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Review article

Efficacy of deprescribing on health outcomes: An umbrella review of systematic reviews with meta-analysis of randomized controlled trials

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ABSTRACT

Background: Deprescribing is an important intervention across different settings in medicine, but the literature supporting such a practice is still conflicting. Therefore, we aimed to capture the breadth of outcomes reported and assess the strength of evidence of the use of deprescribing for health outcomes.
Methods: Umbrella review of systematic reviews of the use of deprescribing searching in Medline, Scopus, and Web of Science until 01 November 2023. The grading of evidence was carried out using the GRADE for intervention studies, whilst data regarding systematic reviews were reported as narrative findings.
Results: Among 456 papers, 12 systematic reviews (six with meta-analysis) for a total of 231 RCTs and 44,193 patients were included. In any setting, deprescribing was able to significantly reduce the number of total and of potentially inappropriate medications (PIMs) in older patients (low certainty of evidence) and to reduce the proportion of participants potentially having several or PIMs (moderate certainty of evidence). In community, supported by a high certainty of evidence, deprescribing was not more effective than standard care in decreasing injurious falls, any falls or number of fallers. In nursing home, deprescribing was associated with a significantly lower PIMs than standard care (very low certainty of evidence). In end-of-life situations, deprescribing significantly reduced mortality rate of approximately 41% (high certainty of evidence).
Conclusions: Deprescribing is a promising intervention across different settings and situations, but a notable gap in the literature concerning its effects on substantial outcomes still exists.

1. Introduction

Increase in life expectancy and presence of multimorbid conditions among older people, associated with guidelines that suggest therapeutic regimens composed of multiple drugs for common pathologies (e.g., hypertension, diabetes, heart failure), has led to the appearance of complex polypharmacological regimens.(Vordenberg et al., 2023) Literature data highlight that one-third of people aged over 65 years live with multi-morbidity and take five or more regular drugs (“polypharmacy”), increasing to 50% in over 85 years old. (Masnoon et al., 2017; Morley et al., 2013) Moreover, polypharmacy is frequently associated with an increased risk of adverse drug reactions (ADRs) that can

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cause hospitalization, fall injuries, frailty and mortality.(Ambrose et al., 2013; Budnitz et al., 2011; Leelakanok et al., 2017; Saum et al., 2017; Veronese et al., 2017).

The chance of occurrence of medication-related problems is increased in older persons because changes in pharmacokinetics and pharmacodynamics, such as reduced hepatic and renal function, prolonged elimination half-life, and increased sensitivity to drugs, which have been shown to be associated with an increased risk of ADRs. (ELDesoky, 2007) For this reason, Stevenson et al. recently suggested that a broad approach is needed to address ADRs and that drug-related harm should be treated as a geriatric syndrome itself.(Stevenson et al., 2020).

Among various medications prescribed for older persons, those that pose a risk of adverse drug reactions (ADRs) surpassing their anticipated benefits are categorized as potentially inappropriate medications (PIMs). PIMs are defined as "medications that should be avoided due to their risk which outweighs their benefit and when there are equally or more effective but lower risk alternatives are available".(Page et al., 2010).

A recent review of 33 studies highlights a 44% increased risk of ADRs/hospitalizations in subjects who have PIMs in their therapy, but no statistically significant association was found with mortality. (Xing et al., 2019) It is interesting to note that the results changed when different continents/criteria were used for the analysis. Compared with the older individuals exposed to one PIM, the risk of adverse health outcomes was much higher for those who took $\geq$2 PIMs.(Xing et al., 2019) Moreover, PIMs use is also associated with an increased cost burden on healthcare system which requires further research to rationalize the use of such medications.(Alhawassi et al., 2019) One strategy to resolve the problem of polypharmacy and PIMs is the medication review and "deprescribing".

Deprescribing is generally defined as a systematic process of drug discontinuation, tapering or even substitution of inappropriate medications, supervised by a health care professional, with the goal of managing polypharmacy and improving outcomes.(Thompson and Farrell, 2013).

