP1A2 substrate (Box), nicotine-mediated central nervous system activation may diminish the effect of beta blockers on blood pressure and heart rate.[9]

Drugs for nicotine dependence

Drugs used to aid smoking cessation are not without their hazards, particularly in patients with psychiatric disorders.

Bupropion, a selective catecholamine reuptake inhibitor, is associated with a dose-related risk of seizures. Predisposing risk factors include concomitant administration of antipsychotics, antidepressants, excessive alcohol or those sedatives which lower the seizure threshold. Psychiatric symptoms, in particular psychosis or mania, have been observed, mainly in patients with a history of psychiatric illness, particularly bipolar disorder.

Bupropion is metabolised by CYP2B6 and inhibits the CYP2D6 pathway. Drugs predominantly metabolised by 2D6 (including metoprolol, many antidepressants and antipsychotics) should be started at the lower end of the dose range if bupropion is used. Co-administration of drugs known to induce metabolism (for example, carbamazepine and phenytoin) or inhibit metabolism (for example, valproate) may affect the activity of bupropion.

Nortriptyline, a tricyclic antidepressant shown to aid smoking cessation, also interacts with other drugs metabolised by CYP2D6.

Varenicline, a partial agonist at neuronal nicotinic acetylcholine receptors, has no known clinically significant drug interactions. However, using nicotine replacement therapy while taking varenicline can exacerbate adverse effects such as nausea and headache. As with bupropion, serious neuropsychiatric symptoms have been reported (although a causal association has not been established).

Conclusion

Cigarette smoking can affect drug metabolism via pharmacokinetic and pharmacodynamic mechanisms, and a change in smoking status can render patients at risk of serious adverse reactions.

Patients should be regularly monitored with regard to their smoking status and extent of cigarette consumption and doses of relevant medications adjusted accordingly. ◁

No relevant potential conflict of interest declared

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A complete list of the references is available at www.australianprescriber.com/magazine/36/3/102/4

Q:

SELF-TEST QUESTIONS

True or false?

9. As smoking induces cytochrome P450 1A2, smokers need lower doses of drugs metabolised by this enzyme.

10. The pharmacokinetic effects caused by stopping smoking can be avoided by giving the patient a nicotine patch.

Answers on page 107

New drugs

Ceftaroline fosamil

Approved indication: complicated skin and soft tissue infections, community-acquired pneumonia

Zinforo (AstraZeneca)

vials containing 600 mg powder for infusion

Australian Medicines Handbook section 5.1.3

Ceftaroline fosamil is a cephalosporin with broad-spectrum in vitro activity against Gram-positive bacteria, including *Staphylococcus aureus*, *Streptococcus pyogenes* and *S. pneumoniae,* and some Gram-negative bacteria, including *Escherichia coli*, *Haemophilus influenzae* and *Klebsiella pneumoniae*. It is also effective against methicillin-resistant *S. aureus* (MRSA) and penicillin non-susceptible *S. pneumoniae* because it binds to the altered penicillin-binding proteins produced by these bacteria.

Ceftaroline fosamil is a prodrug which is converted into active ceftaroline by phosphatases in the plasma. Following a single intravenous dose of 600 mg, almost 90% is excreted by the kidneys with a mean terminal half-life of 2.5 hours. Dose adjustment is required in patients with moderate renal impairment (creatinine clearance >30–50 mL/minute) and it is not recommended in severe renal impairment or end-stage renal disease. Pharmacokinetic drug interactions are not expected as ceftaroline does not inhibit or induce P450 cytochromes and is not metabolised by these enzymes.

The approval of ceftaroline for complicated skin and soft tissue infections is based on two similarly designed phase III randomised controlled trials – CANVAS 1 and 2. A total of 1378 patients requiring intravenous antibiotics received ceftaroline 600 mg or vancomycin 1 g plus aztreonam 1 g as a 60 minute infusion every 12 hours for 5–14 days. Most patients had cellulitis, a major abscess or an infected wound. Patients with diabetic foot ulcers, pressure sores, bites, necrotising fasciitis, gangrene and third degree burns or burns covering more than 5% of their body were excluded, as were those with monomicrobial *Pseudomonas aeruginosa* or anaerobic infections.[1]

In an integrated analysis of the trials, rates of clinical cure – defined as total resolution of infection or improvement that no longer required antibiotics – were similar with ceftaroline and vancomycin plus aztreonam (91.6% vs 92.7%). However, in a subset of patients with infections caused by Gram-negative organisms, ceftaroline was not as effective as the comparator, with clinical cure rates of 85.3% versus 100%.[1]

The most common treatment-emergent adverse events in the skin trials were nausea (5.9%), headache (5.2%), diarrhoea (4.9%), pruritus (3.5%), rash (3.2%) and vomiting (2.9%). Four patients receiving ceftaroline were withdrawn. One patient had *Clostridium difficile*-associated diarrhoea and the others had allergic reactions. There were three deaths in the ceftaroline group – causes included respiratory failure, neck cancer and cardiopulmonary insufficiency.

