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REVIEW

An update on the clinical consequences of polypharmacy in older adults: a narrative review

Jonas W. Wastesson [a], Lucas Morin[a], Edwin C.K. Tan[a,b] and Kristina Johnell[a]

[a]Aging Research Center, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet & Stockholm University, Stockholm, Sweden; [b]Centre for Medicine Use and Safety, Faculty of Pharmacy and Pharmaceutical Sciences, Monash University, Parkville, Australia

ABSTRACT

Introduction: Polypharmacy, the use of multiple medications by one individual, is increasingly common among older adults. Caring for the growing number of older people with complex drug regimens and multimorbidity presents an important challenge in the coming years.

Areas covered: This article reviews the international trends in the prevalence of polypharmacy, summarizes the results from previous reviews on polypharmacy and negative health outcomes, and updates a previous review on the clinical consequences of polypharmacy by focusing on studies published after 2013. This narrative review, which is based on a literature search in MEDLINE and EMBASE from January 1990 to June 2018, was undertaken to identify relevant articles. Search terms included variations of polypharmacy and multiple medications.

Expert opinion: The prevalence of polypharmacy is increasing worldwide. More than half of the older population is exposed to polypharmacy in some settings. Polypharmacy is associated with a broad range of clinical consequences. However, methods to assess the dangers of polypharmacy should be refined. In our opinion, the issue of 'confounding by multimorbidity' has been underestimated and should be better accounted for in future studies. Moreover, researchers should develop more clinically relevant definitions of polypharmacy, including measures of inappropriate or problematic polypharmacy.

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Polypharmacy; aged; drug utilization; mortality; multimorbidity

1. Introduction

The number of older adults is increasing worldwide. As more people have the opportunity to live a long life, many will also experience a period of life characterized by the coexistence of multiple health problems [1]. The increasing number of multimorbid older adults with complex drug regimens will continue to be a challenge for the health-care system in the years to come.

Polypharmacy, the use of multiple medications by one individual, can be a rational response to managing complex health problems in older adults [2]. However, there is a growing concern that many older adults are using an inappropriately high number of medications. In particular, complex combinations of drugs can shift the benefits of individual drugs to become harmful when used in a complex drug regimen. This is especially true in nursing homes [3], among very old people [4] and in the context of end-of-life care [5].

There exists no consensual definition of what constitutes polypharmacy [6]. Some have defined polypharmacy as the use of more drugs than clinically indicated [7]. However, this definition relies on a clinical judgment that is difficult to operationalize in large studies. In pharmacoepidemiology and drug utilization research, a strictly numerical threshold is often used to define polypharmacy (e.g. five or more drugs) [6]. Despite the simplicity of such cut-off values, the measurement of polypharmacy remains highly heterogeneous across studies. Differences regarding the inclusion of short-term drug therapies, the length of the period during which drug use is captured, or how to deal with drug switches within the same drug class make comparisons difficult [8]. In general, the term polypharmacy has a negative connotation suggesting potential overuse of medications. Increasingly, scholars are differentiating between inappropriate/problematic and appropriate polypharmacy, where the appropriateness has often been defined based on explicit criteria for drugs to be avoided in older adults in general (such as Beers criteria [9], STOPP/START criteria [10], and Medication Appropriateness Index [11]) but not specifically for older adults with polypharmacy [12,13]. There is a need for standardized tools to define what constitutes appropriate and inappropriate use of polypharmacy. Recently, a set of indicators to define appropriateness of drug use in persons with polypharmacy was suggested based on expert consensus, but these indicators have not yet been operationalized and validated [14].

A number of reviews on the topic of polypharmacy and negative outcomes have been published to date (for an overview, see Section 4.1.). Polypharmacy has been linked to a broad range of negative health outcomes, including falls, frailty, and mortality [15–18]. In this expert opinion, we will first review the international trends in the prevalence of polypharmacy. Secondly, we will review the evidence regarding

CONTACT Jonas W. Wastesson Jonas.wastesson@ki.se Aging Research Center, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet & Stockholm University, Stockholm, Sweden

Article highlights

- The prevalence of polypharmacy in old age is on the rise in high-income countries.
- Polypharmacy is commonly defined as the use of more than an established number of drugs. More refined definitions of polypharmacy including aspects of appropriateness need to be operationalized and validated to facilitate more precise identification of patients at risk of negative consequences.
- Polypharmacy has been linked to a wide range of negative clinical consequences.
- It is difficult to disentangle the negative consequences of polypharmacy from the underlying health conditions for which the drugs are prescribed ('confounding by multimorbidity').
- Providing comprehensive yet balanced pharmaceutical care to older adults with complex health-care needs is a challenge for the future.

