A workshop on pharmacology in pain management was held at the 37th Annual Scientific Meeting of the Australian Pain Society, in Adelaide South Australia 9-12 April, 2017. There was a strong focus on the fastest expanding area of clinical Pain Medicine – the management of chronic pain in older persons. This is a summary of two presentations that were delivered by geriatricians.

The optimal approach to the management of pain in older persons considers pharmacological and non-pharmacological options, and balances pain relief with side effects of therapy. Pharmacological management is made more difficult because of age-related physiological changes, co-morbidity, polypharmacy, disability and frailty. Further complexity occurs in the settings of cognitive impairment and residential care.

Older persons may have difficulty complying with analgesic medications for many reasons. By the time they present for pain management, they may already be taking a large number of medications, including analgesics. Cognitive impairment and inadequate supervision may worsen compliance, especially if the drugs require doses several times a day, pro re nata (prn) doses according to symptoms (eg. opioids) or frequent changes in dose due to clinical monitoring (eg. insulin and warfarin).

If therapeutic objectives are misunderstood, older persons may stop a medication prematurely or, more commonly, increase the dose inappropriately due to a perceived lack of efficacy. Frequently, symptoms are misinterpreted by older patients and clinicians as new pathology requiring additional medication, rather than drug side effects that will resolve after medication withdrawal. Drugs prescribed only for short-term use, such as opioids and benzodiazepines, may be continued inadvertently over long periods, increasing the risk of adverse effects. If the older person is already experiencing problems with the current regimen, the addition of drugs with a high risk of overuse and side effects is strongly discouraged.
Prior to prescribing an analgesic, clinicians should attempt to rationalise the older patient’s current medications, to minimise complexity, maximise compliance, reduce current side effects and avoid adverse outcomes. Effective communication with older patients (and diplomacy with their other treating clinicians) may determine whether a medication is currently indicated or can be withdrawn safely.

Clinicians have a responsibility to consider a number of factors before prescribing an analgesic, in particular an opioid, to older persons.

1. Characteristics of the pain

In older persons, chronic pain may result from malignancy, musculoskeletal disease, a neuropathic process, or some combination, and can result in mood disturbance, insomnia and loss of independence. In the ideal world, the pain would be treated without recourse to opioids, anti-epileptic drugs and antidepressants. Disease-modifying anti-rheumatic drugs may reduce arthralgia from rheumatoid arthritis and intra-articular steroid injections may alleviate osteoarthritic knee pain. Analgesia is necessary when the underlying cause of pain cannot be alleviated.

The management of pain in the setting of dementia poses additional challenges. Husebo demonstrated that a stepwise approach to pain management in non-verbal nursing home residents led to reduced agitation, aggression and other behavioural problems. The majority of residents were treated with paracetamol (acetaminophen) alone, with less than one-quarter treated with low dose opioid analgesia, predominantly buprenorphine transdermal patch $\leq$ 10 micrograms per hour. (1) A recent Australian study involving 6 nursing homes revealed much higher opioid doses were being used. (2)

2. Treatment goals
Eminence-based medicine (that is, decisions made from the experience of a senior clinician) should complement evidence-based medicine in negotiating appropriate goals of treatment with older persons. (3) Therapeutic goals should be explicit about whether they involve

- Disease prevention,
- Disease control,
- Preservation of function,
- Symptom relief or
- End-of-life care.

With advancing age, the goal is likely to shift to symptom relief, quality of life and maintenance of functional independence. Overly aggressive treatments aimed to eliminate pain may result in intolerable side effects, perhaps worse than the pain itself. An older person may prefer mental alertness over increased analgesia that could exacerbate cognitive impairment. Conversely, pain relief may take priority over cognition in the palliative care setting.

Experienced pain clinicians should identify success and failure criteria that are meaningful to each older patient and recognise when they have achieved their optimal clinical state. Once an optimal clinical state has been achieved, further changes in analgesia will either make no difference or make matters worse. Experienced clinicians should have the insight and humility to reverse therapeutic decisions to return to the optimal state.

3. Non-pharmacological management

Non-pharmacological pain management is more effective in the long term than pharmacotherapy but tends to be under-prescribed by doctors and underused by clients. (4) Older persons may feel that exercise exacerbates pain, in contrast to opioids that alleviate it. When prescribed and monitored expertly, however, exercise benefits mood, memory and mobility, in addition to pain control. Other physical therapies, such as TENS, acupuncture, massage and repetitive transcranial magnetic stimulation, and psychological interventions,
such as meditation and cognitive behavioural therapy, may also be beneficial but can be labour-intensive and require expert supervision.

