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Review

Deprescribing: An umbrella review

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ABSTRACT

This umbrella review examined systematic reviews of deprescribing studies by characteristics of intervention, population, medicine, and setting. Clinical and humanistic outcomes, barriers and facilitators, and tools for deprescribing are presented. The Medline database was used. The search was limited to systematic reviews and meta-analyses published in English up to April 2022. Reviews reporting deprescribing were included, while those where deprescribing was not planned and supervised by a healthcare professional were excluded. A total of 94 systematic reviews (23 meta-analyses) were included. Most explored clinical or humanistic outcomes (70/94, 74 %); less explored attitudes, facilitators, or barriers to deprescribing (17/94, 18 %); few focused on tools (8/94, 8.5 %). Reviews assessing clinical or humanistic outcomes were divided into two groups: reviews with *deprescribing intervention trials* (39/70, 56 %; 16 reviewing specific deprescribing interventions and 23 broad medication optimisation interventions), and reviews with *medication cessation trials* (31/70, 44 %). Deprescribing was feasible and resulted in a reduction of inappropriate medications in reviews with *deprescribing intervention trials*. Complex broad medication optimisation interventions were shown to reduce hospitalisation, falls, and mortality rates. In reviews of *medication cessation trials*, a higher frequency of adverse drug withdrawal events underscores the importance of prioritizing patient safety and exercising caution when stopping medicines, particularly in patients with clear and appropriate indications.

Keywords: deprescription, drug discontinuation, drug withdrawal, drug tapering, umbrella review

INTRODUCTION

Concerns have been raised about the inappropriate use of polypharmacy, especially in older patients who may take a large number of medicines with varying levels of complexity (1). Overtreatment with unnecessary or inappropriate medicines does not represent the best possible medical care for a patient, and one approach to avoid this is through deprescribing. The term "deprescribing" was first introduced in 2003 by Woodward that

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suggested planning and undertaking deprescribing activities to improve health outcomes in older people (2). The article by Reeve *et al.* from 2015 exposed that most papers include deprescribing definitions with terms related to discontinuing medicines (*e.g.*, stop, cease, withdraw), while a limited number included the terms dose reduction, substitution, and tapering (3). Thus, they proposed one definition of deprescribing, which is described as the process of withdrawal of an inappropriate medication, supervised by a healthcare professional, with the goal of managing polypharmacy and improving outcomes. The definition of deprescribing is indeed still ambiguous and raises, for example, the question of whether dose reduction is deprescribing or not.

Moreover, studies evaluating the potential benefits and harms of deprescribing can vary widely in the provided intervention. In general, deprescribing studies can be divided into *medication cessation vs. deprescribing intervention trials* (4). In *medication cessation trials*, a target medicine is discontinued in all participants and it provides direct information on the effectiveness and safety of deprescribing (5, 6). For example, such trials may explore abrupt deprescribing of proton pump inhibitors in all patients, regardless of the indication. On the other hand, *deprescribing intervention trials* examine the implementation of an intervention designed to encourage deprescribing, but not required to do so (7). In these trials, the appropriateness of a medicine is first assessed for each individual patient. Later, deprescribing is proposed only for those patients for whom it is deemed necessary. These studies may involve interventions that focus only on discontinuation of medicine, such as patient education on the cessation of proton pump inhibitors, or a broader medication optimisation intervention that includes adjustment, discontinuation, or even initiation of a more appropriate medicine (*e.g.*, medication review, medicines reconciliation). *Deprescribing intervention trials* typically evaluate the success of the intervention implementation, such as the proportion of participants for whom deprescribing was deemed necessary and who successfully discontinued their proton pump inhibitor. Effectiveness and safety outcomes are also commonly reported, but are likely to depend on the success of the intervention. Additionally, these trials may provide qualitative insights that are important, for example, to understand the potential ineffectiveness, to plan further improvement, or possibly implement deprescribing interventions. Although both types of studies are undoubtedly important, the results may not be directly comparable and require cautious interpretation (1).

Not only can the definition of deprescribing and interventions themselves vary, but deprescribing approaches can also target populations with different characteristics, and be specific to certain medicines, settings, or deprescribing tools. In order to provide insights into the current state of research and potential avenues for future exploration, this umbrella review examined and summarised systematic reviews and meta-analyses of deprescribing studies by characteristics of intervention, population, medicine, and setting. Moreover, clinical and humanistic outcomes, barriers and facilitators to deprescribing, and tools for deprescribing are presented.

EXPERIMENTAL

The PRIOR guidelines 2022 for the overview of reviews were used as a guide in the preparation of this umbrella review.

Data sources

The Medline bibliographic database was used. The search was limited to systematic reviews and meta-analyses published in English up to April 2022. A set of terms was selected prior to beginning the search to cover deprescribing and all possible related terms. Therefore, we used synonyms for discontinuation (*e.g.*, withdraw) in conjunction with terms related to healthcare services (*e.g.*, medication review), treatment with multiple medicines (*e.g.*, polypharmacy), or appropriateness of prescribing (*e.g.*, inappropriate prescription). Additional references were sourced through reviewing bibliographies of identified reviews. A full search strategy is provided in Appendix 1.

Selection of reviews and meta-analyses

Reviews reporting any type of deprescribing approach regardless of the definition of deprescribing were included. Reviews were excluded if deprescribing was not planned and supervised by a healthcare professional, as delineated in the definition by Reeve *et al.* (3). Reviews examining only temporary discontinuation of medicines were also excluded.

Data extraction

A reviewer (NJ) extracted the relevant data using a standard data extraction form designed for this review. The data extracted included general characteristics of the review (population included, target medicines, healthcare settings), methodology (objective, number and type of studies included, review type), deprescribing approach (*medication cessation trials* or *deprescribing intervention trials*), and outcomes. Key findings regarding both clinical and humanistic outcomes were extracted from the reviews analysed. Clinical outcomes included mortality, hospitalisation, medication use, adverse drug withdrawal events, and falls, while the humanistic outcome was quality of life. For reviews describing attitudes, barriers, or facilitators to deprescribing approaches, these qualitative outcomes were retrieved. For reviews with descriptions of the deprescribing tools, the most important results about the reviewed tools were retrieved. For systematic reviews, the narrative conclusions of the authors were extracted. For meta-analyses, the pooled relative risks (RR), odds ratios (OR), or mean differences were extracted along with the 95 % confidence intervals (CI).

Data synthesis and analysis

Regarding the deprescribing approach, reviews were divided into two main categories: reviews that mainly included *medication cessation trials* and reviews that mainly included *deprescribing intervention trials.* The latter were further subdivided into reviews that mainly included *specific deprescribing interventions* with only deprescribing and no probability of a prescribing component (*e.g.*, medication review conducted solely to identify deprescribing targets, excluding the initiation of new medicines) or *broad medication optimisation interventions* with deprescribing and also a high probability of a prescribing component (*e.g.*, starting a new medicine). The reviews describing attitudes, barriers, or facilitators to deprescribing approaches and the reviews describing tools for deprescribing were summarised separately. Findings are presented in a narrative form. Given the variety of deprescribing approaches presented across all reviews, statistical pooling in meta-analyses was not appropriate.

