REVIEW ARTICLE

Drug Safety 2009; 32 (6): 457-474
0114-5916/09/0006-0457/$49.95/0

Treatment of Chronic Non-Malignant Pain in the Elderly

Safety Considerations

Jonathan Bruce Barber and *Stephen J. Gibson*

National Ageing Research Institute, Parkville, Victoria, Australia

Contents

Abstract

Non-malignant pain in the elderly is frequently under-treated, with physicians appearing to be uncertain concerning how best to achieve optimum management of this common problem in individual cases. The aim of this review is to provide a brief overview and discuss the variety of interacting factors that contribute to the continuing under-treatment of chronic non-malignant pain in the older population. The central objective is to encourage safer and more effective pain management in a population that is highly vulnerable to painful conditions and to the consequences of poorly treated pain.

Under-treatment of pain as experienced by the elderly is largely a consequence of uncertainties that arise within a complex environment that is underscored and exacerbated by the progressive and rapid aging of the global population. Uncertainties include the optimum management of pain in geriatric syndromes, frailty and dementia, and their impact on diagnosis, pain assessment and choices of treatment modalities. There is an inadequate

evidence base for pharmacological interventions in older persons with respect to pharmacokinetic and pharmacodynamic changes that occur with aging. In this review, the prevalence of chronic pain and the incidence of adverse drug reactions are identified as factors that encourage conservatism in prescribing, as are major predictors of adverse drug reactions, i.e. aging, inappropriate combinations of medications and polypharmacy.

The major classes of analgesic drugs are summarized with reference to their mechanisms of action, analgesic properties and known adverse effects. Although all medications have associated risks, the use of analgesics in managing persistent pain in elderly people is widely supported and guided on the basis of clinical experience and consensus among specialists in geriatrics and pain management.

It is concluded that the absence of trial data, specific to the elderly, is substantially offset by information based on clinical experience and expert consensus statements. Used appropriately, analgesic and adjuvant treatments can and should be employed to relieve persistent pain in the expanding elderly population.

This review is directed at healthcare professionals who are not specialists in geriatrics or in pain management but who are called upon to treat painful conditions in the older person. The aim is to provide an overview of the many factors that currently contribute to the uncertainties that arise in treating persistent pain in the elderly. While the elderly constitute a discrete and complex treatment population, pharmacological approaches can, and should, be used to treat pain in this vulnerable group by drawing upon available clinical and research evidence with the objective of encouraging better practice without compromising patient safety.

Despite expert recommendations for an increased role of non-pharmacological strategies in the management of persistent pain in the elderly, analgesic drugs are still used more often than any other mode of therapy.[1-4] Prescribed, administered and monitored appropriately, they provide a safe and effective means of treating pain in older adults.[5,6] Nonetheless, there are ongoing concerns about the safety of analgesic use in older patients. Effective treatment of persistent pain is somewhat more hazardous with the elderly because aging introduces a number of compromising factors.

When considering pharmacotherapies for pain management in older persons, age-related changes in biological processes, increased comorbidities, the inherent heterogeneity in health status and disease symptoms found in older populations, the increasing incidence of adverse drug reactions (ADRs), the high prevalence of polypharmacy and the paucity of evidence to support treatment decisions are all important factors to consider.

1. Aging of the Global Population

Between 1950 and 2005, global life expectancy rose from 47 years to 65 years and global fertility fell from 5.0 to 2.6 children per woman.[7] In 2006, one in nine people (688 million) were ≥60 years of age, a ratio predicted to reach one in five (almost 2 billion) by 2050. Of those aged ≥60 years in 2006, 13% were in the oldest old category (≥80 years of age) and this number is expected to triple by 2050.[8] Current and projected changes in aging demography indicate that health problems associated with the elderly will compound over the next few decades.

Aging is strongly associated with an increased prevalence of disease markers, actual disease, disability consequent to disease and an exponential increase in mortality rates.[9,10] A survey of selected chronic health conditions among non-institutionalized Americans aged ≥65 years

revealed that 53.3% had hypertension, 49.5% arthritis, 30.9% heart disease, 21.1% cancer, 18% diabetes, 10.6% asthma, 10% chronic bronchitis or emphysema and 9.3% stroke. With respect to physical function, 19% of men aged >65 years and 31.9% of women had lost at least one of five basic abilities such as stooping and kneeling or walking two to three blocks.[11]

The elderly are disproportionately represented as health services consumers. People ≥65 years of age account for 25% of general practice attendances and 35% of hospital admissions and hospital bed occupancy.[12] Similar figures have been reported in other recent population health surveys.[13] Although pain is not routinely included in such surveys, the high prevalence of arthritis is a useful index of the scale of the problem.

2. Geriatric Syndromes, Frailty and Dementia

While diseases experienced by the elderly may share common features across the lifespan, diagnosis, treatment and treatment outcomes are affected by geriatric syndromes in which one symptom or symptom complex may result from multiple aetiological factors, multiple organ systems and interactions between multiple pathogenetic pathways.[14] For example, the delirium syndrome in the elderly, identifiable by a specific phenomenology, may result from accumulated coexistent impairments such as dementia, dehydration, sensory impairment, medications and sleep disturbance.[15] Aetiologies often overlap and patients may present with two or more concurrent syndromes.[16]

Elderly hospitalized people frequently have undiagnosed coexisting geriatric syndromes that impact on treatment outcomes.[17] Impaired activities of daily living, falls and incontinence are syndromes strongly predictive of adverse outcomes, including increased length of hospital stay, change in residential status on discharge and unplanned readmissions.[18]

Further challenges arise in the presence of frailty, a condition that has both objective and clinical markers but for which diagnostic criteria are yet to be formalized. Part of the difficulty in establishing criteria for frailty is that, despite phenotypic attributes,[19] it is a condition in which multiple system deficits (including undernourishment, loss of lean body mass, reduced physical capacity, loss of endurance and lower homeostatic reserve) combine variously to make diagnosis difficult.

Increasingly prevalent, dementing diseases are typically accompanied by a progressive reduction in the capacity for self-report of pain.[20,21] However, the absence of pain reporting in people with dementia is not a reliable index of the absence of pain.[22] In such cases, assessment of pain and evaluation of treatment outcomes depend upon systematic observation of pain-related behaviours. There are a number valid and reliable observer-rated behavioural instruments designed for assessing pain in people who have dementia.[23-25]

3. An Inadequate Evidence Base for Treatment of Elderly People

Age-related biological changes have the potential to modulate pharmacokinetic and pharmacodynamic processes. Thus, clinical trials must include representative samples of the elderly in order to ensure best practice.[26] Nonetheless, the evidence base for prescribing in that population is disproportionately small. Of 8945 randomized controlled trials, only 3.4% were for people aged >65 years and none were for those aged >85 years.[12] Furthermore, 35% of published clinical trials excluded older people without providing justification.[27] In most clinical trials, exclusion criteria were such that only atypically healthy older subjects were studied.[28] Given that the typical community-dwelling 70-year-old has over three co-morbid medical problems and takes an average of seven different medications, the representativeness of the older samples included in trials can be questioned. The legacy of this selection bias is an inadequate evidence base for pharmacological treatment approaches in the elderly. Currently, much of geriatric practice with respect to drug use is essentially anecdotal and based on extrapolation from studies in younger patients or healthy older people.[29]

This inadequate evidence base may contribute to the apparent conservatism in prescribing for the elderly. Studies consistently report routine under-treatment of pain in older people[30,31] and show that 45–80% of elderly people report inadequate treatment of painful conditions.[2] Under-treatment of pain is more marked in the presence of frailty and dementia,[32-35] and this can lead to other adverse outcomes, including poor sleep,[36] impaired cognition,[37] increased disability,[38] depression[39] and reduced quality of life.[40] While such conservative clinical practice may be intended to reduce the risk of adverse drug reactions, administration of pain-appropriate doses of simple analgesics and adjuvants can provide adequate relief and avoid escalation to opioid analgesics for which there is evidence of more prevalent adverse events and an increase in potentially serious adverse events.[41]

