Abstract

A literature search was carried out to review the influence of ‘ageing’ on pharmacotherapeutic decision-making, specifically how ‘age’ is defined and considered in the utilisation of medication. Embase, Medline, International Pharmaceutical Abstracts, and Google scholar were canvassed in a three-tiered search according to pre-established inclusion criteria. In tier 1, a total of 22 studies were identified highlighting the underutilisation of medication in elderly patients, with a particular focus on warfarin. Four studies highlighted an age-bias in medication-prescribing for elderly patients, specifically in relation to medicines for rheumatoid arthritis, angina, and hypertension. Tier 2 identified diverse definitions for ‘elderly’, including biological age, chronological age, physiological age, as well as various descriptions of ‘elderly’ in clinical trials and guidelines. Finally, medication optimisation tools were identified through the third tier, emphasising the use of chronological age to describe the ‘elderly’. Old age influences pharmacotherapeutic decision-making at various levels, however, what complicates the situation is the absence of a comprehensive definition of ‘elderly’. Clinical recommendations need to be based more on objective factors known to affect medication effectiveness and safety.

Keywords: Elderly, Definition, Medication Optimization, Age-bias

1. Introduction

Various ‘spokes’ underpin the quality use of medicine umbrella, including evidence-based medicine, patient-centred care, and individualisation of medicine. Whilst all health care professionals strive to deliver best practice aligned to these, for some patient populations this alignment is apparently more challenging, for e.g. older persons. Indeed decision-making can be more complex in older persons, however, evidence suggests that decision-making is often based on ‘age’ *per se*, rather than on individualised review of the relevant factors.

Medication prescribing in elderly patients is often a challenge for many clinicians. Age-associated biological, physiological, and pharmacological changes along with the issues of comorbidity and polypharmacy, add to the complexity of medication use in older persons [Mangoni and Jackson 2003, Elliott 2006]. Since these age-associated changes do not present uniformly across older people of the same chronological age, there is some degree of heterogeneity in overall health among the elderly. Moreover, functional and cognitive status decline, and the limited evidence base regarding pharmacotherapy (due to the exclusion of elderly subjects from clinical trials) also add to the challenges of prescribing in older persons [Crome, Lally et al. 2011]. All of these factors, subsequently, affect clinical decision-making in older persons, such that patient age may negatively impact the use of pharmacotherapy.

Ageism, i.e. *prejudice and discrimination on the grounds of an age of a person*, or an age-bias in pharmacotherapeutic decision-making is an important issue associated with medication [Penson, Daniels et al. 2004]. A classic example of such an age-bias in decision-making and subsequent underutilisation of evidence-based medication is atrial fibrillation therapy; warfarin, despite evidence showing its efficacy in older patients, remains underutilised even after accounting for contraindications (e.g. comorbidity) [Bajorek, Krass

et al. 2002, Pugh, Pugh et al. 2011]. Another important area where medication underutilisation raises concern is effective pain management [Auret and Schug 2005].

Medication underutilisation may be the consequence of a well-considered rational decision by the prescribing clinician (rational underprescribing) [Van Den Heuvel, Los et al. 2011]. However, the literature highlights the direct influence of patient age on treatment decisions. Since age *per se* is not a specific risk factor for adverse drug events [Carbonin, Pahor et al. 1991], decision-making should instead be focused on individual patient characteristics and supported by comprehensive patient assessment. A comprehensive assessment of patient characteristics will help the prescriber identify those older patients in whom benefits of medications outweigh the risks [Sergi, De Rui et al. 2011]. This is especially important in high risk medications (e.g., anticoagulants) where the risk-benefit assessment may be skewed by age-based decisions, causing potential harm to the patient from under-treatment (e.g., stroke). Periodic re-reviews can also identify changes in patient characteristics over time, and take into account concepts such as time-to-benefit (duration of prescribing required to achieve benefits from the use of a medication) and time-to-harm (duration of prescribing required for a medication to cause harm) [Holmes, Min et al. 2013].

The aim of this paper is to review the influence of ageing on pharmacotherapeutic decision-making by:

- highlighting the existing age-bias in prescribing (tier 1)
- exploring definitions of ageing and their relevance to use of pharmacotherapy in older patients (tier 2)
- identifying medication prescribing optimisation tools for older patients (tier 3)

2. **Method**

A review of the literature was undertaken using key electronic databases (Embase, Medline, International Pharmaceutical Abstracts and Google Scholar). The search was conducted in 3-tiers. Tier 1 was conducted to specifically showcase studies on the underutilisation of medications in the older population, using the following keywords: “ageism”, “age-bias”, “underutilisation”, “underprescribing”, “inappropriate prescribing”, along with the terms “elderly” and “older”. The search was limited to original research publications in the English language within the time period of 2000 to 2014 (aligned with the World Health Organisation’s definition of elderly presented in *Minimum Data Set* project in year 2000 [World Health Organisation 2000]). Tier 2 involved a broader search criterion to identify papers on the ageing process, descriptions of ‘old’ in clinical practice guidelines, and measures to define ageing (chronological age, biological age, and ageing pharmacology). The search tier was limited to original and review articles published in the English language. Tier 3 focused on tools to rationalise medication prescribing in older patients. In all tiers, reference lists were also searched to identify further literature. For Tier 2 and Tier 3, unrestricted search criteria were utilised (with no major inclusion and exclusion criteria). Articles were included for this review if they were considered relevant to the objectives of the review.

3. Results

3.1 Tier 1: Studies reporting an age-bias in medication prescribing

3.1.1 Number and type of studies

A total of 22 studies were identified (Table 1): nine studies pertained to hospital settings [Bajorek, Krass et al. 2002, Dudley, Bowling et al. 2002, Peake, Thompson et al. 2003, Tran, Laupacis et al. 2004, Avezum, Makdisse et al. 2005, Friberg, Hammar et al. 2006, Perera, Bajorek et al. 2009, Wright, Sloane et al. 2009, Bajorek and Ren 2012]; four studies were based in general practice [Simpson, Wilson et al. 2005, DeWilde, Carey et al. 2006, Leizorovicz, Cohen et al. 2007, Gallagher, Rietbrock et al. 2008]; and three studies utilised disease-specific databases (e.g. disease-specific registries) [Woodard, Nadella et al. 2003, Alibhai, Krahn et al. 2004, Gladstone, Bui et al. 2009]. Thirteen studies focussed on cardiac conditions, of which ten specifically explored medication underutilisation in atrial fibrillation. Four studies investigated the influence of patient age on clinicians' treatment decisions [Hajjar, Miller et al. 2002, Fraenkel, Rabidou et al. 2006, Harries, Forrest et al. 2007, Kievit, van Hulst et al. 2010].