Numerous studies and systematic reviews have examined a variety of strategies to deprescribe in older adults with mixed results.(Linsky et al., 2019; Page et al., 2016b) Among the reasons contributing to the heterogeneity of evidence have included the lack of a consistent definition of deprescribing, different outcome measurement and wide variation in study design. Generally, methods recommended in intervention studies to decrease PIMs include use of check drug-drug interactions and use of specific tools validated in the older population. These tools to detect PIM can be categorized as implicit (judgment based), explicit (criteria based) or combined (both judgment and criteria based). Implicit tools contain questions that are designed to examine the effectiveness and safety of each medication such as the Medication Appropriateness Index (MAI). Explicit tools comprise a list of medications that are known, based on evidence, to be inappropriately prescribed to older patients. Examples of explicit tools are the Beers Criteria and the STOPP/START tool (Screening Tool of Older Persons' Prescriptions/Screening Tool to Alert to Right Treatment).(Rankin et al., 2018) Finally, increasing literature is showing that also patients could be interested in reducing medications and they search for education about the drugs that take and they search for communication with their providers around deprescribing.(Holmes and Todd, 2017).

Considering available randomized clinical trials (RCTs) derived from systematic reviews, this umbrella review sought to determine which interventions of deprescribing, alone or in combination, are effective in improving the outcomes after deprescribing intervention in various clinical setting.

2. Methods

2.1. Protocol and registration

This umbrella review, including systematic reviews with or without meta-analysis, was conducted following the recommendations of the Cochrane handbook for systematic literature reviews to carry out the screening and selection of studies and reported according to the updated 2020 Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines.(Higgins et al., 2019; Page et al., 2021) The protocol is freely available in PROSPERO (CRD42023481063).

2.2. PICO question and eligibility criteria

Following the PICOS (participants, intervention, control, outcomes, study design) question, we included:

- Participants: any;
- Intervention: deprescribing, generally defined as a systematic process of drug discontinuation, tapering or even substitution of inappropriate medications, supervised by a health care professional, with the goal of managing polypharmacy and improving outcomes (Reeve et al., 2015);
- Controls: standard or usual care;
- Outcomes: all health outcomes;
- Study design: systematic reviews with or without meta-analysis of randomized controlled trials.

We excluded the following studies: (i) meta-analyses of intervention studies comparing two active interventions; (ii) specific deprescribing, i.e., the use of this intervention for removing a specific class of medications; (iii) meta-analyses including only one study.

2.3. Information sources and search strategies

For this umbrella review, several relevant bibliographic databases were comprehensively searched, including Medline (via Ovid), Scopus, and Web of Science from database inception up to the 01st of November 2023.

The following search was used in Pubmed: (deprescribing OR Deprescriptions) AND ("meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analysis"[All Fields] OR "systematic review"[Publication Type] OR "systematic review"[All Fields]). The search was then adapted to the other databases.

2.4. Study selection

The selections were independently carried out by two review authors (LC, MC), with consensus meetings to discuss the studies for which divergent selection decisions were made by the two review authors. A third senior member of the review team (NV) was involved, if necessary. The studies selection process involved, first, a selection based on title and/or abstracts, then a selection of studies retrieved from this first step based on the full-text manuscripts by the same two authors. The freely accessible software Rayyan was used for the title/abstract screening. (Ouzzani et al., 2016) The largest systematic review, in terms of number of studies, was included.

2.5. Data collection and data items

From the eligible full-text articles, we extracted: first author name and affiliation, year of publication, journal name, title of the manuscript; data on the characteristics of the population considered, for individual study (e.g., sample size, mean age, gender, population/condition/setting etc.), tools used for deprescribing (then categorized using the classification suggested by Reeve et al., (Reeve, 2020), who performed

the deprescribing, and health outcomes. The data regarding estimates were extracted at single study level and categorized in risk ratio (RR), odds ratio (OR), hazard ratio (HR), mean difference (MD), standardized mean difference (SMD) collected using a standardized Excel data extraction form. Data extraction was led out by some authors (UG, AM, XT, GZ, SC, MC, VB) and systematically double checked by senior authors (NV, AP). Errors found in extraction by the second review author were corrected during a consensus meeting. Discrepancy in terms of two reviews related to the data extraction about one systematic review was solved through a consensus with an expert researcher (NV).

2.6. Assessment of risk of bias

One author (VB) rated the methodological quality of the included systematic reviews using "A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2)"(Shea et al., 2017), which ranks the quality of a meta-analysis in one of 4 categories ranging from "critically low" to "high" according to 16 predefined items. (Shea et al., 2017) Another author (NV) double checked this evaluation.