4. Pharmacokinetics and Pharmacodynamics in Elderly People

Aging is accompanied by biological changes leading to reduced homeostatic efficacy and systemic regulatory changes that affect cardiac, renal, gastrointestinal and neuroendocrine functions. Typically, there is also an increase in relative body fat. These changes have a direct and variable impact on absorption and bioavailability, distribution, binding, biotransformation and elimination of drugs commonly used in the treatment of chronic pain.[10]

There is mounting evidence that age-related biological changes also have complex modulating effects on nociception and antinociception, responses to brief noxious stimuli and responses to pathological pain consequent to tissue inflammation or nerve injury.[42] These appear to be the consequence of functional, structural and biochemical changes, including a loss of both unmyelinated and myelinated fibres involved in the processing of thermal and noxious sensations. Evidence derived from experimentally applied transient noxious stimuli is inconsistent, but there appears to be an age-related increase in pain threshold. This is not simply taken to suggest that the elderly experience less pain sensation when reported. Indeed, it indicates that they may be at greater risk of injury due to reduced efficacy of pain as an early warning system.[43] More pertinent to a discussion of chronic pain is the observation of an association between advancing age, altered sensitivity to stimulation associated with inflammatory processes and impairment of the capacity of the aging nervous system to restore normal response patterns following nerve injury.[42] Many widespread morphological and neurochemical changes occur centrally and peripherally throughout the aging nervous system that have the potential to affect pain perception.[44] The changes in pain nociception that occur in the elderly are compounded by changes in descending endogenous pain inhibitory mechanisms. Both opioid and non-opioid-dependent endogenous analgesic systems undergo age-related decline and this has implications for the choice of treatment strategies. Increases in pain thresholds are likely to be offset by impairments in endogenous mechanisms, suggesting that the experience of pain may be qualitatively different in the elderly, and the assessment and treatment strategies applied to younger populations will not be appropriate. For a comprehensive review see Gibson and Farrell.[43]

5. Prevalence of Chronic Pain in the Elderly

Obtaining accurate estimates of pain prevalence can be difficult. Because pain is a subjective experience, assessment is dependent upon self-report and, in the absence of gold-standard measurement tools, clinical measures are only weakly associated with the subjective experience.[45] Methodological issues notwithstanding, chronic pain appears to show an age-related increase in prevalence until at least the seventh decade of life with a plateau or slight decline into very advanced age.[46] Absolute prevalence figures vary between different studies, depending upon the nature of the questions asked, the time interval sampled (days, weeks, months, lifetime), the time in pain during this interval (everyday, most days, at least weekly, any pain during the period), the severity of pain needed for inclusion

as a case, and the sampling technique (telephone interview, face-to-face interview, questionnaire). Nonetheless, a consensus suggests that about 18% of young adults experience persistent, bothersome pain rising to a peak of 30–65% in those aged 55–65 years and then declining somewhat to about 25–55% of the population in those aged ≥85 years.[45,46] The increased pain prevalence in older segments of the population is primarily attributed to the massive age-related increase in degenerative spinal and joint disease.[47]

6. Incidence of Adverse Drug Reactions

In 1998, Lazarou et al.[48] published a meta-analysis on 39 of 153 prospective pharmacological studies meeting criteria for inclusion. The review included records of 62 705 North American patients between 1966 and 1996. It excluded therapeutic failures (errors), intentional or accidental overdose, drug abuse, errors in administration and noncompliance. The incidence of serious ADRs was 6.7% and the incidence of fatal ADRs was 0.32% of hospitalized patients. Extrapolation of the fatal ADR data led to a national estimate of 106 000 deaths in 1994, placing ADRs as the fourth to sixth largest cause of death. Methodological criticisms have been made,[49] but this study suggests a consistently high pattern of ADRs. The study did not examine ADRs with reference to age or treatment.

A global investigation revealed weighted mean ADR rates of 4.6% (North America), 7.5% (UK and Ireland) and 14.1% (Europe).[50] In English hospitals between 1998 and 2005, 447 071 ADRs accounted for 0.50% of all hospital episodes, and the number increased by 44.5% such that ADRs accounted for 0.56% of all hospital episodes by 2005.[51] A study of 43 380 patients ≥60 years of age admitted to Western Australian public and private hospitals between 1981 and 2002 revealed a more than 5-fold increase in the rate of ADR-related hospital stays over this period, with the rate of increase clearly being associated with progression to the oldest of the elderly population.[52] Analgesics represent one of the most commonly used group of drugs and would be expected to make a significant contribution to these published rates of ADRs.[52] Moreover, as ADRs constitute a major reason for the current under-treatment of pain in older persons, it becomes important to better understand the evidence base relating to this important aspect of clinical care.

7. Analgesic Drug Safety in the Elderly

In the context of pharmacological treatments for chronic pain, safety may be conceptualized as a state of freedom from the adverse effects of medication. Specifically, this may include ADRs associated with the pharmacology of the medicines (such as dry mouth and constipation from drugs with anticholinergic activity), the potential for drug-drug interactions, risk of suicide (accidental or deliberate) and toxicity (damage to organ systems, liver, kidney, stomach, cardiac, respiratory). However, ADRs should not be viewed as a single entity. Some ADRs are common (e.g. constipation from the use of codeine, sedation from the use of morphine) and easily managed. There are predictable adverse effects with some analgesics (e.g. NSAID-induced gastrotoxicity or renal impairment) that are potentially more serious, while other adverse effects are very rare, but very serious and unpredictable (e.g. NSAID-induced anaphylaxis). These issues are discussed in greater detail within the following sections on each analgesic drug class. Regardless of specific drug class, the major generic risk factors of increased ADRs can be summarized as increasing age, inappropriate medication and the use of multiple medications (polypharmacy).

7.1 Aging

Anecdotal reports, clinical experience and the medical literature[53,54] have long indicated that aging is an important risk factor for ADRs. For example, 59% of ADRs in England involved patients >60 years of age.[51] NSAIDs were reported by some studies as the leading cause of ADRs and others as the fourth or fifth leading cause.[50] A study of older Australians ranked NSAID-related repeat ADRs at 14.7%, second

only to cardiovascular treatment-related ADRs (15.6%).[55] It is therefore reasonable to conclude that the issue of drug safety in the elderly is one that requires a high level of vigilance on the part of prescribing physicians and that special care is needed to ensure appropriate medication use. However, vigilance does not automatically mandate conservatism, and while all medications carry risks, the risks need to be carefully assessed in relation to the potential benefits as a means of avoiding under-treatment of treatable conditions.[56] While aging constitutes a risk, it is not a simple one-to-one relationship, and inter-individual variation, disease, frailty and stress may overshadow age-related changes.[57]

7.2 Inappropriate Medication

Inappropriate analgesic medication is a leading cause of ADRs in the elderly. The use of NSAIDs without gastroprotective agents, for example, is identified as a major cause of gastrointestinal bleeding in older patients.[57] To counter the absence of age-specific pharmacological evidence, prescribing practice for the elderly is frequently guided by explicit published criteria based on single research studies, reviews or expert consensus. In 2002, an American Geriatric Society expert panel provided guidelines for the assessment and treatment of persistent pain in the elderly together with specific treatment recommendations.[2] Appropriate updates, where needed, are available from online clinical information services (e.g. Solomon[58]) and other sources. In Australia, the Analgesic Expert Group[59] provide cautions and advice specific to the elderly; in Canada, McLeod et al.[60] and the Improved Prescribing in the Elderly Tool[61] provide specific guidelines; in the US the Beers' criteria[62] have been recently updated;[63] and a recent consensus list has been created in France.[64]

7.3 Polypharmacy

The incidence of ADRs is associated with the number of concurrently administered drugs. A recent study that included over 600 000 people aged ≥75 years revealed a strong association between the number of dispensed drugs and the probability of clinically relevant (26%) and potentially serious (5%) drug interactions, and that osteoarthritis was one of the risk factors for polypharmacy in the elderly.[65] While the interactions of aging, current co-morbidities and polypharmacy are known, Beyth and Shorr[66] argue that the elderly are at increased risk and that NSAIDs are one of the major classes of drugs implicated. The increase in the number of drugs prescribed is associated with the higher incidence of co-morbid disease in older people. However, the use of multiple medications may be entirely appropriate and yield significant benefits.[56] Avoiding treatment on the basis of potential drug interactions is not appropriate. Adverse consequences may be reduced by more careful diagnostic and prescribing procedures in accord with medication guidelines together with vigilant monitoring, especially in the early stages of treatment. There is accumulating evidence that prescriber education, the use of a medication grid to alert providers and the use of geriatric evaluation and management procedures, both with inpatients and outpatients, results in a reduction in the number of medications per patient.[67] This suggests that risks associated with polypharmacy can be reduced by implementing systemic approaches to patient care.