This box summarizes key points contained in the article.

the clinical consequences of polypharmacy, thereby updating an earlier review by Maher et al. [18]. Thirdly, we will highlight some of the major methodological and clinically relevant challenges in assessing and reducing the consequences of polypharmacy in older adults.

2. Methods

This narrative review was based on a literature search in MEDLINE and EMBASE from January 1990 to June 2018 in combination with hand searches of reference lists and citation checking. The key search term was 'polypharmacy' and versions of this ('poly-medication', 'multiple medications', etc.). To investigate the trends in the prevalence of polypharmacy, we included all identified original studies reporting the prevalence of polypharmacy at minimum two time points, with at least one year apart, in a population-based study population of older adults (the majority of the study population aged >60 years). To investigate the clinical consequences of polypharmacy, we included both original studies and reviews investigating the association between polypharmacy and different clinical consequences. We excluded articles written in other languages than English. It should be noted that this review is not a systematic review. Instead, we aimed to map the different clinical consequences that have been studied in relation to polypharmacy, which could provide a roadmap for focused systematic reviews targeting specific outcomes. In this review, we focused on studies not included in the original review from 2014 by Maher [18]. The broad range of outcomes studied in relation to polypharmacy were presented in categories based on the authors' expertise and previous literature. The review did not include outcomes related to the economic costs of polypharmacy or the administration of drugs (e.g. adherence).

3. Trends in polypharmacy prevalence

Over the last few decades, several studies have monitored the secular trends in drug use among older adults. We have reviewed population-based studies reporting the prevalence of polypharmacy among older adults at a minimum of two time points. All identified studies reported an increase in the prevalence of polypharmacy (Figure 1 and Table 1). This includes results from the United States [19–21], Europe [22–27], and New Zealand [28]. For example, a population-based Swedish study of persons aged ≥75 years found the prevalence of polypharmacy to increase from 27% in 1988 to 54% in 2001, and 65% in 2006 [24]. Similarly, a nationally representative survey of noninstitutionalized persons in the United States reported an increase from 24% to 39% between 1999 and 2012 [20]. The prevalence of polypharmacy is also on the rise in the general adult population [29]. It is evident that we are witnessing an international surge in polypharmacy prevalence. However, as the method to define polypharmacy varies across studies, it is difficult to compare the level of polypharmacy across different settings (Table 2). Cross-national surveys provide a framework for how we can compare the level of drug use between countries. In the Survey of Health, Ageing and Retirement in Europe (SHARE), the prevalence of polypharmacy was assessed using a harmonized survey in 18 countries. The prevalence of polypharmacy ranged from 26% in Switzerland to 40% in the Czech Republic among people aged 65 years and older [30]. Less is known about the incidence and duration of polypharmacy across different population [31,32].

This worldwide increase in polypharmacy could be reflective of a 'success story': older people now survive longer with chronic conditions, partly due to more available drug treatments and better diagnostic work-up. However, this increase is also driven by the use of single-disease guidelines that are not adapted for older adults with multimorbidity [33]. There is a need for more guidelines focusing on the specific challenges of treating older adults with many coexisting chronic conditions [34–36]. The composition of drugs used in polypharmacy regimens is relatively concentrated to a relatively small set of drugs [37]. Some specific drug classes that have been linked to the increase in polypharmacy include, among others, cardiovascular drugs (especially statins), antidepressants, and proton pump inhibitors [19,20].

4. Clinical consequences of polypharmacy

4.1. Overview of reviews

Several reviews about polypharmacy and associated negative outcomes have been published to date. In Table 2, we review the results from selected previous reviews. In general, polypharmacy has been linked to a range of negative outcomes, including falls, frailty, and mortality [15–18]. Some reviews have focused on the association between polypharmacy and a number of different health outcomes [17,18], whereas others have focused on polypharmacy and a specific health outcome (such as frailty [15] and mortality [16]). The only systematic review to include a meta-analysis on the negative consequence was the review on polypharmacy and death by Leelakanok et al. [16]. This meta-analysis supported an association between polypharmacy and subsequent mortality. However, the reviews have also highlighted a number of shortcomings with the published articles, such as varying definitions of polypharmacy and difficulties in disentangling the effects of polypharmacy from the underlying health problem that the drugs were prescribed for (confounding by indication).

