Position Statement 29
Prescribing in Older People

Key Points

1. Prescribing in older people is complex. There is a lack of good quality evidence supporting clinical guidelines in this population who are increasingly frail and have multimorbidity.

2. Pharmacokinetic and pharmacodynamic changes in older people influence outcomes by altering drug disposition, metabolism, clearance and responses. Usually this will result in increased exposure and toxicity at standard adult therapeutic doses.

3. Polypharmacy can be a consequence of following clinical practice guidelines that have been developed based on studies performed in younger fitter populations with single disease states.

4. Polypharmacy increases the risk of adverse outcomes. Adverse events can be frequently missed or misattributed to ageing or another disease process and if not recognised can then trigger a prescribing cascade. Adverse drug events may result in hospitalisation and death.

5. A thorough medication history is a key component of the geriatric assessment. The emergence of adverse effects, changes in symptoms and/or goals should prompt a review of medicines.

6. The use of collaborative and consultative approaches for older patients is paramount in optimising prescribing and deprescribing. Medical ethics must guide the prescribing process. These principles include beneficence, non-maleficence, autonomy and justice. Consent from patients or their substitute decision makers must be a cornerstone of the prescribing and deprescribing process.

7. The goals of care once established should be reviewed regularly and when there have been changes in the patient's circumstances including clinical and social. This is an important aspect in prescribing and deprescribing.

8. When prescribing, consider whether medications are necessary and if so select the agent taking into account individual characteristics such as renal impairment. Minimise the overuse as well as the underuse of medications.

9. Monitor safety and efficacy as well as the need to continue the medications. Consider the cost of prescribing the drug to the individual, community and the health system. Once the medication has been selected, choose the appropriate dosage and duration of treatment. Be aware and monitor for drug-drug and drug-disease interactions.

This Position Statement represents the views of the Australian and New Zealand Society for Geriatric Medicine. This Statement was approved by the Council of the ANZSGM on 26th March 2018. This paper was co-authored by Angela Molga, David Le Couteur, Sarah Hilmer, Sally Johns, John Maddison.

INTRODUCTION

This position statement is aimed at providing an approach to quality use of medicines for older people. Prescribing is complex due to multimorbidity and limited evidence in older adults for both effectiveness and safety of
medications recommended by clinical guidelines. Pharmacokinetic and pharmacodynamic variability due to ageing influence the effects of medications, especially in frail individuals. With increasing age and evolving (or changing) health status, goals of care may change and a high level of communication addressing these goals and determining ongoing consent is a core to the ethics of prescribing. A detailed medication history is one of the essential domains of a geriatric assessment with a reduction in drug burden being an effective therapeutic intervention with positive outcomes. Medication management for the older person requires knowledge, skills and reasoning beyond the level applied to prescribing for younger fitter people with single conditions.

**EPIDEMIOLOGY**

The Australian population is predicted to experience a dramatic change with significant increases in ageing over the next five decades. People older than 65 years old are projected to increase from 3.2 million to between 5.7 and 5.8 million in 2031 and 9.0 and 11.1 million by 2061. The highest growth rate is expected in the population aged 85 years and over with the peak growth expected in 2032.(1) Similarly in New Zealand, the proportion of the population aged 65 years old and over in 2014 was 14% (650,000) which is predicted to increase to 24-32% (1.57-1.81 million) by 2068.(2)

**POLYPHARMACY**

Polypharmacy is defined as the use of five or more medications and is associated with an increased rate of adverse outcomes including adverse drug reactions,(3) (4) non-adherence,(5) death,(6) falls,(7) disability(8) and delirium.(9) Although there is limited, if any, evidence for the benefits of polypharmacy, clinicians may feel that polypharmacy is unavoidable as they strive to comply with disease specific clinical guidelines or the recommendations of multiple practitioners involved in patient care. Thus the use of a quantitative definition assists the clinician in screening patients with polypharmacy thus allowing timely evaluation, intervention and optimisation of patient care.

The Australian National Census of Medicines Use (2009-10) observed that polypharmacy was more common with increasing age, especially in people aged 75 years and older and women,(10) and that the prevalence had increased since the 1995 National Health Survey.(11) Risk factors for polypharmacy include old age, female gender, increasing number of diagnoses, hospitalisation and depression,(12) although polypharmacy is the consequence of prescribing habits of doctors more than patient based characteristics. The most commonly used medications by participants in the National Census were antihypertensives, fish oils, glucosamine and lipid-lowering agents.(10) In residential aged care facilities an average of seven drugs are used per patient including those prescribed on an “as required” basis, with the most common being analgesics, antipsychotics, and laxatives.(13)

In New Zealand in 2016, 35 percent of people aged 65 years and 59 percent of people aged 85 years and older received five or more long-term medicines, with four percent receiving 11 or more long term medicines with the highest rates in those aged over 85 years old. There was also an increase in the use of psychotropic agents and benzodiazepines with increasing age and an increase in the dispensing of the ‘triple whammy’ (ACE inhibitor/ARB, diuretic and NSAID) on discharge from public hospitals.(14)

**PHARMACOKINETIC AND PHARMACODYNAMIC VARIATIONS WITH AGEING AND FRAILTY**

There are many pharmacokinetic and pharmacodynamic changes that occur with normal ageing. Changes in the volume of distribution and clearance have the most significant clinical impact because these influence loading doses and maintenance doses of medications, respectively.(15) In general, old age is associated with reduced renal and hepatic clearance of many medications, while the age-related reduction in skeletal muscle and increase in body fat can influence their volume of distribution.

These pharmacokinetic and pharmacodynamic changes are even more pronounced in people with frailty. Frailty is “a state of increased
vulnerability to stressors due to age-related declines in physiologic reserve across neuromuscular, metabolic and immune systems’. (16) Sarcopenia is a key feature of frailty and is associated with a relative increase in body fat and decreased lean body mass, which can markedly influence the volume of distribution of medications. (17) The age-related reduction in albumin which is even greater in frail people, means that total drug levels of albumin-bound drugs (e.g. phenytoin, valproate) can be unreliable with toxic levels occurring at apparently therapeutic levels. (18, 19)

Clearance is affected due to changes in renal and hepatic function. Renal mass decreases with age and renal function is impaired by conditions that frequently coexist such as hypertension, chronic heart failure and diabetes mellitus. (20) Sarcopenic patients have less muscle to produce creatinine, therefore serum creatinine levels that seem to be in normal range may overestimate glomerular filtration rate. In the context of these physiological changes, calculated creatinine clearance using formulas (e.g. Cockcroft-Gault, Chronic Kidney Disease Epidemiology Collaboration CKD-EPI, Modification of Diet in Renal Disease MDRD) to estimate kidney function are more appropriate in older persons than using eGFR. (21, 22) Age-related changes in hepatic drug clearance will lead to increased drug levels and toxicity of many drugs (and reduce the activity of prodrugs that require liver metabolism to be converted to their active metabolites). (23)

Overall, changes in hepatic and renal clearance, body composition and protein binding mean that lower doses of medications are required to achieve similar therapeutic concentrations of medications in older people. In addition to these changes in pharmacokinetics, pharmacodynamic changes result in enhanced effects of medications at ‘standard doses’ and blood levels due to the reduction in EC50 (effective concentration of a drug at which 50% of its maximum response is observed) and Emax (the maximum response). Examples of medications affected by these changes include antihypertensives due to age-related changes in beta-receptors and calcium channels receptors, benzodiazepines due to changes in GABA-receptors, (15, 24) and age associated sensitivity to warfarin(25) and opioids. (26)

It is also important to appreciate that even if an individual has been on a therapeutic agent for many years, changes in pharmacokinetics and pharmacodynamics associated with ageing and multimorbidity may alter the effectiveness and safety of medications. Therefore it is essential to periodically review all medications.

CONSENT AND GOALS

Applying the principles of medical ethics (beneficence, non-maleficence, autonomy and justice) is especially important when prescribing given the paucity of evidence available in prescribing for older people with multimorbidity. Clinical practice guidelines infrequently take into account the individualisation of therapy and goals and neither is there emphasis on the balance between harm and benefit in light of those goals. (18) Useful concepts for practitioners to consider are consent to treatment, time-to-benefit and time-to-harm. Anticholinergics, sedatives, benzodiazepines and psychotropic drugs negatively impact on older people by worsening cognition and increasing the risk of falls. These medications are frequently used in older people who are vulnerable due to impaired cognition and in some circumstances their autonomy and consent is not respected e.g. when medications are concealed due to their refusal. Discussions to prescribe and deprescribe should be held with the substitute decision maker if the individual’s decision-making is considered to be impaired and the potential to cause harm and benefits tailored to each individual should be highlighted. (27) Another example is statins which are frequently prescribed to older people however time to benefit is estimates at 2 to 5 years of continuous therapy therefore they may not be useful in people with limited prognosis or terminal conditions. (28) Older people with HbA1c less than 53 mmol/mol (7%) are at increased risk for falls and hypoglycaemic episodes, and these are also associated with increased risk for development of dementia. An HbA1c greater than 53 mmol/mol (7%) is considered acceptable, with relaxed control in frail patients or those with life expectancy less than 5 years. (29-31) Hypoglycaemia is an
immediate clinical risk, whereas hyperglycaemia presents risk over many years.

When reviewing medications or prescribing consider the individual’s consent, carer autonomy, overall disease burden, short and long term goals and the quality and applicability of evidence for the guideline.(32) Diligently applying the principles of medical ethics will assist greatly in resolving much of the difficulty in prescribing in complex older patients with multimorbidity.

**OPTIMISING PRESCRIBING**

**Considerations in initiating medications**

Quality prescribing involves the quality use of medicines, effective communication, establishing goals and consent and evaluating efficacy, safety and outcomes in order to individualise treatment. The Australian National Strategy for the Quality Use of Medicines lists the principles of Quality prescribing.(33) These are:

1. Ensure that appropriate consent is obtained
2. Conduct a thorough medication history to avoid prescribing cascades and therapeutic duplication
3. Use appropriate dosing regimens by taking into account the relevant pharmacokinetic and pharmacodynamic variations in older people

The use of tools such as the Screening Tool of Older Persons’ Prescriptions (STOPP) and Screening Tool to Alert to Right Treatment (START) criteria(34) assists in prioritising, rationalising, prescribing and deprescribing of medications, especially in multimorbidity. Similarly the Drug Burden Index is a pharmacological risk assessment tool that can help clinicians identify medicines with anticholinergic and sedative effects that have cumulative effects on impairing function in older people.(35) The Beers Criteria(36) are also used to assist in optimising prescribing however there are medications listed that are not used in Australia and New Zealand. The Inappropriate Medication Use and Prescribing Indicators Tool is derived from Australian consensus guidelines.(37) Tools and criteria are to be used as adjuncts to clinical decision-making, taking into account the individual circumstances and choices of the patient. Quality prescribing also involves addressing under-prescribing, as omission of indicated treatment can also result in adverse outcomes including hospitalisation and increased morbidity.(38)

In patients with multimorbidity there is a greater risk of adverse events but the use of multiple medications may appear to be unavoidable on the basis of application of single disease clinical guidelines or the management of symptoms. Goals may differ for the patient if they are approaching end of life as opposed to being in robust health. In addition the goals of the patient/carer and the clinician may differ which requires consideration and discussion.(39-41) Consider whether medications are necessary and if so select the agent taking into account individual characteristics such as renal impairment. Minimise the overuse as well as the underuse of medications.

**Monitoring safety and efficacy**

Conduct a regular review of medications. The review should consider:

4. safety and efficacy as well as the need to continue the medications
5. the emergence of adverse drug reactions (drug-drug and drug-disease interactions), issues with tolerability, geriatric syndromes such as falls, dementia or frailty.
6. changes in clinical and/or psychosocial circumstances – these should prompt a re-evaluation of goals and therapy.(42)
7. adherence to medication regimes prior to uptitration or other changes in therapy

Adherence to medication regimes decreases with the increases in number of medications, regimen complexity and patient specific factors such as economic, cognitive impairment, inadequate patient or carer comprehension, and physical factors preventing them from taking the medications by routes prescribed. For example dexterity affected by arthritis or Parkinson’s disease – rendering them unable
to open the bottle, or swallowing difficulties making it difficult to take tablets. The process of administering a medication should form part of the assessment when prescribing a medication either as a new prescription or a review.

**Deprescribing**

Deprescribing can be defined as ‘the process of withdrawal of an inappropriate medication, supervised by a health care professional with the goal of improving outcomes.’ The principles of deprescribing include identifying when it may be beneficial, developing a plan and monitoring outcomes including withdrawal syndromes, symptom recurrence or improvements. Deprescribing one drug can unmask an underlying drug interaction not previously recognised. It can resolve related adverse drug effects, improve patient satisfaction and quality of life, improve physical and cognitive function as well as reduce financial cost to patient and the community. Withdrawal and rebound syndromes should be considered when deprescribing. These can be avoided by stopping one drug at a time and slow weaning over weeks if necessary. Medications that usually require weaning include most psychotropic medications (including antidepressants, sedatives, opioids, and antiepileptics), beta-blockers, levodopa, steroids and proton pump inhibitors.

A comprehensive geriatric assessment could identify and formulate targeted approaches including clinical pharmacy services – post discharge review, home medicines review – as well as implementing recommendations.

Assessments can also occur in residential care in conjunction with the primary care provider. Recommendations and goals can be formulated and communicated in multidisciplinary case conferences with the aim of providing patient centred care.

**CLINICAL PRACTICE GUIDELINES IN OLDER PEOPLE, ADVERSE DRUG REACTIONS AND HIGH RISK MEDICATIONS**

Clinical management in older people is frequently based on evidence extrapolated from studies in more robust groups with fewer physiological deficits, morbidities and medications. Older people, especially frail older people, are underrepresented in clinical trials. In addition clinical trials usually determine singular outcomes and adverse drug reactions are poorly or underreported in publications, especially those that are often most important to older people such as falls or impairments of physical and cognitive function. Therefore the incidence of adverse drug events in real patients has been reported to be higher than that reported in clinical trial participants. Clinical practice guidelines are usually aimed at managing single diseases, therefore have limited applicability for older people with multimorbidity by failing to account for disease-disease interactions, disease-drug interactions and drug-drug interactions. For example following the UK national clinical guidelines specifically for type 2 diabetes and 11 other commonly coexisting conditions such as hypertension, depression and osteoarthritis, could result in 32 potentially serious drug-disease interactions and 113 potentially serious drug-drug interactions occurring in an individual. Patients with multimorbidity are frequently managed by multiple specialists and primary health care clinicians which increases the risk of duplication, drug interactions and failure to identify adverse drug reactions.

Adverse drug reactions are significant in older people due to physiological changes that occur with ageing and frailty but polypharmacy itself is the major contributor. Adverse drug reactions are frequently reported by older people. If an older person is taking five concurrent medications there is a 50% probability of at least one drug interaction and they are 4 times as likely to be hospitalised as a consequence of the adverse drug event. Twenty to 30% of adverse drug reactions are due to errors in prescribing, dispensing or monitoring and 42% of life-threatening/fatal adverse reactions are preventable. Adverse drug reactions may present atypically in older people – for example as a “geriatric syndrome” such as a fall or confusion. As a result adverse drug events are frequently misdiagnosed and result in prescribing cascades, hospitalisation or death.
If an adverse drug event is not recognised a prescribing cascade may result. For example, cholinesterase inhibitors for the treatment of Alzheimer’s disease may cause or perpetuate urinary incontinence. If this is not recognised an anticholinergic may be inappropriately prescribed – which may in turn worsen cognition. A study of over 20,000 older people with dementia who were prescribed a cholinesterase inhibitor demonstrated that they had an increased risk of receiving an anticholinergic drug to manage urinary incontinence compared with a control group of similar numbers who did not receive cholinesterase inhibitors - 4.5% vs 3.1%; p<0.001; adjusted hazard ratio, 1.55; 95% confidence interval 1.39–1.72).(60) This highlights the importance of recognising a symptom as drug-related as it could be potentially reversible with the cessation of the drug.