In summary, safety considerations in treatment of the elderly are compounded by factors specific to the aging process summarized above. In all cases, patient history, accurate diagnosis, co-morbid conditions, current medications, the known mechanisms of drug actions, precautions, adverse indications and interactions with other drugs collectively impact on choice of treatment.[68] With the elderly, especially the oldest old, the frail and those with serious cognitive disorders, prescribing should account for the additional complexities that arise from age-related changes in biological function.

8. Pharmacological Interventions for the Treatment of Chronic Pain

Drugs with analgesic properties are often classified into three major categories: simple

analgesics, NSAIDs and opioid agents. A fourth category comprises adjuvants that, while not true analgesics, have properties that assist with the provision of pain relief. These include sedatives and hypnotics, anxiolytics, antipsychotics, antidepressants and antiepileptics. The actions of these drugs, their potential adverse effects and drug-drug interactions are generally well defined on the basis of clinical trial data and clinical experience. However, in the absence of trial data for the old and the oldest of the elderly population, a preponderance of clinically derived anecdotal evidence and dose adjustments based on data from younger cohorts are typically used to inform prescribing practice in older patients.

A summary overview of drug treatment used in the management of chronic non-malignant pain in the elderly is provided in table I.

9. Paracetamol

Orally administered paracetamol (acetaminophen) is ubiquitous as the first line of treatment for mild to moderate musculoskeletal pain in the elderly and is recommended as the primary long-term means of managing chronic osteoarthritic pain.[2,69] It is a weak, reversible, nonspecific cyclo-oxygenase (COX) inhibitor with analgesic and antipyretic CNS actions. Analgesia results from inhibition of COX and related changes in hypothalamic and spinal prostaglandin synthesis.

When used at recommended doses, paracetamol is relatively safe because of its low gastrointestinal and renal toxicity.[70,71] Independent of age, absorption via the gastrointestinal tract is rapid and efficient.[72] Although the volume of distribution is lower in elderly compared with young people, it appears to remain consistent between healthy and frail elderly.[73] In contrast, clearance declines with healthy aging and further declines in the frail elderly, suggesting that the altered clearance is beyond that attributable to reduced liver volume.[73] While the resultant prolongation of the half-life in older adults is not thought to warrant routine dosage adjustment,[72] 39% of acute liver failure cases were attributed to paracetamol overdose in a prospective cohort study that concluded that paracetamol overdose and idiosyncratic drug reaction had overtaken viral hepatitis as the leading cause of acute liver failure.[74]

While paracetamol is regarded as a safe analgesic drug, its use is subject to a number of precautions, potential adverse effects and interactions. Precautions include the presence of hepatic and renal impairment and restricted salt intake. Adverse effects, although rare, include dyspepsia, nausea, allergy and haematological changes.[75] Known risk factors for hepatotoxicity include poor nutrition, dehydration and liver disease.[70] Drug interactions include anticoagulants, drugs affecting gastric emptying, hepatic enzyme inducers such as hypnotics and antiepileptics, and alcohol.[75] Clinically significant cases of liver damage in patients taking paracetamol at therapeutic doses are very rare.[76] A recent review of 791 studies, that included 30 865 subjects in prospective studies, reported no cases of fulminant hepatic liver injury, liver transplantation or death due to paracetamol.[77] Retrospective studies reviewed in the same report included 9337 patients and found 96 cases with excessive serum alanine aminotransferase, one case of liver transplant and six deaths. The authors noted information in some retrospective reports suggesting that overdosing may have occurred. Hepatotoxicity occurs because overdose of paracetamol leads to saturation of the detoxifying cytochrome P450 (CYP) enzymes CYP2E1 and CYP3A4 that convert paracetamol to the metabolite *N*-acetyl-p-benzoquinoneimine (NAPQ1). The consequent accumulation of NAPQ1 depletes glutathione via conjugation, resulting in cell damage and death.

While cases of hepatotoxicity are reported to be most frequent among adolescents and young adults, the majority of paracetamol-related deaths occur in people ≥40 years of age, and alcohol abuse is noted as a strong risk factor.[78] Between 1995 and 2004, the elderly accounted for only 4.5% of the total number of cases of paracetamol overdose and, while overall 85% of paracetamol overdose cases were intentional, the incidence of intentional overdose in the elderly was 45%.[79] The major risk of toxicity with paracetamol is inadvertent overdose related to

Table I. Overview of drug classes used for chronic, non-malignant pain in the elderly

Drug	Use	Action	Precautions	Adverse effects	Interactions	Combination therapy
Simple						
Paracetamol (acetaminophen)	First-line analgesic; for mild to moderate pain especially musculoskeletal pain; long-term use for osteoarthritic pain. Dose: maximum 4000 mg/24h four times daily or slow release (8 h)	CNS action, weak reversible COX inhibition; rapidly absorbed; hepatically cleared; $t_{1/2}$ 1–3 h; clearance slows with aging and especially frailty	Hepatic and renal impairment; reduced oral intake	Acute ingestion; chronic use >4 g/day can lead to hepatic necrosis	Anticoagulants; hepatic enzyme inducers; drugs that affect gastric emptying; alcohol	NSAIDs and opioids
NSAIDs						
Aspirin (acetylsalicylic acid)	Analgesic; rheumatoid arthritis. Dose: maximum 3600 mg/24 h	Non-reversible nonspecific COX-1 and COX-2 inhibition	Ibuprofen allergy; low sodium; prolonged use; asthma; peptic ulcer use with other anti-inflammatories	Gastrointestinal adverse effects and gastrointestinal bleeding; renal; hepatic; cardiac; peripheral oedema; cognitive dysfunction	ACE inhibitors; diuretics; methotrexate; anticoagulants; lithium; hypoglycaemics; probenecid	Paracetamol and opioids
Nonselective: includes numerous formulations – diclofenac, ibuprofen, indometacin, ketoprofen, mefenamic acid, naproxen, piroxicam, sulindac, tiaprofenic acid	Anti-inflammatory and analgesic for nociceptive pain; initial doses should be low (50% of normal) for the elderly; titrated and monitored	Reversible nonspecific COX-1 and COX-2 inhibition and reduction in CNS and peripheral prostaglandin synthesis	History of gastrointestinal bleeding or ulcer; renal and cardiac impairment; hypertension; older age	As for aspirin	As for aspirin	Paracetamol and opioids
Selective: e.g. celecoxib, parecoxib, meloxicam (at low dosage)	Anti-inflammatory and analgesic	Reversible specific COX-2 inhibition	History of gastrointestinal bleeding or ulcer; renal and cardiac impairment; hypertension; older age	As for nonselective but lower gastrointestinal adverse effects and increased cardiac risk	As for aspirin	Paracetamol and opioids
Opioid analgesics						
Includes numerous variants: most commonly used in elderly – morphine, codeine and oxycodone; less common in elderly – fentanyl, buprenorphine;	Analgesic; use indicated when simple analgesics and NSAID treatment fail to give pain relief or are contraindicated	Binding to opioid receptors in CNS and gastrointestinal tract	Extensive lists of precautions are associated with opioid drugs. Consult formularies when prescribing	Most common with elderly: nausea, vomiting, constipation, urinary retention, respiratory depression, sedation,	Monoamine oxidase inhibitors, antiepileptics, CNS depressants, antihypertensives, anticholinergics, other opioids, sedatives	Paracetamol and NSAIDs

