**Name of journal: *World Journal of Pharmacology***

**ESPS Manuscript NO: 12847**

**Columns: REVIEW**

**Appropriate prescribing in the elderly - Current perspectives**

Lavan AH *et al*. Appropriate prescribing in the elderly

Amanda Hanora Lavan, John O’Grady, Paul Francis Gallagher

**Amanda Hanora Lavan, John O’Grady, Paul Francis Gallagher,** Department of Geriatric Medicine, Cork University Hospital,Cork,Ireland

**Author contributions:** All the authors contributed to this work.

**Conflict-of-interest:** None.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Correspondence to: Dr. Paul Gallagher, PhD, FRCPI, Consultant Physician,** Department of Geriatric Medicine, Cork University Hospital,Corcaigh, Wilton, Co., Cork,Ireland. pfgallagher77@eircom.net

**Telephone:** +353-21-4921302

**Fax:** +353-21-4922829

**Received:** July 27, 2014

**Peer-review started:** July 28, 2014

**First decision:** September 16, 2014

**Revised:** March 20, 2015

**Accepted:** May 8, 2015

**Article in press:**

**Published online:**

**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

**© The Author(s) 2015.** Published by Baishideng Publishing Group Inc. All rights reserved.

**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.

Lavan AH, O’Grady J, Gallagher PF. Appropriate prescribing in the elderly – Current perspectives. *World J Pharmacol* 2015; In press

**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 (UN) 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 ≥ 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 versus 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 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.

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 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 adverse drug reactions (ADRs) has been shown in numerous studies in Europe[41,42], the 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.

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 a*l[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 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 adverse drug *reaction* (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 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 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 appropriatenes**s**[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 & 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.

**REFERENCES**

1 **United Nations.** World Population Ageing 2013. Available from: URL: http://www.un.org/en/development/desa/population/publications/pdf/ageing/WorldPopulationAgeing2013.pdf

2 **Chrischilles EA**, Foley DJ, Wallace RB, Lemke JH, Semla TP, Hanlon JT, Glynn RJ, Ostfeld AM, Guralnik JM. Use of medications by persons 65 and over: data from the established populations for epidemiologic studies of the elderly. *J Gerontol* 1992; **47**: M137-M144 [PMID: 1512428 DOI: 10.1093/geronj/47.5.M137]

3 **National Centre for Health Statistics.** Health, United States, 2013: With Special Features on Prescription Drugs. Hyattsville (MD): National Center for Health Statistics (US), 2014 [24967476]

4 **O'Connor K,** O'Mahony D. Drugs and Ageing. In: Liston R, Mulkerrin EC, editors. Medicine for older patients: cases and practice. Dublin, Ireland: Eireann Healthcare Publications, 2003: 205

5 **Wynne HA**, Blagburn J. Drug treatment in an ageing population: practical implications. *Maturitas* 2010; **66**: 246-250 [PMID: 20399044 DOI: 10.1016/j.maturitas.2010.03.004]

6 **Richardson K,** Moore P, Pekdar J, Galvin R, Bennett K, Kenny RA. The Irish Longitudinal Study on Ageing. Polypharmacy in adults over 50 in Ireland: Opportunities for cost saving and improved healthcare. [accessed 2012 Dec]. Available from: URL: http://tilda.tcd.ie/assets/pdf/PolypharmacyReport.pdf

7 **Qato DM**, Alexander GC, Conti RM, Johnson M, Schumm P, Lindau ST. Use of prescription and over-the-counter medications and dietary supplements among older adults in the United States. *JAMA* 2008; **300**: 2867-2878 [PMID: 19109115 DOI: 10.1001/jama.2008.892]

8 **Hanlon JT**, Fillenbaum GG, Ruby CM, Gray S, Bohannon A. Epidemiology of over-the-counter drug use in community dwelling elderly: United States perspective. *Drugs Aging* 2001; **18**: 123-131 [PMID: 11346126 DOI: 10.2165/00002512-200118020-00005]

9 **Cheung CK**, Wyman JF, Halcon LL. Use of complementary and alternative therapies in community-dwelling older adults. *J Altern Complement Med* 2007; **13**: 997-1006 [PMID: 18047447 DOI: 10.1089/acm.2007.0527]

10 **Wu CH**, Wang CC, Kennedy J. Changes in herb and dietary supplement use in the U.S. adult population: a comparison of the 2002 and 2007 National Health Interview Surveys. *Clin Ther* 2011; **33**: 1749-1758 [PMID: 22030445 DOI: 10.1016/j.clinthera.2011.09.024]

11 **Meyer BR.** Clinical pharmacology and ageing. In: Evans JG, Williams TF, Beattie BL, Michael JP, Wilcock G, editors. Oxford textbook of geriatric medicine. 2nd ed. Oxford: Oxford University Press, 2003: 127-136

12 **Resnick NM.** Geriatric medicine. In: Fouci AS, Braunwald E, Isselbacher KJ, editors. Harrison's principles of internal medicine, vol 1. 14th ed. New York: McGraw-Hill Companies Inc, 1998: 37-46

13 **Woodhouse KW**, Wynne HA. Age-related changes in liver size and hepatic blood flow. The influence on drug metabolism in the elderly. *Clin Pharmacokinet* 1988; **15**: 287-294 [PMID: 3203484 DOI: 10.2165/00003088-198815050-00002]