3.1.2 Underutilisation of medications and the effect of age on decision-making

Studies have reported the underutilisation of diuretics [Hajjar, Miller et al. 2002], β-blockers [Dudley, Bowling et al. 2002, Hajjar, Miller et al. 2002, Sloane, Gruber-Baldini et al. 2004, Tran, Laupacis et al. 2004, Avezum, Makdisse et al. 2005], statins [Avezum, Makdisse et al. 2005], angiotensin converting enzyme inhibitors [Sloane, Gruber-Baldini et al. 2004], aspirin [Dudley, Bowling et al. 2002, Wright, Sloane et al. 2009], antidepressants [Hanlon, Wang et al. 2011], calcium supplements [Sloane, Gruber-Baldini et al. 2004], and chemotherapy [Peake, Thompson et al. 2003, Woodard, Nadella et al. 2003], 8 studies specifically reported the underutilisation of warfarin in older patients [Bajorek, Krass et al. 2002, Simpson, Wilson et al. 2005, Waldo, Becker et al. 2005, Leizorovicz, Cohen et al. 2007, Gallagher, Rietbrock et al. 2008, Gladstone, Bui et al. 2009, Perera, Bajorek et al. 2009, Bajorek and Ren 2012]. These studies reported that 15-21% of atrial fibrillation patients did not receive any anticoagulation therapy [Waldo, Becker et al. 2005, Gladstone, Bui et al. 2009], despite being

at high risk of stroke and guideline recommendation, and in the absence of any contraindication to the therapy [Friberg, Hammar et al. 2006, Gladstone, Bui et al. 2009, Bajorek and Ren 2012]. Patients aged 80 years or more (compared to younger counter-parts) were approximately 5 times less likely to receive warfarin therapy [Bajorek, Krass et al. 2002, DeWilde, Carey et al. 2006]. The percentage of patients receiving vitamin K antagonists decreased with age, particularly after the age of 70 years with the likelihood of receiving a vitamin K antagonist declined by 9.6% each year of age [Leizorovicz, Cohen et al. 2007].

Among all the studies from tier 1, 11 identified that the chronological age of a patient was an important factor affecting clinical decision-making [Bajorek, Krass et al. 2002, Dudley, Bowling et al. 2002, Hajjar, Miller et al. 2002, Peake, Thompson et al. 2003, Woodard, Nadella et al. 2003, Tran, Laupacis et al. 2004, Avezum, Makdisse et al. 2005, Friberg, Hammar et al. 2006, Harries, Forrest et al. 2007, Kievit, van Hulst et al. 2010]. The cut-off age influencing warfarin utilisation in older patients has ranged between 75-85 years [Bajorek, Krass et al. 2002, Waldo, Becker et al. 2005, DeWilde, Carey et al. 2006, Friberg, Hammar et al. 2006, Gallagher, Rietbrock et al. 2008, Bajorek and Ren 2012]. Being over the age of 75 years also decreases the likelihood of receiving thrombolysis and secondary prevention with aspirin and β-blockers following acute myocardial infarction [Dudley, Bowling et al. 2002]. In residential care settings, 76.2% of acute myocardial infarction patients aged ≥ 65 years do not receive β-blockers [Sloane, Gruber-Baldini et al. 2004]. In the treatment of breast carcinoma (with oestrogen receptor positive status), being over 65 years of age decreases the likelihood of receiving chemotherapy by 62 times (compared to those aged ≤ 50 years). For patients with oestrogen receptor negative breast carcinoma, being 65 years or over is associated with 7-fold lower likelihood of receiving chemotherapy compared to those aged 50 years or less [Woodard, Nadella et al. 2003]. Some studies have specifically

highlighted the impact of medication underutilisation on clinical outcomes (e.g., pain management). For example, in a study of 21,380 nursing home residents aged 65 years and older, 24.5% of those with persistent pain received no treatment with analgesics [Auret and Schug 2005]; being over the age of 70 years has been identified as an important factor contributing to the undertreatment of pain [Denny and Guido 2012].

There is, however, a need to add some substantial caveats. The limited clinical evidence to support the use of some medications in older patients (due to the under-representation of older and frail adults in clinical trials) is, perhaps, one of the key issues underpinning medication underutilisation in older patients. Also, the relationship between polypharmacy and medication underutilisation (i.e., the simultaneous existence of the two phenomena in a patient [Kuijpers, Van Marum et al. 2008, Blanco-Reina, Ariza-Zafra et al. 2015]) further complicates the decision-making process in older patients.

3.1.3 Clinicians' understanding of 'old' age

Studies investigating clinicians' understanding of 'old age' have focused on the management of rheumatoid arthritis [Fraenkel, Rabidou et al. 2006, Kievit, van Hulst et al. 2010], angina [Harries, Forrest et al. 2007], and hypertension [Hajjar, Miller et al. 2002]. Studies have revealed health professionals' biased understanding of 'old age' [Hajjar, Miller et al. 2002, Fraenkel, Rabidou et al. 2006, Harries, Forrest et al. 2007], and that some physicians regard 'old age' a contraindication to treatment [Harries, Forrest et al. 2007]. Their understanding of diseases and subsequent treatment choices change with increasing patient age [Hajjar, Miller et al. 2002]. Clinicians are also reportedly reluctant to use aggressive treatment measures in older patients [Fraenkel, Rabidou et al. 2006, Kievit, van Hulst et al. 2010], for instance, rheumatologists are reluctant to escalate care in patients aged 80 years or above [Kievit, van Hulst et al. 2010].

3.2 Tier 2: Definitions of ageing and their relevance to the use of pharmacotherapy

The basic understanding of the ageing process has advanced significantly over the past decade [Kennedy, Berger et al. 2014] such that the current definition of ageing refers to a progressive functional impairment accompanied by diminishing fertility and an elevated risk of mortality [Kirkwood and Austad 2000, López-Otín, Blasco et al. 2013]. In clinical settings, health professionals and policy makers primarily rely on chronological age to identify elderly patients, although there are various other means to describe being 'old' including biological age, geriatric syndromes, and individual assessment of age-related factors affecting the use of a particular medication.