Continued next page

Table I. Contd

Drug	Use	Action	Precautions	Adverse effects	Interactions	Combination therapy
not recommended for elderly – pentazocine, pethidine, propoxyphene, methadone	Doses in elderly start at 25–50% of adult dose and titrate slowly			dizziness, cognitive impairment		
Adjuvants						
Antidepressants include TCAs, SSRIs, SNRIs. Antiepileptics include carbamazepine, gabapentin, pregabalin, phenytoin, lamotrigine, sodium valproate Anxiolytics Corticosteroids	Co-analgesic use for pain control especially for diabetic neuropathy, post-herpetic neuralgia, and other neuropathic pain conditions Doses are much lower for analgesic use (10–20%) and escalated according to effect and tolerability	Evidence for efficacy and safety of adjuvant drug therapies for chronic pain in the elderly is limited and variable. The analgesic use of antidepressants is widely accepted with some evidence for efficacy in the elderly. Anticholinergic effects of TCAs in the elderly increase the risk of confusion, falls, postural hypotension, bladder problems. Antiepileptic use in the elderly is associated with sedation, ataxia, unsteadiness and falls. Carbamazepine and gabapentin are supported by some efficacy data Anxiolytics are not recommended for chronic non-malignant pain in the elderly. Corticosteroids are not recommended for long-term use in the elderly due to the range of potential adverse effects			NA

COX = cyclo-oxygenase; **h** = hours; **NA** = not applicable; **SNRI** = serotonin-noradrenaline (norepinephrine) reuptake inhibitor; **SSRIs** = selective serotonin reuptake inhibitor; $\mathbf{t_{1/2}}$ = half life; **TCA** = tricyclic antidepressant.

the multiple paracetamol-containing analgesics that are readily available without prescription and are marketed under a variety of different names.

Paracetamol-induced hepatotoxicity can be treated with intravenous *N*-acetylcysteine on the basis of observed serum paracetamol levels. Treatment is initiated preferably within 8–10 hours of ingestion, although treatment even after 24 hours is indicated. If correctly treated, <4% of cases involving severe hepatotoxicity develop hepatic failure, and fatalities or liver transplants are rare.[80]

10. NSAIDs

NSAIDs include nonselective COX inhibitors and COX-2 selective inhibitors. They are used frequently for pain treatment in the elderly, especially those with somatic or visceral nociceptive pain.[81] NSAIDs are also used for inflammatory osteo- and rheumatoid arthritic conditions and other acute and chronic pain states, including headache and postoperative bone pain. Their peripheral and CNS analgesic action occurs via inhibition of COX-1 and COX-2 isoenzymes, resulting in a reduction in the synthesis from arachidonic acid of prostaglandins (pro-inflammatory prostanoic acids). Inhibition of COX-2 is thought to mediate the anti-inflammatory response. Pharmacokinetic properties of different NSAIDs vary substantially according to chemical class, dose and route of administration. Time to peak concentration ranges from half an hour up to 6 hours and the elimination half-life ranges from 1 to 53 hours. Those with a very long half-life (meloxicam, naproxen and piroxicam) should not be prescribed for the elderly. Anti-inflammatory effects occur over several days or longer. Elimination is dependent upon hepatic metabolism in all but two NSAIDs (indometacin, oxaprozin) and clearance can be affected by renal impairment.

As observed above, NSAIDs make a major contribution to the increasing incidence of ADRs in the elderly. In the US, the FDA black-box warning regarding NSAIDs refers in large part to dose-dependent gastrointestinal and renal effects. Gastrointestinal effects derive from two actions,

i.e. direct irritation of the gastric mucosa by acidic molecules and reduction in protective prostaglandin levels consequent to the inhibition of COX-1. Renal effects arise from changes in renal haemodynamics (glomerular perfusion and filtration rates) that are mediated by the vasodilatory actions of some prostaglandins.

Major contraindications to the use of NSAIDs include active gastrointestinal bleeding and peptic ulceration, and NSAID-sensitive or aspirin (acetylsalicylic acid)-sensitive asthma. Some protection, although not complete protection, against gastrointestinal bleeding is gained by the concurrent use of a proton pump inhibitor. Precautions include a history of gastrointestinal bleeding or ulcer, hepatic, renal or cardiac impairment, hypertension, bleeding tendencies and older age. With regard to the latter, ketorolac, mefenamic acid, piroxicam, oxaprozin and naproxen are not recommended for use in the elderly because of their elevated risk of toxicity.[60,63] However, with naproxen this risk may be counterbalanced by evidence that it does not share the increased cardiac risk associated with other NSAIDS.[82] This reduced cardiac risk has not been trialled in the elderly and, since shorter acting NSAIDS are recommended for the elderly,[70,81] the long half-life of naproxen at over 15 hours should be included as a factor in prescribing. Drug interactions include antihypertensives, ACE inhibitors, diuretics, high-dose methotrexate, anticoagulants, lithium, oral hypoglycaemic agents and probenecid.

Selective COX-2 inhibitors are associated with a significantly lower incidence of gastrointestinal adverse effects but have been associated with increased cardiovascular risk. Underlying the increased risk of cardiovascular events are changes in the ratio of prostacyclin (prostaglandin I_2; a vasodilator and potent platelet inhibitor) and thromboxane A_2 (a pre-thrombotic eicosanoid), leading to platelet aggregation, vasoconstriction and prothrombotic events.[83] However, recent reviews have also started to question whether most of the currently available COX-2 inhibitors (i.e. celecoxib) have any worse risk profile for cardiac events than more traditional NSAIDs (particularly diclofenac).[84-86]

The literature on ADRs emphasises NSAIDs as a major source of adverse events, with the largest number being gastrointestinal ADRs[87] including gastrointestinal bleeds.[88,89] Others include peripheral oedema, precipitation of heart failure, cardiovascular disorders, cerebrovascular accidents and cognitive dysfunction.[6] Ranking among the top five causes of ADRs across all age groups,[50] NSAIDS warrant special care when used in older patients among whom their adverse effects are more pronounced. Indeed, several consensus guidelines for the management of persistent pain in older adults recommend against using NSAIDs, particularly in view of evidence that paracetamol offers a similar level of analgesic cover without the elevated ADR risk.[2] Consider alternatives to NSAIDs and COX-2 inhibitors, such as paracetamol, for mild to moderate pain and low-dose corticosteroids for inflammatory arthritides. If NSAIDs/COX-2 inhibitors are considered appropriate, the following recommendations are made for their use in treating persistent pain in the elderly:

1. Consider alternatives to NSAIDs and COX-2 inhibitors (i.e. paracetamol).
2. Use NSAIDs that have a short half-life.
3. Use the smallest possible dose for the shortest possible duration.
4. Do not combine COX-2 inhibitors with nonselective NSAIDs.
5. Concomitant use of NSAIDs (particularly ibuprofen) and COX-2 inhibitors and aspirin may block the cardioprotective function of aspirin.
6. If effective pain reduction is not observed within the first few days of treatment, consider an alternative drug therapy.

Aspirin, a salicylate drug, is often regarded as the first NSAID. Acting as a non-reversible COX inhibitor, it has been superseded by paracetamol and modern NSAIDs. It has no role in the treatment of chronic pain in the elderly, and prolonged use in analgesic doses is the first of a number of precautions found in formularies.[75] Aspirin shares with other NSAIDs similar gastrointestinal effects and it interacts with corticosteroids, anticoagulants and alcohol.

11. Opioid Analgesics

Despite expert endorsement of the use of opioids to reduce pain and improve mood and functioning in people with chronic non-malignant pain, many physicians do not prescribe them due to uncertainty regarding their efficacy and the belief that they have minimal functional benefits and may even worsen outcomes.[68] Given that prolonged administration of high-dose opioids clearly has associated risks, guidelines specifically addressing opioid use in chronic pain have been developed with the aim of maximizing pain control while minimizing adverse outcomes. These guidelines embody a comprehensive approach that details methodical procedures at the initial diagnostic and treatment phase, the dose-adjustment phase and the stable (dose maintenance) phase, together with guidelines for assessment of outcomes.[68] The guidelines are consistent with recommendations for meticulous initial and ongoing review of indications for opioid use with a low starting dose, careful titration and ongoing monitoring with every patient.[90]

Opioids are indicated for severe pain that has not responded to non-opioid treatment. However, pharmacokinetic and pharmacodynamic changes, a higher incidence of co-morbid disease and greater likelihood of polypharmacy in the elderly may increase the potential for adverse effects, drug-drug interactions and drug-disease interactions, thus escalating the issue of safe use in this population.[6]

Opioid action is mediated by binding differentially to high-affinity opioid receptors (μ, κ, δ) in the CNS and gastrointestinal tract – the systems underlying both the pain-relieving attributes and some of the adverse effects of opioids. A significant lack of published information creates a challenge for treating physicians, exposing the need for more research into opioid use in the elderly.[90] Physiological changes in aging together with increased age-related brain sensitivity to opioids mandate lower initial dose requirements and titration until effective analgesia is achieved.