Quality and overlap assessment

The PRISMA 2020 checklist (9) was used to assess the quality of reviews focused on clinical and humanistic outcomes of deprescribing approaches, as well as those concentrating on tools for deprescribing. Meanwhile, the ENTREQ 2012 checklist (10) was used to assess the quality of reviews that reported on attitudes, facilitators, or barriers to deprescribing approaches. The overlap of primary studies within the included reviews was also assessed. Primary studies were extracted, and their overlaps were separately evaluated for reviews focused on the clinical and humanistic outcomes of deprescribing approaches, reviews exploring attitudes, barriers, or facilitators to deprescribing approaches, and reviews examining tools for deprescribing. Additionally, the overlap based on the types of medicines was separately addressed in reviews focused on the clinical and humanistic outcomes and those exploring attitudes, barriers, or facilitators to deprescribing approaches.

RESULTS AND DISCUSSION

A total of 94 systematic reviews, including 23 meta-analyses, were included in the umbrella review. Fig. 1 provides an overview of the selection process.

General characteristics of included reviews and meta-analyses

All 94 reviews were published between 2008 and 2022. Most reviews reported clinical and humanistic outcomes, namely mortality, quality of life, hospitalisation, medication use, adverse drug withdrawal events, or falls (70/94, 74 %). Fewer reviews reported attitudes, facilitators, or barriers to deprescribing approaches (17/94, 18 %). One of the reviews reported both clinical outcomes and qualitative findings related to facilitators and barriers to deprescribing. Few reviews focused specifically on identifying or examining tools for deprescribing approaches (8/94, 8.5 %).

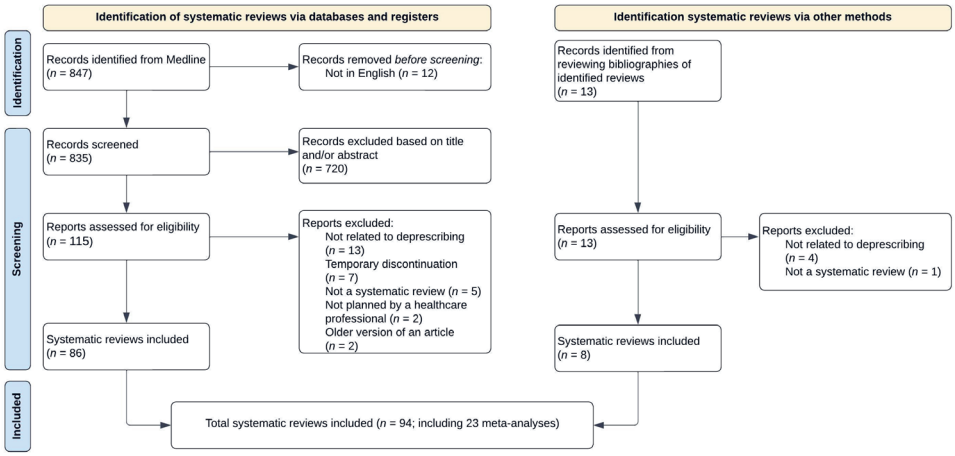

Fig. 1. Flowchart of systematic reviews inclusion.

Reviews describing clinical and humanistic outcomes of deprescribing approaches

Most reviews reported clinical and humanistic outcomes (70/94, 74 %), and 23 of the reviews were upgraded to meta-analysis. The number of randomised or non-randomised studies included in a single review ranged from 2 to as many as 116, on average 17 per review, and the number of participants ranged from 15 to more than 500,000 (Supplementary Table I).

The populations included were of different ages, usually older people over 65 years of age (36/70, 51 %; Table I), adult people over 18 years of age (30/70, 43 %), and only four (4/70, 6 %) reviews addressed younger people under the age of 18. The reviews focusing on an adult population over 18 years of age were not limited to those under 65 years but also included older individuals aged 65 and above, who may even represent the majority of patients in these studies. Slightly less than half of the reviews were limited to patients with specific conditions (33/70, 47 %), most commonly patients with mental disorders (17/70, 24 %), pain (4/70, 6 %), or specific chronic diseases such as diabetes, reflux disease, heart failure and others (Table I). In the older population, the reviews did not focus on a specific disease, with the exception of mental disorders (11–16), especially dementia and sleep disorders. In the adult population, most reviews focused on mental disorders (17–24) or chronic medical conditions (5, 6, 25–34). Of the four reviews that addressed populations younger than 18 years, three focused on children and adolescents with mental disorders such as attention-deficit hyperactivity disorder (35, 36) or epilepsy (37), and one review focused on paediatric patients with asthma (38).

Table I. Number of included systematic reviews describing clinical and humanistic outcomes according to age and characteristics of population

	Characteristic	Age (years)			No. of reviews
		< 18	≥ 18	≥ 65	
No specific condition	no specifics		5	11	16
	limited life expectancy			8	8
	polypharmacy		1	6	7
	critically ill or surgery		4	2	6
Specific condition	mental disorders	3	8	6	17
	pain		4		4
	diabetes		1	2	3
	reflux disease		2		2
	heart failure		1	1	2
	rheumatic disease		2		2
	asthma	1			1
	Crohn's disease		1		1
	osteoporosis		1		1
	Total	4	30	36	70

Most reviews focused on a group of medicines, most commonly medicines for mental disorders (15/70, 21 %), in particular benzodiazepines (13, 16, 21–23) and antipsychotics (15, 18, 35, 36). Two other commonly covered groups of medicines were cardiovascular medicines (7/70, 10 %) (39, 40), including antihypertensives (11, 41, 42) or heart failure medicines (29, 43), and analgesics (5/70, 7 %), especially opioids (14, 27, 31, 33, 34).

The reviews were generally not restricted to a particular setting (46/70, 66 %). Few of the reviews were specifically limited to an inpatient (12/70, 17 %) (31, 34, 44–53) or outpatient setting (11/70, 16 %) (5, 21, 22, 54–61). Long-term care (*e.g.*, nursing homes) was addressed in only one review (62). The main characteristics of reviews and included studies as well as outcomes, namely mortality, quality of life, hospitalisation, medication use, adverse drug withdrawal events, and falls, are summarised in Supplementary Table I.