14 **Mangoni AA**, Jackson SH. Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. *Br J Clin Pharmacol* 2004; **57**: 6-14 [PMID: 14678335 DOI: 10.1046/j.1365-2125.2003.02007.x]

15 **Cockcroft DW**, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976; **16**: 31-41 [PMID: 1244564 DOI: 10.1159/000180580]

16 **Levey AS**, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 1999; **130**: 461-470 [PMID: 10075613 DOI: 10.7326/0003-4819-130-6-199903160-00002]

17 **Corsonello A**, Pedone C, Corica F, Mussi C, Carbonin P, Antonelli Incalzi R. Concealed renal insufficiency and adverse drug reactions in elderly hospitalized patients. *Arch Intern Med* 2005; **165**: 790-795 [PMID: 15824299 DOI: 10.1001/archinte.165.7.790]

18 **Bushardt RL**, Massey EB, Simpson TW, Ariail JC, Simpson KN. Polypharmacy: misleading, but manageable. *Clin Interv Aging* 2008; **3**: 383-389 [PMID: 18686760 DOI: 10.2147/CIA.S2468]

19 **Hanlon JT**, Schmader KE, Ruby CM, Weinberger M. Suboptimal prescribing in older inpatients and outpatients. *J Am Geriatr Soc* 2001; **49**: 200-209 [PMID: 11207875 DOI: 10.1046/j.1532-5415.2001.49042.x]

20 **Holbrook AM**, Pereira JA, Labiris R, McDonald H, Douketis JD, Crowther M, Wells PS. Systematic overview of warfarin and its drug and food interactions. *Arch Intern Med* 2005; **165**: 1095-1106 [PMID: 15911722 DOI: 10.1001/archinte.165.10.1095]

21 **Juurlink DN**, Mamdani MM, Kopp A, Rochon PA, Shulman KI, Redelmeier DA. Drug-induced lithium toxicity in the elderly: a population-based study. *J Am Geriatr Soc* 2004; **52**: 794-798 [PMID: 15086664 DOI: 10.1111/j.1532-5415.2004.52221.x]

22 **Shorr RI**, Ray WA, Daugherty JR, Griffin MR. Concurrent use of nonsteroidal anti-inflammatory drugs and oral anticoagulants places elderly persons at high risk for hemorrhagic peptic ulcer disease. *Arch Intern Med* 1993; **153**: 1665-1670 [PMID: 8333804 DOI: 10.1001/archinte.1993.00410140047006]

23 **Battistella M**, Mamdami MM, Juurlink DN, Rabeneck L, Laupacis A. Risk of upper gastrointestinal hemorrhage in warfarin users treated with nonselective NSAIDs or COX-2 inhibitors. *Arch Intern Med* 2005; **165**: 189-192 [PMID: 15668365 DOI: 10.1001/archinte.165.2.189]

24 **Juurlink DN**, Mamdani M, Kopp A, Laupacis A, Redelmeier DA. Drug-drug interactions among elderly patients hospitalized for drug toxicity. *JAMA* 2003; **289**: 1652-1658 [PMID: 12672733 DOI: 10.1001/jama.289.13.1652]

25 **Onder G**, Pedone C, Landi F, Cesari M, Della Vedova C, Bernabei R, Gambassi G. Adverse drug reactions as cause of hospital admissions: results from the Italian Group of Pharmacoepidemiology in the Elderly (GIFA). *J Am Geriatr Soc* 2002; **50**: 1962-1968 [PMID: 12473007 DOI: 10.1046/j.1532-5415.2002.50607.x]

26 **Goldberg RM**, Mabee J, Chan L, Wong S. Drug-drug and drug-disease interactions in the ED: analysis of a high-risk population. *Am J Emerg Med* 1996; **14**: 447-450 [PMID: 8765105 DOI: 10.1016/S0735-6757(96)90147-3]

27 **Frank C**, Godwin M, Verma S, Kelly A, Birenbaum A, Seguin R, Anderson J. What drugs are our frail elderly patients taking? Do drugs they take or fail to take put them at increased risk of interactions and inappropriate medication use? *Can Fam Physician* 2001; **47**: 1198-1204 [PMID: 11421047]

28 **Prins MC**, Drenth-van Maanen AC, Kok RM, Jansen PA. Use of a structured medication history to establish medication use at admission to an old age psychiatric clinic: a prospective observational study. *CNS Drugs* 2013; **27**: 963-969 [PMID: 23959814 DOI: 10.1007/s40263-013-0103-9]

29 **Gurwitz JH**, Field TS, Harrold LR, Rothschild J, Debellis K, Seger AC, Cadoret C, Fish LS, Garber L, Kelleher M, Bates DW. Incidence and preventability of adverse drug events among older persons in the ambulatory setting. *JAMA* 2003; **289**: 1107-1116 [PMID: 12622580 DOI: 10.1001/jama.289.9.1107]

30 **Tamblyn RM**, McLeod PJ, Abrahamowicz M, Laprise R. Do too many cooks spoil the broth? Multiple physician involvement in medical management of elderly patients and potentially inappropriate drug combinations. *CMAJ* 1996; **154**: 1177-1184 [PMID: 8612253]

