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**Achieving Appropriate Medication for Older Adults: A Multidimensional
Perspective**

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Highlights

- Polypharmacy has a multifactorial cause and, therefore, requires a multidimensional approach.
- Randomised controlled trials must overcome barriers to the inclusion of older people so they can be more representative and informative.
- Drug design must take into consideration older people's needs and preferences.
- Regulation will enforce patient-centric drug design.
- In an age of conflicting guidelines, the individual patient must remain at the centre of care.
- Clinical decision support systems can help clinicians to tailor medication to patients' needs.
- Seamless communication and the involvement of patients and their carers in the review process are central to achieving appropriate medication for older people.

Highlights

- Polypharmacy has a multifactorial aetiology and, therefore, requires a multidimensional approach.
- Drug RTCs must overcome barriers to include older people so they can be representative and informative.
- Drug design must take into consideration older people's needs and preferences from its inception.
- Regulation will enforce patient-centric drug design.
- In an age of conflicting guidelines, the individual patient must remain at the centre of care.
- Clinical decision support systems can effectively help clinicians to tailor medication to patients' needs.
- Seamless communication and involving patients and their carers in the review process is central to achieve appropriate medication in older people.

Abstract

Achieving appropriate medication is a multidimensional process. Current research on polypharmacy mainly focuses on drug appropriateness, but little is devoted to what determines the ongoing challenge. The authors, with their diverse clinical, pharmaceutical and regulatory backgrounds, offer a narrative review on the causes of inappropriate polypharmacy and how to avoid it. Inappropriate polypharmacy may stem from the systematic exclusion of frail older patients from landmark randomised controlled trials, which has prevented the accurate establishment of the clinical benefits of a drug for that ever-growing group of patients. Nonetheless, what may determine the usefulness of a drug in a specific patient cohort is its design. Patient-centric drug product development must, therefore, account for older people's characteristics, so that drugs are better formulated from their inception. This novel drug development process has significant implications for industry and requires adequate regulation. Clinicians must understand and be part of drug development. Explicit criteria such as STOPP/START provide guidance on identifying opportunities and circumstances to review medication but achieving appropriateness is far more complicated. New healthcare technology may pave the way to better-tailored interventions at a healthcare system level, but patient and

advocate voices, as well as communication and continuity of care, must remain at the core. In conclusion, inappropriate polypharmacy results from the combination of multiple factors. Achieving appropriate medication for older adults requires merging different disciplines and a focus on patients' needs and expectations.

Keywords: Older Adults; Patient-centric Medication; Medication Review

Introduction

Ageing is a global phenomenon. Fifty percent of adults aged 75 and older have now at least three concomitant conditions[1]. In the United Kingdom, for instance, the 75 years and older cohort grew by 89% since 1974 and it is now 8% of the total population[2]. Multiple chronic conditions lead to polypharmacy and, currently, 75% of older adults are prescribed more than five different drugs[3].

Older adults have the highest prevalence of polypharmacy, adverse drug reactions, and health care consumption[4, 5]. It is unquestionable that medication appropriateness is at the core of the patient-physician relationship, but deprescribing is still a challenging responsibility with very few pragmatic solutions. Understanding the different dimensions, aspects, and causes of the challenge will potentially empower clinicians in achieving better medication appropriateness for their older patients.

The authors offer a comprehensive narrative review on the causes of inappropriate polypharmacy in older people, exploring the fields that require improvement to achieve medication appropriateness. Figure 1 synthesizes the outline of the article, illustrating what the authors consider to be the primary drivers of inappropriate polypharmacy requiring an integrated approach for better outcomes in older patients.

1. Patient heterogeneity and lack of representation in trials

Inclusion criteria in trials tend to create homogeneous samples, mitigating biases. However, this approach generates distance from the richness and diversity of the real clinical world, which may lead to a lack of reproducibility of the study findings in particular cohorts, such as older adults. Furthermore, outcomes in randomised clinical trials (RCTs) often mirror benchmarks of health care system performance and may not be the relevant ones for the older cohort[6].

Researchers report many barriers to inclusion of older adults in clinical trials. Evidence indicates that low participation levels are often associated with decreased physical and cognitive reserve[7, 8]. Nevertheless, patients report other obstacles, such as impairments on instrumental activities of daily living (e.g., using the telephone or organising transport to research facilities). Additionally, fears of outcome assessment failure due to comorbidity, drug-drug interaction, and the need for age-adapted formulations may be perceived by researchers as compelling arguments to use a chronological age below 65 years as an inclusion criterion[7, 9]. Therefore, to counteract this default position, the ICH E7 regulatory guideline on 'studies in support of special populations: geriatrics' requires older adults to be included in clinical trials[10].

The representation of complex older adults in clinical trials may not only provide a better understanding of therapies but also contribute to the development of improved/gold standards in health care systems, assist in the establishment of optimal dosage in older adults, and help to determine cohort-specific adverse drug reactions.