To summarise, deprescribing approaches were most commonly employed in older populations, with mental disorders, polypharmacy, limited life expectancy, or specific chronic conditions such as diabetes, reflux disease, or heart failure. All the most frequently recognised characteristics in the reviews are expected in the older population and outline patients with high risk for medicine misadventures that should be prioritised for considering deprescribing where appropriate (63). Importantly, successful deprescribing requires more than just considering a patient's age, especially it must address an individual's health condition and medication complexity, including polypharmacy or inappropriate medication use (62, 64). Indeed, patient-specific interventions, such as medication reviews conducted by pharmacists or physicians aimed at identifying deprescribing opportunities in

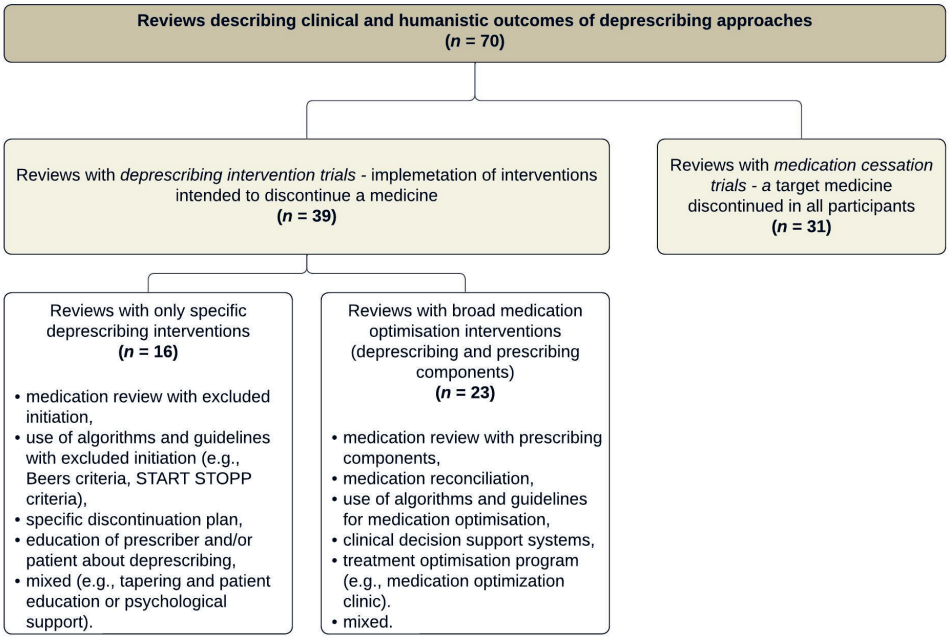

Fig. 2. Distinction between reviews describing clinical and humanistic outcomes of deprescribing approaches.

older patients, have been shown to be more effective at reducing mortality than broad deprescribing educational initiatives directed at healthcare providers or older patients (55, 64).

Type of deprescribing intervention and outcomes

The reviews were divided according to the main type of intervention performed in the studies. In many cases, the reviews did not contain only one type of trial but were classified according to the predominant type. More reviews included *deprescribing intervention trials* (39/70, 56 %; Fig. 2, Supplementary Table I); 16 with specific deprescribing interventions, and 23 with broad medication optimisation interventions. Fewer included *medication cessation trials* (31/70, 44 %).

Reviews which mainly included *deprescribing intervention trials* primarily reported medication use outcomes (34/39, 87 %), as well as adverse drug withdrawal events (19/39, 49 %), hospitalisation (16/39, 41 %), quality of life (15/39, 38 %), mortality (14/39, 36 %), and falls (13/39, 33 %). In addition to clinical and humanistic outcomes, some also reported implementation outcomes such as the feasibility of the interventions in clinical practice (33, 64). These reviews were further divided into reviews that examine *specific deprescribing interventions*, and reviews that include *broad medication optimisation interventions*, which were mostly medication reviews.

Specific deprescribing interventions have been proven to reduce the total number of inappropriate medications (13, 19, 21, 22, 24, 27, 31, 33, 34, 64–66). In particular, educational deprescribing interventions have been shown to reduce opioid use. Additionally, a wide range of interventions, ranging from minimal deprescribing interventions like providing self-help information to patients, to more complex interventions such as cognitive behavioural therapy or mindfulness-based cognitive therapy, have been effective in reducing the use of benzodiazepines or antidepressants. Mostly no detrimental consequences of specific deprescribing interventions were reported, as no increase in adverse events (13, 21, 31, 64, 67), emergency department visits, or rehospitalisations (66, 68), also in the very fragile patients with limited life expectancy were noted. The benefit of deprescribing on other important clinical outcomes was not found, with the exception of two meta-analyses that were able to show a mortality risk-benefit (64, 66) when very targeted patient-specific geriatric interventions were applied. These interventions included medication reviews that excluded initiation but solely focused on identifying targeted medicines for deprescribing, using predefined algorithms such as the Screening Tool of Older Persons Prescriptions (STOPP) in older adults or older adults with limited life expectancy. When interpreting clinical outcomes of deprescribing interventions, it should be noted that it is not always necessary to demonstrate that discontinuation of a medicine leads to improved patient health. Rather, if it can be demonstrated that ceasing the medicine does not result in any deterioration of the patient's health, this can also be considered a favourable outcome (69).

Broad medication optimisation interventions included a variety of interventions, most notably multidisciplinary interventions, pharmacist-led medication reviews, physician-led interventions, prescriber or patient education programmes, and clinical decision support systems. These interventions have been proven to reduce the use of potentially inappropriate medications (45, 48, 53, 55, 57, 62, 70–72) and have also been found to be cost-effective (50, 59). Deprescribing was safe and feasible, and more complex interventions

such as medication reconciliation, medication review, and patient education by pharmacists even reduced potential adverse drug events (45, 57) and hospitalisation rates (43, 46). Medication review-directed deprescribing interventions reduced falls by 24 % in older residents in nursing homes (62). In most cases, no difference in mortality was found after deprescribing, with the exception of two meta-analyses that reported deprescribing interventions within medication review reduced all-cause mortality in older adults in randomised controlled studies (55, 62). Therefore, complex interventions, including medication reconciliation and other services that frequently involved pharmacists, demonstrated improvements in important clinical outcomes. However, due to the wide range of interventions that consider a patient's overall medication regimen, it is challenging to ascertain whether the benefits can be solely attributed to deprescribing. In fact, one review (58) reported a higher medication burden following a comprehensive geriatric assessment, indicating that factors beyond deprescribing alone can influence medication usage and other outcomes.

Reviews which mainly included *medication cessation trials* primarily reported adverse drug withdrawal events (29/31, 93 %) and medication use outcomes (17/31, 54 %), as well as mortality (14/31, 45 %), quality of life (7/31, 23 %), hospitalisation (6/31, 19 %), but rarely falls (4/31, 13 %). Notably, one specific intervention, procalcitonin-guided discontinuation of antibiotics, demonstrated a lower mortality rate (47, 51). Furthermore, deprescribing psychotropic medicines resulted in a reduction in the number of falls (39), and discontinuation of statins showed potential improvement in quality of life (40). Reviews with *medication cessation trials* typically examined the best strategies for discontinuing medicine in all participants, who may differ in the appropriateness and importance of the indication for the medicine to be discontinued. Consequently, the occurrence of adverse events was frequently reported for these strategies. The outcomes varied, ranging from the absence or occurrence of transient adverse drug withdrawal events (6, 11, 14–16, 25, 41, 42, 73) to more severe reactions (5, 12, 20, 28, 29, 35, 36, 74, depending on the specific medicine and individual characteristics. It is important to distinguish between different reasons for deprescribing. Reviews may focus on the discontinuation of potentially inappropriate medications without an existing indication or on the discontinuation of medicines with an existing indication but with a desire to treat the condition less intensively. For example, when proton pump inhibitors were discontinued in patients with reflux disease or mild esophagitis, an increased risk of poor symptom control and lower patient satisfaction was observed (5), whereas, most patients without a clear indication can reduce or completely discontinue proton pump inhibitors without worsening symptom control (6). If the reason for deprescribing is to reduce the intensity of treatment for an existing disease, this must be done with special caution as deprescribing medicines in patients with pre-existing, yet stable, conditions carries the possibility of recurrence. For instance, discontinuing heart failure medicines in patients with stable chronic heart failure (29), ceasing attention-deficit hyperactivity disorder medicines in children diagnosed with the condition (36), or discontinuing biological therapies for rheumatic diseases (28) can potentially lead to relapse. Two reviews even reported higher mortality rates associated with discontinuing heart failure medicines (29) and warfarin in high-risk patients, such as frail individuals or those with limited life expectancy (40). Careful consideration should be given to the appropriateness of indication and the potential for recurrence when deprescribing medicines in cessation trials.