31 **Beard K**. Adverse reactions as a cause of hospital admission in the aged. *Drugs Aging* 1992; **2**: 356-367 [PMID: 1504448 DOI: 10.2165/00002512-199202040-00008]

32 **Lindblad CI**, Hanlon JT, Gross CR, Sloane RJ, Pieper CF, Hajjar ER, Ruby CM, Schmader KE. Clinically important drug-disease interactions and their prevalence in older adults. *Clin Ther* 2006; **28**: 1133-1143 [PMID: 16982290 DOI: 10.1016/j.clinthera.2006.08.006]

33 **Lindblad CI**, Artz MB, Pieper CF, Sloane RJ, Hajjar ER, Ruby CM, Schmader KE, Hanlon JT. Potential drug-disease interactions in frail, hospitalized elderly veterans. *Ann Pharmacother* 2005; **39**: 412-417 [PMID: 15687479 DOI: 10.1345.aph.1E467]

34 **Chin MH**, Wang LC, Jin L, Mulliken R, Walter J, Hayley DC, Karrison TG, Nerney MP, Miller A, Friedmann PD. Appropriateness of medication selection for older persons in an urban academic emergency department. *Acad Emerg Med* 1999; **6**: 1232-1242 [PMID: 10609925]

35 **Giron MS**, Wang HX, Bernsten C, Thorslund M, Winblad B, Fastbom J. The appropriateness of drug use in an older nondemented and demented population. *J Am Geriatr Soc* 2001; **49**: 277-283 [PMID: 11300238 DOI: 10.1046/j.1532-5415-2001.4930277.x]

36 **Gosney M**, Tallis R. Prescription of contraindicated and interacting drugs in elderly patients admitted to hospital. *Lancet* 1984; **2**: 564-567 [PMID: 6147611 DOI: 10.1016/S0140-6736(84)90775-X]

37 **Hanlon JT**, Schmader KE, Boult C, Artz MB, Gross CR, Fillenbaum GG, Ruby CM, Garrard J. Use of inappropriate prescription drugs by older people. *J Am Geriatr Soc* 2002; **50**: 26-34 [PMID: 12028243 DOI: 10.1046/j.1532-5415.2002.50004.x]

38 **Spinewine A**, Schmader KE, Barber N, Hughes C, Lapane KL, Swine C, Hanlon JT. Appropriate prescribing in elderly people: how well can it be measured and optimised? *Lancet* 2007; **370**: 173-184 [PMID: 17630041 DOI: 10.1016/S0140-6736(07)61091-5]

39 **Willcox SM**, Himmelstein DU, Woolhandler S. Inappropriate drug prescribing for the community-dwelling elderly. *JAMA* 1994; **272**: 292-296 [PMID: 8028142 DOI: 10.1001/jama.272.4.292]

40 **Ennis KJ**, Reichard RA. Maximizing drug compliance in the elderly. Tips for staying on top of your patients' medication use. *Postgrad Med* 1997; **102**: 211-213, 218, 223-224 [PMID: 9300029 DOI: 10.3810/pgm.1997.09.323]

41 **Hamilton H**, Gallagher P, Ryan C, Byrne S, O'Mahony D. Potentially inappropriate medications defined by STOPP criteria and the risk of adverse drug events in older hospitalized patients. *Arch Intern Med* 2011; **171**: 1013-1019 [PMID: 21670370 DOI: 10.1001/archinternmed.2011.215]

42 **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 [PMID: 1514459 DOI: 10.1093/ageing/21.4.294]

43 **Lund BC**, Carnahan RM, Egge JA, Chrischilles EA, Kaboli PJ. Inappropriate prescribing predicts adverse drug events in older adults. *Ann Pharmacother* 2010; **44**: 957-963 [PMID: 20460558 DOI: 10.1345/aph.1M657]

44 **Page RL**, Ruscin JM. The risk of adverse drug events and hospital-related morbidity and mortality among older adults with potentially inappropriate medication use. *Am J Geriatr Pharmacother* 2006; **4**: 297-305 [PMID: 17296535 DOI: 10.1016/j.amjopharm.2006.12.008]

45 **Hanlon JT**, Schmader KE. What types of inappropriate prescribing predict adverse drug reactions in older adults? *Ann Pharmacother* 2010; **44**: 1110-1111 [PMID: 20460555 DOI: 10.1345/aph.1P182]

46 **Liu CL**, Peng LN, Chen YT, Lin MH, Liu LK, Chen LK. Potentially inappropriate prescribing (IP) for elderly medical inpatients in Taiwan: a hospital-based study. *Arch Gerontol Geriatr* 2010; **55**: 148-151 [PMID: 21820189 DOI: 10.1016/j.archger.2011.07.001]

47 **Rochon PA**, Berger PB, Gordon M. The evolution of clinical trials: inclusion and representation. *CMAJ* 1998; **159**: 1373-1374 [PMID: 9861206]

48 **Gallagher P**, O'Mahony D. STOPP (Screening Tool of Older Persons' potentially inappropriate Prescriptions): application to acutely ill elderly patients and comparison with Beers' criteria. *Age Ageing* 2008; **37**: 673-679 [PMID: 18829684 DOI: 10.1093/ageing/afn197]

49 **Rochon PA**, Gurwitz JH. Prescribing for seniors: neither too much nor too little. *JAMA* 1999; **282**: 113-115 [PMID: 10411177 DOI: 10.1001/jama.282.2.113]