In order to achieve a more representative participation of older patients in clinical trials, these would need to: (1) consider the appropriateness of the drug design by establishing safety on organs and systems of particular importance in older patients

before phase 2 trials; (2) provide immediate access to medical care should the need arise; (3) improve communication with participants using face-to-face interviews; (4) overcome barriers to follow-up, e.g. organising home visits or embedding research in clinical settings; and (5) allocate acceptable budgets and timeframes to accommodate older adults needs.

2. Lack of drug products tailored to older patients' needs

Drug discovery is the first step of the drug product development endeavour. After identifying a promising drug compound, experiments are conducted to obtain data on the composition, manufacturing method, and appropriate route of administration to deliver the drug to the body, i.e., to convert the drug into a drug product. The design of the drug product may significantly influence pharmacokinetics and pharmacodynamics in different patient groups, leading to different clinical and therapeutic outcomes.

'Patient centric drug (product) development' is a recently coined term to define what needs must be accounted for in an individual patient or distinct populations. The term encompasses targeted patients' physiological, physical, psychological, and social characteristics as the pivotal point in the development of the necessary variety of products within the drug portfolio[11, 12]. The main challenge lies within the heterogeneity of specific patient populations, such as older people. The ageing population has diverse physiological, physical and, cognitive characteristics rendering the individuals from fit to frail[13]. Therefore, an effective patient-centric approach to meet the needs of older patients is required, particularly for the ones with polypharmacy. Messina et al. showed that only a few studies considered the relationship between the drug product design and their senior friendliness[14]. Thus, a comprehensive assessment of the patients' characteristics will require special attention in the overall design of a new drug product.

Physiological, physical, and cognitive functions have significant influence on the drug products performance. Changes associated with ageing have an impact on drug performance[15]. Conversely, physical ability plays a central role at the point of administration. To prevent any unlicensed modification of the drug product, pharmaceutical manufacturers will need to consider features into the design of a new drug to enable older patients to take their drugs as intended.

As an example, in the case of an enteric-coated tablet with high dose strength of a drug used for the treatment of age-related disease, it is important to consider gastrointestinal physiology (e.g., altered gastric pH) and administration-related factors (e.g., difficulty in swallowing or remembering the time to take the drug) at the early stage of drug product design. The interchangeability of (generic) drugs may lead to overdosing and duplication as treatments can have different storage, dosing, and administration requirements. Thus, medication self-management by ageing populations should be a priority for developers. However, for some types of drugs, the development of improved senior-friendly products may only be possible by further strengthening the regulatory provisions.

3. Lack of guidance and education

The 1993 ICH E7 regulatory guideline on 'studies in support of special populations: geriatrics' states that 'patients entering clinical trials should be reasonably representative of the population that will be treated by the drug'[10]. As previously argued, older people are the main drug users and the most relevant population in general hospitals; thus, one might expect the needs of older people to be well catered for in drug product development and upon market entry. The evidence discussed so far shows otherwise.

Since 2011, the European Medicines Agency (EMA) has undertaken efforts to better address older people's needs within the current legislative framework[16]. A Geriatric Medicines Strategy was developed and new guidance documents

increasingly included statements on older people, such as the EMA Good Practice Guide on risk minimisation and prevention of medication errors[17]. Following an earlier concept paper in May 2017, a reflection paper on the pharmaceutical development of medicines for use in the older population was adopted for public consultation.[12] The paper provides an overview of aspects worthy of consideration that are not yet addressed elsewhere, such as the administration of drugs through feeding tubes, drug product modifications to facilitate the intake or to lower the dose, medication management including polypharmacy, multiple compliance aids, and drug-dispensing systems. To take account of clinical practices, all stakeholder parties, including patients and patient representatives, doctors, nurses, and pharmacists were invited to convey their feedback to the EMA.

In the last decades, clinical guidelines targeted the management of a single condition. As the prevalence of multimorbidity increases with age[1], physicians will prescribe a higher number of drugs should they strictly follow guidelines for each independent condition[18]. Additionally, clinical guidelines stem from RCTs that often use less relevant outcome measures in older age (e.g. crude mortality; readmission) or just simply exclude this cohort[19], an issue that may compromise their generalizability to people living with geriatric syndromes, especially frailty[20, 21].

4. Preferences and perceptions

Questioning guidelines in the particular context of older patients with multimorbidity or frailty is a recent topic and mostly based on observational studies. Deprescribing RCTs are still ongoing, and the safety and efficiency have not yet been fully established[22, 23]. Therefore, deprescribing may raise medico-legal concerns among physicians. However, a recent article discussing the matter in the legal context of the United Kingdom concluded that physicians can safely deprescribe and that, legally, deprescribing is not different from prescribing[24]. Lack of training, awareness, time pressures, patient willingness, and past experiences may represent

stronger barriers to deprescribing than legal aspects[25]. In a systematic review, Anderson *et al.* identified several highly interdependent factors influencing the ability of a physician to discontinue a potentially inappropriate medication (PIM). This related to lack of awareness, inertia, or feasibility domains. These results suggest that attention should be given to increase skills and knowledge on safe deprescribing among young and senior doctors[26].