A second set of reviews focused on interventions to reduce polypharmacy/inappropriate polypharmacy. Overall, these reviews have found some support for interventions to reduce

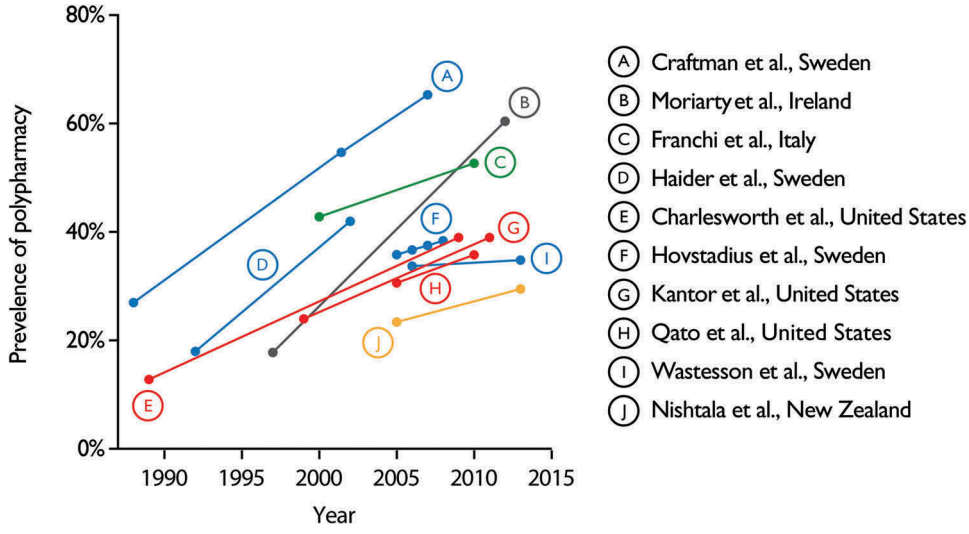

Figure 1. International trends in the prevalence of polypharmacy in older adults.

inappropriateness and the number of drugs in people with polypharmacy, but with unclear effects on clinically relevant outcomes [38,39].

4.2. Update on polypharmacy and clinical consequences

The broad range of clinical consequences that have been studied in relation to polypharmacy complicates a comprehensive summary of the results. In Figure 2, the outcomes have been broadly defined into four categories based on their theoretical *proximity* to polypharmacy. In the inner circle, closest to polypharmacy, are drug-related outcomes, such as drug-drug interactions. As we move to the outer circles, the outcomes could potentially be related to the more proximal outcomes (e.g. drug-drug interactions can contribute to hospital admissions) and are also more likely to be affected by other health-related factors. In this section, we review studies not covered by the highlighted reviews.

4.2.1. Drug-related problems: drug-drug and drug-disease interactions, adverse drug reactions, and potentially inappropriate medications

With polypharmacy comes the risk of health problems directly related to drug utilization. The risk of potential drug-drug interactions increases almost exponentially with the number of drugs used [40]. Hence, polypharmacy is a key risk factor for drug-drug interactions. Additionally, the use of single-disease clinical guidelines in older adults with multimorbidity can result in potentially serious drug-disease interactions [41]. The prevalence of clinically important drug-disease interactions has been reported to be about 15% in a sample of frail older adult veterans in the US [42]. The use of potentially inappropriate drugs and underuse of drugs is also frequent among older adults with polypharmacy, typically defined by explicit criteria (such as STOPP/START) [43–45]. Adverse drug reactions (ADRs) have been proposed to be the leading cause of about 10% of hospitalizations in older adults [46,47], and almost 90% of older adults hospitalized for an ADR have been reported to have polypharmacy upon hospital admission [48]. In a UK study, persons with chronic obstructive pulmonary disease (COPD) were often using multiple medications and also more likely to be prescribed many drugs linked to potential ADRs (such as falls, constipation, urinary retention, bleeding, and renal injury) than those without COPD [49]. Furthermore, adherence to essential medicines is important in the older population. Adherence to medications has been reported to decrease with the number of prescribed drugs [50]. Polypharmacy, and the use of multiple single-disease guidelines, tends to make drug regimens increasingly complex [51–53], which can lower adherence and has been linked to higher mortality [51].

