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HEALTHY AGING RESEARCH

Prescribing appropriately in frail older people

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Abstract

Frailty is one of the most important aspects associated with the elderly. It is defined as a state of increased vulnerability to poor resolution of homeostasis after a stressor event, which increases the risk of adverse outcomes such as falls, institutionalization and death. Frail older adults are more likely to have several concurrent disorders, requiring multiple treatments and hence, considerable medication consumption. The functional reserve of multiple organs deteriorates with ageing and this often leads to changes in drug pharmacokinetics and metabolism. As a result, prescribing medications for frail older people is often complex and challenging. Furthermore, there is a paucity of evidence from clinical trials on the effects of multiple drug consumption in patients aged above 80 years since people from this age group tend to be excluded from such studies. Because of the changes in the pharmacokinetics and pharmacodynamics of drugs in older people, especially in those who are frail, there is an increased risk of adverse drug events for these patients, which can result in hospitalization, increased morbidity and mortality. In this review, appropriate prescribing for frail older people is explored. Consideration will be given to the impact of frailty on medication prescribing and how individualized prescribing could reduce the risk of adverse drug events in at-risk older patients. Tools used to enhance prescribing practice are examined, including those aimed at reducing polypharmacy, underprescribing and inappropriate prescribing. These tools use either explicit (criterion-based) or implicit (judgment-based) criteria. However, most of the current therapeutic guidelines are applicable mainly for the fit older population and cannot be directly applied where frail individuals are concerned. Approaches to improving appropriate prescribing among frail elderly patients, including those with limited life expectancy, are also reviewed.

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Introduction

In developed countries, those aged 65 years and older represent the most rapidly growing segment of the population [1]. More people are living to be old, and older people themselves are living longer [2]. As a result, frailty is increasingly an important aspect of an ageing population.

The concept of 'frailty' is used to identify older adults at high risk of death, disability, and institutionalization [3, 4]. Frailty is characterised by low physiological reserves and vulnerability to illness and other stressors [3]. Based on recent estimates, 10% of community-dwelling older persons are frail and another 42% are pre-frail, with increasing prevalence with age. Frail older adults account for the highest health care costs in industrialized nations [5].

Several terms are used to describe standards that should be achieved in prescribing, including 'safe', 'rational', 'optimal' and 'appropriate'. Appropriate prescribing is a broad term and can be conceptualized as an individual gaining the maximum benefit from medication but not experiencing adverse effects caused by excessive, inappropriate or inadequate

consumption of the medication [6]. In one study of 196 outpatients aged 65 years and above who were taking five or more medications simultaneously, 57% were taking at least one medication that was ineffective, duplicative or not indicated [7]. Ineffective prescribing refers to the prescription of a drug that is not effective for the indication in general or for the specific patient. This concept is distinct from under-prescribing [6]. Under-prescribing is the failure to prescribe a drug that is indicated and appropriate, or the use of an appropriate drug at ineffective doses [6]. Over-prescribing refers to the use of a drug that is unnecessary or at an excessive dosage (too much, too often or too long).

The World Health Organisation defined an adverse drug event (ADE) as a noxious, unintended and undesired effect of a drug, excluding therapeutic failures, intentional or accidental poisoning and drug abuse [8]. Older people are more susceptible to ADEs due to a variety of environmental and physiological factors. Polypharmacy is commonly defined as the use of five or more regular medications and has been recognised as the most important risk factor for ADEs. The probability of ADEs in older people is further increased by age-related changes in the pharmacokinetics and pharmacodynamics of medicines, including increased sensitivity to certain drug classes. Additionally, the consequences of ADEs may be more severe due to the presence of multiple comorbidities, loss of functional independence and reduced homeostatic reserve.

Prescribing appropriately in older people requires a balance between risks and benefits of medications. However this can be complex because of the limited evidence on effectiveness of pharmacological therapy in the older age group. Evidence from randomized, controlled trials for drug efficacy in older people is limited because older people, especially those who are frail, are under-represented in these studies. As a result, the effects of medications among older people are often extrapolated from the younger population.

Definition and assessment of frailty

There are three main approaches to the assessment of frailty. The first identifies frailty as a clinical syndrome or phenotype (a set of signs and symptoms that tend to occur together, thus characterising a specific medical condition). The most well-known and widely used phenotype identifies frailty as the presence of three or more of five criteria: weight loss, exhaustion, weak grip strength, slow walking speed, low physical activity [3]. This phenotype has been validated as a predictor of adverse outcomes in large epidemiological studies [9] and has recently been used to define frailty as the most common condition leading to death in community-dwelling older people [10]. Fried's model for frailty [3] has many strengths: it is clinically coherent, reproducible and identifies frailty as a wasting disorder, with sarcopenia as a key pathophysiological feature. However, its reliance on performance-based tests limits its feasibility for older inpatients [11].

An alternative to phenotypic approaches is the measurement of frailty based on the clinician's subjective opinion [12]. While such measures have strong face validity, their reliance on judgement (which may vary between clinicians and between health systems) and dependence on geriatric expertise (e.g. accurate assessment of functional status) limit their generalisability.

The conceptualisation of frailty as a multidimensional syndrome enables its measurement by the quantity rather than by the nature of health problems [13]. In this model, individuals accumulate deficits throughout their lives: the more health disorders individuals have, the higher the likelihood they will be frail and their frailty can be measured by an index of accumulated deficits or Frailty Index (FI) [14]. This model employs a well-defined methodology to create an index as a proportion of deficits (e.g. someone with six deficits out of 40 counted has a FI of 0.15) [15]. The FI approach is feasible in older inpatients [11] and also predicts a patient's capacity to recover from acute illness [16] and potential for rehabilitation [17]. However, it has yet to be implemented in routine clinical practice.

Drug pharmacokinetics and pharmacodynamic changes in frail older people

Ageing and frailty involves progressive impairments in the functional reserve of multiple organs, which can

affect drug pharmacokinetics (excretion, absorption, distribution and metabolism) and pharmacodynamics (Table 1).

Absorption

Early studies reported significant "age-related" changes affecting drug absorption, including reduced saliva production, reduced gastric acid secretion, delayed gastric emptying and intestinal atrophy [18]. Frailty status has not been explicitly measured in these studies, and we can only speculate that older people described as "healthy" are physiologically robust, with no significant co-morbidities and good functional status. Therefore no consistent effects of increasing age on the bioavailability of drugs have been reported.

Distribution

Ageing is associated with significant changes in body composition [19]. Frailty is associated with increases in body fat and reduction in lean body mass. In a study of 3,055 community dwelling adults aged 65 years and above, those with a high waist circumference were significantly frailer. This finding was consistent across different categories of body mass index (such as lowest prevalence of frailty were in those with BMI 25-29.9 kg/m^2), and using different definitions of frailty [20]. Storage in fat initially limits the effect of drugs but then prolongs it, and the slow release of these drugs from fat storage may result in significant plasma levels, particularly after administration of repeated doses. As body fat increases and total body water decreases, the apparent volume of distribution of polar drugs (such as digoxin and lithium) will decrease [21] while that of lipophilic drugs (such as diazepam) will increase [22].

Table 1. Physiological changes with ageing and the effects on drug pharmacokinetics

Pharmacokinetic parameter	Physiological changes with ageing	Effects on drug pharmacokinetics
Absorption and bioavailability	Increase in gastric pH	Slight decrease in absorption but rarely significant clinically
	Delay in gastric emptying	
	Decrease in splanchnic blood flow	
	Decrease in absorption surface	
	Decrease in gastrointestinal motility	
Distribution	Increase in body fat	Increase in volume of distribution and half-life of lipophilic drugs
	Decrease in lean body mass	
	Decrease in total body water	Increase in plasma concentration of hydrophilic drugs
	Decrease in serum albumin	Increased free fraction in plasma for highly protein-bound acidic drugs
	Increase in α_1-acid glycoprotein	Decrease in free fraction of basic drugs
Hepatic elimination/metabolism	Decrease in hepatic blood flow	First-pass metabolism can be less effective
	Decrease in hepatic mass	Phase I metabolism of some drugs might be slightly impaired
Kidney elimination	Decrease in renal blood flow and glomerular filtration rate	Impaired elimination of renally cleared drugs

While albumin levels do not change with "healthy ageing", frail older people have significantly lower levels of serum albumin [23]. Acidic drugs (such as phenytoin, warfarin, digoxin, naproxen, ceftriaxone, lorazepam, valproic acid) are usually bound extensively to albumin, with unbound drug available for passive diffusion to extravascular or tissue sites where the pharmacologic effects of the drug occur. Since most measured drug levels reflect total drug in serum (bound and unbound), frail older people taking acidic drugs are prone to toxic side effects even with "normal" drug levels. Alpha$_1$-acid glycoprotein tends to increase with age and this can lead to a decrease in the free fraction of basic drugs [24]. However, age-related changes in plasma protein binding are generally regarded to be of little clinical relevance.

Renal elimination

Between the ages of 30 and 80 years, kidney mass and the number of associated glomeruli decrease by about 20-30% [25]. However, in about one third of older patients there is no decrease in kidney function [25]. Although ageing itself has only a minor effect on kidney function, confounding factors such as hypertension, diabetes mellitus and heart diseases account for a decline in kidney function in many older people [26].

A cross-sectional association between frailty and renal impairment has been recognised. The prevalence of the frailty phenotype is 15% in older people with any degree of chronic kidney impairment [27], increasing to 21% for those with moderate to severe chronic kidney disease [28] and 73% at dialysis initiation [29]. Frailty is associated with increased mortality in older people with renal impairment, even after adjustment for chronological age and comorbidities [30]. However, whether frailty is a cause or consequence of renal impairment has yet to be established.

Creatinine has previously been identified as a possible marker to assess kidney function but its suitability has subsequently found to be rather limited because it can be affected by muscle mass, diet and renal tubular secretion. To our knowledge, frailty status has not been considered explicitly in validation studies of equations estimating glomerular filtration rate (GFR). However, since sarcopenia is a core feature of the frailty phenotype [3], GFR estimated from plasma creatinine may overestimate the true GFR for older people who are frail. These individuals may, therefore, be particularly vulnerable to the accumulation of drugs, such as digoxin, which are primarily renally eliminated [18].

Metabolism

Many drugs undergo biotransformation to more polar metabolites by several cytochrome P-450 (CYP)-dependent phase I reactions and/or phase II pathways, such as glucuronidation, acetylation or sulfatation. This drug metabolism occurs mainly in the liver. It is generally accepted that the liver mass and hepatic blood flow decrease by about 20-30% and 20-50%, respectively, with age [31]. These changes might affect the elimination of high-clearance drugs.

However, according to *in vitro* data, no age-related changes in hepatic metabolic activities have been observed [31]. Likewise the content and activities of various CYP450 enzymes in hepatic biopsy samples did not decrease with age in the range of 10-85 years [32, 33]. All these findings would suggest that drug metabolism remains well preserved in older people, at least up to about 80 years.

Pharmacodynamic changes

Pharmacodynamic changes observed with ageing involve altered (usually increased) sensitivity to several classes of drugs such as anticoagulants, cardiovascular and psychotropic drugs. Older people appear to have an increased sensitivity to benzodiazepines [34] and warfarin [35]. Chronological age has also been cited as an important predictor of analgesic response [36]. However, the paucity of evidence relating pharmacodynamic responses to frailty is acknowledged as a limiting factor in establishing optimal dosing regimes in this patient group [37].

Medications in frail older people

Older people often take multiple prescribed medications concurrently and polypharmacy occurs in 20-50% of patients [38, 39]. Older adults in residential

aged care facilities are prescribed, on average, seven different drugs, while hospitalised patients receive an average of eight [40]. Polypharmacy in older people, especially those who are frail, is associated with decreased physical and social functioning, reduced adherence rate to essential medications, increased risk of delirium, falls, hospitalisation and death. Although frailty is not synonymous with comorbidity or disability, many frail older people have multiple chronic diseases and functional impairment and are prescribed many medications. The number of different drugs a person takes is the single most important predictor of inappropriate prescribing and ADEs. One report estimated the risk of ADEs as 13% for two drugs, 38% for four drugs and 82% for seven drugs or more [41].

ADEs leading to hospitalisation occur more frequently in patients over the age of 65 years compared to younger patients (20.1% vs. 9.6%) [42]. In a study of 1756 patients aged 65 years or above, 45.1% of ADEs were classified as definitely avoidable and 31.4% as possibly avoidable [43].

A significant proportion of frail older adults may find it difficult to understand and adhere to complex medication plans. Those with dementia or other types of cognitive impairment are particularly vulnerable to this problem.

Older people, especially those who are frail, are often excluded from drug trials. There is a paucity of high-quality studies among older patients. For example, 60% of patients with cancer are above the age of 65 years but this age group typically make up only 22-36% of trial participants [44, 45]. Therefore treatment decisions are often extrapolated from fitter people groups without physiological decline. Moreover, in one meta-analysis, it was concluded that very little rigorous research has been conducted on reducing unnecessary medications in frail older adults or patients approaching end of life [46].

Assessing the quality of prescribing

When clinicians assess the appropriateness of a prescription, it is important to consider whether this is from a patient-benefit perspective or from a criteria-based perspective. On one hand, what may seem to be inappropriate by the patient's clinician may well be the most acceptable option for a patient; while on the other hand, what may be perceived as appropriate by the patient's clinician may not be by a patient.

As there are no biological age markers available, clinicians still have to rely on the chronological age. However, it is important to differentiate the fit (i.e., "normal" ageing) from the frail older people. And, as such, prescribing in frail older people should differ from that in non-frail.

Prescribing in older people can be assessed using explicit (criteria-based, Table 2) or implicit (judgment-based) tools. Generally, explicit criteria are derived from expert reports or published reviews. These criteria have high reliability and reproducibility but usually focus mainly on specific drugs and disease states. On the other hand, implicit criteria are person-specific and explore patient preferences before the consideration of disease and medications. These criteria rely on the judgment of the assessor and consequently have low reliability and practical utility.

There is also debate about whether these tools are generalisable across different countries due to differences in prescribing practices. It is also important to realise that most of the studies assessing these tools have not been linked with health outcome measures such as benefit in terms of improving morbidity, mortality, hospital admission and quality of life.

Beers criteria

Beers criteria present a list of potentially inappropriate medications for older people, irrespective of patient preferences or disease burden. It was developed in the USA in 1991 and was designed for older residents in nursing homes [47]. It underwent several revisions, the latest in 2012, to enable wider application in older adults [48]. The most recent updated criteria included 53 medications or medication classes.

Table 2. Comparison of explicit tools used to assess appropriate prescribing in older people

Criteria	Description	Strength	Weaknesses
Beers [47, 48]	List of medications to be avoided in older people living in residential care facilities Updated for use in all ambulatory and health care settings	List medications that should be avoided in older people List medications to be avoided with specific medical conditions in older people Updated version include medications to be used with caution in older people	List requires regular updates to be effective A number of medications listed are seldom used Does not address drug-drug interactions, duplication or dosing of renally cleared drugs Does not examine underprescribing
Improving prescribing in the elderly tool [50]	List of medications that should be avoided in older people, drug-disease interactions and drug-drug interactions	Includes drug-disease and drug-drug interactions	Not based on physiological systems Biased towards NSAIDs, cardiovascular and psychotropic drugs
STOPP/START [52, 55]	STOPP has 80 criteria for potentially inappropriate prescribing START has 34 indictors to detect prescribing omission	Includes medications widely used in Europe Addresses drug-drug interactions and duplication	Not an exhaustive list

NSAIDs: Non-steroidal anti-inflammatory drugs; START: Screening Tool to Alert doctors to the Right Treatment; STOPP: Screening Tool of Older Person's Potentially inappropriate Prescriptions

These were divided into three categories of potentially inappropriate medications and drug classes: (a) avoid in older patients, (b) avoid in older people with certain diseases or syndrome, and (c) use with caution in older adults. However it does not address drug-drug interaction, drug duplication, under-prescribing and dosing of renally cleared drugs. Furthermore, there is little evidence to support a clear benefit in relation to clinical outcomes through the use of Beers criteria [49].

Improving prescribing in the elderly tool

Improving prescribing in the elderly tool (IPET), also known as the McLeod criteria, was developed in Canada in 1997 and applied to hospital inpatients [50]. This tool consists of a list of 18 drugs that should generally be avoided in older people, 16 drug-disease interactions and four drug-drug combinations. These criteria are based on risk-benefit ratios and allow the assessment of drug-drug and drug-disease interactions. Excellent inter-rater reliability with a kappa co-efficient of 1.0 has been reported [51].

STOPP and START

The Screening Tool of Older Person's Prescriptions (STOPP) criteria version 1 address 65 indicators of inappropriate prescribing with particular attention to drugs that adversely affect older patients at risk of falls, drug-drug interaction, drug-disease interaction and drug duplication [52]. The Screening Tool to Alert doctors to Right Treatment (START) criteria report 22 evidence-based prescribing indicators and highlight the potentially serious errors of prescribing omission in older people, arranged according to physiological systems [52].

In a previous study of 600 patients aged 65 years or older, detection of serious avoidable ADEs increased when STOPP criteria (odds ratio 1.85) were used compared to Beer's criteria [53]. In the same study, definitely or possibly avoidable ADEs relevant to

admission were 2.76 times more frequently detected with STOPP criteria. Therefore, evidence would suggest that STOPP criteria are more sensitive to detect potentially inappropriate medications that result in ADEs, but a randomized controlled trial is needed to prove their role as a useful interventional tool.

START has a good inter-rater reliability with a kappa coefficient of 0.68 [52]. The validated START tool has been evaluated in a study with 600 older patients over the age of 65 years who were admitted to hospital with an acute illness. One or more prescribing omissions were found in 58% of the patients, without any evidence of contraindications [54]. The probability of omission was related to age, with the highest incidence in the age group above 85 years (72% with one medication omission).

STOPP/START criteria were expanded and updated in 2014 for the purpose of minimizing inappropriate prescribing in older people [55]. The version 2 criteria are based on an up-to-date literature review and consensus validation among a European panel of experts. The new version has 80 STOPP criteria and 34 START criteria. This represents an overall 31% increase in STOPP/START criteria compared with version 1. However, both STOPP and START criteria can be complex, making their application time consuming. Furthermore, these tools have not been linked to clinical outcomes such as hospital admission or morbidity.

Medication Appropriateness Index

The Medication Appropriateness Index (MAI) is a refined implicit method developed in the US [44]. This index rates ten elements of prescribing: indication, effectiveness, dose, correct directions, practical directions, duplication, duration, cost, drug-drug and drug-disease interactions. Medications are rated as appropriate, marginally appropriate or inappropriate for each criterion.

As an implicit indicator, the MAI requires clinical judgement but it also uses more explicit criteria that standardize the process, giving good inter-rater reliability and an overall kappa of 0.83 [44]. Although the MAI has a good reliability in ambulatory settings and community pharmacies, the generalizability of this tool as used by other investigators is unknown [56, 57]. Moreover, it does not evaluate the indication of drugs.

10-step quality use of medicine framework

A quality use of medicine framework was developed in Australia to minimize inappropriate medications in older people [58]. Incorporating 10 steps, this framework aims to decrease the number of medications to the appropriate number of essential drugs. The individualized and systematic approach of this framework identifies the medications that are of little or no benefit in older patients, enabling discontinuation of non-essential ones.

This framework focuses on medication-related and medication management-related aspects of appropriate prescribing that addresses an important gap observed in other tools. However, studies are needed to validate its effectiveness in the treatment of older people in various settings.

Good Palliative-Geriatric Practice Algorithm

The Good Palliative-Geriatric Practice Algorithm is a tool developed in Israel for addressing the problem of polypharmacy and improving the quality of prescribing in older people in residential care facilities [59]. The use of this algorithm indicates that many medications can be discontinued in the frail older people without significant detrimental effects on mortality, morbidity and quality of life. It has been shown to be effective in reducing polypharmacy, morbidity including admission to acute care facilities, and mortality, with a one-year mortality rate of 21% in the study group compared with 45% in the control group [59]. The use of this algorithm was also able to decrease polypharmacy in community-dwelling older people, with discontinuation of 58% of prescribed medications [60]. Successful discontinuation was achieved in 81% of participants in this study, including non-consent and failures. No significant adverse effects or deaths were attributable to discontinuation. Of discontinued medications, only 2% were recommenced because of recurrence of the initial indication. On a modified Likert scale, 88% of patients reported a global improvement in health and

there was evidence of modest improvement in cognitive function.

It has been suggested that the use of both explicit and implicit criteria together may be more advantageous than either one alone [61, 62]. However, there is no specific tool or set of criteria to guide prescribing in frail older people or patients with decreased life expectancy [63]. The next step in this field is to develop a tool that will enable both the evaluation of frailty and appropriateness of medication prescription in this cohort.

Approach to improving quality of prescribing

In Australia, one in four older people living in the community are hospitalised for medication-related problems over a 5-year period [64] and 15% of older adults attending general practice report an ADE in the preceding 6 months [65]. About 25% of these ADEs are thought to be preventable [65]. This indicates that there is still scope for improving appropriate prescribing among older people especially those who are frail.

To reduce or prevent inappropriate prescribing, there is a need for the education of prescribers, development of evidence-based guidelines, involvement of patients and caregivers and effective methods of monitoring and auditing medications regularly.

A Cochrane review has been undertaken to determine which interventions, alone or in combination, are effective in improving the appropriate use of polypharmacy and reducing medication-related problems in older people [66]. Twelve studies were reviewed. One intervention consisted of computerised decision support and 11 complex, multi-faceted pharmaceutical approaches to interventions were provided in a variety of settings. Interventions to improve appropriate polypharmacy, such as pharmaceutical care, appear to be beneficial in terms of reducing inappropriate prescribing but unclear if there was any clinically significant improvement.

Deprescribing is the process of tapering or discontinuing drugs with the goal of minimising polypharmacy and improving outcomes. However, the implementation of deprescribing among clinicians can be challenging for a number of reasons: increasing intensity of medical care, under-appreciation of the scale of polypharmacy-related harm, reluctance of prescribers and ambivalence of patients [40].

The simplest approach to assessing appropriateness of medication is to check the current medication list of an older person during each hospital admission or outpatient attendance. This will identify potential new symptoms related to adverse drug events, eliminate duplication of medications and prevent potential drug-drug interactions [67]. A regular review by general practitioners or pharmacists, at least annually, can be useful to stop inappropriate medications and consider starting any that are potentially beneficial.

Education of prescribers as well as older patients and their caregivers is important in the path towards appropriate prescribing. Prescribers need to be educated on the use of medications in older people, age-related changes in pharmacokinetics and pharmacodynamics as well as the interaction between frailty and medications [68]. Such training should begin at a tertiary education level. In addition, engaging patients and their caregivers in making decisions about drug treatments is also important. A meta-analysis of interventional studies to improve medication adherence have found that educational initiative can improve drug adherence and reduce hospital admission rates [69].

Multidisciplinary team involvement is another approach that has been found to have favourable outcomes in improving the quality of medication prescription in older people [70]. The team may include nurse practitioners, clinical pharmacists specializing in geriatric medicine and other health practitioners who can review drug lists and alert clinicians or the patient about concerns regarding the use of a particular medication.

The use of information technology can alert or remind clinicians and pharmacists of potential drug errors, duplications and interactions. One study has shown that using a drug utilization database to integrate information technology, pharmacists and clinicians can improve prescribing in older people [71]. Other advantages of using electronic prescribing are the elimination of illegible handwriting and enhancement of record keeping. However, the use of information

technology still does not replace the need for prescribers to be well trained in prescribing appropriately to frail older people and to exercise clinical judgment in each individual patient.

Prescribing in frail patients at end-of-life stage

Frailty is an important predictor of adverse outcomes, including death, and should therefore have a significant bearing on decision-making in clinical settings. One model for appropriate prescribing for patients late in life proposes focusing on four components: (a) remaining life expectancy, (b) time until treatment benefit, (c) goals of care and (d) treatment targets [63]. Another model proposed by Scott et al expands this to ten steps [adding (e) ascertainment of current medications; (f) identification of patients at high risk of or experiencing ADEs; (g) estimation of the magnitude of benefit vs. harm in relation to each medication; (h) assessing the relative utility of different drugs; (i) identification of drugs that may be discontinued; (j) ongoing evaluation of drug utility and patient adherence by a single nominated clinician] [58].

In those who are frail, the prolongation of life often becomes a less important therapeutic goal. It is important to remember that the risks of secondary prevention may outweigh benefits in those with limited life expectancy. For example, in one study the median life expectancy for frail older hospitalised patients with delirium was 88 days (95 % confidence interval: 5–171 days) [72]. The homeostatic instability and loss of physiological reserves of these patients renders them vulnerable to ADEs and they may not survive to reap any benefit from treatment with medications such as statins [73], angiotensin-converting enzyme inhibitors [74] or bisphosphonates [75]. Despite recent attention to incorporating patient life expectancy and goals of care into medication prescribing among older people, these criteria have yet to be implemented into medication reduction trials at the end of life.

It is critical that clinicians recognise patients who are entering the end-of-life stage in order to define treatment goals and prescribe the appropriate medications. Despite questionable benefit, a substantial proportion of patients with terminal conditions continue to take medications for preventative measures until death [76]. Algorithms to guide deprescribing and a systematic approach to the discontinuation of medications have been shown to reduce morbidity and mortality [60]. At the same time there is a need to manage symptoms adequately and it is generally viewed that anticipatory prescribing is good practice in the terminal phase of illness.

Conclusions

Appropriate prescribing is often complex and challenging in frail older people. There is a paucity of evidence to guide prescribing in this group of people because of their under-representation in clinical trials. Prescribing tools can enhance prescribing practice and be used for auditing. However, currently available tools have limitations including a lack of evidence for their benefits in terms of clinical outcomes and the absence of any that have been validated for frail older patients. Therefore, further work is required to develop a prescribing evaluation tool that is useful in frail older people. Approaches to improving appropriate prescribing should include regular review of medications and treatment response; education of prescribers, patients and their caregivers; utilisation of multidisciplinary strategies; and using information technology to reduce errors where possible. However, this prescribing tool should not be used in isolation. Good clinical judgment and a thorough understanding of patients' wishes, preferences and treatment goals remain the cornerstone of high-quality and individualized prescribing, especially for those who are at the end-of-life stage.

References

1. Louria DB. Extraordinary longevity: individual and societal issues. J Am Geriatr Soc. 2005;53:S317-9.
2. Christensen K, Doblhammer G, Rau R, Vaupel JW. Ageing populations: the challenges ahead. Lancet. 2009;374:1196-208.
3. Fried LP, Tangen CM, Walston J et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci .2001;56:M146-56.

4. Sternberg SA, Wershof Schwartz A, Karunananthan S et al. The identification of frailty: a systematic literature review. J Am Geriatr Soc. 2011;59:2129-38.
5. Fassbender K, Fainsinger RL, Carson M, Finegan BA. Cost trajectories at the end of life: the Canadian experience. J Pain Symptom Manage. 2009;38:75-80.
6. Aronson JK. Rational prescribing, appropriate prescribing. Br J Clin Pharmacol. 2004;57:229-30.
7. Steinman MA, Landefeld CS, Rosenthal GE et al. Polypharmacy and prescribing quality in older people. J Am Geriatr Soc 2006;54:1516-23.
8. International drug monitoring. The role of the hospital. World Health Organ Tech Rep Ser. 1969;425:5-24.
9. Bandeen-Roche K, Xue QL, Ferrucci L et al. Phenotype of frailty: characterization in the women's health and aging studies. J Gerontol A Biol Sci Med Sci. 2006;61:262-6.
10. Gill TM, Gahbauer EA, Han L, Allore HG. Trajectories of disability in the last year of life. N Engl J Med. 2010;362:1173-80.
11. Hubbard RE, O'Mahony MS, Woodhouse KW. Characterising frailty in the clinical setting--a comparison of different approaches. Age Ageing. 2009;38:115-9.
12. Studenski S, Hayes RP, Leibowitz RQ et al. Clinical Global Impression of Change in Physical Frailty: development of a measure based on clinical judgment. J Am Geriatr Soc. 2004;52:1560-6.
13. Rockwood K, Mitnitski A, Song X et al. Long-term risks of death and institutionalization of elderly people in relation to deficit accumulation at age 70. J Am Geriatr Soc. 2006;54:975-9.
14. Rockwood K, Mitnitski A. Frailty in relation to the accumulation of deficits. J Gerontol A Biol Sci Med Sci. 2007;62:722-7.
15. Searle SD, Mitnitski A, Gahbauer EA et al. A standard procedure for creating a frailty index. BMC Geriatr. 2008;8:24.
16. Singh I, Gallacher J, Davis K et al. Predictors of adverse outcomes on an acute geriatric rehabilitation ward. Age Ageing. 2012;41:242-6.
17. Hubbard RE, Eeles EM, Rockwood MR et al. Assessing balance and mobility to track illness and recovery in older inpatients. J Gen Intern Med. 2011;26:1471-8.
18. Currie GM, Wheat JM, Kiat H. Pharmacokinetic considerations for digoxin in older people. Open Cardiovasc Med J. 2011;5:130-5.
19. Ramsay SE, Whincup PH, Shaper AG, Wannamethee SG. The relations of body composition and adiposity measures to ill health and physical disability in elderly men. Am J Epidemiol. 2006;164:459-69.
20. Hubbard RE, Lang IA, Llewellyn DJ, Rockwood K. Frailty, body mass index, and abdominal obesity in older people. J Gerontol A Biol Sci Med Sci. 2010;65:377-81.
21. Hanratty CG, McGlinchey P, Johnston GD, Passmore AP. Differential pharmacokinetics of digoxin in elderly patients. Drugs Aging. 2000;17:353-62.
22. Weiss M. How does obesity affect residence time dispersion and the shape of drug disposition curves? Thiopental as an example. J Pharmacokinet Pharmacodyn. 2008;35:325-36.
23. Hubbard RE, O'Mahony MS, Savva GM et al. Inflammation and frailty measures in older people. J Cell Mol Med. 2009;13:3103-9.
24. Butler JM, Begg EJ. Free drug metabolic clearance in elderly people. Clin Pharmacokinet. 2008;47:297-321.
25. Glassock RJ, Rule AD. The implications of anatomical and functional changes of the aging kidney: with an emphasis on the glomeruli. Kidney Int. 2012;82:270-7.
26. Fliser D, Franek E, Joest M et al. Renal function in the elderly: impact of hypertension and cardiac function. Kidney Int. 1997;51:1196-204.
27. Shlipak MG, Stehman-Breen C, Fried LF et al. The presence of frailty in elderly persons with chronic renal insufficiency. Am J Kidney Dis. 2004;43:861-7.
28. Wilhelm-Leen ER, Hall YN, M KT, Chertow GM. Frailty and chronic kidney disease: the Third National Health and Nutrition Evaluation Survey. Am J Med. 2009;122:664-71.
29. Bao Y, Dalrymple L, Chertow GM et al. Frailty, dialysis initiation, and mortality in end-stage renal disease. Arch Intern Med. 2012;172:1071-7.
30. Johansen KL, Chertow GM, Jin C, Kutner NG. Significance of frailty among dialysis patients. J Am Soc Nephrol. 2007;18:2960-7.
31. Schmucker DL. Aging and the liver: an update. J Gerontol A Biol Sci Med Sci. 1998;53:B315-20.
32. Shimada T, Yamazaki H, Mimura M et al. Interindividual variations in human liver cytochrome P-450 enzymes involved in the oxidation of drugs, carcinogens and toxic chemicals: studies with liver microsomes of 30 Japanese and 30 Caucasians. J Pharmacol Exp Ther. 1994;270:414-23.
33. Hubbard RE, O'Mahony MS, Calver BL, Woodhouse KW. Plasma esterases and inflammation in ageing and frailty. Eur J Clin Pharmacol. 2008;64:895-900.
34. Trifiro G, Spina E. Age-related changes in pharmacodynamics: focus on drugs acting on central nervous and cardiovascular systems. Curr Drug Metab. 2011;12:611-20.
35. Routledge PA, Chapman PH, Davies DM, Rawlins MD. Factors affecting warfarin requirements. A prospective population study. Eur J Clin Pharmacol. 1979;15:319-22.
36. Pickering G, Jourdan D, Eschalier A, Dubray C. Impact of age, gender and cognitive functioning on pain perception. Gerontology. 2002;48:112-8.
37. McLachlan AJ, Bath S, Naganathan V et al. Clinical pharmacology of analgesic medicines in older people:

impact of frailty and cognitive impairment. Br J Clin Pharmacol. 2011;71:351-64.