50 **Wolf PA**, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke* 1991; **22**: 983-988 [PMID: 1866765 DOI: 10.1161/01.STR.22.8.983]

51 **Lake FR**, Cullen KJ, de Klerk NH, McCall MG, Rosman DL. Atrial fibrillation and mortality in an elderly population. *Aust N Z J Med* 1989; **19**: 321-326 [PMID: 2789508 DOI: 10.1111/j.1445-5994.1989.tb00271.x]

52 **Furberg CD**, Psaty BM, Manolio TA, Gardin JM, Smith VE, Rautaharju PM. Prevalence of atrial fibrillation in elderly subjects (the Cardiovascular Health Study). *Am J Cardiol* 1994; **74**: 236-241 [PMID: 8037127 DOI: 10.1016/0002-9149(94)90363-8]

53 **Elliott RA**, Woodward MC, Oborne CA. Antithrombotic prescribing in atrial fibrillation: application of a prescribing indicator and multidisciplinary feedback to improve prescribing. *Age Ageing* 2002; **31**: 391-396 [PMID: 12242203 DOI: 10.1093/ageing/31.5.391]

54 **Galvin R**, Moriarty F, Cousins G, Cahir C, Motterlini N, Bradley M, Hughes CM, Bennett K, Smith SM, Fahey T, Kenny RA. Prevalence of potentially inappropriate prescribing and prescribing omissions in older Irish adults: findings from The Irish LongituDinal Study on Ageing study (TILDA). *Eur J Clin Pharmacol* 2014; **70**: 599-606 [PMID: 24493365 DOI: 10.1007/s00228-014-1651-8]

55 **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**: 632-638 [PMID: 17881418 DOI: 10.1093/ageing/afm118]

56 **Sengstock D**, Vaitkevicius P, Salama A, Mentzer RM. Under-prescribing and non-adherence to medications after coronary bypass surgery in older adults: strategies to improve adherence. *Drugs Aging* 2012; **29**: 93-103 [PMID: 22239673 DOI: 10.2165/11598500-000000000-00000]

57 **Murray MD**, Morrow DG, Weiner M, Clark DO, Tu W, Deer MM, Brater DC, Weinberger M. A conceptual framework to study medication adherence in older adults. *Am J Geriatr Pharmacother* 2004; **2**: 36-43 [PMID: 15555477 DOI: 10.1016/S1543-5946(04)90005-0]

58 Medicines and Healthcare products Regulatory Agency. Available from: URL: https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency

59 Adverse Drug Events, Adverse Drug Reactions and Medication Errors. VA center for Medication Safety and VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel Nov 2006. Available from: URL: http://www.va.gov/ms/professionals/medications/adverse\_drug\_reaction\_faq.pdf

60 **Hanlon JT**, Schmader KE, Koronkowski MJ, Weinberger M, Landsman PB, Samsa GP, Lewis IK. Adverse drug events in high risk older outpatients. *J Am Geriatr Soc* 1997; **45**: 945-948 [PMID: 9256846]

61 **Hohl CM**, Dankoff J, Colacone A, Afilalo M. Polypharmacy, adverse drug-related events, and potential adverse drug interactions in elderly patients presenting to an emergency department. *Ann Emerg Med* 2001; **38**: 666-671 [PMID: 11719747 DOI: 10.1067/mem.2001.119456]

62 **O'Connor MN,** Gallagher P, Byrne S, O'Mahony D. Adverse drug reactions in older patients during hospitalizations: are they predictable? *Age Ageing* 2012; **41**: 771-776 [PMID: 22456465 DOI: 10.1093/ageing/afs046]

63 **Gurwitz JH**, Field TS, Avorn J, McCormick D, Jain S, Eckler M, Benser M, Edmondson AC, Bates DW. Incidence and preventability of adverse drug events in nursing homes. *Am J Med* 2000; **109**: 87-94 [PMID: 10967148 DOI: 10.1016/S0002-9343(00)00451-4]

64 **Tangiisuran B**, Wright J, Van der Cammen T, Rajkumar C. Adverse drug reactions in elderly: challenges in identification and improving preventative strategies. *Age Ageing* 2009; **38**: 358-359 [PMID: 19420141 DOI: 10.1093/ageing/afp050]

65 **Pirmohamed M**, James S, Meakin S, Green C, Scott AK, Walley TJ, Farrar K, Park BK, Breckenridge AM. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. *BMJ* 2004; **329**: 15-19 [PMID: 15231615 DOI: 10.1136/bmj.329.7456.15]

66 **Rawlins MD,** Thompson JP. Pathogenesis of adverse drug reactions. In: Davies DM, editor. Textbook of adverse drug reactions. Oxford: Oxford University Press, 1977: 44 [DOI: 10.1017/S0033291700016500]

67 **Campbell SM**, Cantrill JA. Consensus methods in prescribing research. *J Clin Pharm Ther* 2001; **26**: 5-14 [PMID: 11286603 DOI: 10.1046/j.1365-2710.2001.00331.x]

68 **Anderson GM**, Beers MH, Kerluke K. Auditing prescription practice using explicit criteria and computerized drug benefit claims data. *J Eval Clin Pract* 1997; **3**: 283-294 [PMID: 9456428 DOI: 10.1046/j.1365-2753.1997.t01-1-00005.x]