3.2.1 Defining elderly in clinical trials

Clinical trials have been criticised for their unjustified exclusion of older persons, often specifying an upper age limit within their inclusion criteria. For instance, Bugeja et al (1997) examined four major medical journals for all published original studies and identified the unjustified exclusion of people aged 75 or above in 35% of those studies that were deemed to be relevant to older persons. Similarly, Cruz-Jentoft et al (2010) examined study protocols submitted to research ethics committees and found that 19% had unjustified upper age limits ranging between 65 to 80 years. The definition of 'elderly', therefore, seems to be often based on chronological age [Aapro, Kohne et al. 2005] with differing age cut-offs across seemingly similar studies. For example, in acute myeloid leukaemia trials, a patient aged 60 years or above was considered 'elderly', whereas in the case of patients with solid tumours, patients aged 70 years or above were regarded 'elderly' [Kohne, Grothey et al. 2001]. A study protocol to compare the risks and benefits of warfarin *vs* aspirin use in stroke prevention, defined elderly as being 75 years or older [Mant, Hobbs et al. 2007]. Even practice standards and guidelines relating to elderly patients have defined 'elderly' according to chronological

age, for example, the European Forum on Good Clinical Practice has previously defined 'elderly' as ≥ 65 years (albeit, has recommended changing this to 75 years or older, alongside the inclusion of geriatric expertise in research ethics committees) [Wrobel, Dehlinger-Kremer et al. 2011, European Forum for Good Clinical Practice 2013].

The results of these evidence-forming clinical studies are presented in the form of clinical guidelines, which have often been discussed as being irrelevant to older patients. O'Hare et al (2009) examined four major US clinical guidelines (addressing the use of angiotensin-converting enzyme inhibitors and angiotensin II-receptor antagonists in chronic kidney disease) for their relevance to older persons and found that most of the clinical trials used to develop these guidelines underrepresented older people. In a cross-sectional study of 703 general practitioners, Lugtenberg et al (2011) identified that a lack of applicability of the recommendations presented in clinical guidelines was an important barrier to guideline adherence. Recently, in a study of 20 Australian clinical guidelines, it was found that most of these guidelines presented no definition for the term 'elderly', while some used only chronological age-based definitions [Singh and Bajorek 2014]. Clinical guidelines also failed to establish a relationship between an individual patient's physical status and the pharmacology of recommended medications. For their disease-driven approach of patient care, clinical guidelines are considered as inappropriate in the care of older patients with comorbidities [Boyd, Darer et al. 2005, Mutasingwa, Ge et al. 2011] where the application of clinical guidelines may lead to polypharmacy, adverse drug reactions, complex treatment regimens, and high financial burdens [Boyd, Darer et al. 2005]. Recently, Dumbreck et al (2015) examined 12 national clinical guidelines in the United Kingdom and identified a potential for drug-disease and drug-drug interactions, especially in patients with comorbid conditions, if the recommendations in these guidelines were adhered to. In older patients who are already using polypharmacy, the application of disease-driven guidelines can lead to

potential adverse drug reactions arising from implicitly unsafe combinations of medications [Boyd, Darer et al. 2005].

Since, clinicians face a dilemma when prescribing medications to older patients [Crome, Lally et al. 2011], clinical guidelines fail to provide enough guidance about caring for older patients especially those with comorbid conditions [Boyd, Darer et al. 2005]. They also often fail to provide robust guidance on the risks and benefits of certain medications in patients aged 75 or above [Bugeja, Kumar et al. 1997]. Clinicians may be reluctant to prescribe medications in the absence of evidence of safety and efficacy in the older population. Likewise, the use of chronological age to guide recommendations within clinical guidelines may also lead to inappropriate medication use, since these recommendations are generalised in a patient population beyond a certain age [Singh and Bajorek 2014]. Such guidelines overlook the divergence that exists in the health status (e.g., comorbidity, frailty) of older patients. Therefore, the 'one size fits all' approach can lead to both medication underutilisation and the inappropriate use of medication in older patients.

3.2.2 Chronological age

Traditionally, 'old age' has been defined using a chronological age (time elapsed since birth) of 65 years or above [World Health Organisation 2010]. The evidence on which this definition is based is unknown. In 1975, Norman Ryder suggested that 'old age' began when the remaining life expectancy of a person was less than 10 years [Warren Sanderson and Sergei Scherbov 2008]. A similar concept of 'old age' appeared a century ago when Prince Otto Von Bismarck, a German Chancellor, considered those aged 65 years or above as eligible for the national pension scheme, because he expected most people to die before this time [Orimo, Ito et al. 2006]. In the present era, when life expectancy has increased significantly, it seems inappropriate to define 'old age' using 65 years as the cut-off [Orimo,

Ito et al. 2006]. Over time, it is not just the life expectancy that has increased, but also healthy life expectancy [Salomon, Wang et al. 2012]. Healthy life expectancy is the number of years of good health that a person can expect to live at any given age (considering age-associated mortality, morbidity, and functional health status) [Salomon, Wang et al. 2012]. For this reason, some researchers have argued the need to review the definition of what is considered 'old' [Orimo, Ito et al. 2006, Jacobs, Maaravi et al. 2012].

Chronological age-based clinical decision-making is a generalised approach which neglects the enormous heterogeneity that exists in the health status and responses to medications in older patients [Hutchison and O'Brien 2007, Cho, Lau et al. 2011]. Moreover, chronological age is not a reliable selection criterion for the identification of patients who need treatment interventions, such that eligible patients may be falsely excluded [Schuurmans, Steverink et al. 2004]. For such limitations, some of the guidelines have recommended the use of biological age (discussed ahead) rather than chronological age for patient management [Bellmunt, Negrier et al. 2009].

3.2.3 Biological age

Although many scientific papers have discussed the concept of biological age, no consensus definition is available [Cho, Park et al. 2010]. While some use this term to describe the rate of ageing [Levine 2013, Levine and Crimmins 2014], others describe it from the perspective of an impairment index [Goggins, Woo et al. 2005]. As an indicator of the rate or extent of ageing of an individual, biological age is calculated using various clinical markers (or biomarkers) to quantify multi-system age-associated physiological alterations. For example, Levine and Crimmins (2014) used ten biomarkers (indicators of metabolic, cardiovascular, inflammatory, renal, hepatic, and lung function) to calculate biological age and the associated rate of ageing among African Americans. In 1988, Baker and Sprott (1988) defined

biomarker as *a biological parameter of an organism that either alone or in some multivariate composite will, in the absence of disease, better predict functional capability at some late age than will chronological age*. The American Federation for Aging Research has proposed criteria to help identify a suitable biomarker of ageing: it must predict an individual's physiological, cognitive, and physical function in an age-related way, must monitor the direct impact of age and not of any disease, tests musts be replicable while causing no harm to the person, and must be applicable to both humans and laboratory animals. Furthermore, a potential biomarker must predict, independent of chronological age, the future onset of age-related diseases [American Federation for Aging Research 2011].