2.7. Data synthesis and grading of the evidence

The data analysis was conducted using STATA 14.0. For each meta-analysis, we estimated the common effect size and its 95%CI (confidence interval) under the assumption of a random-effects model.(Geisser, 1974) Heterogeneity was estimated using the I^2 statistics: values of 50% or greater are indicative of high heterogeneity, while values above 75% suggest very high heterogeneity.(Higgins and Thompson, 2002) Publication bias was assessed using the test proposed by Egger and co--workers.(Harbord et al., 2009).

The evidence from meta-analyses was evaluated using the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) assessment. Where available, we included the GRADE reported by the authors of the meta-analyses. The GRADE framework takes into account several important domains for the judgment of the certainty of the evidence, including study design, risk of bias, inconsistency,

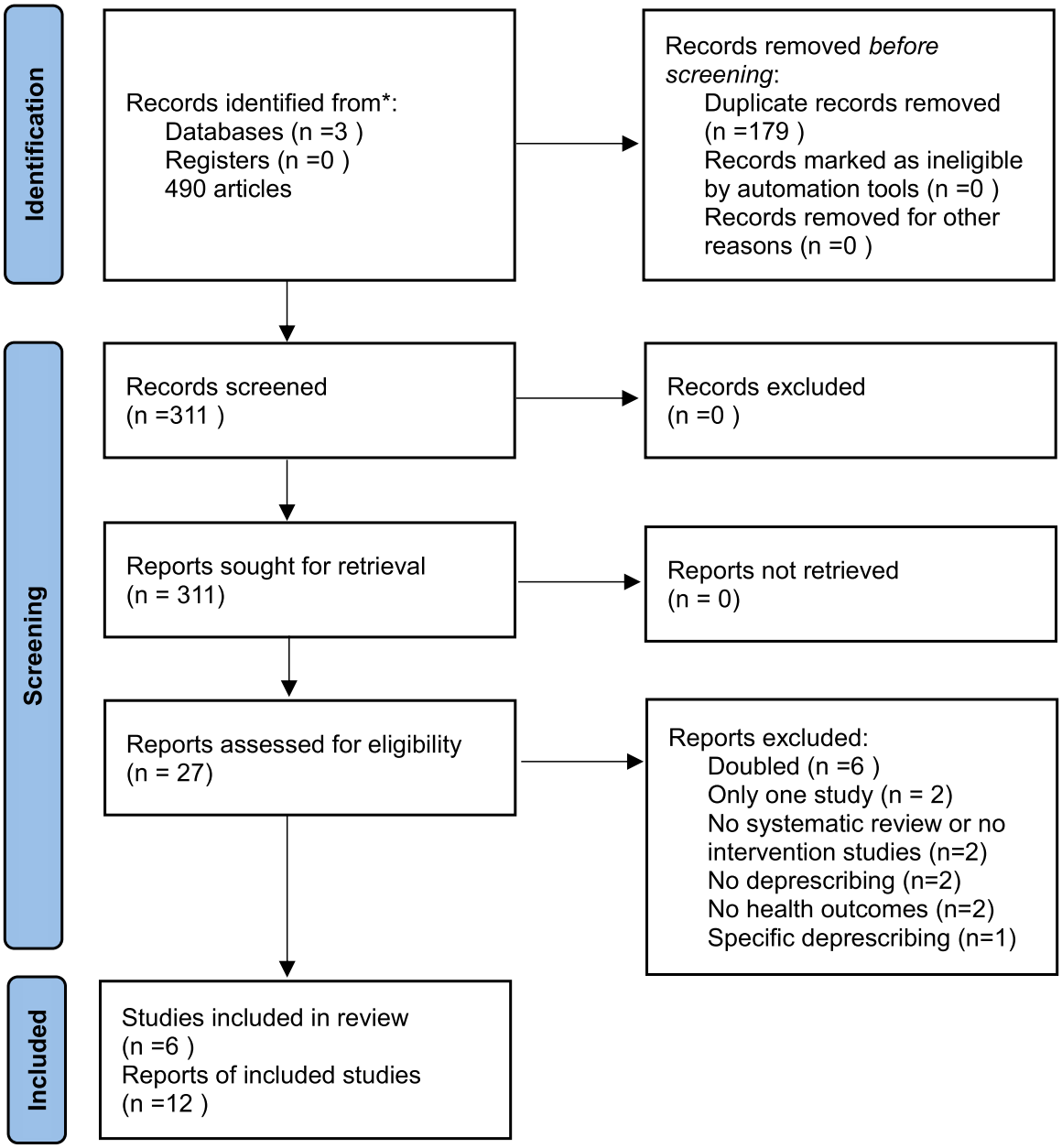

Fig. 1. PRISMA flow.