4.2.2. Adverse drug events: falls, fractures, renal failure

The use of multiple medications can cause adverse drug events. Falls and subsequent fractures have been linked to polypharmacy in a number of studies [17]. A Swedish study based on nationwide registers found that the risk of falls increased with the number of drugs used in a dose-response fashion. However, the association between polypharmacy was attenuated when adjusting for specific fall-inducing drugs [54]. In line with this, an Australian study including only long-term care recipients reported that the number of fall-risk drugs was associated with fall-related hospital admission whereas polypharmacy was not an independent risk factor [55]. Polypharmacy is also reported to be common among people with renal insufficiency, for example among German nursing home residents [56]. A population-based study found that a long duration of polypharmacy was associated with a higher risk of acute renal failure [57]. However, a cross-sectional study from the US did not find an independent association between polypharmacy and chronic kidney disease [58].

4.2.3. Physical function and disability

Physical function is important for independence and quality of life in older adults. Polypharmacy has been found to reduce

Table 1. Overview of studies reporting trends in polypharmacy in older adults.

Author, year of publication	Study design	Country	Study population	Source of medication data	Medication use	Polypharmacy cut-off	Time of polypharmacy assessment	Prevelence, %
Charlesworth et al. (2015) [19]	Repeated cross-sectional survey	USA	Nationally representative sample of the noninstitutionalized US population aged ≥65 years	Self-reported	All prescription drugs used in the last 30 days	≥5 drugs	1988–1991 2009–2010	12.8 39.0
Craftman et al. (2016) [24]	Repeated cross-sectional surveys	Sweden	Radom sample of the population living in one district of Stockholm aged ≥60 years	Self-reported	Current use of prescribed and over-the-counter (OTC) drugs.	≥5 drugs	1987–1989 2001–2003 2007–2009	27.0 53.9 65.3
Franchi et al. (2013)	Repeated cross-sectional register study	Italy	The population aged 65–95 years in the Lombardy region, Italy.	Routinely collected administrative data	Monthly prescription drug use over one year.	≥5 drugs.	2000 2010	42.8 52.7
Haider et al. (2007)	Repeated cross-sectional survey	Sweden	Nationally representative sample of the Swedish population aged ≥77 years	Self-reported	Use of prescribed and OTC drugs during two weeks.	≥5 drugs	1992 2002	18.0 42.0
Hovstadius et al (2010)	Repeated cross-sectional register study	Sweden	The population aged 70–79 in Sweden		All prescribed drugs during three months	Use of ≥5 drugs	2005 2006 2007 2008	35.0 35.9 36.7 37.6
Kantor et al. (2015)	Repeated cross-sectional survey	USA	Nationally representative sample of the noninstitutionalized US population aged ≥65 years	Self-reported	All prescription drugs used in the last 30 days	≥5 drugs	1999–2000 2011–2012	24.0 39.0
Moriarty et al. (2015)	Repeated cross-sectional register study	Ireland	The population aged ≥65 in one health region in Ireland	Routinely collected administrative data	Prescription drugs dispensed for ≥3 consecutive months in a year (regularly used drugs)	≥5 drugs (regularly used)	1997 2012	17.8 60.4
Nishtala et al. (2014)	Repeated cross-sectional register study	New Zealand	The population aged ≥65 in New Zealand.	Routinely collected administrative data	Concurrent prescription drug use during 90 days	≥5 drugs concurrently for ≥90 days	2005 2013	23.4 29.5
Qato (2016) et al	Cohort study	USA	Nationally representative sample of community dwellers in the US population aged 62 to 85 years	Self-reported	Current use of prescribed and OTC drugs.	≥5 drugs (only prescription drugs)	2005–2006 2010–2011	30.6 35.8
Wastesson et al. (2016)	Repeated cross-sectional register study	Sweden	The population aged ≥65 years in Sweden	Routinely collected administrative data	One-day point prevalence based on prescribed drugs during three months	≥5 drugs	2006 2013	33.7 34.8

[1] The paper also provides the prevalence of polypharmacy for other age groups

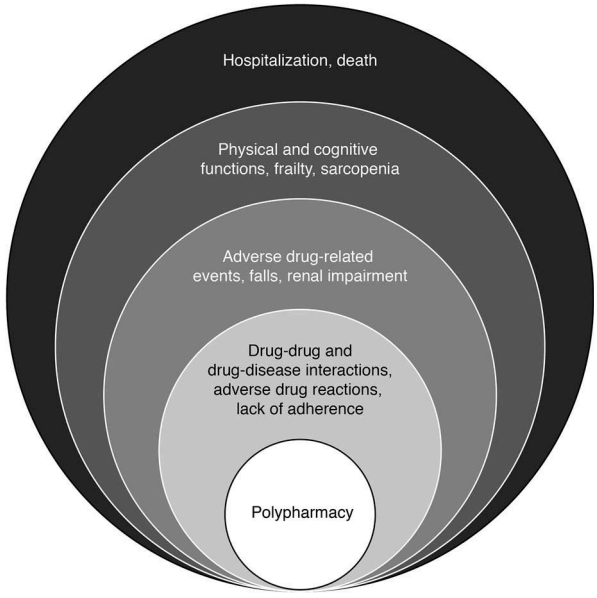

Figure 2. Framework for polypharmacy and conceptual classification of outcomes.