The elementary premise underpinning the use of biomarkers of ageing is that chronological age does not represent the biological age of an individual [Simm, Nass et al. 2008]. The idea to measure the rate of ageing using clinical biomarkers first started to appear in gerontology research in the early 1980s [Ludwig and Smoke 1980], resulting in the exploration of various clinical markers since then. An important issue associated with the identification of potential biomarkers and their use in clinical practice is related to their validity. Until now, only some biomarkers have been validated through detailed longitudinal studies, whilst most are tested in cross-sectional studies [Simm, Nass et al. 2008]. Some examples of biomarkers studied to date include Interleukin-6, tissue necrosis factor α, growth hormone, and testosterone [Simm, Nass et al. 2008]. However, none of these have proven effective in measuring biological age on its own [Bürkle, Moreno-Villanueva et al. 2015].One of the most studied biomarkers of ageing is telomere length (nucleoprotein structures at the ends of chromosomes), since telomere length decreases as age increases. The evidence for and against the use of telomere length as a biomarker of ageing remains equivocal [Mather, Jorm et al. 2011]. Apart from its utilisation as a biomarker in ageing research, telomere length has also been used as a benchmark to select other biomarkers of ageing. Zhang et al (2014) used telomere length and

chronological age, as benchmarks, along with five other biomarkers to develop an equation as a mean of biological age calculation. It was found that telomere length is a more robust benchmark in the selection of biomarkers than chronological age. The use of a combination of biomarkers to measure biological age is also gaining interest in ageing research. In MARK-AGE study, a set of biomarkers of ageing was identified to calculate biological age [Bürkle, Moreno-Villanueva et al. 2015]. Many computational algorithms are also available to calculate biological age based on bio-markers, for example Klemera Doubal's method [Klemera and Doubal 2006].

Another approach to assess biological age is based on the frailty index (accumulated number of deficits a person has) [Rockwood and Mitnitski 2007]. Mitnitski et al [Mitnitski, Graham et al. 2002] suggested the use of frailty index in calculating personal biological age in older populations in Canada; later, the same method was used in a Chinese population [Goggins, Woo et al. 2005].

Various online tools, though crude and not validated, allow people to measure their relative physical fitness in relation to their chronological ages based on their medical history (number of diseases), genetics (ethnic origin, family medical history), lifestyle (smoking, diet and exercise habits), and physical status (obesity) [M.E. Craig, S.M. Twigg et al. 2011]. The availability of such tools on government health websites (Department of Health, Queensland) [The State of Queensland (Department of Health)] and health insurance providers' [M.E. Craig, S.M. Twigg et al. 2011] websites suggests an increasing awareness of these tools as a better prediction of health status. The development of such tools is often carried out by private organisations (e.g., Expert 24 LTD™ [Expert 24]) providing little information regarding the development process**.** Following a general assessment of a person's health profile, these tools provide a relative age at which people on average have a similar health profile as the person under assessment. Some tools are particularly designed to estimate a

person's biological age in respect to their cardiovascular functioning, often known as 'heart age' or 'vascular age'. 'Heart age' is the age of an 'ideal' person (non-smoker, total serum cholesterol to high density lipoprotein ratio of 4, blood pressure of 120/80 mm Hg) with equal risks for cardiovascular disease as the patient under assessment [Boon, Boyle et al. 2014]. Recently, the Joint British Societies have developed a tool (JBS3 risk calculator) [Joint British Societies 2014] which, apart from calculating a person's 'heart age', assists in clinical decision-making process [Boon, Boyle et al. 2014].

Despite the differences in its definition and measurement approaches, biological age highlights physiological differences between two individuals of the same chronological age; the calculated biological age could be higher (relatively poor health status) or lower (relatively good health status) than the chronological age. Therefore, prescribing decisions might be better based on the biological age of a patient [Bellmunt, Negrier et al. 2009].

3.2.4 Geriatric Syndromes

Geriatric patients are a subgroup of elderly people with multiple comorbid conditions, impaired homeostasis, and reduced functional reserve [Hilmer, McLachlan et al. 2007]. In clinical practice, geriatric patients are identified through a set of signs and symptoms, known as geriatric syndromes [Inouye, Studenski et al. 2007]. These geriatric syndromes include delirium, falls, incontinence, and frailty [Inouye, Studenski et al. 2007]. An important application of geriatric syndromes lies in the risk-benefit assessment of medications in older patients, whereby the number of geriatric syndromes decides whether medications, for example, cancer therapy, are to be prescribed or not [Rikkert, Rigaud et al. 2003]. Comprehensive geriatric assessment could help clinicians in identifying older patients at high risk of severe toxicity and/or side effects [Ferrucci, Guralnik et al. 2003] and can assist in the decision-making process [Tucci, Ferrari et al. 2009, Caillet, Canoui-Poitrine et al. 2011].

Frailty is a state of increased vulnerability to stressors, involving multisystem alterations that lead to impaired homeostasis reserve and resiliency [Clegg, Young et al. 2013]. Frailty has a well-established theoretical basis; however, its practical application in clinical setting is still controversial. A part of this controversy is regarding the two major scales to measure frailty: the frailty phenotype [Fried, Tangen et al. 2001] and the frailty index [Rockwood, Song et al. 2005]. Researchers or clinicians often consider these scales as alternatives or substitutes (and usually have preferences for one or the other scale), when these scales are complementary to each other and work effectively at different levels of patient evaluation [Cesari, Gambassi et al. 2014]. Frailty has been associated with pharmacokinetic and pharmacodynamic changes [Wynne, Cope et al. 1990, Hilmer, Tran et al. 2011], therefore, it may be appropriate to consider in the decision-making surrounding pharmacotherapy. Another important consideration regarding the medication use in frail older patients is polypharmacy. An association between polypharmacy and frailty has been highlighted in the literature, specifically that polypharmacy may lead to frailty [Morley 2014]. It has also been suggested that keeping the number of prescribed medication less than 6 may reduce the risk of frailty in older patients [Rolland, Morley et al. 2014]. Hence, medication underutilisation may be required as a strategy to decrease the risk of frailty, resulting in the need to prioritise medications.