Reviews describing attitudes, barriers, or facilitators to deprescribing approaches

The reviews describing attitudes, barriers, or facilitators to deprescribing approaches (17/94, 18 %) included from 2 to 42 randomised or non-randomised studies in a single review, on average 19 per review (Supplementary Table II). The number of participants ranged from 48 to as many as 400.000. Participants were patients (13/17, 76 %) (75–87), healthcare professionals (12/17, 71 %) (45, 79–83, 85–90), such as prescribers, nursing home staff, or caregivers (11/17, 65 %) (75, 76, 78–80, 82–87). Most reviews did not address a specific medicine or were limited to any long-term medicine (10/17, 59 %), five reviews were focused on a specific medicine, such as cancer therapy (86, 87), benzodiazepines (83), psychotropic medicines (90), and anticholinergics (85), two reviews were tied to a group of potentially inappropriate medications (45, 89). The reviews were generally not restricted to a particular setting (12/17, 71 %), three were specifically limited to inpatient settings (45, 86, 87), one to outpatient settings (80), and one to long-term care settings (*e.g.*, nursing homes) (90).

The main findings related to attitudes, barriers, or facilitators to deprescribing approaches are summarised in Supplementary Table II. The reviews examining attitudes toward deprescribing with the patients' attitudes towards deprescribing questionnaire (PATD) or modifications, reported that 70–88 % of patients are willing to discontinue medicines if told to do so by a healthcare professional (75–78). Additionally, patients showed a willingness to specifically discontinue benzodiazepines (83). In contrast, it is worth noting that healthcare professionals consider the discontinuation of benzodiazepines particularly challenging (83). This highlights the importance of a collaborative approach that involves patients, carers, and multiple healthcare professionals to successfully navigate the deprescribing process. The niche area of cancer therapy discontinuation for end-of-life situations further emphasizes the critical need for patient care that is empathetic, well--informed, and consistent with the patient's values and desires (86, 87). Effective communication is essential when presenting deprescribing also to other patients in late palliative care, highlighting the need for these strategies to be embedded in deprescribing tools (91).

Facilitators and barriers to deprescribing are mostly organisational, professional, and patient-related. The establishment of other clinical pharmacy services, such as the involvement of multidisciplinary teams in the process, medication reconciliation, medication review, as well as the presence of a clinical pharmacist in the clinical setting, may serve as a framework for deprescribing interventions and was the most frequently cited facilitator of deprescribing (45, 82, 88, 89). Patient-related facilitators primarily included patient's or family's involvement, good communication with the patient, especially about possible adverse drug withdrawal events (78, 83, 90), and shared decision-making about stopping medicines (76, 79, 89). Professional-related facilitators included awareness of deprescribing, self-confidence and skills of healthcare professionals, good collaboration between healthcare professionals (*e.g.*, nurses and physicians), follow-up with monitoring (78, 80, 82, 88–90), and other factors listed in Supplementary Table II. Barriers included factors similar to those of facilitators, only in a negative direction. Additionally, unawareness of the benefits of deprescribing, fear of cessation, or fear of missing out on future benefits of treatment were highlighted as important barriers (78, 79, 84). Addressing fears and concerns about deprescribing is critical to overcoming barriers to deprescribing and should be done through effective patient education and open communication between patients and healthcare professionals. Shared decision-making with patients plays a vital role in this regard.

Reviews describing tools for deprescribing approaches

Eight reviews described tools for deprescribing approaches and are summarised in Supplementary Table III. Three of the reviews examined all of the tools developed for deprescribing and reported the following types of tools: general framework, detailed tools for medicine assessment, and comprehensive discontinuation guidelines (91–93). One of these reviews focused on frail older populations and one on palliative care patients, including cancer patients. Three other reviews focused on guidelines for discontinuation of specific medicines, *e.g.*, cholinesterase inhibitors (94), statins (95), and dermatological therapy (96). One review described only educational materials on deprescribing one or more medicines (97), and another review determined the applicability of the N-of-1 trial method (98).

Tools for deprescribing approaches could be applied in different stages of deprescribing, *e.g.*, preparation, which includes assessment of the current status of the patient and his medication history, medicine evaluation, decision making, and implementation (91). The identified weaknesses of the tools in the reviews include poor descriptions of development methodology and their limited application in clinical practice (92), no or few specific recommendations for the discontinuation of specific medicines (94–96), and in the case of educational material, a requirement of high levels of reading, thus making it inappropriate for populations with low health literacy (97). An N-of-1 or single-subject clinical trial is a randomized crossover study design in which a single patient acts as their own control (98). This design uses the random allocation of an experimental and a control intervention while keeping the patient unaware of the sequence (98). This method, considered safe, may be particularly useful for studying deprescribing in specific individuals, such as older adults who are cognitively impaired, addressing the inherent complexities and variabilities of this group (98). However, while the overall feasibility of N-of-1 trials remains to be evaluated, it is important to note that they are not suitable for investigating long-term outcomes, risks, or benefits (98). Practical and validated tools are needed to provide clinicians with guidance on the discontinuation process, communication aspects, and to encourage patient involvement in order to align with patients' evolving priorities and care goals (91). Patients with certain medical conditions such as cancer patients or near the end of life may have unique opportunities and challenges to deprescribing.

Quality and overlap assessment

Reviews focusing on clinical and humanistic outcomes had an average score of 0.77, while those concentrating on tools for deprescribing scored an average of 0.79 out of a maximum of 1.00, reflecting a robust reporting approach. Reviews exploring attitudes, barriers, or facilitators to deprescribing approaches had a notably lower average score of 0.54 out of 1.00, highlighting areas for improvement in reporting and methodology. Regarding ENTREQ guidelines, deficiencies were noted in approaches to searching and in the use of quotations. Reviews focusing on qualitative research could benefit from more structured search strategies and more effective integration of direct evidence, such as quotations. Detailed assessments of the quality are available in Supplementary Tables IV to VIII. The overlap of all primary studies was 28 % between reviews focused on the clinical and humanistic outcomes of deprescribing approaches, 24 % between reviews exploring attitudes, barriers, or facilitators to deprescribing approaches, and only 3 % between

reviews examining tools for deprescribing. The low overlap in reviews examining tools for deprescribing indicates diverse research in this area, with potential for new studies. The overlap based on the types of medicines is reported in Supplementary Tables I and II.