objective measures of physical function (e.g. gait speed, chair rise, and grip strength) in older adults [59–61]. In a study of 482 community-dwelling older adults, polypharmacy was associated with lower gait speed even when accounting for multimorbidity and high-risk drugs [61]. In a British birth cohort, it was found that polypharmacy was associated with poorer physical function and that people exposed to polypharmacy at two time points were more likely to have low physical function than persons exposed at a single time point [60]. In contrast, a multicenter study of European nursing homes did not find that polypharmacy was associated with a faster decline in functional status [62]. Disability, measured as activities of daily living, has also been positively associated with polypharmacy [63,64]. In a population-based study of 772 Spanish older adults, having polypharmacy and frailty was associated with incident disability [64]. Although most of the reviewed studies found an association between polypharmacy and different measures of physical function, it should be noted that it is inherently difficult to establish a causal relationship between the two factors as general health status is associated with both polypharmacy and physical function (a confounding factor) [17].

4.2.4. Frailty, sarcopenia, and quality of life

Similar to physical function and disability, it is difficult to establish causality regarding the association between polypharmacy and frailty. The relationship between polypharmacy and frailty was the focus of a 2018 systematic review [15]. A majority of the reviewed studies found support for a positive association between polypharmacy and frailty; however, many of these studies were cross-sectional in nature and thus the directionality of the associations could not be established. A paper not included in the systematic review found that polypharmacy was associated with a higher risk of incident frailty in a sample of relatively young Northern Americans when followed for up to 8 years [65]. The concept of frailty is interrelated with the concept of sarcopenia. Whereas frailty relates more to a general reduction in homeostatic reserves while sarcopenia relates to the loss of muscle mass, both concepts are often clinically manifested in reduced physical function/disability as a part of the aging process [66]. Although the loss of muscle mass is sometimes included in the definition of frailty, some authors have attempted to study the specific effect of polypharmacy on sarcopenia. Indeed, polypharmacy has been associated with sarcopenia in a cross-sectional analysis of 1,502 participants from the Berlin Aging Study II [67]. Furthermore, two small cross-sectional studies investigating the association between multiple medications and health-related quality of life found no statistically significant effect of polypharmacy on quality of life [68,69].

4.2.5. Cognitive functions

Polypharmacy has been linked to lowered cognitive functions and dementia. Some of these studies have analyzed cognitive status at one time point, and others have analyzed if polypharmacy is associated with a decline in cognitive status. In a cross-sectional study of community-living Japanese older adults, polypharmacy was associated with lower cognitive status [70]. A longitudinal register-based nested case-control study matching incident dementia cases with dementia-free cases found that polypharmacy was associated with receiving a dementia diagnosis. The association remained also after adjusting for a number of health conditions and potentially inappropriate medications [71]. Being exposed to polypharmacy at two time points, compared to one time point, was found to be associated with a stronger negative association between polypharmacy and cognitive function in an aforementioned British study, suggesting a cumulative negative effect of polypharmacy [60]. Two studies have investigated if polypharmacy is associated with a faster decline in cognition. Polypharmacy was associated with a faster cognitive decline in a multicenter study of European nursing homes [62]. A US-

Table 2. Overview of selected systematic reviews on polypharmacy and negative consequences and on the clinical outcomes of reducing polypharmacy.

Author, year	Topic	No. of included studies	Exposure/interventions	Outcomes	Summary of results	Comments
Fried, 2014 [17]	The relationship between polypharmacy and negative health outcomes	50	Polypharmacy	-Falls or fall-related outcomes -Adverse drug events -Hospitalization or mortality -Other outcomes	Mixed results for the association between polypharmacy and negative health outcomes.	The authors note the heterogeneity in the definitions of polypharmacy and the inadequate adjustment for chronic conditions in many studies.
Gutiérrez-Valencia, 2018 [15]	The relationship between polypharmacy and frailty	25	Polypharmacy	Frailty	A positive association between polypharmacy and frailty was found in 21 out of the 25 studies.	A majority of the included studies were cross-sectional, thus the directionality of the association could not be established.
Leelakanok, 2017 [16]	The relationship between polypharmacy and mortality	47	Polypharmacy	Mortality	Pooled estimate suggested a positive association between both the continuous number of drugs and different polypharmacy cut-offs and mortality.	The authors conclude that unmeasured/residual confounding from multimorbidity could affect the pooled estimates.
Maher, 2014 [18]	The relationship between polypharmacy and clinical consequences	≈50	Polypharmacy	-Health-care costs -Adverse drug events -Drug interactions -Medication nonadherence -Functional status -Cognitive impairment -Falls -Urinary incontinence -Nutrition - Potentially inappropriate prescribing	The review finds support for a strong association between polypharmacy and a broad range of consequences.	Polypharmacy is a growing concern as the prevalence is increasing, and varies across studies and settings. The authors urge for more interventions to reduce polypharmacy.
Clinical consequences of reducing polypharmacy						
Rankin et al. 2018 [38]	Effect of interventions to improve prescribing for older adults (people aged 65 years and older, prescribed polypharmacy.	32	Interventions (using validated tools) affecting prescribing aimed at improving appropriate polypharmacy	-Medication appropriateness. -Potentially inappropriate medications -Potential prescribing omissions -Hospital admissions -Medication-related problems -Adherence to medication. -Quality of life	Uncertain if the interventions improved appropriateness of medicines Little or no difference in hospitalization and quality of life. The interventions may interventions may lead to a slight reduction in potential prescribing omissions	Unclear if the interventions improved appropriateness of medicines. The authors suggest that the improving timing, duration, and multifacetedness of the intervention may lead to more success.

(*Continued*)

Table 2. (Continued).

Author, year	Topic	No. of included studies	Exposure/interventions	Outcomes	Summary of results	Comments
Johansson, 2016 [39]	Impact of strategies to reduce polypharmacy on clinically relevant endpoints	25	Electronic and nonelectronic strategies to reduce polypharmacy	-Mortality -Hospitalization -Number of drugs -New morbidity -Quality of life -Physical and mental functioning -Adverse drug event -Adverse drug reaction -Medication error -Inappropriate medication -User/patient satisfaction/ acceptance -Adherence to medication -Resource utilization -Costs	Little evidence for interventions to improve quality or appropriateness of drug therapy to have an effect on all-cause mortality or hospitalizations among older adults with polypharmacy.	The author found some support for a reduction in the number of drugs in the intervention group compared to the control group. Furthermore, many interventions were complex and not clearly defined.

based study also found some support for a more pronounced cognitive decline among polypharmacy users but this was not statistically significant [72]. In the context of polypharmacy and cognition, it is of great importance to also consider specific drug types; for example, psychotropics and drugs with anticholinergic properties are known to have negative effects on cognition [62,71].

4.2.6. Hospitalizations

Polypharmacy has been linked with hospital admission in studies including general older adults [73], nursing home residents [68], and in people diagnosed with dementia [74]. The association has been found for any hospital admission [32,73–75], unplanned hospital admissions [74,76], and re-hospitalization in hospital-based samples [77]. A notable example is a Korean study using administrative data to follow people up to 10 years applying polypharmacy as a time-varying exposure [73]. The study found an independent association between the exposure to polypharmacy and subsequent all-cause and fall-related hospitalization while adjusting for the use of potentially inappropriate medications and anticholinergic burden. Another interesting finding is that Payne et al. [76] observed that the risk of unplanned hospital admissions increased with the number of medications used; however, this effect was less evident for people with a high number of chronic conditions. Future studies should also include measures of the length of hospital stay. This would provide a more detailed picture of health-care consumption and is easily compared across studies and health-care systems [78].

4.2.7. Mortality

In 2017, a systematic review withmeta-analysis was published investigating the association between polypharmacy and mortality [16]. In all, 47 articles were included in the meta-analysis. Pooled estimates were presented for papers using the number of drugs as a continuous variable, and the odds ratio for mortality was 1.08 (95% confidence interval [CI] 1.04–1.12) for each additional drug used. In addition, pooled estimates from papers using different categorical cut-offs for the number of drugs were also presented; these analyses suggested a potential dose–response relationship, where a higher cut-off yielded a higher estimate for the association between polypharmacy and death. For the cut-off of five or more drugs, the pooled estimate was 1.31 (95% CI 1.17–1.47). The authors noted a large variety in how the included studies addressed confounding by indication (e.g. that people with polypharmacy are also more likely to have many chronic conditions that can also increase the risk of mortality). Hence, the authors did not rule out the possibility of residual confounding affecting the pooled estimates. A notable example of a study addressing the issue of confounding by indication was published after this systematic review. In the ESTHER study, Schöttker et al. [79,80] addressed confounding by indication by adjusting for chronic conditions and by using propensity score matching. Interestingly, they observed that the association between polypharmacy and non-cancer mortality was found when adjusting for chronic conditions (hazard ratio (HR) 2.01; 95% CI 1.15–3.51) but largely attenuated in the model using propensity score matching (HR 1.26; 95% CI 0.70; 2.28). The authors thus suggest that solely adjusting for chronic condition is insufficient to avoid confounding by indication when relating polypharmacy to subsequent clinical consequences.

5. Challenges in assessing and reducing the clinical consequences of polypharmacy

Three major challenges for extending the research on polypharmacy and potential negative outcomes have been identified in this review. First, there is a need to further refine the definition of polypharmacy. Second, the methodological challenges in assessing the association between polypharmacy and negative outcomes should be better acknowledged in future studies. Third, we need to further develop interventions to reduce polypharmacy in order to produce successful and scalable strategies. These issues are further discussed in the following sections.

5.1. Developing a clinically meaningful definition of polypharmacy

No standard definition exists for what constitutes polypharmacy. In general, polypharmacy can be defined as a count of drugs, or include some kind of clinical judgment about the quality/appropriateness of polypharmacy. When polypharmacy is defined as a count of the number of drugs, a cut-off of five or more concurrently is most frequently used [6]. The cut-off of five drugs has been validated in some settings [81,82]; however, it is questionable if the cut-off is appropriate across all settings and times. With the international surge in polypharmacy prevalence, with almost 50% of the older population exposed to polypharmacy, a cut-off of 10 drugs (sometimes referred to as 'excessive polypharmacy') could potentially be a more appropriate cut-off to define high-risk drug use. Defining polypharmacy as a specific number of drugs is useful for monitoring drug use in large populations and as a crude marker of polypharmacy in epidemiological studies of the harms of polypharmacy when it might not be practically feasible to make a more detailed assessment of the appropriateness of polypharmacy. Definitions such as 'more drugs than clinically indicated' or appropriate polypharmacy requires clinical judgment and is more feasible in a clinical context. In these situations, considering the composition of drugs in the regimen in relation to the needs of the patient is crucial to make a personalized optimization of the current drug regimen. There are promising initiatives to combine the cut-off approaches and the clinical judgment approach in a meaningful way. Burt et al. have initiated the development of a polypharmacy appropriateness measure that can be used in both clinical practice and in informatics systems [14].

5.2. From 'confounding by indication' to 'confounding by multimorbidity'

It is inherently difficult to correctly estimate the negative health outcomes related to polypharmacy given that polypharmacy itself is most often a consequence of poor health. The challenge is to prove a negative effect of polypharmacy beyond the already existing health problems that the polypharmacy drug regimen is intended to treat. This conundrum is usually referred to as 'confounding by indication'.

Confounding by indication is a well-described bias in the medical literature [83]. The specific challenge with polypharmacy is that we need to expand the concept of 'confounding by indication' to several indications, i.e. 'confounding by multimorbidity'. Common strategies to reduce the risk of this bias are to adjust for general health status or some composite score of general health status (for example, Charlson Comorbidity Index [84] and multimorbidity scales [85]). Nevertheless, far from all published papers on the negative health risks of polypharmacy adjust for health factors [17]. The strong correlation between number of drugs and number of health problems may not only be solved by solely adjusting for health status. The use of novel methods including propensity score matching, instrumental variables, and quasi-experimental designs are strongly encouraged to improve the assessment of causal effects of polypharmacy on negative health outcomes [79]. Study designs mimicking randomized control trials can strengthen the evidence as a classical trial randomizing polypharmacy to patients would not be ethically feasible. However, novel translational work randomizing polypharmacy in mice is currently ongoing [86,87]; this can provide knowledge about whether medications that are generally well tolerated in mice become risky when used in combination. To increase the potential of making causal claims about the association between polypharmacy and clinical outcomes, temporality is a key issue. The consequences of polypharmacy ought to be studied at a time point later than when polypharmacy status is assessed, and more efforts should be directed to accounting for intra-individual changes in polypharmacy status over time; for example, by using polypharmacy as a time-varying exposure [73,88]. This could provide important insights into whether a persistent exposure to polypharmacy may lead to a cumulative risk of negative outcomes as suggested in a recent study [60].