69 **Boyd CM**, Darer J, Boult C, Fried LP, Boult L, Wu AW. Clinical practice guidelines and quality of care for older patients with multiple comorbid diseases: implications for pay for performance. *JAMA* 2005; **294**: 716-724 [PMID: 16091574 DOI: 10.1001/jama.294.6.716]

70 **Beers MH**, Ouslander JG, Rollingher I, Reuben DB, Brooks J, Beck JC. Explicit criteria for determining inappropriate medication use in nursing home residents. UCLA Division of Geriatric Medicine. *Arch Intern Med* 1991; **151**: 1825-1832 [PMID: 1888249 DOI: 10.1001/archinte.1991.00400090107019]

71 **Beers MH**. Explicit criteria for determining potentially inappropriate medication use by the elderly. An update. *Arch Intern Med* 1997; **157**: 1531-1536 [PMID: 9236554 DOI: 10.1001/archinte.1997.00440350031003]

72 **Fick DM**, Cooper JW, Wade WE, Waller JL, Maclean JR, Beers MH. Updating the Beers criteria for potentially inappropriate medication use in older adults: results of a US consensus panel of experts. *Arch Intern Med* 2003; **163**: 2716-2724 [PMID: 14662625 DOI: 10.1001/archinte.163.22.2716]

73 **American Geriatrics Society 2012 Beers Criteria Update Expert Panel.** American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc* 2012; **60**: 616-631 [PMID: 22376048 DOI: 10.1111/j.1532-5415.2012.03923.x]

74 **Gallagher P**, Ryan C, Byrne S, Kennedy J, O'Mahony D. 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 [PMID: 18218287 DOI: 10.5414/CPP46072]

75 **Gallagher PF**, O'Connor MN, O'Mahony D. Prevention of potentially inappropriate prescribing for elderly patients: a randomized controlled trial using STOPP/START criteria. *Clin Pharmacol Ther* 2011; **89**: 845-854 [PMID: 21508941 DOI: 10.1038/clpt.2011.44]

76 **Hanlon JT**, Schmader KE, Samsa GP, Weinberger M, Uttech KM, Lewis IK, Cohen HJ, Feussner JR. A method for assessing drug therapy appropriateness. *J Clin Epidemiol* 1992; **45**: 1045-1051 [PMID: 1474400 DOI: 10.1016/0895-4356(92)90144-C]

77 **Samsa GP**, Hanlon JT, Schmader KE, Weinberger M, Clipp EC, Uttech KM, Lewis IK, Landsman PB, Cohen HJ. A summated score for the medication appropriateness index: development and assessment of clinimetric properties including content validity. *J Clin Epidemiol* 1994; **47**: 891-896 [PMID: 7730892 DOI: 10.1016/0895-4356(94)90192-9]

78 **Hajjar ER**, Hanlon JT, Sloane RJ, Lindblad CI, Pieper CF, Ruby CM, Branch LC, Schmader KE. Unnecessary drug use in frail older people at hospital discharge. *J Am Geriatr Soc* 2005; **53**: 1518-1523 [PMID: 16137281 DOI: 10.1111/j.1532-5415.2005.53523.x]

79 **Hanlon JT**, Artz MB, Pieper CF, Lindblad CI, Sloane RJ, Ruby CM, Schmader KE. Inappropriate medication use among frail elderly inpatients. *Ann Pharmacother* 2004; **38**: 9-14 [PMID: 14742785 DOI: 10.1345/aph.1D313]

80 **Lipton HL**, Bero LA, Bird JA, McPhee SJ. The impact of clinical pharmacists' consultations on physicians' geriatric drug prescribing. A randomized controlled trial. *Med Care* 1992; **30**: 646-658 [PMID: 1614233 DOI: 10.1097/00005650-199207000-00006]

81 **Steinman MA**, Landefeld CS, Rosenthal GE, Berthenthal D, Sen S, Kaboli PJ. Polypharmacy and prescribing quality in older people. *J Am Geriatr Soc* 2006; **54**: 1516-1523 [PMID: 17038068 DOI: 10.1111/j.1532-5415.2006.00889.x]

82 **Bossart W**, Loeffler H, Bienz K. Enucleation of cells by density gradient centrifugation. *Exp Cell Res* 1975; **96**: 360-366 [PMID: 249 DOI: 10.1111/jgs.12891]

83 **Pasina L**, Djade CD, Tettamanti M, Franchi C, Salerno F, Corrao S, Marengoni A, Marcucci M, Mannucci PM, Nobili A. Prevalence of potentially inappropriate medications and risk of adverse clinical outcome in a cohort of hospitalized elderly patients: results from the REPOSI Study. *J Clin Pharm Ther* 2014; **39**: 511-515 [PMID: 24845066 DOI: 10.1111/jcpt.12178]

84 **Schmader KE**, Hanlon JT, Pieper CF, Sloane R, Ruby CM, Twersky J, Francis SD, Branch LG, Lindblad CI, Artz M, Weinberger M, Feussner JR, Cohen HJ. Effects of geriatric evaluation and management on adverse drug reactions and suboptimal prescribing in the frail elderly. *Am J Med* 2004; **116**: 394-401 [PMID: 15006588 DOI: 10.1016/j.amjmed.2003.10.031]

85 **Saltvedt I**, Spigset O, Ruths S, Fayers P, Kaasa S, Sletvold O. Patterns of drug prescription in a geriatric evaluation and management unit as compared with the general medical wards: a randomised study. *Eur J Clin Pharmacol* 2005; **61**: 921-928 [PMID: 16307267 DOI: 10.1007/s00228-005-0046-2]

86 **Crotty M**, Halbert J, Rowett D, Giles L, Birks R, Williams H, Whitehead C. An outreach geriatric medication advisory service in residential aged care: a randomised controlled trial of case conferencing. *Age Ageing* 2004; **33**: 612-617 [PMID: 15385274 DOI: 10.1093/ageing/afh213]

87 **Strandberg TE**, Pitkala KH, Berglind S, Nieminen MS, Tilvis RS. Multifactorial intervention to prevent recurrent cardiovascular events in patients 75 years or older: the Drugs and Evidence-Based Medicine in the Elderly (DEBATE) study: a randomized, controlled trial. *Am Heart J* 2006; **152**: 585-592 [PMID: 16923435 DOI: 10.1016/j.ahj.2006.02.006]

88 **Holland R**, Smith R, Harvey I. Where now for pharmacist led medication review? *J Epidemiol Community Health* 2006; **60**: 92-93 [PMID: 16415254 DOI: 10.1136/jech.2005.035188]

89 **Hanlon JT**, Weinberger M, Samsa GP, Schmader KE, Uttech KM, Lewis IK, Cowper PA, Landsman PB, Cohen HJ, Feussner JR. A randomized, controlled trial of a clinical pharmacist intervention to improve inappropriate prescribing in elderly outpatients with polypharmacy. *Am J Med* 1996; **100**: 428-437 [PMID: 8610730 DOI: 10.1016/S0002-9343(97)89519-8]

90 **Crotty M**, Rowett D, Spurling L, Giles LC, Phillips PA. Does the addition of a pharmacist transition coordinator improve evidence-based medication management and health outcomes in older adults moving from the hospital to a long-term care facility? Results of a randomized, controlled trial. *Am J Geriatr Pharmacother* 2004; **2**: 257-264 [PMID: 15903284 DOI: 10.1016/j.amjopharm.2005.01.001]

91 **Spinewine A**, Swine C, Dhillon S, Lambert P, Nachega JB, Wilmotte L, Tulkens PM. Effect of a collaborative approach on the quality of prescribing for geriatric inpatients: a randomized, controlled trial. *J Am Geriatr Soc* 2007; **55**: 658-665 [PMID: 17493184 DOI: 10.1111/j.1532-5415.2007.01132.x]

92 **Eleazer GP**, Doshi R, Wieland D, Boland R, Hirth VA. Geriatric content in medical school curricula: results of a national survey. *J Am Geriatr Soc* 2005; **53**: 136-140 [PMID: 15667390 DOI: 10.1111/j.1532-5415.2005.53023.x]

93 **Bragg EJ**, Warshaw GA. ACGME requirements for geriatrics medicine curricula in medical specialties: progress made and progress needed. *Acad Med* 2005; **80**: 279-285 [PMID: 15734811 DOI: 10.1097/00001888-200503000-00014]

94 **Warshaw GA**, Bragg EJ. The training of geriatricians in the United States: three decades of progress. *J Am Geriatr Soc* 2003; **51**: S338-S345 [PMID: 12823665 DOI: 10.1046/j.1365-2389.2003.51345.x]

95 **van Eijk ME**, Avorn J, Porsius AJ, de Boer A. Reducing prescribing of highly anticholinergic antidepressants for elderly people: randomised trial of group versus individual academic detailing. *BMJ* 2001; **322**: 654-657 [PMID: 11250852 DOI: 10.1136/bmj.322.7287.654]

96 **Stein CM**, Griffin MR, Taylor JA, Pichert JW, Brandt KD, Ray WA. Educational program for nursing home physicians and staff to reduce use of non-steroidal anti-inflammatory drugs among nursing home residents: a randomized controlled trial. *Med Care* 2001; **39**: 436-445 [PMID: 11317092 DOI: 10.1097/00005650-200105000-00004]

97 **Pimlott NJ**, Hux JE, Wilson LM, Kahan M, Li C, Rosser WW. Educating physicians to reduce benzodiazepine use by elderly patients: a randomized controlled trial. *CMAJ* 2003; **168**: 835-839 [PMID: 12668540]

98 **Fick DM**, Maclean JR, Rodriguez NA, Short L, Heuvel RV, Waller JL, Rogers RL. A randomized study to decrease the use of potentially inappropriate medications among community-dwelling older adults in a southeastern managed care organization. *Am J Manag Care* 2004; **10**: 761-768 [PMID: 15623266]

99 **Lutters M**, Harbarth S, Janssens JP, Freudiger H, Herrmann F, Michel JP, Vogt N. Effect of a comprehensive, multidisciplinary, educational program on the use of antibiotics in a geriatric university hospital. *J Am Geriatr Soc* 2004; **52**: 112-116 [PMID: 14687324 DOI: 10.1111/j.1532-5415.2004.52019.x]