Limitations

The diversity of the terminology in the field of deprescribing represented a major challenge and has made an effective retrieval of all published reviews uncertain. Intentionally, the search was extensive and the search profile broad, hence ensuring the majority of applicable reviews were identified and included. During the writing of this paper, additional strategies for searching deprescribing literature were published (99), but the search profile of this umbrella review was not compared with these recommended strategies. Reviews were classified by the predominant intervention type and may include different types of studies, including both *deprescribing intervention trials* and *medication cessation trials*. The wide range of qualitative and quantitative reviews did not allow comparability or correlation between specific interventions and outcomes. The list of excluded reviews is not provided. The protocol of this umbrella review was not registered.

Practice, policy, and future research

In clinical practice, it's crucial to acknowledge that successful deprescribing requires individualized approaches that consider the patient's health conditions and medication complexity, including inappropriate medication use. Collaboration among patients, care -givers, and healthcare professionals is essential for successful deprescribing. This should be followed also on a policy level. The policy should support the implementation of deprescribing in clinical practice by producing practical and validated tools for deprescribing, considering factors like health literacy and patient populations with unique needs. Future systematic reviews on deprescribing should carefully differentiate between *deprescribing intervention trials* and *medication cessation trials* and then focus on the composition and clear description of the deprescribing approach examined in specific populations, medicines, and settings. The description of the study design of included studies in future reviews must be carefully considered, especially the selection of deprescribing intervention, to ensure sufficient quality of evidence and the implementation of evidence-based interventions into routine practice (69). Researchers should focus more on one type of medicine and, when appropriate, also on patients' groups, to make a specific recommendation for discontinuation in the absence of compelling indications.

CONCLUSIONS

The current umbrella review provides a comprehensive and nuanced overview of the existing evidence and identifies specific reviews that can inform clinical practice and researchers in the field of deprescribing. A total of 94 systematic reviews were included. Most reviews examined outcomes related to mortality, quality of life, hospitalisation, medication use, adverse drug withdrawal events, or falls of deprescribing approaches (70/94, 74 %). Reviews with *deprescribing intervention trials*, qualitative findings, and tools provide insights into successful implementation in clinical practice, considering factors

such as individual patient needs and overall treatment goals. Reviews with *medication cessation trials* aim to identify the safest deprescribing strategies in all participants, including those who may have an appropriate and established indication and therefore these reviews primarily examined adverse drug withdrawal events. Distinguishing between *deprescribing intervention trials* and *medication cessation trials* in a systematic review is crucial, as it ensures an accurate assessment of the evidence to inform decisions regarding deprescribing strategies.

The datasets generated during and/or analysed during the current study are available from the corresponding author upon reasonable request.

In the supplementary file, the search profile, characteristics of the included reviews, and the quality assessment of the reviews are available.

Availability of data and materials. – The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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Conflict of interest. – N. Japelj, N. Horvat, and M. Kos declare that they have no competing interests. L. Knez has received a speaker honorarium from MSD, Pfizer, and Roche.

Authors contributions. – Conceptualization, N.J., N.H., L.K., and M.K.; methodology, N.J. and M.K.; investigation, N.J.; analysis, N.J. and M.K.; writing, original draft preparation, N.J.; writing, review and editing, N.J., N.H., L.K. and M.K. All authors have read and agreed to the published version of the manuscript.

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Deprescribing: an umbrella review

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Appendicies

Appendix 1: Search profile

Search: ("deprescribed"[All Fields] OR "deprescriptions"[All Fields] OR "deprescription"[All Fields] OR "deprescribing"[All Fields] OR (("withdraw"[Title/Abstract] OR "cease"[Title/Abstract] OR "cessation"[Title/Abstract] OR "discontinue"[Title/Abstract] OR "stop"[Title/Abstract]) AND ("Therapy Management"[Title/Abstract] OR "medication review"[Title/Abstract] OR "service"[Title/Abstract] OR "process"[Title/Abstract] OR "care"[Title/Abstract] OR "Pharmaceutical Preparations"[MeSH Terms] OR ("Polypharmacy"[Title/Abstract] OR "multidrug regimen"[Title/Abstract] OR "multidrug treatment"[Title/Abstract] OR "multidrug therapy"[Title/Abstract]) OR (("inappropriate"[Title/Abstract] OR "appropriate"[Title/Abstract]) AND ("prescribe"[Title/Abstract] OR "prescription"[Title/Abstract])))) AND "systematic review"[Filter]

Supplementary Table 1 – Characteristic of reviews reporting outcomes related to mortality, quality of life, hospitalisation, medication use, adverse drug withdrawal events, or falls of deprescribing approaches.

Author	Population	Deprescribing approach; medicine	Setting	N of studies (N of RCTs); N of participants	Outcomes
Any medicine (overlap of primary studies within the reviews: 30%)					
Pruskowski, 2019 [68]	>65 yrs life-limiting illness limited life expectancy	deprescribing intervention; any	any	12 (8) N= 2195	• Quality of life: deprescribing may not significantly improve quality of life or satisfaction with care. • Hospitalisation: deprescribing may not contribute to additional emergency department visits and hospitalisations.
Shrestha, 2021* [66]	>65 yrs life-limiting illness limited life expectancy	deprescribing intervention; any dual-purpose medicines	any	5 (4) N= 689	• Mortality: deprescribing lowered the risk of mortality (RR 0.59, 95% CI 0.44 to 0.79). • Quality of life: no significant difference. • Hospitalisation: deprescribing lowered the risk of referral to acute care facilities (RR 0.40, 95% CI 0.22 to 0.73), but not impact the risk of emergency presentation, unplanned hospital admission, or general practitioner visits. • Medication use: overall success of deprescribing 75.7%, varied between 33.3% for beta-blockers to 100% for nitrates. • Adverse drug withdrawal events: insufficient evidence. No significant difference in physical and cognitive functions. • Falls: deprescribing had no impact on the risk of falls, or non-vertebral fracturs.
Ostini, 2011 [65]	>18 yrs	deprescribing intervention; any	any	12 (6) N=NR	• Medication use: possible to stop prescribing various medicines with different deprescribing interventions. Involvement of patient in the stopping process a common theme in effective interventions.
Page, 2016* [64]	>65 yrs polypharmacy	deprescribing intervention; any	any	116 (56) N=34.143	• Mortality: MA of RCTs showed deprescribing polypharmacy (≥3 medicines) had no mortality benefit (OR 0.82; 95% CI: 0.61–1.11). MA of non-RCTs showed deprescribing polypharmacy reduced mortality (OR 0.32; 95% CI: 0.17–0.60). In subgroup analysis, patient-specific interventions reduced mortality (OR 0.62, 95% CI 0.43–0.88), educational programmes had no mortality benefit (OR 1.21, 95% CI 0.86–1.69). Deprescribing of single medicine or medication classes not associated with a difference in mortality. • Quality of life: RCTs showed deprescribing polypharmacy had no impact on quality of life. Deprescribing of single medicine or medication classes not associated with a difference in quality of life in RCTs and non-RCTs. • Medication use: MA of RCTs showed deprescribing polypharmacy reduced both total number of medicines (MD −0.99; 95% CI: −1.83 to −0.14) and PIMs (MD −0.49; 95% CI: −0.70 to −0.28). • Adverse drug withdrawal events: RCTs showed deprescribing polypharmacy did not increase adverse drug withdrawal events. • Falls: MA of RCTs showed deprescribing polypharmacy had no impact on falls (OR 0.65; 95% CI: 0.40–1.05).