4. Choice of analgesic

There is little evidence on which to base therapeutic decisions in old age. There is no ideal analgesic, opioid or non-opioid. Subjects aged over 80 are often excluded from drug trials, even when this is not required for the objectives of the trial. When older subjects are included in these studies, they may not be representative of the older population in general. Therapeutic decisions are often extrapolated from studies involving younger or more robust subjects. Pain management guidelines habitually recommend agents that are poorly tolerated by older subjects and may aggravate other geriatric syndromes such as falls, cognitive impairment, urinary symptoms and postural hypotension.

While the World Health Organization suggests paracetamol as initial and ongoing therapy for pain, there is minimal evidence of long-term efficacy to support this recommendation. Oral non-steroidal anti-inflammatory medications (NSAIDs) may be beneficial for musculoskeletal pain but have gastrointestinal, cardiovascular and renal adverse effects that limit their use in older persons and should only be used for short durations to manage acute exacerbations of pain. Serotonin and noradrenaline reuptake inhibitors (such as duloxetine), anticonvulsants (pregabalin) and tricyclic antidepressants may be useful for neuropathic pain but increase risk of falling. Furthermore, tricyclic antidepressants are best avoided due to anticholinergic side effects and delirium.

Opioids remain the most commonly used analgesic in the management of chronic pain, although there is little evidence to support long-term opioid use at any age. Over recent decades, the increasingly prevalent use of opioids has been associated with a disproportionate increase in opioid use in people over 80, despite the higher risk of adverse effects such as falls, fractures and death. The (mis)use of opioids in Australia has not reached North American proportions, yet Australian data show wide regional variation in opioid consumption, with higher use in areas with limited multidisciplinary and specialist services.
5. Current diseases and possible side effects

When the age of 85 is reached, one-half of the population will have 3 or more chronic conditions, and one quarter will have 5 or more, in addition to age-related physiological changes. Advancing age is also associated with an increased prevalence of frailty, which may occur independently of co-morbidities. Frailty increases the prevalence of pain, vulnerability to physiological stressors and risk of suboptimal outcomes including hospitalisation, residential aged care placement and death.

While a sort course of opioid therapy may be appropriate for an acute exacerbation of musculoskeletal pain, injury, or in post operative settings, the long-term opioid use (ie. longer than four weeks) is discouraged due to the development of tolerance, side effects, opioid-induced hyperalgesia and withdrawal syndromes. The mu opioid receptor (MOR) mediates most of the supraspinal analgesic effects of opioids but is also responsible for sedation, respiratory depression and bradycardia. Activation at delta and kappa receptors may provide spinal analgesia but also predisposes to reduced gastric motility, constipation, hypotension and diuresis.

Opioids may exacerbate syndromes of ageing in patients. As opioids cause sedation, dizziness and delayed reaction time, they may increase the incidence of fracture by predisposing to falls or by increasing the risk of fracture once a fall has occurred.(8) The risk of fracture in older adults with arthritis appears to be higher in the first two weeks after drug commencement, for opioids of shorter duration of action and for higher opioid doses.(9) While pain and suboptimal analgesia are themselves risk factors for delirium,(10) opioids increase the risk of delirium due to their central nervous system effects, particularly in people with cognitive impairment.(11)

6. Pharmacodynamic, -kinetic and –genetic interactions

Older persons are frequently prescribed more than one opioid to treat pain, leading to complex pharmacodynamic interactions. For example, buprenorphine has higher affinity for and potency at the MOR but lower intrinsic activity and efficacy (partial agonism) than
morphine and oxycodone. Buprenorphine can act as a competitive antagonist, displacing morphine, oxycodone and other more potent opioids from the MOR and limiting their analgesic efficacy.(12)

In addition to opioid receptor agonism, some opioids are also agonists and antagonists at other receptors. For example, tramadol causes noradrenaline (NRI) and serotonin reuptake inhibition (SRI) and NMDA, 5HT2c and cholinergic receptor antagonism. Methadone and tapentadol have NRI and SRI properties, while methadone is also an antagonist at NMDA receptors. These drugs may potentiate the toxicity of other drugs in the older patient’s regimen. For example, SRI enhances some of the analgesic properties of tramadol but predisposes to the serotonin syndrome if the older person is also taking a selective serotonin reuptake inhibitor, monoamine oxidase inhibitor or tricyclic antidepressant.