There are also common examples of drug-drug interactions which commonly occur in older people and are under recognised. For example, increased statin levels due to inhibition of liver CYP3A4 by drugs such as verapamil, diltiazem or macrolides, increases the risk of myopathy in older people. Resources such as the P450 drug interaction table (61) or the Australian Medicines Handbook (62) provide prescribers with easy-to-access information regarding a drug’s potential interactions. Hyponatraemia from SSRIs,(63) tendon rupture from steroids,(64) and acquired potentially fatal prolongation of the QT interval are also seen more commonly in older people.(65)

Adverse drug reactions may be related to not starting at lower doses in older people; however there is limited clinical evidence for using lower doses than those recommended in clinical practice guidelines.(66) The majority of reported presentations due to adverse drug events in older people are due to anticoagulants, diuretics, analgesics and hypoglycaemics.(67) Other commonly implicated high risk medications with a large percentage of fatal and non-fatal events include methotrexate, digoxin, aspirin, beta blockers and anticonvulsants.(68) Adverse effects of other medicines, such as falls and impaired physical and cognitive function from benzodiazepines, antipsychotics, anti-depressants and other sedating and anticholinergic medicines are under-recognised and under-reported.(8) In addition to those adverse events, there has been an association between the use of antipsychotics and increased mortality, stroke and pneumonia. This is concerning due to the observed frequent use of these medications for behavioural and psychological symptoms in older people with major neurocognitive disorders in residential care facilities.(69)

When completing the medication history it is important to include dietary supplements, over-the-counter, complementary and alternative medicines, as these contribute to polypharmacy, as well as drug interactions.(70) The use of these agents has increased over the last decade in addition to significant increases in prescribed medications such as statins and antiplatelet agents. This trend in polypharmacy and the increased use of alternative therapy was highlighted in the United States over a 5 year period between 2005 and 2010. At the end of the study period twice as many older people were at higher risk of drug-drug interactions between complementary/alternative therapy and prescribed medications.(71)

Due to the heterogeneity of older people with multimorbidity it is a complex task to anticipate, identify and appropriately manage adverse drug reactions, drug-drug and drug-disease interactions, and withdrawal. In addition adverse effects can present as geriatric syndromes such as falls or confusion or be misinterpreted as ‘ageing’ leading to a failure to identify the cause. It is critical to consider whether changes in clinical status are related to medications, whether these be recent or long-term medications. Every opportunity should be taken to review the entire medication regime and potentially reduce, cease or switch medications.(72)

**CONCLUSIONS**

Older people are the highest users of multiple medications and have highest disease burden. Prescribing in older people is complex due to physiological variations, multimorbidity, numerous drug-drug and drug-disease interactions and difficulty in identifying adverse drug reactions. Polypharmacy puts individuals
at increased risk of adverse events including hospitalisations, falls, disability and death. The principles of medical ethics and of quality use of medicines, combined with knowledge of pharmacological changes with old age can provide frameworks for prescribing in older people where the clinical evidence base for prescribing is often very limited. Prescribers can empower their patients by ensuring informed consent is obtained throughout the prescribing and deprescribing process with the aim of improving health outcomes and overall quality of life.

REFERENCES


40. Scott IA, Le Couteur DG. Physicians need to take the lead in deprescribing. Internal medicine journal. 2015;45(3):352-6.