There is the potential for an extensive range of adverse effects involving cardiovascular, neurological, dermatological, gastrointestinal, musculoskeletal, neuroendocrine, respiratory and urinary functions.[59] Close monitoring is therefore essential. However, when used appropriately for persistent pain in the elderly, the most common adverse effects are constipation, nausea and vomiting, sedation and cognitive changes. Constipation should be anticipated and, as a matter of routine, treated prophylactically with laxatives.[81] Nausea, sedation and cognitive changes usually resolve within a few days.

It should be noted that the direct adverse effects of opioids are functional in nature and the potential for organ damage is markedly less than those of paracetamol and NSAIDs. Furthermore, their ongoing use in treating chronic pain in the elderly may involve a lower level of life-threatening risk than that of NSAIDs.[2] This may be a factor underlying a widespread increase in the use of opioids in treating non-cancer pain in recent years[91] and the evidence suggesting that opioid prescribing increases with increasing age such that prevalence is highest in those >70 years of age.[92] While neuroendocrine effects (hypothalamic and antidiuretic) are apparent, more research is needed to determine whether long-lasting endocrine effects occur.

Codeine, morphine and oxycodone are commonly used in the elderly. Oral delivery is the most common mode of administration for these drugs, although controlled-release fentanyl and buprenorphine are increasingly being administered via transdermal patch.

Codeine is a weak opioid analgesic metabolized to morphine by CYP2D6. Between 7% and 10% of Caucasians and 1% to 2% of Asians do not metabolize codeine and thus gain no analgesic effect from its use. Taken orally, codeine 180–240 mg is required to achieve equi-analgesia with morphine 30 mg. When used for persistent pain, the lowest effective dose should be used, starting with 15–30 mg 6-hourly and not exceeding 60 mg in a single dose. As with other opioids, codeine should be co-administered with laxatives to avoid constipation. Codeine has a ceiling dose effect in which increasing the dose will yield no further analgesic benefit. A small increase in analgesic effect of approximately 5% is achieved

using a combination codeine/paracetamol formulation.

Transdermal fentanyl was observed to significantly reduce pain and significantly improve function in a cohort of older osteoarthritis patients.[93] Among an older group, transdermal fentanyl was over seven times less likely to cause constipation than controlled-release oxycodone.[94] It has been shown that low-dose transdermal fentanyl yields therapeutic benefit in chronic non-malignant pain and may therefore have particular benefit for the elderly.[95] The evidence to support transdermal fentanyl is, nonetheless, very limited.

This is even more the case with transdermal buprenorphine. While not universally available, it is being increasingly used for the treatment of chronic pain in residential aged-care facilities in countries that have approved its use. This may largely be due to its relative convenience when administered as a 7-day release system, which reduces administration time and daily staffing requirements. Therapeutic guidelines in Australia[59] suggest caution on the basis of both limited evidence and limited experience with buprenorphine compared with other opioids.

Slow-release opioids should not be prescribed for opioid-naïve elderly patients before using immediate-release opioid formulations to establish dose requirements and effects.

Tramadol is a weak synthetic opioid that combines μ-opioid receptor binding with enhanced noradrenergic and serotonergic nociceptive inhibition. It has a lower sedative and respiratory impact than other opioids and has a lower risk of constipation. Tramadol has the potential to induce seizures and is therefore contraindicated for those with epilepsy, those who have risk factors for seizures or those who are taking other serotonergic drugs. It has limited analgesic effect, which may encourage the use of higher doses, thereby substantially increasing the likelihood of serotonin toxicity. Beyond a possible lower constipating effect, it has little advantage over codeine.[81]

Several opioids are not recommended for the elderly. These include pentazocine (neuropsychiatric toxicity), pethidine (seizure risk), dextropropoxyphene (neural and cardiac toxicity risks) and methadone (long half-life).[6,59] Others not recommended include combination drugs for which there is a lack of pharmacokinetic and efficacy information in older people.[6]

Formularies and published guidelines identify an extensive array of potential ADRs associated with opioid analgesics. These may occur in multiple systems including cardiovascular, neurological, dermatological, gastrointestinal, musculoskeletal, neuroendocrine, respiratory and urinary systems. The elderly are more likely to be sensitive to opioid effects and they are more susceptible to adverse outcomes. As a consequence, extra care is recommended at all phases – diagnosis and evaluation, prescribing, administering and monitoring.

12. Adjuvant Analgesics

Adjuvants are medications often used in the management of both musculoskeletal and neuropathic persistent pain, although their usual role is for conditions other than pain. They include antidepressants, antiepileptics, anxiolytics and corticosteroids. A study of 987 community-dwelling people aged ≥65 years found that people with chronic pain used psychotropics, antidepressants and sedative-hypnotics at rates 2- to 3-fold higher than those without chronic pain.[96]

The most commonly prescribed antidepressant adjuvants include tricyclic antidepressants (TCAs) and serotonin-noradrenaline (norepinephrine) reuptake inhibitors (SNRIs). A systematic review of antidepressants used for neuropathic pain concluded that both TCAs and venlafaxine, an SNRI, provide at least moderate pain relief for one in three people with neuropathic pain.[97] There were too few data to evaluate efficacy in the other antidepressant drugs. One in five patients on these drugs discontinue treatment because of adverse events, although limited evidence suggests that selective serotonin reuptake inhibitors (SSRIs) are better tolerated.[97] Numbers needed to treat (NNT) for SNRIs and SSRIs are 4 and 7, respectively. That one in every four, or one in every seven people treated are predicted to gain the

desired therapeutic outcome from the use of these medications raises questions about their value as therapeutic options.[98] Of the TCAs, nortriptyline is preferred for the elderly over amitriptyline. While all TCAs can cause significant adverse effects in older people, hypotension and anticholinergic responses are less likely with nortriptyline.

Antiepileptics include carbamazepine, gabapentin, pregabalin, phenytoin, lamotrigine, sodium valproate and others. A 2005 review found that efficacy data are limited to that supporting the use of carbamazepine and gabapentin to treat neuropathic pain, where 66% of patients received good pain relief. Nonetheless, the review concluded that antiepileptics should not be used as a first-line treatment and should be withheld until other interventions have been tried.[99]

Anxiolytics are not recommended for non-malignant chronic pain,[97] but, if used, caution should be exercised in combining them with TCAs to avoid toxicity.[100]

Corticosteroids are administered locally (via intralesional or intra-articular injection) or systemically. They have a long half-life and extensive dose-related adverse effects, which include metabolic effects, osteoporosis, psychological disturbances, skin atrophy, pituitary-adrenal suppression, gastrointestinal effects and immunosuppression. With variable data on their efficacy when used for epidural, sacroiliac and facet joint treatment, the use of corticosteroids may yield palliative benefits but their use is controversial in light of limited evidence.[101]

13. Approaches to Improving Safety

The realistic goal in treating chronic pain is to reduce pain levels to the extent that patients can achieve their highest functional potential. This includes cognitive, psychological and physical function, and optimal independence in activities of daily living.