5.3. Interventions to reduce polypharmacy and deprescribing

Interventions aimed at reducing the inappropriateness of polypharmacy or to reduce the risk of negative outcomes of polypharmacy have in general been unsuccessful in having an impact on clinically relevant end points [13,39]. Furthermore, many of these interventions are complex and might therefore have limited scalability [39]. In a large cluster-randomized trial of 1,546 multimorbid patients in the UK allocated to usual care or patient-centered care (optimized for management of multimorbidity), the authors found that the intervention did not reduce the number of drugs 11.0 (8.0–15.0) in the usual care group vs 11.0 (8.0–15.0) in the intervention group (adjusted IRR: 1 · 02, 95% CI 0 · 97 to 1 · 06), treatment burden, or medication adherence [89]. On a more positive note, interventions aimed at reducing ADRs in older adults have been more successful and a recent systematic review found a 35% risk reduction in ADRs for interventions led by a pharmacist [90]. Furthermore, the increasing sophistication of computerized decision support systems for the optimization of drug therapy for older adults will likely lead to a larger uptake of these important tools. Decision support systems have been found to reduce the risk of potential inappropriate medication use [91,92]. By combining decision support tools with relevant patient data regarding, for example, kidney function (creatinine clearance rate) and genetic ability to metabolize drugs (e.g. CYP450 enzymes), there is a great potential to provide more tailored prescribing – moving closer to the concept of personalized medicine [93,94]. The mounting interest in deprescribing is highly pertinent also for older adults with polypharmacy, and especially for the large group of older adults with polypharmacy at the end of life [5] and very old people with a limited remaining life expectancy [4,95]. The systematic study of the process of deprescribing in older adults with polypharmacy will be another important area in the years to come [96].

6. Conclusion

The prevalence of polypharmacy in older adults is increasing in most countries. This is a cause for concern given the observed association between polypharmacy and a wide spectra of negative health outcomes, including drug-related problems, adverse drug events, physical and cognitive function, hospitalization, and mortality. In our mapping of the literature on polypharmacy and negative health outcomes, we have identified a large number of studies. However, to our knowledge, only the association between polypharmacy and mortality has been subjected to a systematic review with meta-analysis. Moreover, scalable interventions to reduce polypharmacy (by deprescribing or other interventions) is needed to revert the trend of increasing levels of polypharmacy in the older population.

7. Expert opinion

The prevalence of polypharmacy in old age is on the rise in high-income countries, which leads to increasingly complex drug regimens. Providing optimal care for the growing number of older adults with multimorbidity and polypharmacy is a challenge for the years to come. The majority of the studies included in this review show an association between polypharmacy and a range of negative clinical outcomes in older adults. In our opinion, however, important methodological challenges need to be addressed to verify whether this association between polypharmacy and harms is causal or not. We believe that the main challenge is that of 'confounding by multimorbidity': the necessity to manage multiple chronic conditions is often the reason for polypharmacy, and this could be a source of bias in observational studies that attempt to establish a relationship between polypharmacy and the risk of subsequent adverse outcomes. Future studies should incorporate recent methodological advances in other fields of clinical epidemiology pertaining to the use of novel epidemiological methods to better address causal inference. These include propensity score-matching procedures, quasi-experimental and self-controlled designs, longitudinal assessment of the exposure to polypharmacy, and translational research. Moreover, we believe there is a need for more systematic reviews targeting polypharmacy and specific outcomes. Such efforts could enrich the discussions about the potential mechanisms between polypharmacy and the selected outcome, and provide more information about how analytical strategies might influence the results found in individual studies.

Interventions targeted at reducing the negative outcomes of polypharmacy have not proven to be successful or are difficult to scale-up. In our opinion, further research is needed to develop more refined definitions of the appropriateness of polypharmacy; this could improve the targeting of interventions and their likelihood of success in an aging population where polypharmacy is a growing universal concern. To better personalize drugs treatments and avoid some of the risks of polypharmacy, we also need to continue developing and implementing tools (e.g. computerized decision support systems) and tests (e.g. genetic variants that effects metabolization of drugs) that can help clinicians tailor prescriptions to the specific needs of their individual patient. The rising prevalence of polypharmacy in older adults is partly driven by the use of preventative drugs with substantial benefits at the population level but large number needed to treat. We encourage continuous discussions, educational activities, and guidelines on when and how to stop medications, especially in groups with limited life expectancy (end-of-life situations or among the very old).

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ORCID

Jonas W. Wastesson http://orcid.org/0000-0001-7601-4319

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