The degree of age-related physiological change varies greatly between individuals, and between organ systems within the same individual. Age-related changes in drug metabolism lead to the accumulation of active drugs and metabolites and increase the risk of toxicity. Opioids are metabolised in the liver through phase I and II processes, both of which decline with age. Phase I metabolism involves the cytochrome p450 enzyme pathway, in particular CYP2D6 and CYP3A4.

It is uncertain to what extent CYP2D6 metabolism declines with age. However, reduced enzyme function, due to polymorphism in cytochrome p450 alleles, persists into old age. Reduced CYP2D6 metabolism can lead to accumulation of enzyme substrates, including oxycodone, methadone, morphine and tapentadol. Reduced CYP2D6 function can also limit the efficacy of inactive drugs, such as tramadol and codeine that rely on that enzyme for conversion to an active metabolite.

CYP3A4 appears prone to greater age-related decline in function. Drugs reliant on this enzyme for metabolism, such as methadone, fentanyl and buprenorphine, will have reduced systemic clearance, prolonged elimination half-lives and tendencies to accumulate in older persons. (13)

Older persons may be taking medications that inhibit cytochrome p450 function, leading to opioid accumulation and toxicity. Antihypertensive drugs, such as the calcium antagonists verapamil, nifedipine and diltiazem, and the antiarrythmic amiodarone inhibit CYP3A4.
CYP2D6 is inhibited by the antidepressants duloxetine, paroxetine, sertraline, escitalopram and doxepin; while reboxetine, citalopram, fluoxetine and venlafaxine inhibit both CYP2D6 and CYP3A4. With respect to antipsychotic medications, CYP2D6 is inhibited by risperidone and haloperidol, while both CYP2D6 and CYP3A4 are inhibited by quetiapine. The combination of an opioid and a cytochrome p450 inhibitor should be avoided if possible, or closely monitored for toxicity if not.

Age-related decline in renal function also leads to the accumulation of active and inactive parent opioids and metabolites. The active metabolites of tramadol (O-desmethy tramadol, M1) codeine, morphine and hydromorphone are mostly excreted in the kidneys. Buprenorphine has metabolites with minimal analgesic activity that can accumulate in renal impairment. While Fentanyl is extensively converted by the liver to inactive metabolites, a small fraction (5 to 10%) of the drug is still excreted unchanged by the kidneys. Even opioids such as methadone and oxycodone, which have active metabolites that are mainly eliminated by the liver, should be monitored for accumulation and toxicity.

All opioids need some degree of lipid solubility to cross the blood-brain barrier. As people age, the percentage of body fat rises, increasing the volume of distribution of lipid-soluble drugs. Fentanyl, which is substantially more lipophilic than morphine, accumulates in fat stores, thereby increasing its volume of distribution, half-life, duration of effect and potential for toxicity.

7. **Other Geriatric Medicine principles and recommendations**

Guidelines for the management of pain in older persons recommend the combination of non-pharmacological with pharmacological therapies. Unpublished data from a multidisciplinary pain clinic for older persons was presented. The mean age was over 80 years, two thirds of whom were frail and 40% had cognitive impairment. Patients with frailty, multi-morbidity and cognitive impairment were able to achieve meaningful improvements in pain scores and activity interference with a multidisciplinary approach.
When prescribing opioids, or indeed any drug, to older persons, it is safer to ‘start low and go slow’ and to use the least number of drugs in the lowest doses and for the shortest durations necessary to achieve pain control.

While opioid doses are being titrated, short acting formulations (ie. with more frequent doses) are generally preferred as they can address exacerbations of pain more promptly.

Once pain has been improved and stabilised, regular doses of a longer acting preparation is preferable, due to more sustained analgesia, with a short-acting opioid used prn to handle breakthrough pain or acute flares.

Doses of analgesics, especially opioids should be adjusted to the older person’s comorbidities, existing drug regimen, age-related changes in metabolism and vulnerability to side effects, especially in the presence of frailty.

Pain can be a difficult problem to manage and clinicians should enlist the aid of older patients’ carers, pharmacists, general practitioners and allied health practitioners when required.

References: