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REVIEW

Appropriate prescribing in the elderly: Current perspectives

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Abstract

Advances in medical therapeutics have undoubtedly contributed to health gains and increases in life expectancy over the last century. However, there is growing evidence to suggest that therapeutic decisions in older patients are frequently suboptimal or potentially inappropriate and often result in negative outcomes such as adverse drug events, hospitalisation and increased healthcare resource utilisation. Several factors influence the appropriateness of medication selection in older patients including age-related changes in pharmacokinetics and pharmacodynamics, high numbers of concurrent medications, functional status and burden of co-morbid illness. With ever-increasing therapeutic options, escalating proportions of older patients worldwide, and varying degrees of prescriber education in geriatric pharmacotherapy, strategies to assist physicians in choosing appropriate pharmacotherapy for older patients may be helpful. In this paper, we describe important age-related pharmacological changes as well as the principal domains of prescribing appropriateness in older people. We highlight common examples of drug-drug and drug-disease interactions in older people. We present a clinical case in which the appropriateness of prescription medications is reviewed and corrective strategies suggested. We also discuss various approaches to optimising prescribing appropriateness in this population including the use of explicit and implicit prescribing appropriateness criteria, comprehensive geriatric assessment, clinical pharmacist review, prescriber education and computerized decision support tools.

Key words: Elderly; Inappropriate prescribing; Polypharmacy; Beers criteria; Screening Tool of Older Person's potentially inappropriate Prescriptions/Screening Tool to Alert to Right Treatment; Adverse drug reactions

Core tip: In this paper we discuss the challenges and complexities of prescribing for older people. We describe the important age-related changes in pharmacokinetics and pharmacodynamics that influence prescribing decisions and we highlight commonly encountered examples of drug-drug and drug-disease interactions. We present a detailed analysis of a complex clinical case in which several instances of potentially inappropriate prescribing exist and we suggest corrective actions. We explore a range of strategies aimed at optimizing prescribing appropriateness for older people including prescribing criteria, comprehensive geriatric assessment, clinical pharmacy interventions and computerized decision supports.

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INTRODUCTION

Over the last century, there have been dramatic increases in life expectancy owing largely to improvements in living standards and advances in diagnostics, pharmaceutical medicine and therapeutics. This is reflected in worldwide changes in population demographics, with ever-increasing numbers of older people. The United Nations define "older people" as being aged 60 years or older with the oldest old being 80 years or older. In 1990, 9.2% of the world's population was aged at least 60 years old. In 2013, this proportion was 11.3% and by 2050, it is estimated that 21.2% of the world's population will be aged 60 years and over[1]. The largest numbers of older adults currently reside in developed countries, however by 2050 it is estimated they will reside in developing countries. Presently the older population is predominantly female with an expected improvement in male mortality expected in the coming years[1].

Though increased longevity is to be celebrated, it is well established that increasing age brings with it an increase in the burden of co-morbidity and a corresponding increase in the consumption of medications. Appropriate selection and prescription of curative and preventative medicines is an essential element of high quality healthcare for older people, who are the greatest consumers of healthcare resources in most developed nations[2]. One in eight Americans is aged over 65 years, but this small proportion of the population consumes the greatest proportion of prescription medications[3]. Similarly, older Europeans consume over twice as many healthcare resources than their younger counterparts[4]. In the United Kingdom approximately one fifth of the population is aged over 65 years, but this group receives 45% of all dispensed drugs[5]. In Ireland, 11% of the population is over 65 years but account for up to 50% of medications dispensed through its reimbursement service[6]. In the United States approximately 30% of community-dwelling older adults are regularly prescribed five or more medications[7]. This number rises in hospitalized older patients and in nursing home residents, perhaps reflecting a greater disease burden.

It is estimated that older people consume approximately 40% of all over-the-counter (OTC) medications sold in the United States[8]. Concurrent use of OTC medication with regular prescription medications places patients at higher risk of adverse outcomes; one study reported that 46% of older patients were concurrently taking OTC medications with regular prescription medications and 1 in 25 of these patients were at risk of significant drug interactions[7]. In addition, there is emerging evidence that the consumption of complementary and alternative medicines amongst older adults is steadily increasing[9]. A recent study showed a significant rise in the use of herbal remedies in those aged $\geqslant$ 65 years from 13.2% in 2002 to 19.5% in 2007[10].

Prescribing for older patients with multiple chronic illnesses, especially frailer older patients with cognitive and functional impairments, presents many unique challenges, particularly with respect to the following variables: (1) polypharmacy; (2) altered pharmacokinetic and pharmacodynamic responses; (3) balancing the risk of harm *vs* long term therapeutic benefit; and (4) paucity of robust scientific evidence for use of commonly prescribed medications in older, frail patients with limited life expectancy.

Prescribers must be cognizant of important age-related anatomical, biochemical and physiological changes that affect drug pharmacokinetics, pharmacodynamics and homeostatic mechanisms. They must also be aware of the potential for interaction with concurrently prescribed drugs and co-existing disease states. Prescribers should have an appreciation of the potentially low therapeutic yield in very frail older patients with poor life expectancy where the risk of certain treatments can exceed the potential clinical benefit. These important tenets of appropriate prescribing for older patients are briefly summarised below.

Pharmacokinetics and ageing

The key pharmacokinetic changes commonly associated with ageing are summarized in Table 1. A more detailed description follows. Drug absorption is generally unaltered in healthy older people; however certain conditions may affect the rate of drug absorption. Drugs with anticholinergic effects may reduce saliva secretion, thus impeding the rate, but not necessarily the amount of drug absorbed through the oral mucosa, *e.g.,* buccal midazolam and sublingual nitrate. The rate of absorption of subcutaneous, intramuscular and transdermal medications can be affected by reduced tissue perfusion. Conversely, prokinetic agents such as domperidone or erythromycin can increase the rate of delivery of an oral drug to its absorption site. Reductions in small bowel active transport mechanisms can affect the extent of absorption of iron and vitamin B12. Intravenous absorption is generally not affected.

Plasma drug concentration is inversely related to its volume of distribution (Vd), which in turn, is dependent on the hydrophilic and lipophilic volumes in the body. As people age, there is a reduction in muscle mass and body water content with a proportionate increase in body fat[11]. Consequently, the Vd for hydrophilic drugs (*e.g.,* lithium) is reduced; this may result in toxicity if drugs are not dose-adjusted. Lipophilic drugs (*e.g.,* antipsychotic medications) have a higher Vd in older people, and therefore have an increased elimination

Table 1 Pharmacokinetics and ageing

Absorption	↓ amount of saliva
	↑ gastric pH
	↓ gastric acid secretion
	↑ gastric emptying time
	↓ gastric surface area
	↓ gastrointestinal motility
	↓ active transport mechanisms
Distribution	↓ cardiac output
	↑ peripheral vascular resistance
	↓ renal blood flow
	↓ hepatic blood flow
	↓ body water
	↑ body fat tissue
	↓ serum albumin levels
	↑ for lipid soluble and decrease for water soluble drugs
Metabolic	↓ microsomal hepatic oxidation
	↓ clearance
	↑ steady state levels
	↑ half lives
	↑ levels of active metabolites
	↓ first pass metabolism due to reduced ↓ blood flow
Excretion	↓ in renal perfusion
	↓ in renal size
	↓ in glomerular filtration rate
	↓ tubular secretion
	↓ in tubular reabsorption

↑: Increased; ↓: Reduced.

half-life, prolonged drug effect and accumulation with continued use thus increasing the potential for toxicity and adverse drug events (ADEs)[12].

Most drugs bind to protein (*e.g.,* albumin and α-1 glycoprotein) when circulating in plasma compartments, with only the unbound drug being pharmacologically active. In healthy older people, changes in serum albumin concentrations are minimal. In older people with chronic illnesses and malnutrition, serum albumin concentrations can be significantly reduced, leading to a reduction in bound drug concentrations and higher serum levels of free drug. This affects commonly prescribed drugs such as sodium valproate, warfarin and antipsychotics, thus increasing the potential for drug toxicity and adversity in patients with diminished circulating albumin. This is particularly relevant to frail, older hospitalised patients.

Hepatic mass and perfusion declines with age, thus reducing the liver's capacity for first pass metabolism[13]. Commonly prescribed drugs such as verapamil, amitriptyline and morphine may have higher bioavailability at standard doses in older people, thus leading to greater potential for adverse effects if not dose-adjusted. An example of this includes the risk of first dose hypotension with antihypertensive medications that have a high extraction ratio. This ratio would be reduced in older patients thus leading to greater bioavailability after hepatic extraction and thus greater potential for significant first-dose hypotension, so caution is needed when initiating antihypertensive treatment in an older patient with respect to dose and time of administration.

Table 2 Common cytochrome P450 isoenzyme inhibitors and inducers

Enzyme inhibitors	Enzyme inducers
Amiodarone	Carbamazepine
Allopurinol	Ethanol
Cimetidine	Isoniazid
Citalopram, sertraline	Phenytoin
Ciprofloxacin	Phenobarbital
Diltiazem, verapamil	Rifampcin
Fluxetine, paroxetine	St. Johns Wort
Erythromycin, clarithromycin	
Fluconazole, ketoconazole	
Omeprazole	
Sulphonamides	
Grapefruit Juice	

Another important consideration is the possibility of drugs interacting through inhibition and induction of cytochrome p450 isoenzymes. Commonly encountered enzyme inducers and inhibitors are detailed in Table 2. Enzyme induction may take several weeks to occur and may result in treatment failure in those taking multiple medications, *e.g.,* a patient may fail to respond to "drug A" because "drug B" has induced a cytochrome p450 isoenzyme which metabolizes "drug A".

With ageing, well-documented changes occur in renal size, perfusion and function (see Table 1)[14]. This is of particular relevance to older patients who are prescribed renally excreted drugs where reduced elimination can lead to increased and potentially toxic drug accumulation (Table 3). Glomerular filtration rate (GFR) should be estimated using readily available formulas such as the Cockcroft and Gault[15] and Modification of Diet in Renal Disease[16]. Prescribers should be aware that serum creatinine concentration alone is an unreliable marker of renal function in the elderly owing to reductions in muscle volume. Indeed, approximately 50% of those with normal creatinine levels have a reduced estimate GFR (eGFR)[17].

Pharmacodynamics and ageing

Older people often have significantly different pharmacodynamic responses than their younger counterparts to similar drug concentrations. Differences can be caused by a shift in receptor affinity, density, post-receptor events at the cellular level, or in adaptive homeostatic response mechanisms. Pathologic organ changes may also affect pharmacodynamic responses, particularly in frail older patients[17]. Prescribers should be aware of commonly encountered age-related pharmacodynamic differences as listed in Table 4. Some clinically relevant examples are present in Table 5. Generally, it is recommended to initiate medications at the smallest possible dose and titrate slowly according to response.

Polypharmacy

Polypharmacy is often defined by the number of prescribed medications, with ⩾ 6 drugs being a common

Table 3 Common used drug classes which require dose adjustment with chronic kidney disease

Drug class	Adjust dose in CKD stage 1-3	Avoid in CKD stages 4 and 5
ACE-inhibitors and Angiotensin 2 receptor blockers	All ACE inhibitors	Olmesartan
Diuretics	Potassium-sparing and thiazide diuretics	Potassium-sparing and thiazide diuretics
Beta-blockers	Acebutolol, atenolol, bisoprolol, nadolol, sotalol	Sotalol
Lipid lowering agents	Pravastatin, rosuvastatin, fibrates	Glyburide, metformin, exanitide
Hypoglycaemic agents	Gliclazide, acarbose, insulin, gliptins	
Analgesia (NSAIDs and opioids)	Codeine, tramadol, morphine, oxycodone,	All NSAIDs, pethidine
Psychotropic agents	Lithium, gabapentin, pregabalin, topiramate, vigabatrin, bupropion, duloxetine, paroxetine, venlafaxine	
Miscellaneous	Allopurinol, colchicine, digoxin	Dabigatran Rivaroxaban (CI stage 5, dose adjust in stage 4 CKD) Apixaban (CI stage 5, dose adjust in stage 4)

CKD: Chronic kidney disease; ACE-inhibitors: Angiotensin-converting-enzyme inhibitor; NSAIDs: Non-Steroidal anti-inflammatory drugs; CI: Contraindicated.

Table 4 Age-associated changes in pharmacodynamic response to commonly prescribed drugs

Drug type	Specific drug	Pharmacodynamic response in older people	Potential clinical consequence
Analgesia	Morphine	↑	Excessive sedation, confusion, constipation, respiratory depression
Anticoagulant	Warfarin	↑	Increased bleeding risk
	Dabigatran in those ⩾ 75 yr with a body weight of < 50 kg)		
Cardiovascular system drugs	Angiotensin II receptor blockers	↑	Hypotension
	Diltiazem	↑	
	Enalapril	↑	
	Verapamil	↑	
	Propranolol	↓	
Diuretics	Frusemide	↓	Reduced diuretic effect at standard doses
	Bumetanide	↑	
Psychoactive drugs	Diazepam	↑	Excessive sedation, confusion, postural sway, falls
	Midazolam	↑	
	Temazepam	↑	
	Haloperidol	↑	
	Traizolam	↑	
Others	Levodopamine	↑	Dyskinesia, confusion, hallucinations

↑: Increased pharmacodynamic response; ↓: Reduced pharmacodynamic response.

Table 5 Commonly used drugs - comparison of prescription between older and younger patients

Drug	Typical dose in younger patient (< 65 yr)	Typical dose in older patient (⩾ 65 yr)	Reason for different dose in the elderly
Anti-arrhythmics			
Digoxin	Loading dose is 1-1.5 mg in divided doses over 24 h Maintenance dose 125-250 mcg OD	Loading dose is 1 mg in divided doses over 24 h Maintenance dose 62.5-125 mcg OD	Water soluble contributing to increased plasma levels in the elderly
Anti-coagulants			
Warfarin	Standard initiation dose, *e.g.*, 10 mg daily for two days	Lower initiation dose, *e.g.*, 5 mg daily for two days	Increased sensitivity to anticoagulant effect
Dabigatran	150 mg BD	Patient > 80 yr 110 mg BD Patient 75-80 yr 150 mg BD in setting or normal eGFR	Increased sensitivity to anticoagulant effect
Anti-hypertensive			
Ramipril	Initiation dose 2.5 mg	Initiation dose 1.25 mg	Lower initial dose and gradual dose titration required (higher risk of ADE in the elderly)
Psychoactive drugs			
Diazepam	2 mg TDS	1 mg BD	Lipid soluble with higher volume of distribution in older people thus contributing to a prolonged duration of effect

OD: Once daily; BD: Twice daily; TDS: Three time daily.

Table 6 Important drug interactions in older patients

Drug	Drug	Interaction	Effect
Anti- hypertensive agents	NSAID	NSAID antagonizes hypotensive effect	↓ antihypertensive effect
Aspirin	NSAID, oral corticosteroids	↑ risk of peptic ulceration	Peptic ulceration
Calcium channel blockers	Enzyme inducers	↑ clearance of calcium channel blocker	↓ anti-hypertensive effect
Digoxin	Diuretics	Diuretic-induced hypokalaemia	↑ effect of digoxin (arrhythmia, toxicity)
Digoxin	Amiodarone, Ditiazem, Verapamil	↓ clearance of digoxin	↑ effect of digoxin (arrhythmia, toxicity)
TCA	Enzyme inhibitors	↓ clearance of TCA	Arrhythmia, confusion, orthostatic hypotension, falls
Phenytoin	Enzyme inhibitors	↓ clearance of phenytoin	↑ effect of phenytoin, toxicity
Thyroxine	Enzyme inducers	↑ clearance of thyroxine	↓ effect of thyroxine

NSAID: Non-steroidal anti-inflammatory drug; TCA: Tricyclic anti-depressants.

cut-off point[18]. Another definition of polypharmacy is the prescription of at least one drug without valid clinical indication[19]. Increasing numbers of medications is associated with a higher risk of ADEs with resultant increased frequency of hospitalisation, negative health outcomes and increased healthcare resource utilisation[20-25]. The risk of an adverse drug reaction (ADR) when taking two concurrent medications is 13%[26]. This risk rises to 38% in patients taking 4 medications and to 82% in those taking ⩾ 7 medications[26]. Polypharmacy can often be indicative of prescribing cascades, *i.e.,* where a new drug is used to treat a negative effect of an existing drug. Clearly, prescription of medications in such circumstances is inappropriate.

Prescription of multiple drugs impacts negatively on adherence and compliance. Clinicians are sometimes unaware of their patients complete prescription record perhaps because of multiple prescribers or under-reporting by patients at time of consultation. Frank *et al*[27] reported that almost 4 out of 10 patients were taking drugs unbeknownst to their doctors, and approximately 1 out of 20 patients were not taking medications listed on their prescription record. Prescribers should make every effort to obtain an accurate medication list. Pharmacy reconciliation protocols are useful for this purpose in hospital environments. Tools such as the Structured History of Medications can also be very useful in this regard, though they are time consuming to complete[28].

Drug interactions

One drug can interact with another drug through pharmacokinetic or pharmacodynamic mechanisms. Gurwitz *et al*[29] reported that drug interactions accounted for 13% of preventable prescribing errors. The risk increases with rising numbers of prescribed drugs and with multiple attending prescribers[30]. A study of over sixteen hundred older outpatients across six European countries found that 46% had at an important drug interaction with 1 in 10 having the potential for severe consequence[31]. Table 6 details some commonly encountered and potentially significant drug-drug interactions in older people.

Drugs can often worsen co-existing medical conditions. The risk of drug-disease interactions is higher in older adults who are on multiple medications to treat multiple conditions. Lindblad *et al*[32,33] reported that 15%-40% of hospitalized older adults were prescribed a drug that could potentially exacerbate a co-existing condition, *e.g.,* use of non-dihydropyridine calcium antagonists with heart failure. In the community-dwelling elderly, the prevalence of drug-disease interactions ranges from 6% to 30%[34-37]. Commonly encountered drug-disease interactions, which have the potential for clinically significant negative outcomes in older patients, are presented in Figure 1. Prescription of these medications in these clinical circumstances is potentially inappropriate, particularly if safer alternatives are available.

Appropriate prescribing

So far, we have described circumstances where prescribing decisions in older patients can be considered to be potentially inappropriate, *i.e.,* where the risk of a negative outcome exceeds the potential therapeutic gain. The term "appropriate prescribing" extends well beyond the aforementioned pharmacological principles to encompass a range of actions and attitudes that characterise the quality of prescribing that should be achieved in everyday practice[38] (summarised in Figure 2). This term encompasses several important domains including patient choice, therapeutic expectation, scientific and technical rationalisation and the general good for society[38]. A discussion of pharmacoeconomic rationalisation is beyond the scope of this paper, but it is becoming increasingly important that prescribers are economically just in their decisions so that the greatest number can receive the greatest benefit and that older individuals can be offered the least expensive available therapeutic options.

Inappropriate prescribing (IP) is a commonly used term. It pertains to use of medications that may cause more harm than good and perhaps, more importantly, the under-prescription of clinically indicated medications[38]. IP has been identified in 12%-40% of residents in long-term care facilities and in 14%-23% of community-dwelling older people[39,40]. The association between IP and negative outcomes such as ADRs has been shown in numerous studies in Europe[41,42], the

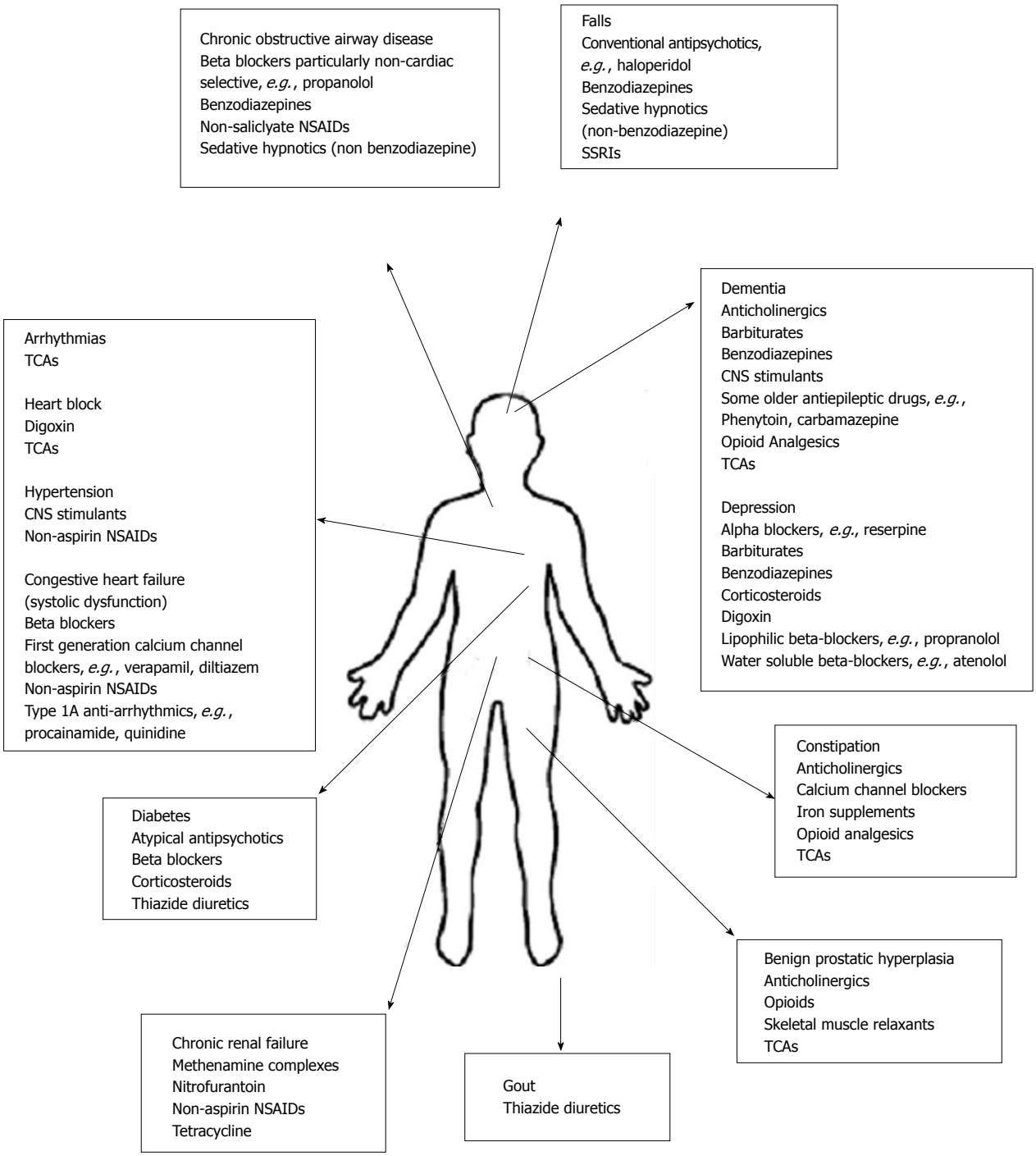

Figure 1 Common encountered clinically significant drug-disease interactions in older patients. The following conditions may be exacerbated by prescription of the *drug classes* listed below.TCA: Tricyclic anti-depressants; NSAID: Non-steroidal anti-inflammatory drug; SSRIs: Selective serotonin reuptake inhibitors.

United States[43-45] and Asia[46].

Clinical judgments of prescribing appropriateness with respect to therapeutic benefit are often difficult to make because of insufficient scientific evidence for the older population. Those with multiple co-morbidities and multiple medications are often poorly represented in clinical trials and physicians often have to extrapolate scientific evidence from the use of medications in younger, unrepresentative patient populations, with fewer illness and fewer concurrent medications. Only 2.1% of patients recruited to trials investigating the efficacy of non-steroidal anti-inflammatory drugs (NSAIDs) were aged 65 years and over, with less than 0.1% over 75 years[47]. Nonetheless, NSAIDs are commonly used to treat musculoskeletal disorders in older patients. It is well established that the risk of adverse events of NSAIDs such as peptic ulcer disease is much higher in older people. Indeed, inappropriate use of NSAIDs is a commonly encountered ADR in elderly inpatients[48], usually through incorrect dose, prolonged duration or failure to recognize impairment of renal function.

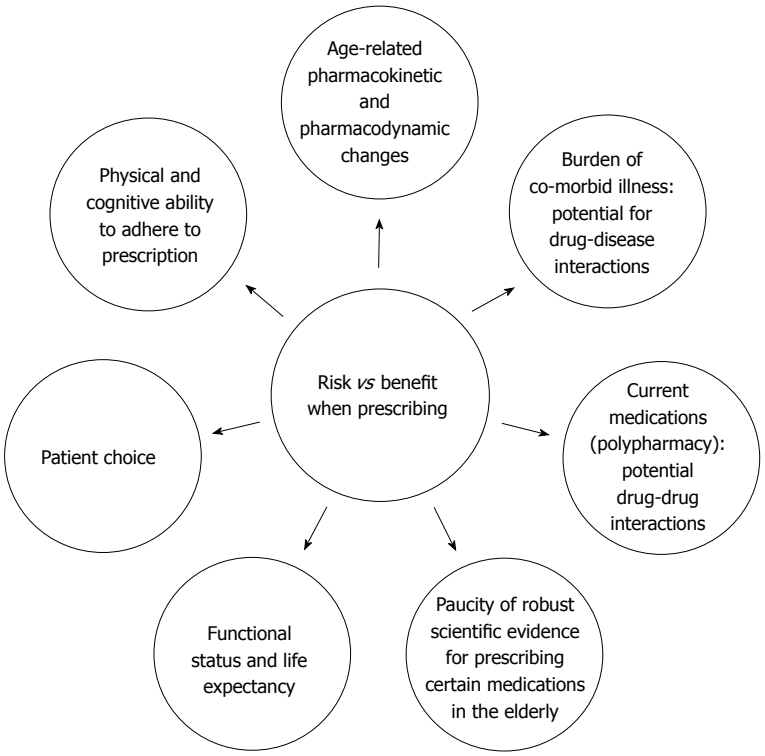

Figure 2 Important considerations when evaluating the quality of prescribing decisions in older people.

Under-prescribing of essential, often preventative medication is perhaps an even bigger concern than misuse of medications in older patients, particularly when the potential outcome of not treating the condition can be catastrophic[49]. The risk of cardio-embolic stroke in those with atrial fibrillation increases with age (1.2% to 2.5% annual risk in persons aged 60-69 years *vs* 7.3%-13.7% annual risk in persons aged 80 years and over)[50-52] but many do not receive evidence-based preventative anticoagulation[53]. The Irish Longitudinal Study on Ageing recently reported that 30% of patients had a potential prescribing omission (PPO), the most common PPO being appropriate anti-hypertensive therapy[54]. Prescribing omissions were twice as common as inappropriate prescriptions[55]. Even greater proportions of hospitalised older patients are reported to have potentially inappropriate prescribing omissions, with Barry *et al*[55] reporting 57% prevalence of prescribing omissions in one prospective study of over 600 hospitalised older patients in Ireland. The elderly have a higher burden of co-morbid illnesses, *e.g.,* a single patient may have hypertension, diabetes mellitus, chronic obstructive airways disease, dementia and recurrent falls. Every effort should be made to appropriately treat all illnesses bearing in mind the principles of appropriate prescribing as previously discussed.

Other considerations

Prescribing appropriateness must also take into account a patient's capacity to comply with the prescription as well as their physical ability to take the medication. In older adults post coronary artery bypass grafting it was found that in-hospital education was paramount in helping patients adhere to their medication regimens[56]. However, it must be acknowledged that almost 25% of patients aged ⩾ 80 years will have significant cognitive deficits and memory deficits can often contribute to improper medication use as patients can have difficulty understanding instructions[57]. Patients may fail to remember to take their medicines or may even take multiple doses concurrently thus placing them at an increased risk of adverse drug events[42]. Prescribers have a responsibility to ensure that medications can be taken safely and reliably. Sometimes this requires simple written instructions, the use of doset boxes or blister-packs, or direct supervision of administration by a carer or relative. Physical impairments such as hearing loss, visual loss and impaired manual dexterity can also impact on adherence to prescribed medications, thus resulting in poor therapeutic yield and consequent negative outcomes.

Clearly, prescribing for older patients is complex and sometimes time-consuming particularly when all of the aforementioned variables are considered. In addition, older patients are a heterogeneous group, with wide variation in physical, cognitive and functional status. The most important clinical question when deciding on prescribing appropriateness is whether or not there is a clear clinical indication for the treatment. This requires a clear diagnosis and a clear expectation of the therapeutic goal. Evaluation of the therapeutic goal must take into account the scientific rational of using a drug as well as the potential benefit to improving the

Table 7 Key considerations when prescribing for older patients

Use non-pharmacological treatment whenever possible
Include the patient (and carer where appropriate) in prescribing decisions
Ensure each medication has an appropriate indication and a clear therapeutic goal (this involves careful clinical assessment and appreciation of time to obtain treatment effect and life expectancy)
Start at the smallest dose and titrate slowly according to response and efficacy
Use the simplest dosing regimen (*e.g.*, once a day preferable to three times per day) and most appropriate formulation
Provide verbal and written instructions on indication, time and route of administration and potential adverse effects of each medication
Regularly review prescriptions in the context of co-exiting disease states, concurrent medications, functional and cognitive status and therapeutic expectation
Be aware that new presenting symptoms may be due to an existing medication, drug-drug interaction or drug-disease interaction (avoid prescribing cascade)
When stopping a medication check that it can be stopped abruptly or whether it needs to be tapered, *e.g.*, long-term steroids, benzodiazepines

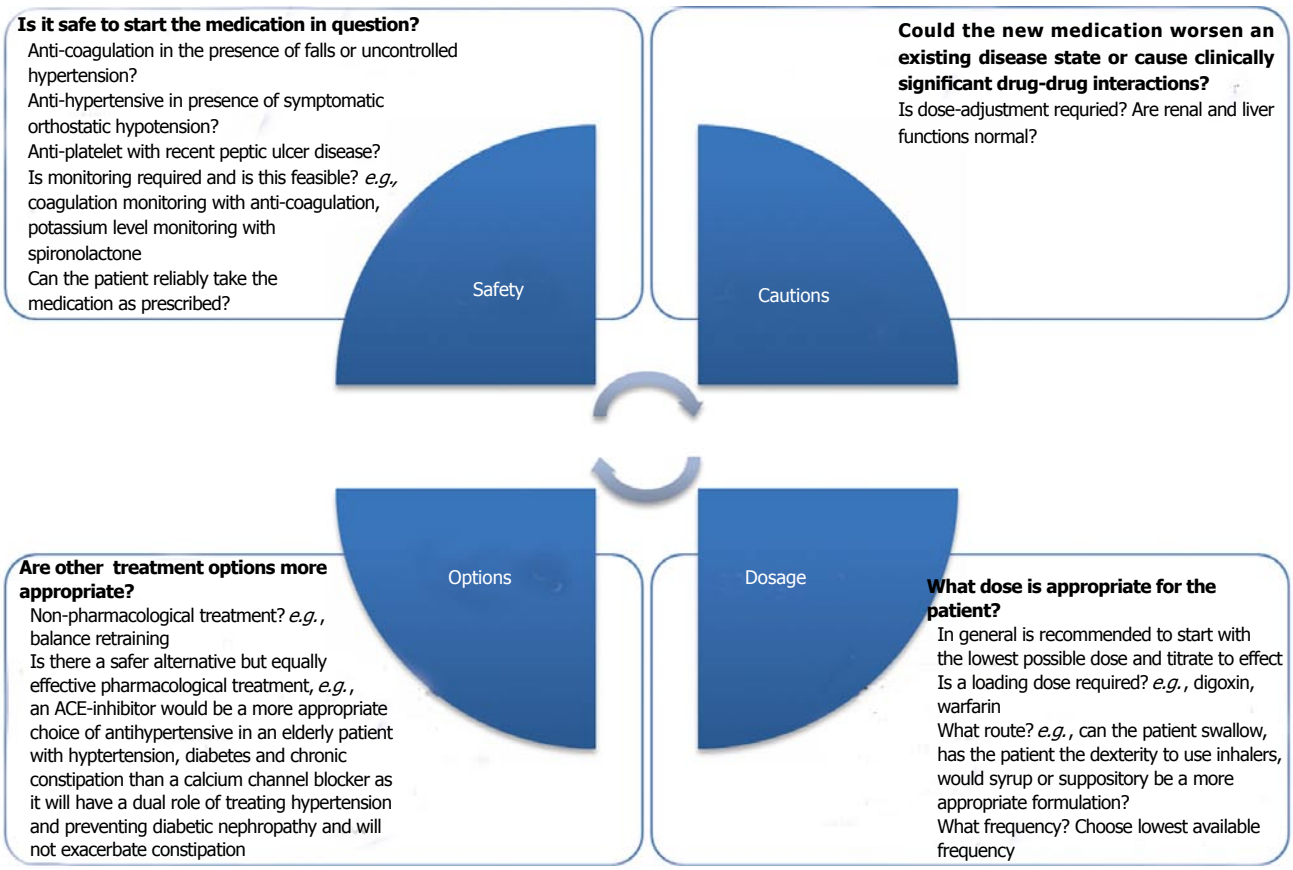

Figure 3 Influential factors when prescribing for the elderly with some examples.

condition. Prescribers must ensure that people take the appropriate medicine at the correct dose; thereby minimizing risks of adversity (see Table 7).

A case history, displayed in Table 8, illustrates the complexities of making appropriate prescribing decisions in older people and also some of the negative clinical consequences of IP decisions. Other examples of important considerations with respect to prescribing safety, cautions, dosage and therapeutic options are presented in Figure 3.

ADVERSE DRUG EVENTS AND ADRS

An adverse drug event (ADE) is defined as "any injury resulting from the use of a drug"[58]. This broad definition encompasses any harm caused directly by the medication and any event that occurs during its use (including dose reductions and harm from discontinuation of the drug). An ADR is defined as a "response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the modification of physiologic function"[58,59].

Unsurprisingly, ADEs are highly prevalent in the elderly. Those with multiple co-morbidities and who are prescribed multiple medications are at the highest risk. It is widely accepted that the crude prevalence rate of ADEs in community-dwelling older people is approximately 30%[60]. One study reported that ADEs accounted for 1 in 10 of all emergency

Table 8 Clinical example

An 80-year-old lady is referred with a four day history of general malaise, nausea, vomiting and recurrent falls. Her past medical history includes paroxysmal atrial fibrillation, non-obstructive coronary artery disease, hypertension, recurrent episodes of acute gout, dependent lower limb edema and "vertigo/dizziness". Prior to this episode she was functionally independent and had normal cognition

Her medications were as follows: Simvastatin 40 mg daily; Verapamil 240 mg daily; Quinine Sulphate 300 mg daily, Perindopril 5 mg/Indapamide 1.5 mg daily; Digoxin 250 mcg daily; Diclofenac 75 mg twice daily; Frusemide 40 mg daily; Betahistine 16 g three times per day; Paracetamol 1 g as required; Warfarin as per INR (target INR 2-3); Flurazepam 30 mg nocte. She was not taking OTC medications

On assessment she was pale and tired. Supine blood pressure was 122/70 mmHg; erect blood pressure after one minute was 92/62 mmHg

Pulse was 52 beats per minute. She had no clinical signs of congestive cardiac failure. She scored 9/10 on a short mental test score

Investigations showed a eGFR of 38 mL/min, serum potassium 2.8 mmol/L (low) and serum sodium 126 mmol/L (low). Haemoglobin was 10.2 g/dL with MCV 72fl (hypochromic microcytic anemia)

When evaluating the appropriateness of an older person's prescription medications it is important to consider the following two questions:

1 Is there a clinical indication for the drug?

2 Could the drug be contributing to the presenting symptoms?

Using this approach each medication should be evaluated in turn and corrective action implemented

Medication	Clinical indication?	Contributing to presenting symptoms?	Action taken?
Simvastatin 40 mg	Yes (hyperlipidaemia, high cardiovascular risk)	Could cause muscle cramps and myopathy which could lead to falls (note patient prescribed quinine)	Check fasting lipid profile and creatine phosphokinase. Revise dose according to target lipid levels
Verapamil 240 mg	Yes (hypertension, arrhythmia)	Could cause hypotension and bradycardia. Increased risk of myopathy when prescribed with simvastatin	Consider discontinuation. Beta-blocker may be more appropriate choice as rate controlling agent
Quinine 300 mg	No clear indication	No	Muscle cramps may be due to statin. Review choice of statin. Discontinue Quinine
Perindopril 5 mg	Yes (hypertension)	Could contribute to postural hypotension and acute renal injury	Consider temporary withdrawal while investigating cause of renal dysfunction
Indapamide 1.5 mg	Yes (hypertension)	Could contribute to postural hypotension, acute renal injury, hyponatraemia and hypokalaemia. Can precipitate digoxin toxicity, hyperuricaemia and recurrent episodes of gout	Discontinue
Digoxin 250 mcg	Yes (atrial fibrillation)	Symptoms of digoxin toxicity. Dose too high given level of renal dysfunction	Discontinue. Beta-blocker may be more appropriate choice of rate controlling agent
Diclofenac 75 mg	Yes (acute gout)	Yes. Diclofenac may be causing renal impairment. Gastritis/peptic ulcer disease should also be considered because of nausea, vomiting and microcytic anemia. NSAIDs should not be prescribed with warfarin because of significantly increased risk of bleeding	Discontinue. Consider addition of allopurinol for gout prophylaxis
Frusemide 40 mg	Yes (hypertension)	Yes (hypotension, hyponatraemia, hypokalaemia, renal impairment)	Frusemide is not required as an anti-hypertensive in this patient. It has been prescribed to treat dependent lower limb edema. Leg elevation and compression stockings would be more appropriate
Betahistine 16 mg	No (prescribed for dizziness which is actually related to orthostatic hypotension)	No	Discontinue. No indication
Paracetamol 1 g	Yes (pain)	No	Continue
Warfarin	Yes (atrial fibrillation embolic prophylaxis)	May be contributing to anemia. Should not be co-prescribed with diclofenac as there is an increased risk of bleeding	Investigate cause of anemia. Consider future suitability for anticoagulation if high falls risk persists
Flurazepam 30 mg	No	Yes (falls, malaise)	Contact GP and pharmacy for prescription history. Do not suddenly discontinue because of risk of benzodiazepine withdrawal

INR: International normalized ratio; OTC: Over-the-counter; eGFR: Estimated glomerular filtration rate; MCV: Mean corpuscular volume.

department attendances in those aged ⩾ 65 years[61]. Approximately one third of those with an ADE had a potential drug interaction. The most common offending medications were NSAIDs, antibiotics, anticoagulants, diuretics, hypoglycemic agents, β-blockers, calcium-channel blockers, and chemotherapeutic agents[61]. ADEs are common in hospitalized older patients, with prevalence rates of up to 25% being reported in some studies[44,62-64]. Most ADEs are predictable with 27% of ADEs in community-dwelling older patients[30] and 42% of ADEs in nursing home facilities thought to be avoidable[63].

One large study of over 18000 hospital admissions found that ADRs were responsible for 1 in 16 hospitalisations (6.5%), 4% of hospital bed capacity and 0.15% of deaths[65]. In the United States, it has been

reported that ADRs are amongst the leading causes of death[59]. The majority of ADRs (> 80%) in older people are predictable in that they are related to the known pharmacological effect of the drug and often escalate with increasing dose[66].

PRESCRIBING APPROPRIATENESS CRITERIA

With changing demographics and ever-increasing availability of therapeutic agents, the frequency of IP in older patients is not abating. Various strategies to identify, measure and reduce potentially inappropriate prescribing have been the focus of worldwide research endeavors over the last thirty years. A detailed analysis of all such endeavors is beyond the scope of this paper. Instead we will focus on the principal prescribing appropriateness criteria, their relationship to adverse healthcare outcomes and the evidence to support their role in optimising prescribing appropriateness.

Explicit criteria for appropriate prescribing comprise lists of medications that are known to cause harm in older adults; either through predictable pharmacological or predictable physiological mechanisms. In general, they have been developed from expert consensus techniques[67]. Explicit criteria can often be utilised in the absence of detailed clinical data[68]. However, this may also be a limitation, particularly in older patients, where clinical detail is an essential requirement for any treatment decision, particularly in relation to burden of co-morbidity[69], patient preference and consideration of previously unsuccessful treatment approaches. Furthermore, explicit criteria need regular updating so as to incorporate emerging evidence.

Beers criteria focus principally on over-prescribing and mis-prescribing. They comprise a list drugs that are inappropriate to prescribe for the elderly under any circumstances and a list of drugs that should be avoided with particular clinical illnesses and syndromes[70-73]. Screening Tool of Older Person's potentially inappropriate Prescriptions (STOPP)/Screening Tool to Alert to Right Treatment (START) Criteria are organised according to physiological system and include criteria that highlight when medications should be considered in older people, with certain conditions, where no contraindication exists, *e.g.,* anticoagulation in patients with atrial fibrillation and calcium and vitamin D supplementation in patients with osteoporosis[74,75]. Table 9 summarises the principal explicit prescribing criteria, their advantages and disadvantages.

Implicit criteria focus on several domains of prescribing appropriateness. The medication appropriateness index (MAI) is the most widely cited implicit tool which measures prescribing appropriateness according to 10 criteria including indication, effectiveness, dose, administration, drug-drug and drug-disease interactions and cost[76,77]. Clinical expertise and detailed clinical and pharmaceutical information is required to apply some of the criteria, thus making this tool time consuming to use in everyday clinical practice. The MAI does not address prescribing omissions. Three of the MAI criteria (indication, effectiveness and duplication) can be combined as a measure of unnecessary polypharmacy, one study of 384 frail older patients at the point of hospital discharge showing that 44% were prescribed at least one unnecessary drug, the most common drug classes being gastrointestinal, central nervous system and therapeutic nutrients or minerals[78]. Another study of 397 frail elderly inpatients showed that 365 patients (92%) met at least one MAI criterion, the most common problems being use of the most expensive drugs (70%), impractical directions (55%), and incorrect dosages (51%)[79]. One advantage of the MAI is that it encompasses elements for drug prescribing that are applicable to any medication and to any clinical condition in any clinical setting. The Assessment of Underutilisation (AOU) of Medications tool is based on an instrument reported by Lipton *et al*[80] and simply requires the user to match the patient's active illnesses to his/her prescription drugs thus establishing if a condition is under-treated by omission of an indicated medication. One study showed that 64% of older patients had evidence of under prescribing according to the AOU instrument[81]. The labeling of a prescription as "potentially inappropriate" implies that the prescription in question should be predictive of an adverse outcome. Ideally, the drugs highlighted by explicit IP criteria should be associated with preventable ADEs. Prospective use of IP screening criteria should, theoretically curtail the occurrence of ADEs.

The reported prevalence rates of potentially inappropriate prescribing according to various explicit criteria range from 24% to 44% depending on the populations and proportions of criteria applied[82]. The reported associations between IP and adverse outcomes also vary. Pasina *et al*[83] showed the prevalence of at least one PIM was 20.1% and 20.3% according to the 2003 and 2012 iterations of Beers' criteria respectively. However an association between IP and health outcomes was not demonstrated. Conversely, medications listed in STOPP[48] criteria have been associated with a higher proportion of patients requiring admission to hospital because of IP-related adverse events than those listed in Beers' criteria (11.5% *vs* 6%, respectively). A recently published randomised controlled trial of 400 older hospitalized patients showed that unnecessary polypharmacy, incorrect dosing, and potential drug-drug and drug-disease interactions were significantly lower at time of discharge and for up to 6 mo post discharge when patients were screened with STOPP/START criteria within 72 h of hospitalization (absolute risk reduction 37.5%, number needed to screen to yield improvement in MAI = 2.8)[75]. Reduction of underutilisation of clinically indicated medications was also observed (absolute risk reduction 21.2% with a number need to yield reduction of 4.7). However, a recent systematic review of the application

Table 9 Explicit criteria for potentially inappropriate prescribing in older patients

Explicit criteria	Advantages	Disadvantages
Beers criteria[70]	Assesses prescribing quality Useful for education	Several drugs unavailable outside United States Does not include underuse of drugs, drug-drug interactions or duplicate drugs No under-prescribing indicators
Beers criteria[71]	Concise explanation of inappropriateness Severity ratings of adverse outcomes Assesses prescribing quality Useful for education	Several drugs unavailable outside United States Does not include underuse of drugs, drug-drug interactions or duplicate drugs No under-prescribing indicators
Beers criteria[72]	Concise explanation of inappropriateness Severity ratings of adverse outcomes Can be used by computerized clinical information systems	Several drugs unavailable outside the United States Controversy over some drugs labeled as inappropriate No drug to drug interaction No drug disease interactions No under prescribing
Beers criteria[73]	Concise explanation of inappropriateness Structured according to therapeutic classes and organ systems Drug disease interactions	Several drugs unavailable outside United States No drug-drug interaction No under prescribing
STOPP/START[74]	Organised by physiological system Concise list on inappropriate medications Includes drug and disease interactions, therapeutic duplications and prescribing omissions	Does not suggest safer alternatives Does not address certain domains of prescribing, *e.g.*, indication
McLeod criteria[113]	Concise list of inappropriate medications with safer alternatives suggested Useful for education	Obsolete indicators, *e.g.*, beta blockers in heart failure No under-prescribing indicators Several drugs unavailable outside United States
IPET 2000 (Improved prescribing in the elderly tool)[114]	Concise Useful for education	Not comprehensive Predominantly cardiovascular and psychotropic drugs No under-prescribing indicators
Zhans criteria[115]	Less restrictive than previous criteria	Several drugs unavailable outside United States No drug to drug interaction No drug disease interactions No under-prescribing indicators
French Consensus Panel List[116]	Concise explanation of inappropriateness Includes drug duplications Safer alternatives suggested	No clinical studies to date No under prescribing
Rancourt[117]	26 Drug drug interactions 10 drug duplications	Large number of criteria to get through in clinical practice Data only on long term care setting
Australian Prescribing Indicators Tool[118]	Includes drug duplication Includes under-prescribing	Not validated and time consuming Derived from Australian data sources limiting international applicability
Norwegian General Practice (NORGEP) Criteria[119]	Can be applied to medication list with no clinical information	No drug prescribing No drug-disease interactions No studies to date outside Norway
Priscus List[120]	Provides therapeutic alternatives Recommendations on dose adjusting and monitoring	No studies to date published outside Germany
Thailand Criteria[121]	Drug interactions Drug disease interactions	No studies to date outside country of origin

of STOPP/START criteria concluded that there was limited evidence found in relation to the clinical and economic impact of the STOPP/START criteria. This is the subject of ongoing research endeavors as described below.

All prescribing appropriateness criteria are designed to assist decision-making and not to substitute good clinical decision-making. However, for prescribing appropriateness criteria to continue to facilitate decision-making they will need to remain clinically valid *via* regular updates in tandem with evolving clinical evidence and new medications. No criteria exist specifically for guidance of prescribing in frail older long term care residents with reduced life expectancy and indeed this cohort is likely to increase with changing demographics and prolonged survival[66].

OTHER APPROACHES TO OPTIMIZING PRESCRIBING APPROPRIATENESS IN OLDER PATIENTS

Comprehensive geriatric assessment

Geriatric medicine multidisciplinary teams comprise doctors, nurses, pharmacists and other allied health professionals who offer detailed assessment of older patients' physical, cognitive and functional abilities as well as optimization of medications. Several trials have shown improvements in all domains of prescribing appropriateness following comprehensive geriatric assessment (CGA). Schmader *et al*[84] demonstrated a significant reduction in the prevalence of potentially inappropriate prescribing, including under-prescribing,

in older inpatients that were randomised to receive CGA when compared to routine inpatient care. In the same study, outpatients who received CGA were shown to have a 35% reduction in the risk of a serious ADEs and prescribing omissions when compared with standard care[84].

Saltvedt *et al*[85] reported a lower prevalence of anticholinergic drug use and potential drug interactions at hospital discharge in acutely ill elderly patients who were randomized to receive inpatient CGA compared with standard hospital care. In addition, antipsychotic drugs were more likely to be withdrawn in the intervention cohort. An Australian study of 154 long term care residents with challenging behavior showed that an intervention comprising two case conferences between a care of the elderly physician, general practitioner, pharmacist and nursing home staff resulted in significant improvements in the prevalence of IP, particularly with respect to the use of benzodiazepines[86]. A Finnish study of 400 patients with cardiovascular disease showed a significant improvement in the use of evidence-based cardiovascular medications following geriatrician review with subsequent improvement in risk factor profile, but no improvement in three year cardiovascular morbidity or mortality[87].

CGA affords a complete overview of an older patient's health status and functional abilities and enables the prescriber to make informed prescribing decisions in the context of such variables. However, comprehensive geriatric assessment is time-consuming and resource intensive and is, in reality, only applicable to patients attending hospital, either as an inpatient or as an outpatient. It is not feasible in most health services for all older patients to undergo comprehensive geriatric assessment, thereby limiting the value of this approach at the population level.

Clinical pharmacy intervention

Clinical pharmacists perform systematic assessments of a patients' medication regimen and generate pharmaceutical care plans with the aim of optimizing the clinical impact of treatment, minimizing adverse effects of treatment and reducing waste[88]. An intervention comprising detailed review of medications by a clinical pharmacist with subsequent recommendations for the attending physician including patient counseling showed significant improvement in MAI scores over a twelve month period when compared to usual outpatient care[89]. However, there were no improvements in other outcomes including ADEs and healthcare use. Similarly, Crotty *et al*[90] reported improvements in MAI scores and a lower hospital re-admission rate in older patients whose medications were reviewed and discussed in detail by doctors and pharmacists. However, significant reductions in ADEs and other adverse outcomes were not identified. In Belgium, one hospital-based study has shown that a combined pharmacy and geriatrician intervention improves prescribing appropriateness[91].

Similar to CGA, specialist pharmacy input is resource intensive and is, in reality, confined to patients attending the hospital. Not all pharmacists have specialist training in geriatric pharmacotherapy and the success of this intervention depends upon the availability of the medical record to the pharmacist as well as the acceptance of the pharmaceutical care plan by both the patient and the prescribing physician. Therefore, clinical pharmacists need to work in close liaison with prescribers. The impact of the community pharmacist with no specialist training in geriatric pharmacotherapy on prescribing appropriateness has not been studied.

Prescriber education, audit and feedback

Several studies have shown that most physicians receive inadequate training in geriatric pharmacotherapy at an undergraduate and postgraduate level[92-94]. Therefore, educational strategies targeted specifically at those who prescribe for older patients would appear to be highly relevant. Numerous studies have investigated the impact of different educational approaches on the quality of prescribing in older patients, with mixed results. In general, interactive approaches with direct feedback that target multiple disciplines[53,95,96] are more effective than passive approaches involving didactic lectures and written dissemination of educational and feedback material[97,98]. However, most of these studies pertain to specific drugs or drug classes, *e.g.*, antibiotics[99], psychotropic drugs[100,101] analgesics[101] or avoidance of potentially inappropriate anticholinergic drugs[95]. The effect of educational interventions on broader measures of prescribing appropriateness and on health-related outcomes remains to be seen.

A recent systematic review investigated whether education interventions improved prescribing by undergraduate students and postgraduate junior physicians. No definitive answer was found. The trials included were small and flawed in their methodology. The better quality studies used the World Health Organization guide that directs students through a six-step problem-solving process when prescribing. Improvement in prescribing skills has been demonstrated in simulated environments. However, further research is required into the long-term benefits of such educational interventions[102].

Electronic prescribing and computerized alerts

Electronic prescribing systems provide user-guidance in relation to medication selection, dosage, price, potential interactions and need for monitoring[103,104]. They have the added potential of reducing prescribing errors of transcription when transferring between places of care, *e.g.,* from hospital to community, or from community to nursing home thereby improving communication[105]. Though challenging and costly to install, these tools can be applied at the point of medication initiation with great potential to minimize ADEs[106].

Existing electronic prescribing systems have been developed for the general adult population and are not specifically refined for elderly patients with complex co-morbidities and altered pharmacokinetics

and pharmacodynamics. Therefore, existing tools may not be suitable for use in older patients. Furthermore, physicians often over-ride the therapeutic flags generated by computerised systems[107] perhaps because many of them are perceived as being falsely positive or clinically unimportant, *e.g.*, a sodium level only marginally below the laboratory reference range may be acceptable in clinical practice. If physicians are overloaded with computerised alerts, they are unlikely to respond to true high-risk safety situations. A disadvantage of computerised prescribing systems is that they are dependent on the quality of the computer programming. There have been reports that computerized decision support systems have themselves resulted in medication errors and related adverse drug events[107-109]. Therefore, computerized decision support systems should be used to enhance a prescribing decision or to flag a potentially inappropriate prescription but can never substitute a comprehensive clinical assessment.

Several exiting research projects are currently underway in Europe[110,111] and the United States[112], the aim being to develop software engines to optimize prescribing appropriateness and to investigate the clinical and economic impacts of their utilisation. A new Software ENgine for the Assessment and optimization of drug and non-drug Therapy in Older persons (SENATOR) trial is presently recruiting throughout seven European centres (http://www.senator-project.eu/). It will assess and optimise drug and non-drug therapy in older persons with multimorbidity and provide recommendations to the attending clinician. The software engine aims to simultaneously reduce inappropriate prescribing, ADRs, and costs alongside optimising medications.

CONCLUSION

Prescribing for older patients presents many unique challenges. Prescribers must be aware of the key pharmacological differences in older people and the principal domains of prescribing appropriateness as described in this paper. Criteria are available to assist prescribers in appropriate decision making, but cannot replace good clinical judgment and cannot be applied in a "one size fits all" manner. Data are limited as to the health-outcome and economic effects of prescribing appropriateness criteria, but important research is ongoing into these areas. Continuous prescriber education at undergraduate and postgraduate level and regular audit of prescribing practice is very important. CGA and clinical pharmacist input are clearly of benefit in optimizing prescribing appropriateness, particularly in hospitalised older patients. However, these interventions are resource intensive. Exciting research into computerized prescribing supports for older people is ongoing. Finally, more older patients with complex co-morbidities should participate in clinical trials to ensure that evidence-based practice and guideline development is based on the testing and use of drugs in representative populations.

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