100 **Crotty M**, Whitehead C, Rowett D, Halbert J, Weller D, Finucane P, Esterman A. An outreach intervention to implement evidence based practice in residential care: a randomized controlled trial [ISRCTN67855475]. *BMC Health Serv Res* 2004; **4**: 6 [PMID: 15066200 DOI: 10.1186/1472-6963-4-6]

101 **Rahme E**, Choquette D, Beaulieu M, Bessette L, Joseph L, Toubouti Y, LeLorier J. Impact of a general practitioner educational intervention on osteoarthritis treatment in an elderly population. *Am J Med* 2005; **118**: 1262-1270 [PMID: 16271911 DOI: 10.1016/j.amjmed.2005.03.026]

102 **Ross S**, Loke YK. Do educational interventions improve prescribing by medical students and junior doctors? A systematic review. *Br J Clin Pharmacol* 2009; **67**: 662-670 [PMID: 19594535 DOI: 10.1111/j.1365-2125.2009.03395.x]

103 **Bates DW**, Gawande AA. Improving safety with information technology. *N Engl J Med* 2003; **348**: 2526-2534 [PMID: 12815139 DOI: 10.1056/NEJMsa020847]

104 **Garg AX**, Adhikari NK, McDonald H, Rosas-Arellano MP, Devereaux PJ, Beyene J, Sam J, Haynes RB. Effects of computerized clinical decision support systems on practitioner performance and patient outcomes: a systematic review. *JAMA* 2005; **293**: 1223-1238 [PMID: 15755945 DOI: 10.1001/jama.293.10.1223]

105 **Weiner M**, Callahan CM, Tierney WM, Overhage JM, Mamlin B, Dexter PR, McDonald CJ. Using information technology to improve the health care of older adults. *Ann Intern Med* 2003; **139**: 430-436 [PMID: 12965971 DOI: 10.7326/0003-4819-139-5\_Part\_2-200309021-00010]

106 **Tamblyn R**, Huang A, Perreault R, Jacques A, Roy D, Hanley J, McLeod P, Laprise R. The medical office of the 21st century (MOXXI): effectiveness of computerized decision-making support in reducing inappropriate prescribing in primary care. *CMAJ* 2003; **169**: 549-556 [PMID: 12975221]

107 **Koppel R**, Metlay JP, Cohen A, Abaluck B, Localio AR, Kimmel SE, Strom BL. Role of computerized physician order entry systems in facilitating medication errors. *JAMA* 2005; **293**: 1197-1203 [PMID: 15755942 DOI: 10.1001/jama.293.10.1197]

108 **Zhan C**, Hicks RW, Blanchette CM, Keyes MA, Cousins DD. Potential benefits and problems with computerized prescriber order entry: analysis of a voluntary medication error-reporting database. *Am J Health Syst Pharm* 2006; **63**: 353-358 [PMID: 16452521 DOI: 10.2146/ajhp050379]

109 **Horsky J**, Kuperman GJ, Patel VL. Comprehensive analysis of a medication dosing error related to CPOE. *J Am Med Inform Assoc* 2005; **12**: 377-382 [PMID: 15802485 DOI: 10.1197/jamia.M1740]

110 Development and clinical trials of a new Software ENgine for the Assessment & Optimization of drug and non-drug Therapy in Older peRsons. Available from: URL: http://www.senator-project.eu/

111 **University College Cork.** Clinical Trial of a New Software ENgine for the Assessment & Optimization of Drug and Non-drug Therapy in Older peRsons (SENATOR). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). [updated 2014 Mar 28]. Available from: URL: <https://clinicaltrials.gov/ct2/show/NCT02097654> NLM Identifier: NCT02097654

112 **Baystate Medical Center.** Using Clinical Alerts to Decrease Inappropriate Medication Prescribing. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). [updated 2014 Mar 7]. Available from: URL: <https://clinicaltrials.gov/ct2/show/NCT01034761> NLM Identifier: NCT01034761

113 **McLeod PJ**, Huang AR, Tamblyn RM, Gayton DC. Defining inappropriate practices in prescribing for elderly people: a national consensus panel. *CMAJ* 1997; **156**: 385-391 [PMID: 9033421]

114 **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**: 103-107 [PMID: 10958706]

115 **Zhan C**, Sangl J, Bierman AS, Miller MR, Friedman B, Wickizer SW, Meyer GS. Potentially inappropriate medication use in the community-dwelling elderly: findings from the 1996 Medical Expenditure Panel Survey. *JAMA* 2001; **286**: 2823-2829 [PMID: 11735757 DOI: 10.1001/jama.286.22.2823]

116 **Laroche ML**, Charmes JP, Merle L. Potentially inappropriate medications in the elderly: a French consensus panel list. *Eur J Clin Pharmacol* 2007; **63**: 725-731 [PMID: 17554532 DOI: 10.1007/s00228-007-0324-2]

117 **Rancourt C**, Moisan J, Baillargeon L, Verreault R, Laurin D, Grégoire JP. Potentially inappropriate prescriptions for older patients in long-term care. *BMC Geriatr* 2004; **4**: 9 [PMID: 15488143 DOI: 10.1186/1471-2318-4-9]

118 **Basger BJ**, Chen TF, Moles RJ. Inappropriate medication use and prescribing indicators in elderly Australians: development of a prescribing indicators tool. *Drugs Aging* 2008; **25**: 777-793 [PMID: 18729548 DOI: 10.2165/00002512-200825090-00004]

119 **Rognstad S**, Brekke M, Fetveit A, Spigset O, Wyller TB, Straand J. The Norwegian General Practice (NORGEP) criteria for assessing potentially inappropriate prescriptions to elderly patients. A modified Delphi study. *Scand J Prim Health Care* 2009; **27**: 153-159 [PMID: 19462339 DOI: 10.1080/02813430902992215]

120 **Holt S**, Schmiedl S, Thürmann PA. Potentially inappropriate medications in the elderly: the PRISCUS list. *Dtsch Arztebl Int* 2010; **107**: 543-551 [PMID: 20827352 DOI: 10.3238/arztebl.2010.0543]

121 **Winit-Watjana W**, Sakulrat P, Kespichayawattana J. Criteria for high-risk medication use in Thai older patients. *Arch Gerontol Geriatr* 2000; **47**: 35-51 [PMID: 17675177 DOI: 10.1016/j.archger.2007.06.006]

**P-Reviewer:** Baba H, Guan YS, M’Koma A, Yanev SG **S-Editor:** Tian YL

**L-Editor: E-Editor:**

**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.

**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 |  |

**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, nadalol, 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, vigabatran, 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  Dabigatran in those ≥ 75 yr with a body weight of < 50 kg) | ↑ | Increased bleeding risk |
| Cardiovascular system drugs | Angiotensin II receptor blockers  Diltiazem  Enalapril  Verapamil  Propranolol | ↑  ↑  ↑  ↑  ↓ | Hypotension |
| Diuretics | Frusemide  Bumetanide | ↓  ↑ | Reduced diuretic effect at standard doses |
| Psychoactive Drugs | Diazepam  Midazolam  Temazepam  Haloperidol  Traizolam | ↑  ↑  ↑  ↑  ↑ | Excessive sedation, confusion, postural sway, falls |
| 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 1mg 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  Dabigatran | Standard initiation dose, *e.g.,* 10 mg daily for two days  150 mg BD | Lower initiation dose, *e.g.*, 5 mg daily for two days  Patient > 80 yr 110mg BD  Patient 75-80 yr 150 mg BD in setting or normal eGFR | Increased sensitivity to anticoagulant effect  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 |

NSAIDs: Non-steroidal anti-inflammatory drugs; TCA: Tricyclic anti-depressants.

**Table 7** **Key considerations when prescribing for older patients**

|  |
| --- |
| **1 Use non-pharmacological treatment whenever possible**  **2 Include the patient (and carer where appropriate) in prescribing decisions**  **3 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)**  **4 Start at the smallest dose and titrate slowly according to response and efficacy**  **5 Use the simplest dosing regimen (***e.g.,* **once a day preferable to three times per day) and most appropriate formulation**  **6 Provide verbal and written instructions on indication, time and route of administration and potential adverse effects of each medication**  **7 Regularly review prescriptions in the context of co-exiting disease states, concurrent medications, functional and cognitive status and therapeutic expectation**  **8 Be aware that new presenting symptoms may be due to an existing medication, drug-drug interaction or drug-disease interaction (avoid prescribing cascade)**  **9 When stopping a medication check that it can be stopped abruptly or whether it needs to be tapered,** *e.g.,* **long-term steroids, benzodiazepines** |

**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 40mg 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 10.2g/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.

**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 |

**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.

**Falls**

Conventional antipsychotics, *e.g.,* haloperidol

Benzodiazepines

Sedative hypnotics (non-benzodiazepine)

SSRIs

TCAs

**Chronic Obstructive Airway Disease**

Beta blockers particularly non- cardiac selective, *e.g.,* propanolol

Benzodiazepines

Non-saliclyate NSAIDs

Sedative hypnotics (non benzodiazepine)

**Dementia**

Anticholinergics

Barbiturates

Benzodiazepines

CNS stimulants

Some older antiepileptic drugs, *e.g.,* Phenytoin, carbamazepine

Opioid Analgesics

TCAs

**Depression**

Alpha blockers, *e.g.,* reserpine

Barbiturates

Benzodiazepines

Corticosteroids

Digoxin

Lipophilic beta-blockers, *e.g.,* propranolol

Water soluble beta-blockers, *e.g.,* atenolol

**Arrhythmias**

TCAs

**Heart Block**

Digoxin

TCAs

**Hypertension**

CNS stimulants

Non-aspirin NSAIDs

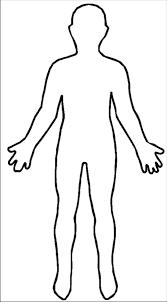
**Congestive Heart Failure (systolic dysfunction)**

Beta blockers

First generation calcium channel blockers, *e.g.,* verapamil, diltiazem

Non-aspirin NSAIDs

Type 1A anti-arrhythmics, *e.g.,* procainamide, quinidine

****

**Constipation**

Anticholenergics

Calcium channel blockers

Iron supplements

Opioid analgesics

TCAs

**Benign Prostatic Hyperplasia**

Anticholinergics

Opioids

Skeletal muscle relaxants

TCAs

**Diabetes**

Atypical antipsychotics

Beta blockers

Corticosteroids

Thiazide diuretics

**Chronic Renal Failure**

Methenamine complexes

Nitrofurantoin

Non-aspirin NSAIDs

Tetracycline

**Gout**

Thiazide diuretics

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

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