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Review

Pharmacotherapy in the ageing patient: The impact of age *per se* (A review)

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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.

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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 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 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 et al., 2002; 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 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 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 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 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 2000–2014 (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 Tiers 2 and 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 et al., 2002; Dudley et al., 2002; Peake et al., 2003; Tran et al., 2004; Avezum et al., 2005; Friberg et al., 2006; Perera et al., 2009; Wright et al., 2009; Bajorek and Ren, 2012); four studies were based in general practice (Simpson et al., 2005; DeWilde et al., 2006; Leizorovicz et al., 2007; Gallagher et al., 2008); and three studies utilised disease-specific databases (e.g. disease-specific registries) (Woodard et al., 2003; Alibhai et al., 2004; Gladstone 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 et al., 2002; Fraenkel et al., 2006; Harries et al., 2007; Kievit 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 et al., 2002), β -blockers (Dudley et al., 2002; Hajjar et al., 2002; Sloane et al., 2004; Tran et al., 2004; Avezum et al., 2005), statins (Avezum et al., 2005), angiotensin converting enzyme inhibitors (Sloane et al., 2004), aspirin (Dudley et al., 2002; Wright et al., 2009), antidepressants (Hanlon et al., 2011), calcium supplements (Sloane et al., 2004), and chemotherapy (Peake et al., 2003; Woodard et al., 2003), 8 studies specifically reported the underutilisation of warfarin in older patients (Bajorek et al., 2002; Simpson et al., 2005; Waldo et al., 2005; Leizorovicz et al., 2007; Gallagher et al., 2008; Gladstone et al., 2009; Perera et al., 2009; Bajorek and Ren, 2012). These studies reported that 15–21% of atrial fibrillation patients did not receive any anticoagulation therapy (Waldo et al., 2005; Gladstone et al., 2009), despite being at high risk of stroke and guideline recommendation, and in the absence of any contraindication to the therapy (Friberg et al., 2006; Gladstone et al., 2009;

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