38. Kennerfalk A, Ruigomez A, Wallander MA et al. Geriatric drug therapy and healthcare utilization in the United kingdom. Ann Pharmacother. 2002;36:797-803.
39. Yong TY, Lau SY, Li JY et al. Medication prescription among elderly patients admitted through an acute assessment unit. Geriatr Gerontol Int. 2012;12:93-101.
40. Scott IA, Anderson K, Freeman CR, Stowasser DA. First do no harm: a real need to deprescribe in older patients. Med J Aust. 2014;201:390-2.
41. Atkin PA, Veitch PC, Veitch EM, Ogle SJ. The epidemiology of serious adverse drug reactions among the elderly. Drugs Aging. 1999;14:141-52.
42. Merten H, Zegers M, de Bruijne MC, Wagner C. Scale, nature, preventability and causes of adverse events in hospitalised older patients. Age Ageing. 2013;42:87-93.
43. Franceschi M, Scarcelli C, Niro V et al. Prevalence, clinical features and avoidability of adverse drug reactions as cause of admission to a geriatric unit: a prospective study of 1756 patients. Drug Saf. 2008;31:545-56.
44. Hanlon JT, Schmader KE, Samsa GP et al. A method for assessing drug therapy appropriateness. J Clin Epidemiol. 1992;45:1045-51.
45. Hutchins LF, Unger JM, Crowley JJ et al. Underrepresentation of patients 65 years of age or older in cancer-treatment trials. N Engl J Med. 1999;341:2061-7.
46. Tjia J, Velten SJ, Parsons C et al. Studies to reduce unnecessary medication use in frail older adults: a systematic review. Drugs Aging. 2013;30:285-307.
47. Beers MH, Ouslander JG, Rollingher I et al. Explicit criteria for determining inappropriate medication use in nursing home residents. UCLA Division of Geriatric Medicine. Arch Intern Med. 1991;151:1825-32.
48. American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc. 2012;60:616-31.
49. Spinewine A, Schmader KE, Barber N et al. Appropriate prescribing in elderly people: how well can it be measured and optimised? Lancet. 2007;370:173-84.
50. McLeod PJ, Huang AR, Tamblyn RM, Gayton DC. Defining inappropriate practices in prescribing for elderly people: a national consensus panel. CMAJ. 1997;156:385-91.
51. Naugler CT, Brymer C, Stolee P, Arcese ZA. Development and validation of an improving prescribing in the elderly tool. Can J Clin Pharmacol. 2000;7:103-7.
52. Gallagher P, Ryan C, Byrne S et al. STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment). Consensus validation. Int J Clin Pharmacol Ther. 2008;46:72-83.
53. Hamilton H, Gallagher P, Ryan C et al. Potentially inappropriate medications defined by STOPP criteria and the risk of adverse drug events in older hospitalized patients. Arch Intern Med. 2011;171:1013-9.
54. Barry PJ, Gallagher P, Ryan C, O'Mahony D. START (screening tool to alert doctors to the right treatment)--an evidence-based screening tool to detect prescribing omissions in elderly patients. Age Ageing. 2007;36:632-8.
55. O'Mahony D, O'Sullivan D, Byrne S et al. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. Age Ageing. 2015;44:213-8.
56. Fitzgerald LS, Hanlon JT, Shelton PS et al. Reliability of a modified medication appropriateness index in ambulatory older persons. Ann Pharmacother. 1997;31:543-8.
57. Kassam R, Martin LG, Farris KB. Reliability of a modified medication appropriateness index in community pharmacies. Ann Pharmacother. 2003;37:40-6.
58. Scott IA, Gray LC, Martin JH, Mitchell CA. Minimizing inappropriate medications in older populations: a 10-step conceptual framework. Am J Med. 2012;125:529-37.
59. Garfinkel D, Zur-Gil S, Ben-Israel J. The war against polypharmacy: a new cost-effective geriatric-palliative approach for improving drug therapy in disabled elderly people. Isr Med Assoc J. 2007;9:430-4.
60. Garfinkel D, Mangin D. Feasibility study of a systematic approach for discontinuation of multiple medications in older adults: addressing polypharmacy. Arch Intern Med. 2010;170:1648-54.
61. Lindley CM, Tully MP, Paramsothy V, Tallis RC. Inappropriate medication is a major cause of adverse drug reactions in elderly patients. Age Ageing. 1992;21:294-300.
62. Buetow SA, Sibbald B, Cantrill JA, Halliwell S. Appropriateness in health care: application to prescribing. Soc Sci Med. 1997;45:261-71.
63. Holmes HM, Hayley DC, Alexander GC, Sachs GA. Reconsidering medication appropriateness for patients late in life. Arch Intern Med. 2006;166:605-9.
64. Kalisch LM, Caughey GE, Barratt JD et al. Prevalence of preventable medication-related hospitalizations in Australia: an opportunity to reduce harm. Int J Qual Health Care. 2012;24:239-49.
65. Miller GC, Britth HC, Valenti L. Adverse drug events in general practice patients in Australia. Med J Aust. 2006;184:321-4.
66. Patterson SM, Cadogan CA, Kerse N et al. Interventions to improve the appropriate use of polypharmacy for older people. Cochrane Database Syst Rev. 2014;10:CD008165.

67. Shrank WH, Polinski JM, Avorn J. Quality indicators for medication use in vulnerable elders. J Am Geriatr Soc. 2007;55:S373-82.

68. Jackson SH, Mangoni AA, Batty GM. Optimization of drug prescribing. Br J Clin Pharmacol. 2004;57:231-6.

69. Peterson AM, Takiya L, Finley R. Meta-analysis of trials of interventions to improve medication adherence. Am J Health Syst Pharm. 2003;60:657-65.

70. Crotty M, Halbert J, Rowett D et al. An outreach geriatric medication advisory service in residential aged care: a randomised controlled trial of case conferencing. Age Ageing. 2004;33:612-7.

71. Monane M, Matthias DM, Nagle BA, Kelly MA. Improving prescribing patterns for the elderly through an online drug utilization review intervention: a system linking the physician, pharmacist, and computer. JAMA. 1998;280:1249-52.

72. Eeles EM, White SV, O'Mahony SM et al. The impact of frailty and delirium on mortality in older inpatients. Age Ageing. 2012;41:412-6.

73. Berthold HK, Gouni-Berthold I. Lipid-lowering drug therapy in elderly patients. Curr Pharm Des. 2011;17:877-93.

74. Hines LE, Murphy JE. Potentially harmful drug-drug interactions in the elderly: a review. Am J Geriatr Pharmacother. 2011;9:364-77.

75. Hollick RJ, Reid DM. Role of bisphosphonates in the management of postmenopausal osteoporosis: an update on recent safety anxieties. Menopause Int. 2011;17:66-72.

76. O'Mahony D, O'Connor MN. Pharmacotherapy at the end-of-life. Age Ageing. 2011;40:419-22.