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Polypharmacy and Polytherapy: Current Perspectives on Risk–Benefit Balance and Strategies for Optimization of Multidrug Treatment in Patients

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ABSTRACT:

Introduction

Thanks to the current state of medical knowledge and established clinical guidelines, healthcare professionals can provide patients with comprehensive pharmacotherapy. This is particularly important for individuals with multimorbidity or those for whom monotherapy is insufficient to achieve the desired therapeutic outcomes. However, it is essential to recognize that polypharmacy can pose significant risks to patient safety, especially when care is provided by multiple healthcare providers. Therefore, it is crucial to distinguish rational polypharmacy from inappropriate and undesirable practices, and to be able to identify and avoid adverse effects associated with poorly managed pharmacotherapy and harmful drug interactions.

Aim of the Study

This study aims to explore and assess the potential benefits and risks of multidrug therapy in clinical practice, with particular attention to the therapeutic rationale of polypharmacy and the adverse consequences associated with it.

Materials and methods

A comprehensive review of the literature was performed using electronic databases such as PubMed, Google Scholar, and ScienceDirect to identify pertinent publications. The keywords used in the search strategy included “polypharmacy”, “polypragmasia”, “multidrug therapy”.

Conclusion

The use of multiple medications in the treatment of chronic diseases, as well as other serious medical conditions, is a common and often necessary aspect of modern patient care. The careful selection and combination of several drugs to achieve the desired therapeutic outcomes is essential in contemporary clinical practice. However, pharmacotherapy must be closely monitored to ensure that each prescribed medication contributes positively to the patient’s health. It is the responsibility of the multidisciplinary healthcare team to collaboratively manage the patient’s treatment, oversee polypharmacy, prevent potential adverse drug reactions, and discontinue medications that are no longer necessary.

Key words

Polypharmacy, polypragmasia, multigrug therapy

INTRODUCTION

Polytherapy is a common approach in modern pharmacotherapy. It involves the use of two or more pharmacological agents with the aim of achieving an enhanced therapeutic effect. The synergistic action of drugs allows for increased treatment efficacy without a corresponding significant rise in the risk of adverse effects. This approach benefits patients and becomes necessary when monotherapy proves insufficient or ineffective. Selecting the most appropriate and effective therapy remains a significant challenge for healthcare providers [1]. However, when a patient is prescribed more medications than clinically indicated, and significant interactions between them occur, the phenomenon is referred to as polypharmacy. It may result from consultations with multiple physicians, a lack of understanding of drug mechanisms, or insufficient knowledge about drug-drug and drug-disease interactions [2]. Polypharmacy contributes to poor medication adherence and increases the incidence of adverse drug reactions [3]. This issue is particularly concerning in the elderly due to the high prevalence of multimorbidity in this population. According to current data, the healthcare burden related to

multimorbidity is expected to increase significantly, driven by both the aging population and the growing number of individuals living with multiple chronic conditions [4], [5]. In Europe, the proportion of individuals aged 65 and older is projected to rise from 34.1% in 2019 to 56.7% by 2050 [6]. Older patients are especially susceptible to side effects due to decreased renal and hepatic function, which alters drug metabolism and elimination [7]. Age-related changes in body composition and physiology also affect drug pharmacokinetics and pharmacodynamics, further influencing both dosage and mode of drug administration in geriatric patients [8]. Moreover, age-related cognitive decline may lead to difficulties in medication adherence [9]. Nearly 50% of elderly patients are prescribed at least one medication that is not medically necessary [10]. Additionally, more than half of medications are prescribed, dispensed, or sold inappropriately - often without a prior review of the patient's current pharmacological regimen [11].

AIM OF THE STUDY

Given the rapidly aging population and the increasing prevalence of chronic diseases, this article aims to present both the benefits and risks of polypharmacy in elderly patients, as well as its growing significance and potential risks in individuals with chronic conditions.

THE STATE OF KNOWLEDGE:

Polytherapy in contemporary clinical practice

The use of polytherapy is associated with numerous benefits. Medications may belong to the same or different therapeutic classes, and their actions can be complementary or based on different mechanisms of action. A rational combination of drugs can lead to improved health outcomes. Appropriate treatment involving multiple medications may help prevent unplanned hospital admissions. Notably, patients taking four to six medications were not found to be at greater risk of unplanned hospitalization compared to those taking one to three drugs [12]. The primary goal of effective combination therapy is to prescribe only those medications that are necessary for the treatment of a specific condition [13]. This remains a significant challenge due to the lack of clear guidelines on prescribing patterns and prioritizing treatments in patients with multimorbidity. One example of such a guideline is the structured medication review procedure developed by a Scottish research group [14]. Similarly, the Polish Pharmaceutical Society issued national guidelines for conducting medication reviews in 2023 [15]. These reviews enable the collection of a comprehensive patient history and allow for a thorough evaluation of the pros and cons of ongoing pharmacotherapy. This process is especially critical

in elderly and multimorbid patients, due to the high number of medications they often use. Such a consultation should include the identification and assessment of drug-drug and drug-disease interactions, recognition of inappropriate pharmacotherapy, evaluation of the necessity of each drug, and assessment of patient adherence. If any irregularities are identified, adjustments in the treatment plan should be implemented [16].