Author	Population	Deprescribing approach; medicine	Setting	N of studies (N of RCTs); N of participants	Outcomes
Bužančić, 2021 [56]	>18 yrs	deprescribing intervention (broad); any	outpatient	24 (9) N=4231	• Mortality: medication review by community-based pharmacist do not affect the mortality. • Quality of life: medication review by community-based pharmacist do not affect the quality of life. • Hospitalisation: medication review by community-based pharmacist do not affect the rate of hospitalisations. • Medication use: medication review by community-based pharmacist can lead to successful deprescribing of high-risk medication. All types of interventions resulted in greater discontinuation of medications. Educational interventions reported financial benefits. Pre-defined pharmacist-led deprescribing did not reduce healthcare resource consumptions but contributed to financial savings. • Falls: medication review by community-based pharmacist do not affect the risk or rate of falls.
Dills, 2018 [58]	>18 yrs multimorbidity	deprescribing intervention (broad); any	outpatient	58 (58) N=NR	• Mortality: deprescribing with or without focusing on a specific medicine or chronic condition may not lead to expected improvement in mortality. • Quality of life: no difference. • Hospitalisation: no difference. • Medication use: interventions with the most success in reducing polypharmacy included pharmacist interventions. Cardiovascular drugs the most successfully deprescribed. Psychotropic medicines and proton pump inhibitors most resistant to deprescribing. Medication burden could be higher after a comprehensive geriatric assessment. • Adverse drug withdrawal events: unmasking of heart failure with diuretic withdrawal, increase in fractures with bisphosphonate withdrawal, decline in cognition, worsening of behaviour with polypharmacy reduction. • Falls: no difference.
Kua, 2019* [62]	>65 yrs	deprescribing intervention (broad); any	long-term care	41 (41) N=18.408	• Mortality: MA (30 RCTs) showed deprescribing reduced all-cause mortality (OR 0.90, 95% CI 0.82 to 0.99). In subgroup analysis, medication review-directed deprescribing interventions reduced all-cause mortality (OR 0.74, 95% CI 0.65 to 0.84). • Hospitalisation: MA (30 RCTs) showed deprescribing had no effect on hospitalisation (OR 0.72; 95% CI 0.31 to 1.66). • Medication use: MA (30 RCTs) showed deprescribing reduced the number of residents with PIMs by 59% (OR 0.41; 95% CI: 0.19–0.89). • Falls: MA (30 RCTs) showed deprescribing had no effect on falls (OR 0.85; 95% CI 0.73 to 1.00). In subgroup analysis, medication review-directed deprescribing interventions reduced falls (OR 0.76, 95% CI 0.62 to 0.93).
Christopher, 2021* [57]	>65 yrs	deprescribing intervention (broad); any	outpatient	13 (13) N=6173	• Quality of life: inconclusive evidence. • Hospitalisation: medication review did not reduce the number of older who require hospitalisation (RR 0.72; 95% CI 0.47 to 1.12). • Medication use: pharmacy-based interventions improved clinical outcomes, including reducing uncontrolled health outcomes, and improving appropriate medication use. Patient education increased discontinuation of sedative–hypnotics use (RR 1.28, 95% CI 1.20 to 1.36). • Adverse drug withdrawal events: reduced with pharmacy-based interventions (patient education). • Falls: medication review did not reduce the number of older who fall (RR 1.25; 95% CI 0.78 to 1.99).
Romano, 2022 [59]	>65 yrs	deprescribing intervention (broad); any	outpatient	14 (11) N=8045[a]	• Medication use: cost effectiveness ranged from dominant to an incremental cost-effectiveness ratio of $112,932 per quality-adjusted life-year. 85% of the interventions were cost saving, dominated usual care or were cost effective considering 1 gross domestic product per capita.

Author	Population	Deprescribing approach; medicine	Setting	N of studies (N of RCTs); N of participants	Outcomes
Johansson, 2016* [100]	>65 yrs polypharmacy	deprescribing intervention (broad); any	any	25 (21) N=10.980	• Mortality: MA showed deprescribing had no effect on all-cause mortality (OR 1.02, 95% CI: 0.84 to 1.23). • Hospitalisation: no difference. • Medication use: deprescribing reduced total number of medicines (3 RCTs).
Bloomfield, 2020* [55]	>65 yrs polypharmacy	deprescribing intervention (broad); any	outpatient	38 (38) N>400.000[b]	• Mortality: medication review reduced all-cause mortality (OR 0.74, 95% CI 0.58 to 0.95). Educational interventions little to no effect on effect on all-cause mortality. No evidence for CDSS. • Quality of life: medication review or educational interventions little to no effect on quality of life. No evidence for CDSS. • Hospitalisation: medication review or educational interventions little to no effect on hospitalisations. No evidence for CDSS. • Medication use: medication review and educational interventions reduced PIMs. Mixed evidence for CDSS. • Falls: comprehensive medication review little to no effect on falls. The effect of educational interventions on falls uncertain. No evidence for CDSS.
Ulley, 2019 [61]	>65 yrs polypharmacy	deprescribing intervention (broad); any	outpatient	22 (12) N=5118	• Medication use: insufficient evidence that deprescribing improves adherence (13 studies reported improved adherence, 5 were RCTs). Four studies reported reduction in medicines and all corresponded with improved adherence.
Ali, 2020** [54]	>65 yrs multimorbidity polypharmacy	deprescribing intervention (broad); any	outpatient	9 (7) N=2424[a]	• Mortality: intervention including role (e.g., pharmacist), program (e.g., medication optimization clinic), tools, decision aids, CDSS, or tapering had comparable rates of mortality. • Quality of life: potential improvement on physical function tests in observational studies. • Hospitalisation: comparable rates of hospitalisation between interventions. • Adverse drug withdrawal events: adverse effects trivial and mainly associated with adverse medicine withdrawal events (limited evidence). • Falls: No difference in incidence for interventions compared with usual care in RCTs (RR 0.87, 95 % CI, 0.57 to 1.31). In observational study, a reduction of 52 % in falls in intervention group.
Ibrahim, 2021 [101]	>65 yrs frail	deprescribing intervention (broad); any	any	6 (2) N=657	• Mortality: no difference. • Quality of life: no impact. Positive impact on clinical outcomes including depression, mental health status, function and frailty. • Hospitalisation: no difference. • Medication use: reduction in PIMs and the total number of medicines per-patient, potential cost savings. • Adverse drug withdrawal events: no difference. • Falls: mixed findings.
Lee, 2021 [49]	>65 yrs undergoing surgery	deprescribing intervention (broad); any	inpatient	16 (2) N=3555	• Hospitalisation: inconsistencies in outcomes related to healthcare utilization. Similarities noted among studies that showed positive results: participants vulnerable or at-risk 65 and older with multimorbidity, elective cases, intervention through interdisciplinary teams, and intervention delivery during the inpatient period. • Adverse drug withdrawal events: inconsistencies in outcomes related to postoperative complications. • Medication use: using STOPP/START criteria demonstrated significant findings in reduction of PIMs (limited evidence).