Pharmacological interventions occupy a central role in treatment of chronic non-malignant pain in the elderly, but the aging process introduces a unique set of factors that make drug interventions in this population potentially more hazardous than is the case in other age groups. The over-representation of the elderly in surveys of ADRs suggests that the guiding aphorism *primum non nocere* – first, do no harm – which underscores daily practice in medicine is frequently challenged. One consequence of this challenge is that many older people are, in fact, under-treated and the goal of reduced pain and optimal functionality is denied. When considering the ADRs associated with analgesic use it is important to recognize and balance the risks versus the potential benefits of treatment. Under-treated pain is known to have serious adverse effects on the person, including problems with sleep, mood disturbance, reduced function and quality of life. The International Association for the Study of Pain recognizes the relief of pain as a fundamental human right. An appropriate balance can be difficult to ascertain, particularly in older adults, but the widespread use of over-the-counter analgesics and the documented patient preference for pain reduction even in the presence of adverse effects, emphasizes the importance of at least trialling this therapeutic option. In this regard, the focus should be on the benefits of good assessment and good pharmacological management for relief of pain, rather than to discourage prescribing and discourage treating pain in older people. It is clear that treatment of the elderly is under-informed, and the literature abounds with calls for high quality studies using representative cohorts of elderly people. In the meantime, other approaches are being adopted with the aim of improving treatment outcomes.

As noted above (see section 7.2; Inappropriate Medication), existing guidelines for the treatment of chronic pain in the elderly are updated from time to time and clinicians and researchers initiate new guidelines. These, used in conjunction with published formularies and therapeutic guidelines, have the potential to reduce the incidence of adverse reactions.

Individual practitioners – based on clinical experience, pharmacological knowledge, familiarity with the literature and collegial interactions – are a potentially valuable source of guidance for colleagues. In one such example, 28 principles

of pharmacological pain management were proposed.[81] The principles first define the nature and scope of the diagnostic and assessment procedures recommended for each patient. These include the use of self-assessment pain instruments and the recording of pain history, physical status, functional status and screening for psychological and cognitive status. Such practice ensures comprehensive evaluation and yields comprehensive baseline data against which treatment can be evaluated. Subsequent treatment principles recommend the combination of pharmacological and non-pharmacological therapies (e.g. mobilization and goal orientation of the patient), and that analgesic prescription takes into account renal and hepatic indices and employs the 'start low, go slow' principle, with titration according to tolerance and efficacy. Approximately half the subsequent principles refer to known precautions, interactions and adverse effects of analgesics, with the final principles addressing procedures for change of medication and the need for monitoring in the form of re-assessment, continuity and persistence. Thus, safety issues, in part, are potentially addressed collegially, although the uptake of such information remains unclear.

Are ADRs preventable? Gurwitz et al.[102] determined in a 12-month study that 42.2% of serious, life-threatening or fatal ADRs were preventable after observing that the most common errors were found in the prescribing and monitoring stages. Patient errors in adherence were also common.

In addressing the high incidence of preventable ADRs, differentiating a systems-centred approach from a person-centred approach has taken the focus away from a wholly individual accountability and acknowledged that systems issues have a powerful role in improving patient safety.[103] Changes at systems levels include implementation of pharmacist-led medication reviews, educational outreach programmes and the development of computer-based monitoring systems.[103]

The rate of preventable ADRs was reduced in one general hospital by 78% during a single-blind, controlled study in which a pharmacist was included in a rounding team.[104] Similarly, a review of evidence favouring an increased role for pharmacists found that pharmacists working with other health professionals did affect physician prescribing practices.[105] Nonetheless, further evidence is needed to support systemic changes that expand the pharmacist role beyond the dispensing of medications.

Education outreach visits have been seen to change prescribing behaviours, and audit and feedback techniques have been shown to increase physician reporting of ADRs and improve medical practice. The cost effectiveness of these approaches is unclear.[106]

Evidence is accumulating in support of the use of computer systems that involve physician order entry and the provision of support for clinical decision making. Better and more usable records can be made available by computer systems that provide extensive and timely access to patient information and bar coding systems for patient wristbands and medication packs.[107]

14. Conclusions

Pharmacological interventions remain by far the most common mode of treatment for chronic, non-malignant pain in the elderly. The ongoing demographic aging of the global population will ensure that problems in healthcare of that ever-expanding cohort will compound.

Physiological changes that accompany the aging process yield greater heterogeneity in disease symptom profiles, which may manifest as geriatric syndromes of considerable complexity. Accompanying those changes are age-related alterations in pharmacokinetic and pharmacodynamic processes. The elderly population therefore constitutes a unique challenge to health professionals in that the goal of reducing levels of persistent pain and maximizing function while avoiding treatment-related harm represents a fine balancing act.

The deficits in current pharmacological evidence with regard to potential drug-induced adverse effects in older people are persistent and pervasive. For many health professionals it can be an intimidating problem leading to

widespread under-treatment of disease in the elderly. Nonetheless, the absence of trial data specific to the elderly is substantially offset by information based on clinical experience and expert consensus statements. Used appropriately, analgesic and adjuvant treatments can and should be employed to relieve persistent pain in this expanding population.

Acknowledgements

The preparation of this manuscript was in part supported by a project grant from the National Health and Medical Research Council of Australia (# 285103) and a project grant from the Department of Health and Ageing, Australia (Evidence Based Practice in Residential Aged Care), both of which provide salary support for the authors. The authors have no other financial disclosures or conflicts of interest and do not receive any funding from the pharmaceutical industry.

References

1. Hadjistavropoulos T, Herr K, Turk DC, et al. An interdisciplinary expert consensus statement on assessment of pain in older persons. Clin J Pain 2007; 23 Suppl.: S1-43
2. American Geriatrics Society Panel on Persistent Pain in Older Persons. The management of persistent pain in older persons. J Am Geriatr Soc 2002; 50: S205-24
3. Kung F, Gibson SJ, Helme RD. Development of a pain management strategies survey questionnaire: preliminary findings. Pain Clinic 2000; 12: 299-315
4. Feinberg SD. Prescribing analgesics: how to improve function and avoid toxicity when treating chronic pain. Geriatrics 2000; 55: 44, 49-50, 53 passim
5. Helme RD. Chronic pain management in older people. Eur J Pain 2001; 5 Suppl. A: 31-6
6. Hanlon JT, Guay DRP, Ives TJ. Oral analgesic: efficacy, mechanism of action, pharmacokinetics, adverse effects, drug interactions, and practical recommendations for use in older adults. In: Gibson SJ, Weiner DK, editors. Pain in older persons. Seattle (WA): IASP Press, 2005: 3-22
7. United Nations, Department of Economic and Social Affairs. World economic and social survey 2007: development in an ageing world [online]. Available from URL: http://www.un.org/esa/policy/wess/wess2007files/wess2007.pdf [Accessed 2009 Mar 26]
8. United Nations, Department of Economic and Social Affairs, Population Division. Population ageing 2006 [online]. Available from URL: http://www.un.org/esa/socdev/ageing/documents/ageing2006chart.pdf [Accessed 2009 March 26]
9. Kirkwood TB, Austad SN. Why do we age? Nature 2000; 408: 233-8
10. McLean AJ, Le Couter DG. Aging biology and geriatric clinical pharmacology. Pharmacol Rev 2004; 56: 163-84
11. Federal Interagency Forum on Aging-Related Statistics. Older Americans 2008: key indicators of well-being. Federal Interagency Forum on Aging-Related Statistics. Washington, DC: US Government Printing Office, Mar 2008
12. Nair BR. Evidence based medicine for older people: available, accessible, acceptable, adaptable? Aust J Ageing 2002; 21 (2) 58-60
13. National health survey: summary of results, Australia 2004-05. Canberra (ACT): Australian Bureau of Statistics, 2006
14. Inouye SK, Studenski S, Tinetti MD, et al. Geriatric syndromes: clinical, research, and policy implications of a core geriatric concept. J Am Geriatr Soc 2007; 55: 780-91
15. Flacker JM. What is a geriatric syndrome anyway? J Am Geriatr Soc 2003; 51: 574-6
16. Olde Rikkert MGM, Rigaud A-S, van Hoeyweghen RJ, et al. Geriatric syndromes: medical misnomer or progress in geriatrics. J Med 2003; 61 (3): 83-7
17. Flood KL, Rohlfing A, Le CV, et al. Geriatric syndromes in elderly patients admitted to an inpatient cardiology ward. J Hosp Med 2007; 2: 394-400
18. Anpalahan M, Gibson SJ. Geriatric syndromes as predictors of adverse outcomes of hospitalization. Intern Med J 2008; 38: 16-23
19. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. Cardiovascular Health Study Collaborative Research Group. J Gerontol Series A Biol Sci Med Sci 2001; 56 (3): M146-56
20. Parmalee PA, Smith B, Katz IR. Pain complaints and cognitive status among elderly institution residents. J Am Geriatr Soc 1993; 41: 517-22
21. Hadjistavropoulos T, Craig T, Martin N, et al. Toward a research outcome measure of pain in frail elderly in chronic care. Pain Clin 1997; 10: 71-9
22. Cole LJ, Farrell MJ, Duff EP, et al. Pain sensitivity and fMRI pain-related brain activity. Brain 2006; 129: 2957-65
23. Abbey J, Piller N, De Bellis A, et al. The Abbey pain scale: a one minute numerical indicator for people with end stage dementia. Int J Palliat Nurs 2004; 10: 6-13
24. Feldt KS. The checklist of non-verbal pain indicators (CNPI). Pain Manag Nurs 2000; 1: 13-21
25. Snow AL, Weber JB, O'Malley KJ, et al. NOPPAIN: a nursing assistant-administered pain assessment instrument for use in dementia. Dement Geriatr Cogn Disord 2004; 17: 240-6
26. McMurdo ME. Including older people in clinical research: benefits shown in trials in younger people may not apply to older people. BMJ 2005; 331: 1036-7
27. Bugeja G, Kumar A, Banerjee AK. Exclusion of elderly people from clinical research: a descriptive study of published reports. BMJ 1997; 315: 1059-60
28. Vogt TM, Ireland CC, Black D, et al. Recruitment of elderly volunteers for a multicenter clinical trial: the SHEP pilot study. Control Clin Trials 1986; 2: 118-33
29. Bowes SG, Dobbs SM, Dobbs RJ, et al. Outcome criteria in clinical trials with elderly subjects. Age Ageing 1990; 19: 353-5