A meta-analysis of 295 studies conducted between 1997 and 2022 found that the prevalence of polypharmacy in the general population was 37%, increasing to 45% in older adults. The highest prevalence was observed in Europe, reaching 68% [5]. In the United States, during 2021–2022, 88.6% of individuals aged 65 and older were taking prescription medications [17]. According to data from the SHARE WAVE 6 European study conducted in 2015, more than five medications were used by 26.7% of individuals aged 65–74, and by 43.1% of those aged 85 and older [18]. The most commonly prescribed medications in patients over 70 years of age in the United States and Canada between 2015 and 2017 included anticoagulants, beta-blockers, loop diuretics, sedatives, and non-opioid analgesics [19].

In certain medical conditions, polypharmacy is desirable to ensure better control of health parameters. By appropriately combining medications, improved therapeutic outcomes can be achieved compared to monotherapy.

Multidrug Strategies in Diabetes Management

For many individuals with type 2 diabetes, the use of more than one medication is necessary to effectively control blood glucose levels and prevent complications associated with the disease [20]. According to the American Diabetes Association (ADA) guidelines, combination therapy may be employed to achieve and maintain target glycemic levels. Metformin, along with lifestyle modification, is recommended as the first-line treatment, while additional oral antidiabetic agents or injectable therapies should be introduced as needed [21].

Oral medications used in the treatment of type 2 diabetes have different, complementary mechanisms of action; therefore, their combination can result in improved glycemic control compared to the use of a single agent at its maximum dose [22]. An increasing number of studies confirm that combination therapy, as compared to monotherapy, provides significant clinical benefits. Various combinations—such as metformin with a DPP-4 inhibitor, a thiazolidinedione, an SGLT-2 inhibitor, or a GLP-1 receptor agonist—have demonstrated efficacy in improving glycemic outcomes [23].

In selected cases, initiating treatment with combination therapy may also be considered [21]. A 2018 review demonstrated that initial combination therapy with metformin and another antidiabetic agent leads to a more pronounced reduction in glycated hemoglobin (HbA1c) levels than metformin monotherapy [24]. Numerous studies have confirmed the effectiveness of combining basal insulin with a GLP-1 receptor agonist. This therapeutic approach is already implemented in clinical practice and is reflected in current guidelines. Moreover, the availability of fixed-ratio combination preparations of these agents makes this an appealing therapeutic option for patients who have not achieved satisfactory outcomes with previous treatment regimens [25].

Combination Therapy in Hypertension

In the case of secondary prevention of myocardial infarction, treatment with agents from four therapeutic classes is recommended: beta-blockers, statins, ACE inhibitors, and antiplatelet agents [26]. The 2024 guidelines of the European Society of Hypertension for the management of elevated blood pressure and hypertension recommend that initial therapy should consist of either an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB), combined with a thiazide/thiazide-like diuretic or a calcium channel blocker (CCB) [27]. The guidelines also emphasize using fixed-dose combination therapies in a single tablet to enhance patient adherence.

Optimizing Pain Control Through Polytherapy

Another example of a beneficial drug combination is in the treatment of chronic pain [28]. The synergistic effect of opioid and non-opioid analgesics can reduce the required opioid dose and thereby decrease adverse effects such as constipation, drowsiness, and vomiting. One such combination is paracetamol with tramadol.

Multimodal Treatment in Depressive Disorders

According to researchers, one-third of psychiatric patients require polypharmacological treatment, taking three or more medications concurrently [29]. For instance, clinical practice may involve the co-prescription of multiple agents from the same pharmacological class - for example, two selective serotonin reuptake inhibitors during a depressive episode - or the use of medications from distinct drug classes at full therapeutic doses to address a single symptom cluster, such as combining valproate with an atypical antipsychotic for the management of mania [29], [30]. Additional factors contributing to the use of multiple medications may involve the necessity to address specific symptom domains, the co-management of separate but

comorbid psychiatric conditions, the persistence of symptoms unresponsive to monotherapy, or the mitigation of side effects resulting from primary pharmacological agents [31].