Table 1
GRADE profile of deprescribing versus standard care in any setting.

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Deprescribing	Control	Relative (95% CI)	Absolute	
Number of total and inappropriate prescription (older people) (Better indicated by lower values)											
11	randomised trials	no serious risk of bias	very serious[a]	no serious indirectness	no serious imprecision	none	1517	1520	-	MD 0.743 lower (1.265–0.211 lower)	LOW
Proportion of participants with a reduction in number of total and inappropriate prescriptions (older people)											
7	randomised trials	no serious risk of bias	serious[b]	no serious indirectness	no serious imprecision	none	257/876 (29.3%)	329/813 (40.5%)	RR 0.59 (0.39–0.91)	166 fewer per 1000 (from 36 fewer to 247 fewer)	MODERATE
Mortality (older people)											
10	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[c]	NA/1689 (0%)	NA/1462 (0%)	OR 0.82 (0.61–1.11)	Not reported	MODERATE
Adverse drug events (older people)											
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[d]	none	33/89 (37.1%)	50/112 (44.6%)	OR 1.22 (0.51–2.93)	446 fewer per 1000 (from 155 fewer to 256 more)	LOW
Effects of medications (older people)											
3	randomised trials	no serious risk of bias	very serious[e]	no serious indirectness	serious[f]	none	62/223 (27.8%)	34/224 (15.2%)	OR 1.39 (0.22–9.02)	47 more per 1000 (from 114 fewer to 466 more)	VERY LOW

[a] I2 >75%
[b] I2 between 50% and 75%
[c] Egger's test with a p-value <0.05
[d] Less than 200 participants and wide 95% confidence intervals
[e] I2 >75%
[f] Wide 95% confidence intervals

indirectness, imprecision and other aspects, such as publication bias and the outcomes of interest.(Guyatt et al., 2008) The certainty of the evidence was then evaluated in very low (the true effect is probably markedly different from the estimated effect), low (the true effect might be markedly different from the estimated effect), moderate (the true effect is probably close to the estimated effect) or high (there is a lot of confidence that the true effect is similar to the estimated effect). (Guyatt et al., 2008) The results of data analysis were imported into the GRADEpro Guideline Development Tool (McMaster University, 2015; developed by Evidence Prime, Inc.). The findings of systematic reviews without meta-analysis was reported only descriptively. The data are reported by the setting originally declared in the systematic review.

3. Results

3.1. Literature search

As shown in Fig. 1, among 456 papers initially screened, we evaluated 23 full texts. After excluding 11 full texts, mainly because the outcomes were already included in the meta-analyses of our umbrella, we finally included 12 systematic reviews, six with meta-analyses and six not. (Kua et al., 2019; Lee et al., 2021; Narayan and Nishtala, 2017; Page et al., 2016a; Pruskowski et al., 2019; Saeed et al., 2022; Seppala et al., 2022; Shrestha et al., 2021; Ulley et al., 2019) The list of excluded references is reported in Supplementary Table 2.

3.2. Main findings of the umbrella review

The 12 systematic reviews included, approximately, 231 RCTs with 44,193 patients. Tables 1 to table 5 show the main findings of the umbrella review in meta-analyses (first four tables divided according to the setting) and systematic reviews. Supplementary Table 3 summarizes the main descriptive findings of the meta-analyses.

3.2.1. Tools used for deprescribing

Supplementary Table 4 and 5 report data about the tools used for deprescribing and who performed this task for meta-analyses and systematic review, respectively. Briefly, across the 162 RCTs included in meta-analyses, 63/162 used deprescribing as discontinuation of a drug according to the Summary of Product Characteristics, 34 studies used explicit criteria such as START/STOPP criteria, 24 used deprescribing according to indications specific for that medication, for example, Beers' criteria, 13 general tools, such as national guidelines available, three RCTs used implicit criteria (i.e., Medication Appropriateness Index), one electronic tools, and 24/162 (14.8%) did not enter in these categories. About the professional doing deprescribing, in 62 RCTs we found that two or more disciplines were involved (such as physician, nurse, pharmacist), in 20 only pharmacists, in 17 only physicians, in 3 RCTs only nurses, in one only general practitioner, in one only geriatrician, but in 58/162 studies (35.8%) this information was not reported in the meta-analyses included (Supplementary Table 4**)**.