30. Pahor M, Guralnik JM, Wan JY, et al. Lower body osteoarticular pain and dose of analgesic medications in older disabled women: the women's health and aging study. Am J Public Health 1999; 89: 930-4
31. Chodosh J, Solomon DH, Roth CP, et al. The quality of medical care provided to vulnerable older patients with chronic pain. J Am Geriatr Soc 2004; 52: 756-61
32. Gibson SJ. IASP global year against pain in older persons: highlighting the current status and future perspectives in geriatric pain. Expert Rev Neurother 2007; 7: 627-35
33. Scherder EJ, Bouma A. Is decreased use of analgesics in Alzheimer disease due to change in the affective component of pain? Alzheimer Dis Assoc Disord 1997; 11: 171-4
34. Horgas AL, Tsai PF. Analgesic drug prescription and use in cognitively impaired nursing home residents. Nurs Res 1998; 47: 235-42
35. Won AB, Lapane KL, Vallow S, et al. Persistent nonmalignant pain and analgesic prescribing patterns in elderly nursing home residents. J Am Geriatr Soc 2004; 52: 867-74
36. Lamberg L. Chronic pain linked with poor sleep: exploration of causes of treatment. JAMA 1999; 281: 691-2
37. Duggleby W, Lander J. Cognitive status and postoperative pain: older adults. J Pain Symptom Manage 1994; 9: 19-27
38. Scudds RJ, Robertson JM. Empirical evidence of the association between the presence of musculoskeletal pain and physical disability in community-dwelling senior citizens. Pain 1998; 75: 229-35
39. Kroenke K, Shen J, Oxman TE, et al. Impact of pain on outcomes of depression treatment: results from the RESPECT trial. Pain 2008; 134: 209-15
40. Rabenda V, Burlet N, Ethgen O, et al. A naturalistic study of the determinants of health related quality of life improvement in osteoarthritic patients treated with nonspecific non-steroidal anti-inflammatory drugs. Ann Rheum Dis 2005; 64: 688-93
41. Moore RA, McQuay HJ. Prevalence of opioid adverse events in chronic non-malignant pain: systematic review of randomised trials of oral opioids. Arthrit Res Ther 2005; 7 (5): R1046-51
42. Gagliese L, Farrell MJ. The neurobiology of aging, nociception and pain: an integration of animal and human experimental evidence. In: Gibson SJ, Weiner DK, editors. Pain in older persons. Seattle (WA): IASP Press, 2005: 25-44
43. Gibson SJ, Farrell M. A review of age differences in the neurophysiology of nociception and the perceptual experience of pain. Clin J Pain 2004; 20: 227-39
44. Gibson SJ, Helme RD. Age differences in pain perception and report: a review of physiological, psychological, laboratory and clinical studies. Pain Rev 1995; 2: 111-37
45. Jones GT, Macfarlane GA. Epidemiology of pain in older persons. In: Gibson SJ, Weiner DK, editors. Pain in older persons. Seattle (WA): IASP Press, 2005: 3-22
46. Gibson SJ, Helme RD. The epidemiology of pain in elderly people. Clin Geriatr Med 2001; 3: 417-31
47. Unwin M, Symmons D, Allison T, et al. Estimating the burden of musculoskeletal disorders in the community: the comparative prevalence of symptoms at different anatomical sites, and the relation to social deprivation. Ann Rheum Dis 1998; 57: 649-55
48. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients. JAMA 1998; 279: 1200-5
49. Kvasz M, Allen IE, Gordon MJ, et al. Adverse drug reactions in hospitalized patients: a critique of a meta-analysis [abstract]. Med Gen Med 2000 Apr 27; 2 (2): E3
50. Wiffen P, Gill M, Edwards J, et al. Adverse drug reactions in hospital patients: a systematic review of the prospective and retrospective studies, June 2002 [online]. Available from URL: http://www.ebandolier.com [Accessed 2008 Feb 12]
51. Patel H, Bell D, Molokhia M, et al. Trends in hospital admissions for adverse drug reactions in England: analysis of national hospital episode statistics 1998–2005 [abstract]. BMC Clin Pharmacol 2007 Sep 25; 7: 9
52. Burgess CL, D'Arcy C, Holman J, et al. Adverse drug reactions in older Australians: 1981–2002. Med J Aust 2005; 182: 267-70
53. Ogilvie RI, Ruedy J. Adverse drug reactions during hospitalization. Can Med Assoc J 1967; 97: 1450-7
54. Carbonin P, Pahor M, Bernabei R, et al. Is age an independent risk factor of adverse drug reactions in hospitalised medical patients? J Am Geriatr Soc 1991; 39: 1093-9
55. Zhang M, Holman CDJ, Preen DB, et al. Repeat adverse drug reactions causing hospitalisation in older Australians: a population-based longitudinal study 1980–2003. Brit J Clin Pharm 2007; 63: 163-70
56. Steinman MA. Polypharmacy and the balance of medication benefits and risks. Am J Geriatr Pharmacother 2007; 5: 314-5
57. Barry PJ, Gallagher P, Ryan C. Inappropriate prescribing in geriatric patients. Cur Psychiatr Rep 2008; 10: 37-43
58. Solomon DH. NSAIDs: cardiovascular effects. UpToDate®, the clinical information service on the web, desktop, and PDA devices [online]. Available from URL: http://www.uptodate.com/home/store/index.do [Accessed 2008 Nov 11]
59. Analgesic Expert Group. Therapeutic guidelines: analgesia. Version 5. Melbourne: Therapeutic Guidelines Ltd, 2007
60. McLeod PJ, Huang AR, Tamblyn RM, et al. Defining inappropriate practices in prescribing for elderly people: a national consensus panel. CMAJ 1997; 156: 385-91
61. Naugler CT, Brymer C, Stolee P, et al. Development and validation of an improved prescribing for the elderly tool. Can J Clin Pharmacol 2000; 7: 103-17
62. Hanlon JT, Schmader KE, Samsa GP. A method for assessing drug therapy appropriateness. J Clin Epidemiol 1992; 45: 1045-51
63. Fick DM, Cooper JW, Wade WE, et al. Updating the Beers criteria for potentially inappropriate medication use in older adults: results of a US consensus panel of experts. Arch Intern Med 2003; 163: 2716-24
64. Laroche ML, Charmes JP, Merle L. Potentially inappropriate medications in the elderly: a French consensus panel list. Eur J Clin Pharmacol 2007; 63: 725-31
65. Johnell K, Klarin I. The relationship between number of drugs and potential drug-drug interactions in the elderly:

a study of over 600 000 elderly patients from the Swedish Prescribed Drug Register. Drug Safety 2007; 30: 911-8