Recent advances in the understanding of frailty pathogenesis have led to the identification of specific physiological markers of frailty [Chen, Mao et al. 2014]. Leng et al (2002) reported an elevated level of serum interleukin (IL)-6 (a pro-inflammatory cytokine) in community-dwelling frail adults. Since then, many studies have revealed an association between chronic inflammation or immune system activation and frailty [Puts, Visser et al. 2005, Li, Manwani et al. 2011]. The elevated level of C-reactive protein and tumour necrosis factor-α in the frail

elderly further strengthens the relationship between inflammation and frailty [Walston, McBurnie et al. 2002, Hubbard, O'Mahony et al. 2009].

3.2.5 Age-associated physiological alterations (physiological age)

Various physiological changes are associated with the 'normal' ageing process, which affect both pharmacokinetic (absorption, distribution, metabolism, and excretion) and pharmacodynamic properties of a medication [Turnheim 2003, McLean and Le Couteur 2004, Corsonello, Pedone et al. 2010]. Such alterations, although frequently observed in elderly people, are not dependent on age *per se*. However, certain clinical features of older people (for e.g., comorbidity, polypharmacy, poor functional status) significantly contribute towards these physiological changes [Wildiers, Highley et al. 2003].

Pharmacokinetic alterations: In older people, diminished medication absorption can occur due to atrophic gastritis, reduced gastric motility and secretions, and reduced intraluminal surface area. However, many studies suggest that these physiological alterations are absent in healthy elderly people [Mangoni and Jackson 2003]. Johnson et al studied xylose absorption in healthy people aged between 32 to 85 years and found no change in gastrointestinal absorption [Johnson, Mayersohn et al. 1985]. Similar studies reported no alterations in absorption as a function of age for acetaminophen [Triggs, Nation et al. 1975], phenylbutazone [Triggs, Nation et al. 1975], aspirin [Melander, Bodin et al. 1978], and lorazepam [Greenblatt, Allen et al. 1979]. The volume of distribution of a medicine depends on body composition and plasma protein profile [McLean and Le Couteur 2004]. An increase in body fat and a decline in body water content occur from the age of 25 to 75 years [Wildiers, Highley et al. 2003]. Even though alterations in protein binding have negligible clinical significance [McLean and Le Couteur 2004], the plasma protein levels often change due to disease states rather than age alone [Yuen 1990]. The metabolism of a medicine is

affected by changes in liver size, liver blood flow, and cytochrome P450 enzyme activity [McLean and Le Couteur 2004]. Phase I reactions (e.g., oxidation, reduction) are particularly affected in older people, while no significant effect of age on Phase II reactions (e.g., glucuronidation) has been observed [Wildiers, Highley et al. 2003]. Even for Phase I metabolising enzymes (e.g., esterases), the effect of age itself has been debated. In a study of 113 healthy subjects aged between 18-85 years, no correlation was found between esterase enzyme activity and increasing age [Abou-Hatab, O'Mahony et al. 2001]. Similarly, for phase II reactions, physical status has a significant effect on the hepatic drug clearance of medications. Wynne et al [Wynne, Cope et al. 1990] studied the urinary clearance of acetaminophen conjugates and identified that the clearance values (corrected for liver size) remained unchanged between healthy young subjects and healthy elderly subjects; however, frail elderly subjects showed a significant reduction in the clearance values. However, recently the role of protein binding has been highlighted in the metabolic clearance of drugs. Intrinsic metabolic clearance is impaired in older patients, however the effect can remain unnoticed if medications are assessed using total drug clearance (especially for highly protein bound drugs) [Butler and Begg 2008].

In the case of renal function, declined glomerular filtration rate (GFR) is considered to be the most important age-associated pharmacokinetic change [McLean and Le Couteur 2004]. After the age of 40 years, GFR has been reported to fall by 1ml/min/year [Wildiers, Highley et al. 2003]; however, in longitudinal studies, almost one-third of the patients showed no change in renal function, even up to the age of 89 years [Rowe, Andres et al. 1976, Lindeman, Tobin et al. 1985]. Some studies have reported that kidney mass declines by 20-25% between 30-80 years of age [McLean and Le Couteur 2004]. Some researchers have argued that disease state or conditions, such as hypertension, chronic heart failure, diabetes mellitus, can significantly affect renal function in older people [Klotz 2009]. In a cross-

sectional study, several aspects of renal function were compared between healthy young subjects, healthy elderly subjects, elderly hypertensive patients, and elderly patients with confirmed mild to moderate heart failure; it was identified that cardiovascular diseases (hypertension and heart failure) had a major impact on renal hemodynamics and other renal functions [Fliser, Franek et al. 1997]. Another important concern associated with renal function in the elderly is its measurement. Many equations have been developed (e.g., Cockcroft-Gault equation, chronic kidney disease epidemiology collaboration (CKD-EPI)), however, their practical use in assessing renal function in older patients is complex [Ungar, Iacomelli et al. 2015]. Many of these equations have been developed and validated in younger patients. For instance, the CKD-EPI equation was based on 12,000 subjects with a mean age of 47 years, while only 13% of the subjects were aged 65 years or older [Levey, Stevens et al. 2009]. Two new equations have been recently developed (BIS1: creatinine-based and BIS2: creatinine and Cystatin-C based) for their use in estimation of GFR in persons aged 70 years or older [Schaeffner, Ebert et al. 2012]. Compared to other equations, these two equations have shown improved precision and accuracy in GFR measurement of elderly persons [Schaeffner, Ebert et al. 2012].

Pharmacodynamic alterations: Physiological changes that affect the pharmacodynamic behaviour of a medication include altered receptor number, receptor affinity, and homeostatic reserve [Bowie and Slattum 2007]. The altered sensitivity of β1-adrenergic receptors is a classic example of pharmacodynamic alterations in the elderly, presenting as a decreased response to β1-adrenergic agonists and an increased response to β1-adrenergic blockers [Hutchison and O'Brien 2007]. The number of cardiac muscarinic receptors also decreases with advancing age [Poller, Nedelka et al. 1997]. Any change in pharmacodynamic response for medications acting on central nervous system will be of special interest considering the high use of, and potential risks (e.g., falls risk, hip fractures) arising from, such medications

in older patients. With advancing age, the major physiological changes that may lead to altered pharmacodynamic responses include altered neurotransmitters and/or receptors, hormonal changes, and impaired glucose metabolism [Bowie and Slattum 2007]. Many studies have found increased sensitivity to the effect of benzodiazepines in older people in the absence of any attributable pharmacokinetic change [Kanto, Kangas et al. 1981, Albrecht, Ihmsen et al. 1999], whereas for some benzodiazepines no changes in pharmacodynamic response have been observed [Pomara, Tun et al. 1997].The exact mechanism of these pharmacodynamic changes for benzodiazepines are not well established; GABA receptor binding itself is not affected by the ageing process [Ruano, Araujo et al. 1996, Sundman, Allard et al. 1997, Bickford and Breiderick 2000]

Since most of these pharmacodynamic studies have examined older patients only, the altered disease pathophysiology in older patients (compared to younger patients) may be a reason for the observed changes in the pharmacodynamic behaviour of medications [McLean and Le Couteur 2004]. Only a few studies, to the present time, have examined changes in pharmacodynamics independently of age.

3.3 Tier 3: Measures to rationalise prescribing in older patients

3.3.1 To identify inappropriate medication use screening tools

A number of screening tools have been developed to rationalise medication prescribing in the elderly; some frequently used tools to screen potentially inappropriate prescribing include Beers' criteria [Beers, Ouslander et al. 1991], Medication Appropriateness Index (MAI) [Hanlon, Schmader et al. 1992], Improving Prescribing in the Elderly Tool (IPET) [Naugler, Brymer et al. 1999], Screening Tool of Older Persons' Potentially inappropriate prescriptions (STOPP) [Gallagher and O'Mahony 2008], and the prescribing indicators tool for elderly Australians [Basger, Chen et al. 2008]. A few tools specifically identify medication

omissions in older patients, for example, the Screening Tool to Alert doctors to the Right Treatment (START) [Barry, Gallagher et al. 2007]. Both, the STOPP and the START tool have been recently updated, giving rise to second generations of these tools [O'Mahony, O'Sullivan et al. 2014]. Whilst most of these tools have defined elderly as those aged 65 years and above, the IPET and the MAI do not provide any specific definition of 'elderly'. A major limitation of some tools is their potential lack of relevance to other countries (different from their origin), since the listed medications may not be available for use [Schubert, Küpper-Nybelen et al. 2013]. For example, Beers' criteria was modified to generate its country-specific versions, for example, the PRISCUS list – Germany [Holt, Schmiedl et al. 2010] and the French consensus panel list – France [Laroche, Charmes et al. 2007].

3.3.2 Clinical decision support tools

Clinical decision support tools are algorithms designed to assist clinical decision-making and may be presented as paper-based clinical pathways or data-input pathways in a computerised form. Some examples include the 'Computerised Antithrombotic Risk Assessment Tool' (CARAT) [Bajorek, Noman et al. 2012], Asthma Crystal Byte [Neville, McCowan et al. 2000], 'clinical decision support of hypertension management' [Montgomery, Fahey et al. 2000], pharmacokinetic-based gentamicin prescribing [Hwang, Chang et al. 2004], and the 'decision support for primary care' tool [Short, Frischer et al. 2003]. For such tools to be effective and relevant, they need to enable comprehensive patient assessment, so that decision-making is patient-oriented; to this end, patient age should only be one of many factors involved in the assessment. Such tools play a key role in optimising medication use in the elderly; for instance, Monane et al [Monane, Matthias et al. 1998] showed improvements in medication use in elderly patients using a computerised drug utilisation review intervention. Similarly, a decision support tool for the use of psychotropic medications in

elderly hospital patients optimised the dose, reduced prescribing of unnecessary medications, and reduced in-hospital falls [Peterson, Kuperman et al. 2005].

3.3.3 Medication review services

Medication review services, for example medication management review (MMR) and home medicines review (HMR), are targeted interventions that evaluate a patient's pharmacotherapeutic requirements, document the findings, and provide evidence-based recommendations to optimise the medication regimen [Krska, Cromarty et al. 2001, Bajorek 2011, Castelino, Bajorek et al. 2011]. These services ensure periodic re-review of prescribed medications, since the risk-benefit profile in a patient may change over time, and this is an important consideration in older patients [Bajorek 2011]. Randomised controlled trials to assess the effectiveness of these review services have identified a significant reduction in medication-related problems [Vinks, Egberts et al. 2009], less use of inappropriate medications [Roberts, Stokes et al. 2001], lower medication expenditure [Roberts, Stokes et al. 2001, Zermansky, Petty et al. 2001], fewer hospital admissions [Krska, Cromarty et al. 2001], and less falls [Zermansky, Alldred et al. 2006]. In a recent meta-analysis conducted to assess the impact of pharmaceutical care interventions on the utilisation of medications in older patients, medication review services were found to significantly reduce medication underuse in older patients [Meid, Lampert et al. 2015].

4. Discussion

This review considers how 'old age' influences the use of pharmacotherapy on various levels (Figure 1). Medication prescribing in older people is not a simple process and requires specific attention. The potential benefits of a medication must be weighed against possible

risks arising from its use [Cherubini, Corsonello et al. 2012], and this is an important consideration regarding medication use in elderly patients. However, along the continuum of initiating pharmacotherapy, from the initial information gaining process (clinical trials) to the prescribing stage, chronological age has traditionally underpinned treatment use in elderly patients [Cherubini, Oristrell et al. 2011, Crome, Lally et al. 2011, Cherubini, Corsonello et al. 2012]. The exclusion of older participants from clinical studies limits the presentation of required evidence in clinical guidelines, which eventually complicates the decision-making at the prescribing stage.

The apparent underutilisation of evidence-based medications in older patients raises some concerns. The influence of patient age on clinical decision-making has been highlighted, with age-based treatment decisions more pronounced for high-risk medications (e.g., warfarin), suggesting a greater emphasis on 'risk' than "benefit' in this process [Bajorek 2011]. The consequences of medication underutilisation are likely to impact on morbidity, disability, and mortality [Cherubini, Corsonello et al. 2012]. Nonetheless, only a few studies have explicitly explored the influence of medication underutilisation on health outcomes. In atrial fibrillation patients, the underutilisation of antithrombotic therapy has been associated with an increased likelihood of ischaemic strokes [Pisters, van Oostenbrugge et al. 2010]. Similarly, in the context of treating older patients with cancer, the underutilisation of analgesics has been associated with an increased incidence of daily pain [Bernabei, Gambassi et al. 1998]. It is, however, worthwhile to discuss the exploding rates of opioid use in non-cancer older patients. In older patients, there are increased chances of opioid-associated adverse drug events, e.g., falls risk, fractures, constipation, respiratory depression. In a study of 19,581 people (mean age 77 years), 12% were found to be using opioid doses higher than guideline recommended maximum dose [Veal, Bereznicki et al. 2015]. Perhaps, it is the initial

suboptimal management of pain that ultimately leads to the over-use of more problematic analgesics as the pain worsens.

Medication underutilisation may be necessary in some cases. In such situations, the clinician may take an informed decision to not prescribe certain medications, a process known as rational under-prescribing [Van Den Heuvel, Los et al. 2011]. A comprehensive assessment of the patient's characteristics is integral to decision-making here.

This paper also explored alternative definitions of 'old age'. Biological age considers interpatient variability in persons of the same chronological age according to current health status [Mitnitski, Graham et al. 2002]. Geriatric syndromes are distinct from definitions of 'older' persons [Hilmer, McLachlan et al. 2007]. Although many physiological changes can affect the pharmacokinetic and pharmacodynamic behaviour of a medication throughout the ageing process, the effect of age *per se* is minimal [Hubbard, O'Mahony et al. 2013].

Various strategies to optimise the use of pharmacotherapy in older patients have shown positive results [Yourman, Concato et al. 2008, Kaur, Mitchell et al. 2009, Patterson, Hughes et al. 2012]. However, the inclusion of an age-based criterion in some tools affects their potential application to practice. Some tools specifically monitor those issues which are often faced by elderly patients (e.g., frailty, functional and cognitive status) through comprehensive geriatric assessment, rendering them valuable aids in the decision-making process. Some strategies are of special importance in older patients with a limited remaining life expectancy and/or multimorbidity. An example of such strategies are consideration of the time-to-benefit and time-to-harm which help in the prioritisation of medications based on patient characteristics [Holmes, Min et al. 2013] and risks and benefits of prescribing.

Therefore, to support best practice based on individualisation of medicine in older people, clinical recommendations need to be more based on objective factors known to affect

medication effectiveness and safety. This will assist risk-benefit assessment and a more patient-centred approach to medication prescribing.

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Table 1 Summary of studies reporting an underutilisation of medications in elderly patients

Reference (year)	Study subjects/setting	Key findings
a) Studies investigating clinicians' understanding of 'old' age		
Hajjar et al (2002) [Hajjar, Miller et al. 2002]	A cross-sectional survey involving 412 health care professionals	• 35% of the health professionals believed that increase in blood pressure with age was a normal aspect of ageing, whilst 25% described hypertension treatment in **patients aged ≥ 85 years** as more harmful than beneficial • Health professionals were reluctant to use diuretics ($p = 0.032$) and β-blockers ($p = 0.005$) as first-line medications in a patient aged 85 years compared to a patient aged 65 years
Kievit et al (2010) [Kievit, van Hulst et al. 2010]	A computer-based survey of 135 rheumatologists	• Patients age influenced rheumatologists' decisions to escalate care in older patients (aged 80 years) compared to younger patients (aged 25 and 50 years)
Fraenkel et al (2006) [Fraenkel, Rabidou et al. 2006]	A survey on a random sample of 204 rheumatologists	• A greater proportion of rheumatologists preferred aggressive DMARD treatment in younger patients (aged 28 years) *vs* in older patients (82 years) (87% *vs* 71%, p=0.007) • Younger patients were 3 times more likely to be prescribed aggressive DMARD therapy compared to older patients
Harries et al (2006) [Harries, Forrest et al. 2007]	Semi-structured interviews using electronic, fictional patients of 85 doctors (29 cardiologists, 28 elderly specialists, and 28 general practitioners)	• For those **patients aged ≥ 65 years**, the treatment preferences of 46% general practitioners and elderly specialists, and 48% of cardiologists changed significantly compared to younger patients
b) Studies associated with atrial fibrillation		
Bajorek et al (2002)[Bajorek, Krass et al. 2002]	Retrospective study of medical records of 262 AF patients aged 65 or more	• **Patients aged 80 years** or more were 5.46 times less likely to receive warfarin compared to those aged 65-79 years (OR 5.46, 95% CI 2.57-11.57)
Perera et al (2009) [Perera, Bajorek et al. 2009]	A prospective study of 220 AF **patients aged 70** or more	• In frail patients (older than non-frail patients), the likelihood to receive warfarin on hospitalisation and discharge from hospital decreased by 2.9 times (95% CI 1.5-6.0) and 8.6 times (95% CI 4.3-17.5) compared to non-frail patients
Gladstone et al	Analysis of data from a prospective database of stroke patients	• 39% of the AF patients (**mean age 77 years**) with a previous

(2009) [Gladstone, Bui et al. 2009]		ischaemic stroke were using warfarin with subtherapeutic normalised ratio, • 15% were not using any antithrombotic medication
Gallagher et al (2008) [Gallagher, Rietbrock et al. 2008]	Analysis of patient data from computerised medical records of general practitioners	• **In Patients aged ≥ 85 years** the likelihood to receive warfarin therapy was 0.16 times compared to patients aged 40-65 years (RR 0.16, 95% CI 0.15-0.18)
Bajorek and Ren (2012) [Bajorek and Ren 2012]	A retrospective audit of medical records of 201 AF patients at a teaching hospital	• Compared to patient aged < 80 years, **those aged 80 ≥ years** were less likely to receive warfarin therapy (52.5% vs 40.2%, p = 0.03) • Of those 155 patients found eligible for warfarin use, only 55% actually received the therapy
Simpson et al (2005) [Simpson, Wilson et al. 2005]	A retrospective study of 377439 patients using a computerised database	• **In Patients aged >75 years** with ischemic stroke, the odds of receiving statin therapy were 0.43 times compared to patients aged < 65 years (95% CI 0.38-0.49) • **In Patients aged > 75 years** with ischaemic stroke and AF**,** the likelihood to receive warfarin therapy was 0.30 compared to those aged < 65 years (95% CI 0.18-0.50)
Waldo et al (2005) [Waldo, Becker et al. 2005]	A retrospective study of 954 inpatients	• **Patient age of > 80 years** was identified as a strong predictor of warfarin underuse (OR 0.663, CI 0.48-0.90, p=0.008)
The FALSTAF Study Group (2007) [Leizorovicz, Cohen et al. 2007]	A prospective study with 5893 outpatients with AF	• The proportion of patients treated with vitamin K antagonists decreased with age (86% of those aged 60-70 years vs 63% of those aged ≥ 80 years) • **Patients aged ≥ 70 years** were 0.90 times more likely not to receive vitamin K antagonists compared to younger patients (95% CI 0.89-0.92)
Friberg et al (2006) [Friberg, Hammar et al. 2006]	A retrospective study of 2800 AF patients using a hospital data with both inpatients and outpatients included	• **In AF patients aged ≥ 80 years** (with indication for, and no contraindication to, warfarin therapy), the likelihood to receive the therapy was 0.3 times compared to those aged 60-74 years (95% CI 0.2-0.5)

DeWilde et al (2002) [DeWilde, Carey et al. 2006]	A retrospective electronic data analysis available from general practices	• Compared to patients aged 55-64 years, those **aged ≥ 85 years** were 0.28 times more likely to not receive warfarin therapy
c) Studies associated with other clinical conditions		
Dudley et al (2002) [Dudley, Bowling et al. 2002]	A retrospective study of 1790 patient records	• Compared to patients aged < 75 years, a smaller proportion of **patients aged ≥ 75 years** received thrombolysis (47% vs 27%), β-blockers (53% vs 26%), and aspirin (80% vs 59%) ($p < 0.01$)
Avezum et al (2005) [Avezum, Makdisse et al. 2005]	Data analysis from the Global Registry of Acute Coronary Events (GRACE) observational study	• **After the age of 65 years,** the percentage of patients receiving aspirin, statins, β-blockers, and thrombolytic therapy decreased ($p < 0.001$) with increasing patient age
Peake et al (2003) [Peake, Thompson et al. 2003]	A questionnaire-based study conducted across 48 hospital trusts.	• The rate of histological diagnosis, active treatment, and survival decreased after **the age of 65 years**
Tran et al (2004) [Tran, Laupacis et al. 2004]	A retrospective, chart review based cohort study of 5131 acute myocardial infarction patients	• The odds of receiving aspirin therapy within 6 hours of hospital arrival in patients aged ≥ 65 years (with no contraindications) were 0.48 times compared to younger patients (95% CI 0.39-0.57)
Woodard et al (2003) [Woodard, Nadella et al. 2003]	A retrospective data analysis of 480 women with breast carcinoma	• Compared to women aged < 50 years, in women **aged ≥ 65** (with oestrogen receptor positive breast carcinoma) the odds of not receiving chemotherapy were 62 times greater
Alibhai et al (2003) [Alibhai, Krahn et al. 2004]	A retrospective cohort study of 347 patients with newly diagnosed prostate carcinoma	• **In Patients aged ≥ 80 years,** the odds of receiving potentially curative therapy were 0.05 times compared to patients aged < 60 years (95% CI 0.01-0.24)
Hanlon et al (2011) [Hanlon, Wang et al. 2011]	A longitudinal study of 3692 **older veterans aged ≥ 65 years**	• 25.4% of patients with depression did not receive antidepressant treatment
Sloane et al (2004) [Sloane, Gruber-Baldini et	Data gathered for 2014 **patients aged ≥ 65 years** living in assisted living settings	• 328 patients with CHF: 62.2% did not receive an ACE inhibitor • 172 patients with prior MI: 60.5% did not receive aspirin and

al. 2004]	76.2% did not receive β-blockers • 435 patients with history of stoke: 37.5% did not receive an anticoagulant or antiplatelet therapy • 315 patients with osteoporosis: 61.0% did not receive calcium supplementation and 51.1% did not receive any treatment

AF: Atrial Fibrillation, DMARD: Disease-Modifying Anti-Rheumatic Drugs, OR: Odds Ratio, RR: Relative Risk, CHF: Congestive Heart Failure, MI: Myocardial Infarction, ACE: Angiotensin-Converting Enzyme, CI: Confidence Interval, p: Probability value

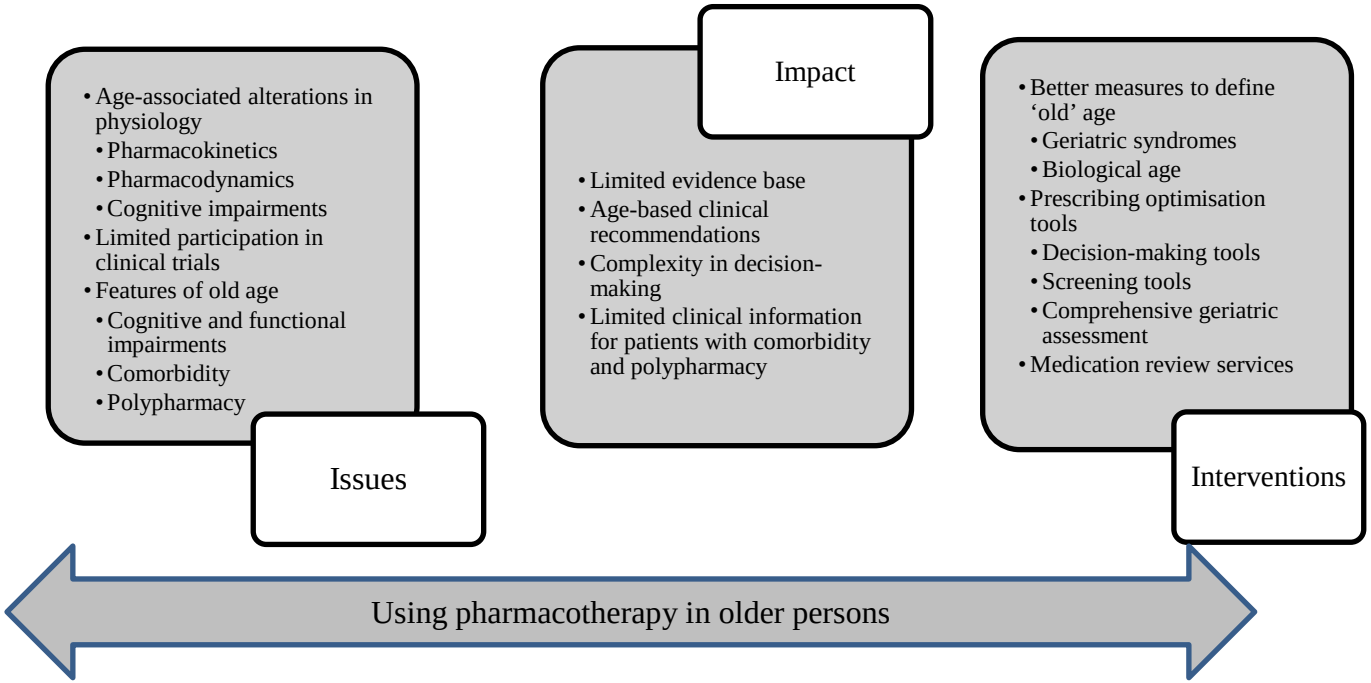

Figure 1 Factors influencing the use of pharmacotherapy in the elderly