Supplementary Table 5 reports data about deprescribing's tools for systematic reviews without meta-analysis. Among 79 RCTs included in this category, 19 RCTs used explicit criteria such as START/STOPP criteria, 18 general tools, such as national guidelines available, 16 electronic tools, such as electronic algorithms to take decisions, 12 used deprescribing as discontinuation of a drug according to the Summary of Product Characteristics, one general tools such as national guidelines, one RCT used a tool specific to engage patients, and for 12 RCTs the information about which tool was used was not clearly reported. About the figure proposing deprescribing, in 44 a multidisciplinary team, 11 RCTs physician alone was involved, in 3 studies pharmacists, but in 21 no information about this aspect was reported (Supplementary Table 5**)**.

3.2.2. Effect of deprescribing in any setting

Considering no prespecified/any setting, as summarized in Table 1,

deprescribing was able to significantly reduce the number of total and of potentially inappropriate medications (PIMs) in older patients in 11 RCTs comparing 1517 subjects randomized to intervention vs. 1520 controls (MD=−0.743; 95%CI: −1.265 to −0.211; low certainty of evidence according to the GRADE) and to reduce the proportion of participants potentially having several or PIMs (RR=0.59; 95%CI: 0.39–0.91; moderate certainty of evidence according to the GRADE). In any setting, deprescribing did not reduce mortality or adverse drug events in older people (Table 1). As reported in Table 5, systematic reviews indicated that in any setting, considering 276 frail older people, one RCT reported significantly lower prescription of PIMs and the other a reduced number of PIMs, while 1/9 of the RCTs included in another systematic review reported that deprescribing was associated with better quality of life than standard care.

3.2.3. Effect of deprescribing in community

Table 2 shows the effect of deprescribing among community-dwellers. A high certainty of evidence, according to the GRADE, supported the idea that deprescribing was not more effective than standard care in decreasing injurious falls, any falls or number of fallers. In systematic review, without meta-analysis, deprescribing was associated with a significant improvement in medications' adherence compared to standard care in five over 12 RCTs included (Table 5).

3.2.4. Effect of deprescribing in nursing home

In nursing home setting, as shown in Table 3, deprescribing was associated with a significantly lower PIMs than standard care (OR=0.41; 95%CI: 0.19–0.88), even if supported by a very low certainty of evidence according to the GRADE, mainly driven by a very high heterogeneity and a serious imprecision. In systematic review without a formal meta-analysis, including 1122 older frail patients, deprescribing was associated with a significant improvement in appropriateness in 3 RCTs (Table 5). The effect of deprescribing on PIMs was, however, not associated with any reduction in mortality, falls, or hospitalization rate (Table 3).

3.2.5. Effect of deprescribing in hospital at end of life

As summarized in Table 4, the meta-analyses considered in our umbrella review, included mainly patients at the end of their life. Overall, deprescribing significantly reduced mortality rate of approximately 41% (RR=0.59; 95%CI: 0.44–0.80) in four RCTs including 308 patients randomized to deprescribing and 265 to standard care. This finding was exempt from any bias. On the contrary, deprescribing was not associated with any decreased risk in falls, hospitalizations, or non-vertebral fractures in end of life in hospital setting (Table 4). As shown in Table 5, in end-of-life situations in hospital setting, deprescribing was like standard care in drug cessation, in reducing inappropriate medications or adverse events.

3.3. Assessment of risk of bias

Using the criteria suggested by the AMSTAR-2, among the six meta-analyses included, one reported a high quality, four moderate and only one low quality (Supplementary Table 6). A similar picture was evident for systematic reviews without a formal meta-analysis. The most common potential sources of biases were a not clear definition of the PICO question (question 1), not clearly reporting the funding sources in the studies included (question 10), and that the authors poorly considered the quality of the studies when discussing their findings (question 13).

4. Discussion

In this umbrella review, including 12 systematic reviews for a total of 231 RCTs and about 50,000 patients, we explored, for the first time, the effect and safety of deprescribing across different settings, including community, nursing home and hospital. Overall, the available

Table 2
GRADE profile of deprescribing versus standard care in community setting.

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Deprescribing	Control	Relative (95% CI)	Absolute	
Injurious fall (older people)											
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/1408 (0%)	0/1595 (0%)	RR 0.95 (0.70–1.27)	-	HIGH
Incidence of falls (older people)											
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	190/499 (38.1%)	170/472 (36%)	RR 1.05 (0.87–1.26)	18 more per 1000 (from 47 fewer to 94 more)	HIGH
Number of fallers (older people)											
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/398 (0%)	0/411 (0%)	RR 0.89 (0.69–1.14)	-	HIGH

[1]Between 10% and 30% of the RCTs at high risk of bias.
[2]Wide 95% confidence intervals.

Table 3
GRADE profile of deprescribing versus standard care in nursing home.

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Deprescribing	Control	Relative (95% CI)	Absolute	
Mortality											
26	randomised trials	no serious risk of bias	serious[a]	no serious indirectness	no serious imprecision	none	1282/5466 (23.5%)	1282/6782 (18.9%)	OR 1.02 (0.85–1.23)	3 more per 1000 (from 24 fewer to 34 more)	MODERATE
Falls											
8	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	470/1733 (27.1%)	497/1651 (30.1%)	OR 0.85 (0.72–1.02)	33 fewer per 1000 (from 64 fewer to 4 more)	HIGH
Hospitalizations											
4	randomised trials	no serious risk of bias	serious[a]	no serious indirectness	serious[b]	none	81/502 (16.1%)	95/500 (19%)	OR 0.85 (0.4–1.79)	190 fewer per 1000 (from 104 fewer to 106 more)	LOW
Potentially inappropriate medications											
3	randomised trials	no serious risk of bias	very serious[c]	no serious indirectness	serious[b]	none	153/872 (17.5%)	247/839 (29.4%)	OR 0.41 (0.19–0.88)	148 fewer per 1000 (from 26 fewer to 221 fewer)	VERY LOW

[a] I2 between 50% and 75%
[b] Wide 95% confidence intervals
[c] I2 > 75%

interventions for deprescribing in daily clinical practice are numerous, but only a few are supported by a high/moderate level of certainty, indicating a high risk of bias affecting certainty around the effects of most available interventions. We believe that our findings are novel from different points of view since, to the best of our knowledge, it is the first attempt to systematically summarize the current literature about deprescribing in terms of health outcomes across different settings and conditions.

We observed the prevalent use of various deprescribing tools in the literature. Among these tools, the discontinuation of a medication based on the summary of product characteristics emerged as one of the most frequently employed strategies. On the contrary, the use of explicit criteria for deprescribing, such as START/STOPP criteria is still limited to a few studies. Recently these criteria were revised at an international level in order to give more solid information for older people, particularly when affected by frailty and multimorbidity. (O'Mahony et al. 2023)Again, it is worth emphasizing that electronic tools remain underutilized in deprescribing research, despite the potential promise of artificial intelligence in this domain, especially within primary care settings.(Damiani et al., 2023) Another crucial aspect is that multidisciplinary teams are involved in deprescribing more often than single figures. The multidisciplinary approach to deprescribing seems to be more effective than single figures making deprescribing as shown by some literature. (Radcliffe et al., 2023).

Considering any setting, the use of deprescribing is associated with a reduction in the number of total medications and of PIMs, even if supported by low-to-moderate certainty of evidence. Recognizing and addressing PIMs is crucial to ensure the safety and health of older persons, as well as to enhance their overall quality of life.(Beck et al., 2022) In fact, PIMs can exacerbate existing health conditions, cause falls, cognitive impairment, or adverse drug interactions. (Beck et al., 2022) This can result in hospitalizations and a reduced quality of life for older individuals. (Beck et al., 2022) Thus, reducing the impact of PIMs holds pivotal significance in the field of geriatric medicine. In response to this challenge, various resources have been created to support healthcare professionals in the practice of deprescribing. These tools exhibit a wide range of formats, encompassing general deprescribing frameworks, drug-specific deprescribing guidelines, and specialized tools designed for facets of the deprescribing process, such as the identification of inappropriate medications or patient engagement. Some of these tools were even converted in mobile applications, available for both healthcare professionals and patients.(Molokhia and Majeed, 2017) Although numerous tools exist, the majority offer minimal insights into their development processes, and there has been a scarcity of research on their practical implementation.(Reeve, 2020) For years, the American Geriatric Society has played a major role in this goal through the release of the Beers Criteria as well as in Europe the STOPP criteria are widely used.

It is also important to recognize that in older and vulnerable population, PIMs use is also associated with an increase in public health costs [11]. Collectively, reducing public health costs related to inappropriate drug use in the older population not only benefits the financial aspects of healthcare but, more importantly, it improves the health and well-being of older individuals. By the way, our data further show that in any setting deprescribing is not better than standard care in reducing mortality, despite epidemiological evidence that associates polypharmacy to poorer health outcomes in older adults.(Gnjidic et al., 2012; Huizer-Pajkos et al., 2016; Turner et al., 2016) Previous studies showed that polypharmacy is a strong predictor of falls, mostly affecting older people (Seppala et al., 2018). However, it becomes evident that the stronger correlation lies in the type of medications taken, especially those known to increase the risk of falls, rather than polypharmacy alone. In fact, some specific medications, including opioids and antiepileptics, are specifically associated with a significant increased risk in falling.

Table 4
GRADE profile of deprescribing versus standard care for end of life situations in hospital.

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Deprescribing	Control	Relative (95% CI)	Absolute	
Falls (end of life)											
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[a]	none	39/97 (40.2%)	45/95 (47.4%)	RR 0.87 (0.65–1.16)	62 fewer per 1000 (from 166 fewer to 76 more)	MODERATE
Hospitalizations (end of life)											
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[a]	none	32/110 (29.1%)	29/113 (25.7%)	OR 1.08 (0.69–1.7)	15 more per 1000 (from 64 fewer to 113 more)	MODERATE
Non vertebral fractures (end of life)											
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[b]	none	4/97 (4.1%)	6/95 (6.3%)	OR 0.67 (0.1–4.56)	20 fewer per 1000 (from 56 fewer to 172 more)	LOW
Mortality (end of life)											
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	57/308 (18.5%)	77/265 (29.1%)	OR 0.59 (0.44–0.80)	96 fewer per 1000 (from 44 fewer to 138 fewer)	HIGH

[a] Wide 95% confidence intervals
[b] Less than 200 participants and wide 95% confidence intervals

(Seppala et al., 2018).

Our umbrella review further shows that in the community setting, deprescribing is not more effective than standard care in decreasing injurious falls, any falls or number of fallers. Our findings can be substantiated through the examination of several hypotheses. Firstly, the limited number of studies available for each outcome raises questions regarding the methodology, as this scarcity could be a limiting factor. Secondly, it is crucial to recognize that falls are a complex, multifactorial occurrence, especially in frail individuals. It is plausible that solely revising medications without implementing additional interventions might not be adequate to sufficiently reduce the risk of falling. Simultaneously, it is worth acknowledging that even multicomponent interventions do not consistently demonstrate effectiveness in reducing the risk of falls among community-dwelling individuals. (Hopewell et al., 2018) Preventing falls in the context of geriatric medicine, is an aspect that frequently remains unaddressed. Despite its unquestionable relevance, it appears that the emphasis on fall prevention is often less than it should be, underscoring the imperative for sustained education, and intervention (Lee et al., 2013). It is of great importance to establish whether the connection between polypharmacy and falls is indeed causal, as this determination is pivotal for the promotion of interventions. (Morin et al., 2019).

The issue of polypharmacy in nursing home settings is a complex and significant concern in healthcare. In nursing homes, where residents are typically older and have multiple chronic conditions, polypharmacy is particularly prevalent. Accordingly, it has been recently estimated that nursing home residents consume the highest number of medications among all the settings in which older people live. (Veronese et al., 2021a) A regular evaluation of drug prescribing in nursing home residents is necessary to minimize PIMs. Interestingly, in this setting, we found that deprescribing, compared to standard care, is associated with a significant decrease in PIMs incidence that is, again as in other settings, not associated with any effect on falls, hospitalization rate or mortality. Considering that for this setting several studies are available for each outcome, it is possible to hypothesize that the use of heterogeneous tools might lead to non-statistically significant results. In this sense, many clinicians and researchers are proposing standardized protocols for deprescribing in such a setting. (Thorpe et al., 2023).

Indeed, the most evident findings about deprescribing were found in hospital at end of life, i.e., in patients with a life expectancy less than six months. In this situation, deprescribing is associated with an approximate reduction in mortality of 41%, even if, again, no effect was found on other important outcomes such as falls, fractures or hospitalizations. These findings carry significant importance, particularly in light of the well-established knowledge that older patients, even at the end of their lives, frequently contend with the burden of substantial and often inappropriate medication regimens. In a recent study involving 244 older patients at the end of life, it was reported that patients took, in mean, 11 medications at death or study termination.(McNeil et al., 2016) Many of these medications may lack clear benefits, and some are employed for primary prevention of chronic medical conditions. This highlights the critical need for a more patient-centered approach to prescribing practices for older individuals, emphasizing the necessity for deprescribing and a thorough evaluation of the risks and benefits associated with each medication, especially in the context of end-of-life care. Our findings offer a compelling basis for reinforcing the practice of deprescribing toward the end of life. This is particularly pertinent because it is plausible that the presence of organ failure, which frequently precedes the final stages of life, could significantly influence the pharmacokinetics and pharmacodynamics of medications. This alteration may lead to an acceleration of mortality, making it imperative to reconsider and, when necessary, reduce medication regimens in line with the evolving needs and physiology of individuals in their final phase of life.(Pasina et al., 2020) Deprescribing, guided by careful assessment and consideration of these factors, becomes a crucial element in optimizing the quality of care and life for those nearing the

Table 5
Findings from systematic reviews.

Setting	Population	Outcome	Number of RCTs	Sample size	Main findings
Any	Frail older patients aged 65 years and overs	Medication-related outcomes	2	276	One RCT reported significantly lower prescription of PIMs; the other a reduced number of medications
Any	Adults aged ≥65 years	QoL	9	1836	Only 1/9 RCTs included, reported that deprescribing was associated with a better QoL than controls
Community	community dwelling adults	improved adherence	12	2794	5/12 RCTs reported that deprescribing was better than standard care in improving adherence
Secondary or acute care settings	Frail older patients	Appropriateness of prescribing	3	1122	All reported significant improvements in prescribing appropriateness.
Hospital	End of life	Drug cessation or improvement	3	180	One of the three RCTs reported a significant lower number of prescriptions compared to the control group
Hospital	End of life	Inappropriate medications	2	546	Both RCTs reported that deprescribing is better than control group in reducing inappropriate medications
Hospital	End of life	Adverse events	2	240	All the RCTs reported that the rate of adverse events was similar between deprescribing and control group

end of their life. Emphasizing the benefits of discontinuing inappropriate medications, aligning criteria with deprescribing guidelines tailored for end-of-life patients, and facilitating multidisciplinary dialogues involving not only healthcare professionals but also patients and their family caregivers can serve as valuable tools in rationalizing drug therapy. By leveraging these approaches, we can promote a more patient-centered and prudent approach to prescribing medications, particularly in the context of palliative care, where the focus is on improving the overall quality of life.

Collectively, our umbrella review provides a comprehensive perspective on the significance of deprescribing within diverse contexts and across a substantial body of RCTs and patient populations. Nevertheless, it is crucial to approach the findings considering some limitations. First, our analysis underscores the prevailing heterogeneity in the tools employed for deprescribing, often with varying degrees of validation. This diversity can introduce complexities when attempting to draw generalized conclusions. Secondly, our selection of RCTs may not always include populations that are paradoxically more susceptible to polypharmacy, such as frail older individuals. The potential omission of this particular demographic in some RCTs must be taken into consideration when evaluating the generalizability of our findings.(Veronese et al., 2021b) Lastly, it is important to acknowledge the possibility that the same RCT may have been incorporated into one or more of our analyses. Nevertheless, given our considered stratification of analyses based on settings and populations, it is possible to hypothesize that the likelihood of such bias to be low.

In conclusion, through this comprehensive umbrella review, we have emphasized the significance of deprescribing in addressing common scenarios encountered in our routine clinical practice. While the evidence supports the positive impact of deprescribing on reducing PIMs and enhancing medication adherence, there remains a notable gap in the literature concerning the effects of deprescribing on substantial outcomes, such as fall prevention. Further research in this domain is warranted to provide a more comprehensive understanding of the broader benefits of deprescribing.

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Declaration of Competing Interest

none.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.arr.2024.102237.

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