Author	Population	Deprescribing approach; medicine	Setting	N of studies (N of RCTs); N of participants	Outcomes
Thio, 2018 [60]	>18 yrs	medication cessation; any chronic medicines	outpatient (long-term care)	27 (27) N=8773[a]	• Mortality: decreased risk of mortality in intervention group (placebo or discontinuation) or no difference. • Quality of life: mixed findings. • Medication use: discontinuation rate 20%-100%. • Adverse drug withdrawal events: relapse rate 1.9%-80%. Greater relapse risk in intervention groups. • Falls: mixed findings.
Proton pump inhibitors (overlap of primary studies within the reviews: 0%)					
Wilsdon, 2017 [7]	>65 yrs no indication	deprescribing intervention (broad); proton pump inhibitors	any	21 (6) N>100.000[b]	• Medication use: more successful deprescribing strategies were population-wide education and promotion strategy, academic detailing for general practitioners, and inpatient geriatrician-led deprescribing.
Boghossian, 2017 [5]	>18 yrs nonerosive reflux disease or mild esophagitis	medication cessation; proton pump inhibitors	outpatient	6 (6) N=1758	• Quality of life: on-demand use may reduce patient satisfaction compared with continuous use. No evidence for abrupt discontinuation. • Medication use: on-demand use reduced drug burden compared with continuous use. No evidence for abrupt discontinuation. • Adverse drug withdrawal events: on-demand use may increase risk of lack of symptom control compared with continuous use. Insufficient evidence for abrupt discontinuation. No evidence of positive drug withdrawal effects for any strategy.
Haastrup, 2014 [6]	>18 yrs gastroesophageal reflux disease, dyspepsia, or unknown indication	medication cessation; proton pump inhibitors	any	6 (3) N=687[a]	• Medication use: discontinuation rate 14%-64% without deteriorating symptom control. Tapering more effective than abrupt discontinuation. • Adverse drug withdrawal events: most patients without a clear indication can step down or completely off proton pump inhibitors without deteriorating symptom control.
Medicines for mental disorders (overlap of primary studies within the reviews: 11%)					
Mugunthan, 2011* [21]	>18 yrs	deprescribing intervention; benzodiazepines	outpatient	3 (3) N=615	• Medication use: reduction/ cessation in benzodiazepine consumption in the intervention groups compared to usual care (RR 2.04, 95% CI 1.5 to 2.8/ RR 2.3, 95% CI 1.3 to 4.2) with minimal intervention (letter, self-help information, or short consultation with a general practitioner). • Adverse drug withdrawal events: minimal interventions improved general health status. Minimal intervention by general practitioner effective strategy to decrease or stop benzodiazepine without causing adverse consequences.
Reeve, 2017 [13]	>65 yrs	deprescribing intervention; benzodiazepines, Z-drugs	any	7 (5) N=1059[a]	• Quality of life: 1 study reported reduced quality of life for continued use of benzodiazepine. • Medication use: benzodiazepine discontinuation rates 27% to 80%, differed according to intervention (the highest for mixed interventions, e.g., patient education and tapering, medicine substitution and psychological support, or tapering and psychological support). • Adverse drug withdrawal events: probably no difference in withdrawal symptoms or sleep quality.

Author	Population	Deprescribing approach; medicine	Setting	N of studies (N of RCTs); N of participants	Outcomes
Van Leeuwen, 2021 [24]	>18 yrs depressive and anxiety disorders	deprescribing intervention; antidepressant	any	33 (33) N=4995	• Medication use: stopping in combination with providing cognitive therapy was possible for 40% to 75% of participants in the group tapering (very low to low certainty evidence). Prompt letter and guidance on tapering sent to the general practitioner may have no effect on the number of people who stop their antidepressant (low certainty evidence). • Adverse drug withdrawal events: no conclusions about withdrawal symptoms after abrupt or gradual stopping. Abrupt stopping may lead to higher risk of relapse (very low-certainty evidence) and insufficient evidence of its effect on occurrence of side effects compared to continuation. Tapering over a few weeks may lead to higher risk of a return (very low-certainty evidence) and may have little or no effect on side effects compared to continuation. Stopping in combination with providing cognitive therapy may show no difference in effects on relapse (very low to low certainty evidence).
Maund, 2019 [19]	>18 yrs anxiety disorders	deprescribing intervention; antidepressant	any	12 (8) N>4900[b]	• Quality of life: mindfulness-based cognitive therapy with tapering vs maintenance antidepressants showed no difference in quality of life at one year or longer. • Medication use: discontinuation rates 6-7% for prompted primary care clinician patient review and tapering, to 40-95% for specialist psychological or psychiatric interventions. Most effective interventions cognitive behavioral therapy or mindfulness-based cognitive therapy. • Adverse drug withdrawal events: Relapse/ recurrence rates similar for mindfulness-based cognitive therapy with tapering and maintenance antidepressants (44% to 48% vs 47% to 60%).
Parr, 2008* [22]	>18 yrs	deprescribing intervention; benzodiazepines	outpatient	32 (32) N=16.019 [a]	• Medication use: gradual dose reduction (OR 5.96, CI 2.08 to 17.11) and brief interventions such as letter to physician or self-help booklet (OR 4.37, CI 2.28 to 8.40) provided superior cessation rates at post-treatment to routine care. Psychological treatment plus gradual dose reduction superior to both routine care (OR 3.38, CI 1.86 to 6.12) and gradual dose reduction alone (OR 1.82, CI 1.25 to 2.67). Substitutive pharmacotherapies did not add to the impact of gradual dose reduction (OR 1.30, CI 0.97 to 1.73), and abrupt substitution by other medicine less effective than gradual dose reduction alone (OR 0.30, CI 0.14 to 0.64). Providing an intervention is more effective than routine care.
Ribeiro, 2021 [23]	>18 yrs	deprescribing intervention (broad); benzodiazepines	any	11 (3) N=178.048[a]	• Medication use: interventions focused on patient education had good discontinuation rates (18% to 43% after 6 months, control groups 5% to 9%) and had a great potential to motivate discussions about deprescribing with physicians. This kind of intervention is usually faster, cheaper and more effective if combined with encouragement from healthcare professionals.
Paquin, 2014 [16]	>40 yrs	medication cessation; benzodiazepines	any	28 (NR) N=3000[a]	• Medication use: protocols included taper alone (32%), taper plus cognitive behavioral therapy (32%) and taper plus medicine substitution (36%). Success rates favorable for all modalities (mean 60%, median 67%, CI 25% to 85%) and independent of dose or duration of use. Common schedules included a 25% dose reduction over 1-2 weeks until drug-free. • Adverse drug withdrawal events: withdrawal symptoms included mainly mild psychological and somatic concerns. No serious safety events were reported. Expert opinion was benzodiazepine reduction protocols among older adults are feasible and successful.
Matsui, 2019* [18]	>18 yrs schizophrenia spectrum disorder	medication cessation; antipsychotics	any	6 (6) N=341	• Medication use: significant difference in study discontinuation due to all causes in favor of staying on antipsychotic polypharmacy (RR 2.28, 95% CI 1.50 to 3.46) vs to antipsychotic monotherapy. • Adverse drug withdrawal events: no significant differences in discontinuation due to lack of efficacy or side effects, relapse, psychopathology, neurocognition, extrapyramidal symptoms, and body weight.
Monahan, 2021 [20]	>18 yrs psychiatric diagnosis	medication cessation; quetiapine	any	13 (0) N=15	• Adverse drug withdrawal events: immediate cessation of quetiapine associated with onset of somatic symptoms or choreiform movements (limited evidence, only case reports).