General Practitioners (GPs) play a noteworthy role in patients and caregivers' perception of the appropriateness of a given drug and should take a central role in the deprescribing process[27]. A recent study in nursing homes revealed that healthcare professionals and patients did not share the same priorities regarding deprescribing, but agreed that the adequacy of medication history and identifying patients' goals of care were the most important ones[28]. Therefore, shared-decision making appears to be the core element of a safe and well-accepted deprescribing strategy, a valuable contribution to the control of ever expanding health care budgets.

5. No systematic use of medication review support tools

Easy-to-use software to guide geriatricians and other clinicians in drug therapy has the potential to improve patient care. However, while some existing resources help clinicians to improve appropriate prescribing, such as explicit screening criteria and drug-drug interaction databases, there are fewer applications available to combine different resources to streamline a comprehensive medication review. This process consists of a review of over- and underprescribing, ineffective prescribing, side-effects, contra-indications, drug-drug interactions, drug-disease interactions, excipient overload, incorrect dosing, product modifications, and dosing frequency[29, 30].

Web-based clinical decision support systems, such as the STRIP Assistant, can enable physicians and pharmacists to assess the medication appropriateness in daily

practice. The information used to generate the advice report includes clinical interactions, double-medication, contra-indications, side effects, dosage and dose frequency, and specific implementations of the STOPP/START criteria. The rules incorporate not only patients' conditions and drugs, but also their contra-indications, complaints, and relevant physiological determinants (e.g. renal function). The report results in items of advice recommending users to add new drugs, to remove extra ones, or to adjust doses. Different barriers, such as the need for additional information beyond the medication list, were encountered and addressed in the development process [31].

Broad use of the STRIP Assistant aims at improving clinical outcomes and reducing health care use, consumption, and costs. The evaluation and review of users' feedback in the ongoing OPERAM (OPTimising thERapy to prevent Avoidable hospital admissions in the Multimorbid elderly) trial, a large European project, will enable the production of a practical and efficient decision support tool. So far, the STRIP Assistant showed to improve medication appropriateness from 58% to 76% ($p < .001$) and to reduce inappropriate drug-choice decisions from 42% to 24% ($p < .001$) [31].

6. Ineffective shared-decision making process

Older patients, their relatives, and carers often feel too many drugs are prescribed and are willing to decrease this number [32]. However, acceptance of deprescribing may not be straightforward. Several barriers to deprescribing have been identified among patients, such as disagreeing with the appropriateness of the cessation decision, the influence of relatives, or non-specific fears about stopping a drug [33]. Nonetheless, it is possible to overcome many of these perceived fears delivering patient-centred care in a structured multidisciplinary intervention focusing on the patient perspective [34]. This finding highlights the need for placing communication at the centre of medication review. Figure 2 explores a possible stepwise approach to a real life medication review based on a shared-decision process. It builds on the Pharmacist's Patient Care Process from the Joint Commission of Pharmacy

Practitioners (JCPP) but stresses the importance of communication, consensus, and continuity of care[35].

Conclusion

The nature of inappropriate polypharmacy is multifactorial and requires a sound knowledge of its causes to be effectively addressed. Although practical solutions integrating shared-decision processes correspond to state-of-the-art patient-centred care and address patients' expectations, a definite answer for this increasingly challenging problem in the older population will always reside in a combination of regulatory affairs, drug development, and a shift from disease-centred to patient-centred guidelines.

The current screening tools and web-based clinical decision support systems require further elaboration. Nonetheless, an advanced comprehensive approach would maximise the benefit of these tools and provide a better therapeutic outcome for older patients with polypharmacy.

Regardless technological enhancement, achieving medication appropriateness in older people will always require excellent communication skills and continuity of care.

Contributors

Luis Mieiro conceptualised, drafted, reviewed and edited the paper.

Mine Orlu conceptualised, drafted, reviewed and edited the paper.

All other authors contributed to the original drafting of the paper.

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Conflict of interest

Diana van Riet-Nales is an expert of the European Medicines Agency (EMA). The authors declare that they have no other competing interests.

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Figure captions

Figure 1: Primary drivers of inappropriate polypharmacy in older people

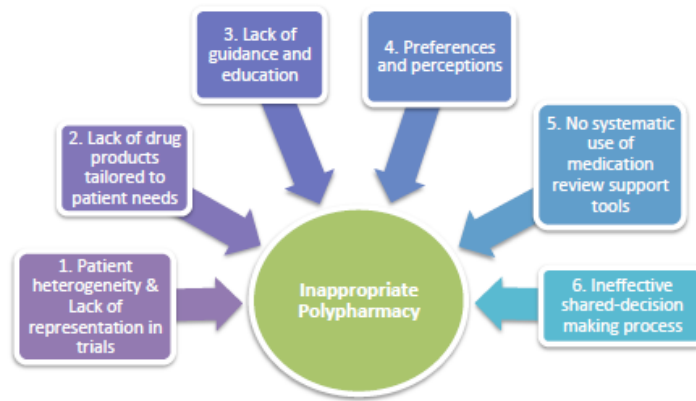


Figure 2: The shared-decision medication review cycle. Legend: PIM – Potentially Inappropriate Medication; PPO – Potential Prescribing Omission.