Risks and Challenges of Polypharmacy

A systematic review from 2013 demonstrated a strong and well-established association between polypharmacy and adverse clinical outcomes [32]. Older adults constitute a particularly vulnerable population, frequently affected by multimorbidity and polypharmacy. Age-related physiological changes influencing drug absorption, metabolism, and pharmacodynamic responses present significant challenges in optimizing pharmacological treatment in this group. Consequently, polypharmacy becomes a major concern, potentially leading to adverse outcomes and increased healthcare costs [33], [34].

Numerous studies have shown that polypharmacy is associated with adverse drug reactions, drug-drug interactions, and nonadherence to medical recommendations. Furthermore, it contributes to deteriorating health outcomes, including falls, fractures, malnutrition, and increased rates of hospitalization [34], [35], [36].

Adverse Drug Reactions (ADRs): Adverse drug reactions (ADRs) can be defined as harmful or unpleasant effects resulting from the use of a medication, which may pose a potential risk if the therapy is continued and require appropriate interventions, such as prevention, specialized treatment, dosage adjustment, or complete discontinuation of the drug [37]. One study demonstrated that patients taking multiple medications had an 88% higher risk of experiencing adverse reactions [38]. It is also noteworthy that adverse events are reported ten times more frequently in older adults than in younger individuals [39].

Polypharmacy can trigger a vicious cycle, where an increasing number of medications leads to adverse drug reactions that are misinterpreted as symptoms of new or existing conditions. This misinterpretation often results in the prescription of additional drugs, further exacerbating the problem [40].

Drug–drug interactions (DDIs): Older adults who take multiple medications are particularly vulnerable to adverse drug interactions [41]. A study conducted among an elderly outpatient population revealed that nearly half were at risk of experiencing drug-drug interactions [42]. When assessing the likelihood of such interactions, it is crucial to take into account multiple factors, including age-related pharmacokinetic and pharmacodynamic alterations, overall physical frailty, and psychosocial aspects [41]. In a study of hospitalized patients taking at least five medications, potential interactions involving cytochrome P450 liver enzymes were

identified in up to 80% of cases. These findings highlight alterations in drug biotransformation processes that may significantly affect treatment efficacy and safety [43]. Drug–drug interactions are a common cause of adverse drug events (ADEs) and often result in patient hospitalizations [44].

Nonadherence: It is estimated that every second elderly patient does not fully adhere to therapeutic recommendations, often due to the complexity of pharmacotherapy regimens and the necessity of taking multiple medications [45]. Moreover, cognitive and sensory impairments frequently pose further challenges to maintaining proper medication adherence [46].

Hospitalizations: Among hospitalized older adults, polypharmacy is observed in 20–60% of cases, depending on the criteria used for patient selection. Hospitalization poses significant risks, particularly for the elderly, as it is often associated with a permanent decline in physical function, cognitive abilities, and overall quality of life [47]. A systematic literature review analyzing factors influencing the effectiveness of treatment in hospitalized elderly patients found that polypharmacy is a statistically significant predictor of hospital length of stay, mortality, and the risk of rehospitalization [48].

Geriatric Syndromes: Patients using multiple medications are more likely to experience cognitive impairment and reduced functional capacity [49], [50]. Studies have also demonstrated a significant impact of polypharmacy on the increased risk of lower urinary tract symptoms, including urinary incontinence, particularly in older women [51], [52]. A cohort study involving 885 Connecticut residents aged over 72 years demonstrated a correlation between the use of a higher number of medications and an increased risk of adverse outcomes, including weight loss and balance disorders, which may subsequently lead to falls—events that pose a significant threat to the health and lives of older adults [53]. Moreover, a 2013 study reported that the risk of falls among older individuals increases by 7% with each additional medication taken [54].

Increased Healthcare Costs: Polypharmacy contributes to increased healthcare expenditures for both individual patients and the healthcare system as a whole. Studies conducted in Japan and Sweden have demonstrated that the concurrent use of multiple medications is associated with elevated pharmacotherapy costs, a higher frequency of outpatient visits, and more frequent hospitalizations. These factors collectively lead to a significant rise in overall treatment expenditures [32], [55], [56].

The term *polypharmacy* remains ambiguous and lacks a universally accepted definition. A narrative review published in 2021 identified approximately 143 definitions of polypharmacy and related terms, the majority of which are based solely on the number of concurrently used medications. These definitions vary and often include gradations of polypharmacy severity - such as minor, mild, moderate, major, or excessive [57]. The most commonly used definition refers to the concurrent use of five or more medications [57], [58], a criterion also endorsed in the 2019 WHO report [59].

In the future, the establishment of a clear threshold criterion will be essential to facilitate a standardized and globally applicable definition of polypharmacy [60].

Healthcare Professional Interventions in Managing the Risks of Polypharmacy

Assessing the effectiveness of pharmacotherapy involving multiple medications and identifying potential risks to patients related to polypharmacy can be challenging for healthcare professionals [61]. Contrary to expectations, broad access to healthcare services - including consultations with various specialists - may actually contribute to the complexity and risks associated with polypharmacy [61], [62]. Therefore, it is crucial to implement systemic measures aimed at preventing the negative consequences of polypharmacy. It is also essential that patients maintain an up-to-date list of all medications and supplements they are taking and bring it with them to every medical appointment [62]. The collection of such data is possible through the implementation of medication reviews.

From Review to Action: The Role of Medication Reviews in Guiding Deprescribing Decisions

Medication reviews can be conducted based solely on the patient's medical records or supplemented with a detailed patient interview. This procedure can be carried out in various healthcare settings, including pharmacies, primary care clinics, and hospitals [15]. Researchers point out, however, that conducting a medication review alone may not be sufficient to reduce the rate of hospital readmissions. However, when a medication review is combined with medication reconciliation and patient education, the likelihood of readmission within 30 days is lower compared to performing the medication review as a standalone intervention. [63]. A clinically relevant medication review requires access to key patient information, including diagnosis, a complete list of prescribed and over-the-counter medications, dietary supplements, and medical devices, as well as detailed data on dosage, frequency, timing, and route of administration. Diagnostic test results, if relevant to therapeutic outcomes, and lifestyle factors

- such as substance use and diet - should also be considered due to their influence on treatment safety and efficacy. Such comprehensive data enable the identification of drug-related problems and support evidence-based pharmacotherapy optimization [3]. Moreover, the literature suggests that, based on a professional analysis such as a medication review, it is worth considering the implementation of deprescribing [62].

Deprescribing is the planned and supervised process of dose reduction or discontinuing medications that may no longer be beneficial or might be causing adverse drug reactions, with the goal of managing polypharmacy and improving patient outcomes [62], [64], [65]. To ensure the effectiveness and clinical benefit of this process, it is essential to incorporate patient education and promote appropriate lifestyle changes [62]. Researchers propose that the process of deprescribing should follow a structured, multi-step approach. It should begin with a comprehensive medication review. Based on the information gathered regarding the patient's current pharmacotherapy and the clinical indications for each medication, a risk–benefit assessment should be conducted to evaluate the therapeutic value and potential adverse effects of drug combinations. This analysis forms the basis for designing a deprescribing plan and initiating dose reduction or drug discontinuation, carried out by qualified healthcare professionals. In this context, collaboration between physicians and pharmacists is particularly valuable and can significantly enhance the safety and effectiveness of the intervention [64], [66].

CONCLUSION

In contemporary medical practice, polypharmacotherapy has become a standard approach, particularly in managing complex or chronic conditions where monotherapy proves insufficient [61]. For certain diseases, achieving optimal patient outcomes necessitates the concurrent use of multiple medications. However, administering more than five drugs simultaneously can increase the risk of adverse drug events, interactions, and diminished therapeutic efficacy [66]. In contemporary clinical practice, managing complex conditions such as hypertension, diabetes, psychiatric disorders, and chronic pain often necessitates the use of multiple medications. This approach, known as polypharmacy, is particularly common among patients with multimorbidity, where monotherapy may be insufficient to achieve optimal therapeutic outcomes. [2], [24], [28], [30]. To ensure safe and effective pharmacotherapy, coordinated efforts among healthcare professionals are essential [63]. Regular medication reviews, deprescribing strategies, and maintaining an up-to-date list of all medications and supplements taken by the patient—coupled

with patient education—are critical components in optimizing polypharmacotherapy. These interventions help mitigate the risks associated with polypharmacy and enhance treatment outcomes [15], [63]. Without implementing these measures, polypharmacotherapy may not only fail to provide the intended therapeutic benefits but could also pose significant health risks to the patient.

DISCLOSURE

Authors' contribution

Conceptualization: JMM, AS and JN;

Methodology: KS and BR;

Software: BR and JN;

Check: JMM and KS;

Formal analysis: BR;

Investigation: JMM and AS;

Resources: JMM and AS;

Data curation: JN;

Writing - rough preparation: BR and AS;

Writing - review and editing: KS, JMM and JN;

Visualization: KS and BR;

Supervision: AS and JN;

Project administration: KS;

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