66. Beyth RJ, Shorr RI. Epidemiology of adverse drug reactions in the elderly by drug class. Drugs Aging 1999; 14: 231-9
67. Hajjir ER, Cafiero AC, Hanlon JT. Polypharmacy in elderly patients. Am J Geriatr Pharmacother 2007; 5: 345-51
68. Ballantyne JC, Mao J. Medical progress: opioid therapy for chronic pain. N Engl J Med 2003; 349: 1943-53
69. Jordan KM, Arden NK, Doherty M, et al. EULAR Recommendations 2003: an evidence based approach to the management of knee osteoarthritis: report of a task force of the Standing Committee for International Clinical Studies Including Clinical trials (ESCISIT). Ann Rheum Dis 2003; 62: 1145-55
70. Gloth FM. Pain management in older adults: prevention and treatment. J Am Geriatr Soc 2001; 49: 188-99
71. Weiner DK, Hanlon JT. Pain in nursing home residents: management strategies. Drugs Aging 2001; 18: 119-21
72. Divoll M, Ameer B, Abernethy DR, et al. Age does not alter acetaminophen absorption. J Am Geriatr Soc 1982; 30: 240-4
73. Wynne HA, Cope LH, Herd B, et al. The association of age and frailty with paracetamol conjugation in man. Age Aging 1990; 19: 419-24
74. Ostapowicz G, Fontana RJ, Schiedt FV, et al. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. US Acute Liver Failure Study Group. Ann Intern Med 2002; 137: 947-54
75. Donohoo E, managing editor. MIMS, issue no. 1. Sydney (NSW). CMPMedica Australia Pty Ltd, 2009 Feb/Mar
76. Pearce B, Grant IS. Acute liver failure following therapeutic administration in patients with muscular dystrophies. Anaesthesia 2008; 63: 89-91
77. Dart RC, Bailey E. Does therapeutic use of acetaminophen cause acute liver failure? Pharmacotherapy 2007; 27: 1219-30
78. Schmidt LE. Age and paracetamol self-poisoning. Gut 2005; 54: 686-90
79. Myers RP, Li B, Fong A, et al. Hospitalizations for acetaminophen overdose: a Canadian population-based study from 1995 to 2004 [abstract]. BMC Pub Health 2007; 7: 143
80. Farrell SE. Toxicity acetaminophen. Harvard Medical School, Department of Emergency Medicine, Brigham and Women's Hospital [online]. Available from URL: http://www.emedicine.com/emerg/topic819.htm [Accessed 2008 Apr 14]
81. Davis MP, Srivastava M. Demographics, assessment and management of pain in the elderly. Drugs Aging 2003; 20: 23-57
82. Brophy JM. Cardiovascular effects of cyclooxygenase-2 inhibitors. Curr Opin Gastroenterol 2007; 23: 617-24
83. Bing RJ, Lomnicka M. Why do cyclo-oxygenase-2 inhibitors cause cardiovascular events? J Am Coll Cardiol 2002; 39 (3) 521-2
84. Moore RA, Derry S, McQuay HJ. Cyclooxygenase-2 selective inhibitors and non-steroidal anti-inflammatory drugs: balancing gastrointestinal and cardiovascular risk [abstract]. BMC Musculoskelet Disord 2007; 8: 73
85. McGettigan P, Henry D. Cardiovascular risk and inhibition of cyclooxygenase: a systematic review of observational studies of selective and non-selective inhibitors of cyclooxygenase-2. JAMA 2006; 296: 1633-44
86. McGettigan P, Han P, Jones L, et al. Selective COC-2 inhibitors, NSAIDs and congestive heart failure: differences between new and recurrent cases. Br J Clin Pharmacol 2008; 65: 927-34
87. Cunningham G, Dodd TRP, Grant DJ, et al. Drug-related problems in elderly patients admitted to Tayside hospitals: methods for prevention and subsequent reassessment. Age Aging 1997; 26: 375-82
88. Larmour I, Dolphin RG, Baxter H, et al. A prospective study of hospital admissions due to drug reactions. Australian J Hosp Pharm 1991; 21: 90-5
89. Chan TYK, Critchley JAJH. Drug-related problems as a cause of hospital admissions in Hong Kong. Pharmacoepidemiol Drug Saf 1995; 4: 165-70
90. Wilder-Smith OHG. Opioid use in the elderly. Eur J Pain 2005; 9: 137-40
91. Sullivan MD, Edlund MJ, Fan MY, et al. Trends in opioid use for non-cancer pain conditions 2000–2005 in commercial and Medicaid insurance plans: the Troup Study. Pain 2008; 138: 440-9
92. Kelly JP, Cook SF, Kaufman DW, et al. Prevalence and characteristics of opioid use in the US adult population. Pain 2008; 138: 507-13
93. Langford R, McKenna F, Ratcliffe S, et al. Transdermal fentanyl for improvement of pain and functioning in osteoarthritis. Arth Rheum 2006; 54: 1829-37
94. Ackerman SJ, Knight T, Schein J, et al. Risk of constipation in patients prescribed fentanyl transdermal system or oxycodone hydrochloride controlled-release in a California Medicaid population. Consult Pharm 2004; 19: 118-32
95. Otis J, Rothman M. A phase III study to assess the clinical utility of low-dose fentanyl transdermal system in patients with chronic non-malignant pain. Curr Med Res Opin 2006; 22: 14493-501
96. Kung F, Gibson SJ, Helme RD. Factors associated with analgesic and psychotropic medications use by community-dwelling older people with chronic pain. Austral NZ J Pub Health 1999; 23: 471-4
97. Saarto T, Wiffen PJ. Antidepressants for neuropathic pain. Cochrane Database Syst Rev 2007; (4): CD005454
98. Neurology Expert Group. Therapeutic guidelines: neurology. Version 3. Melbourne (VIC): Therapeutic Guidelines Ltd, 2007
99. Wiffen P, Collins S, McQuay H, et al. Anticonvulsant drugs for acute and chronic pain. Cochrane Database Syst Rev 2005; (3): CD001133
100. Schmader KE, Dworkin RH. Clinical features and treatment of postherpetic neuralgia and peripheral neuropathy in older adults. In: Gibson SJ, Weiner DK, editors. Pain in older persons. Seattle (WA): IASP Press, 2005: 355-75
101. Bernstein C, Lateef B, Fine P. Interventional pain management procedures in older patients. In: Gibson SJ,

Weiner DK, editors. Pain in older persons. Seattle (WA): IASP Press, 2005: 263-83

102. Gurwitz JH, Field TS, Harrold LR, et al. Incidence and preventability of adverse drug events among older persons in the ambulatory setting. JAMA 2003; 298: 1107-16
103. Cresswell KM, Fernando B, McKinstry B, et al. Adverse drug events in the elderly. Br Med Bull 2007; 83: 259-74
104. Kucukarslan SN, Peters M, Mlyarek M, et al. Pharmacists on rounding teams reduce preventable adverse drug events in hospital general medical units. Arch Intern Med 2003; 163: 2014-8
105. Beney J, Bero LA, Bond C. Expanding the roles of outpatients pharmacists: effects on health services utilisation costs, and patient outcomes. Cochrane Database Syst Rev 2000; (2): CD000336
106. O'Brien MA, Rogers S, Jamtvedt G, et al. Educational outreach visits: effects on professional practice and health care outcomes. Cochrane Database Syst Rev 2007; (4): CD000409
107. Smith DH, Perrin N, Feldstein A, et al. The impact of prescribing safety alerts for the elderly in an electronic medical record: an interrupted time series evaluation. Arch Intern Med 2006; 166: 1098-104

Correspondence: Dr *Jonathan Bruce Barber*, National Ageing Research Institute, PO Box 2127, Royal Melbourne Hospital, Carlton, VIC 3050, Australia.
E-mail: b.barber@nari.unimelb.edu.au