The approval of ceftaroline for community-acquired pneumonia is also based on two phase III randomised trials – FOCUS 1 and 2.[2] In total, 1228 hospitalised patients requiring intravenous antibiotics (but not in the intensive care unit) received ceftaroline 600 mg every 12 hours or ceftriaxone 1 g every 24 hours for 5–7 days. (The design of the trials was similar except that in FOCUS 1 all patients also received two doses of oral clarithromycin 500 mg on day 1). Patients with an infection caused solely by an atypical pathogen such as *Mycoplasma pneumoniae* or *Legionella* species were excluded. In an integrated analysis, clinical cure rates were 82.6% for ceftaroline and 76.6% for ceftriaxone.[2]

The most common pathogens isolated in patients with pneumonia were *S. pneumoniae* and methicillin-sensitive *S. aureus*. (Patients with MRSA infections were excluded from the trials because ceftriaxone does not have activity against MRSA. Thirteen patients were infected with *S. pneumoniae* strains which were resistant to two or more antibiotics including penicillin, macrolides, tetracycline, flouroquinolones, chloramphenicol, trimethoprim-sulfamethoxazole and cephalosporins. Of these, clinical cure was achieved in all four patients treated with ceftaroline and two of the nine patients treated with ceftriaxone.[2]

The most common treatment-emergent adverse events in the pneumonia trials were diarrhoea (4.2%), headache (3.4%) and insomnia (3.1%). One of the 15 deaths in the ceftaroline group was possibly related to the study drug and occurred in a 73-year-old woman after two days of treatment. She had a history of smoking and an abnormal ECG at baseline.[2]

Over 10% of patients in the phase III trials developed a positive Coombs test (a direct antiglobulin test). Although none of the patients had signs of haemolysis, haemolytic anaemia is a possibility with

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

ceftaroline, as it is with other cephalosporins. Doctors should be aware that patients allergic to penicillins may also be allergic to ceftaroline.

There are no human data for ceftaroline in pregnancy or lactation so it should only be used if the benefits outweigh the potential harms. Interruption of breastfeeding is recommended. The safety and efficacy of ceftaroline in children is currently unknown.

Ceftaroline was non-inferior to comparative treatments in phase III trials and provides another option for hospitalised patients with complicated skin infections or community-acquired pneumonia. It has efficacy against infections caused by MRSA and drug-resistant *S. pneumoniae*, but is less effective against some Gram-negative pathogens. It should only be used for infections that are proven or are strongly suspected to be caused by susceptible bacteria. Antibiotic stewardship is important, particularly as ceftaroline has broad-spectrum activity.

T manufacturer provided the product information

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First published online 26 April 2013

Tapentadol

Approved indication: analgesia
Palexia IR 50, 75 and 100 mg tablets (CSL)
Palexia SR 50, 100, 150, 200 and 250 mg (CSL)
Australian Medicines Handbook section 3.2

Tapentadol is a centrally-acting synthetic opioid which is structurally similar to tramadol. It is thought to bind to the mu opioid receptor and inhibit the reuptake of noradrenaline.

The immediate-release form of tapentadol is indicated for moderate to severe pain. In a trial of 603 patients, tapentadol (50, 75 or 100 mg every 4–6 hours) was compared to immediate-release oxycodone (15 mg every 4–6 hours) or placebo for acute pain after bunionectomy. Tapentadol and oxycodone were significantly better than placebo at relieving pain over the first 48 hours. The analgesic effects of tapentadol seemed to be dose-dependent with tapentadol 100 mg being comparable to oxycodone 15 mg. However, at these doses nausea and vomiting appeared to be less common with tapentadol than with oxycodone (nausea 49% vs 67%; vomiting 32% vs 42%) and somnolence seemed to be more common (21% vs 10%).[1]

The efficacy of immediate-release tapentadol (50 and 75 mg) was also similar to immediate-release oxycodone (10 mg) for osteoarthritis pain due to moderate to severe joint disease (in 659 patients). Again, gastrointestinal effects were less for tapentadol than oxycodone.[2]

A sustained-release formulation of tapentadol has also been approved in Australia for moderate chronic pain unresponsive to non-narcotic analgesia. It has been compared to controlled-release oxycodone for chronic low back pain and osteoarthritis in several trials. In a pooled analysis of three trials (2968 patients), tapentadol (100–250 mg twice daily) was not inferior to oxycodone (20–50 mg twice daily) for pain associated with osteoarthritis of the knee and low back pain over 12 weeks of maintenance treatment.[3]

The adverse effects of tapentadol are similar to other opioids. The most common effects are nausea, dizziness, vomiting, somnolence, constipation and pruritus. These events seemed to be dose-related and some people discontinued treatment because of them.

After a single oral dose of tapentadol immediate-release, serum concentrations peak at 1.25 hours. It is extensively metabolised, mainly by glucuronidation, and to a lesser extent by CYP2C9 and CYP2C19, so drug interactions mediated through cytochrome P450 are unlikely. Most of the metabolites are excreted in the urine and the terminal half-life is four hours.

The maximum serum concentrations of the sustained-release formulation are reached in 3–6 hours. Its half-life is approximately six hours.

Tapentadol is not recommended in people with severe renal or hepatic impairment. Caution is urged in those with moderately impaired liver function or a history of seizures.

As tapentadol increases noradrenaline, it should not be taken with monoamine oxidase inhibitors. Drugs that may contribute to serotonin toxicity should also be avoided with tapentadol. Additive central nervous system depression can occur if tapentadol is taken with other centrally-acting drugs, including alcohol.

Prescribers should be aware that tapentadol is not recommended for labour pain and there are inadequate data to support its use for cancer pain. Like other opioids, there is a risk of drug dependence.

The efficacy of tapentadol appears to be similar to oxycodone, but with less gastrointestinal adverse

effects. It is not known how it will compare to other opioids such as tramadol.

T manufacturer provided the AusPAR and/or the product information

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

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

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

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ANSWERS TO SELF-TEST QUESTIONS

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