Author	Population	Deprescribing approach; medicine	Setting	N of studies (N of RCTs); N of participants	Outcomes
Van Leeuwen, 2018* [15]	>65 yrs dementia	medication cessation; antipsychotics	any	10 (10) N= 632	• Mortality: uncertain evidence. • Quality of life: little or no effect. • Medication use: insufficient evidence whether discontinuation has any effect on time until repeat prescription for any psychotropic or any antipsychotic agent. • Adverse drug withdrawal events: discontinuation may have no effect on adverse events and little or no important effect on behavioural and psychological symptoms.
Van de Loo-Neus, 2011 [36]	6 to 18 yrs attention-deficit hyperactivity disorder	medication cessation; attention-deficit hyperactivity disorder medications	any	53 (11) N=NR	• Medication use: annual medicine-free periods are recommended for children and adults. A medicine-free period should last a week or longer. Clinical decisions about continuing or stopping be made on an individual basis. • Adverse drug withdrawal events: some children with attention-deficit hyperactivity disorder continue to benefit from long-term medical treatment in terms of symptom control, whereas in others the beneficial effects of the medicine fail after 1 or 2 years.
Lohr, 2021 [35]	<18 yrs attention deficit hyperactivity disorder	medication cessation; attention-deficit hyperactivity disorder medications	any	35 (13) N=1004[b]	• Quality of life: RCTs support the use of medicines to improve quality of life. • Adverse drug withdrawal events: Most RCTs show early re-emergence of disease symptoms for most children discontinuing stimulants. However, a significant subpopulation (around 30%) may tolerate discontinuation without relapse.
Davies, 2019 [17]	all ages any diagnosis	medication cessation; antidepressant	any	24 (6) N>4500[b]	• Adverse drug withdrawal events: withdrawal incidence rates ranged from 27% to 86% with a weighted average of 56% (14 studies). Nearly half (46%) of people experiencing withdrawal effects describe them as severe (4 studies). Withdrawal effects last for several weeks or months (mean duration between 5 days to 79 weeks).
Parsons, 2021* [12]	>65 yrs dementia	medication cessation; cholinesterase inhibitors or memantine	any	6 (6) N=759	• Mortality: no clear evidence of an effect of discontinuation on mortality (OR 0.75, 95% CI 0.36 to 1.55). No trials investigated stopping memantine only. • Quality of life: little to no change in quality of life of patients or caregivers (limited evidence). • Adverse drug withdrawal events: no clear evidence of an effect of discontinuation on number of adverse events (OR 0.85, 95% CI 0.57 to 1.27) or serious adverse events (OR 0.80, 95% CI 0.46 to 1.39). Discontinuing cholinesterase inhibitors may result in worse cognitive, neuropsychiatric and functional status (limited evidence).
Group of potentially inappropriate medications (overlap of primary studies within the reviews: 13%)					
Lee, 2021* [48]	>65 yrs	deprescribing intervention; FRIDs	inpatient	5 (5) N=1305	• Hospitalisation: no trials evaluated the impact of deprescribing FRIDs on fall-related fractures or hospitalisations. • Adverse drug withdrawal events: no trials evaluated adverse effects related to a FRID deprescribing. • Falls: deprescribing FRIDs did not change the rate of falls (rate ratio 0.98, 95% CI 0.63 to 1.51), the incidence of falls (risk difference 0.01, 95% CI −0.06 to 0.09; RR 1.04, 95% CI 0.86 to 1.26) or rate of fall-related injuries (rate ratio 0.89, 95% CI 0.57 to 1.39) over a follow-up period of 6–12 months.

Author	Population	Deprescribing approach; medicine	Setting	N of studies (N of RCTs); N of participants	Outcomes
Lindsay, 2013 [103]	>65 yrs (mostly) palliative cancer or noncancer patients	deprescribing intervention; PIMs	any	9 (1) N=544.241[a]	• In cancer patients no interventional, follow-up or RCTs, and no studies that have identified the impact of ceasing PIMs in palliative cancer patients. The incidence of PIMs approximately 20%.
Monteiro, 2019 [71]	>65 yrs	deprescribing intervention (broad); PIMs	any	16 (10) N=266.562	• Medication use: CDSS interventions reduced PIMs.
Cardona, 2021 [46]	>65 yrs hospitalised palliative patients near the end of life	deprescribing intervention (broad); PIMs	inpatient	7 (5) N=1747	• Mortality: no evidence of reduction in mortality. • Quality of life: no evidence of reduction in long-term impact on quality of life or physical functioning. • Hospitalisation: interventions by multidisciplinary teams reduced drug-related hospitalisations. No evidence of reduction in all-cause hospital admissions, mortality, long-term impact on quality of life or physical functioning. • Medication use: multi-component interventions reduced PIMs. • Adverse drug withdrawal events: no evidence of long-term impact on reducing adverse events. Three studies reported no difference between intervention and control groups in adverse events or falls at either two or three months.
Saeed, 2022 [50]	>65 yrs frail	deprescribing intervention (broad); PIMs	inpatient	3 (3) N=1122[a]	• Mortality: medication optimisation had no impact on mortality (some concerns of bias). • Quality of life: no differences. • Hospitalisation: no differences in hospital presentations. • Medication use: reduced use of PIMs and cost of medicines. • Adverse drug withdrawal events: medication optimisation interventions are safe and feasible among frail hospitalised older patients. • Falls: no differences in falls, fractures.
Thillainadesan, 2018 [53]	>65 yrs hospitalised	deprescribing intervention (broad); PIMs	inpatient	9 (9) N=2522	• Mortality: impact unclear. • Quality of life: impact unclear. • Hospitalisation: impact unclear. • Medication use: electronic and non-electronic deprescribing interventions, pharmacist-led medication reviews, physician-led interventions, prescriber education programmes, multidisciplinary interventions, and CDSS reduced PIMs. • Adverse drug withdrawal events: deprescribing interventions were safe and feasible. • Falls: impact unclear.
Bourne, 2022* [45]	>18 yrs intensive care unit patients transition to a hospital ward	deprescribing intervention (broad); PIMs	inpatient	17 (1) N>11.000[b]	• Mortality: no difference in mortality rate (limited evidence). • Hospitalisation: no differences in intensive care unit readmission rate or hospital length of stay (limited evidence). • Medication use: reduced risk of use of PIMs at intensive care unit discharge (OR 0.45, 95% CI 0.31 to 0.63) and hospital discharge (OR 0.39, 95% CI 0.2 to 0.76). Multicomponent interventions based on education and guidelines were effective at achieving almost four times more deprescribing of PIMs by the time of patient hospital discharge. • Adverse drug withdrawal events: more complex interventions such as medication review and medicines reconciliation reduced potential adverse drug events (limited evidence).

Author	Population	Deprescribing approach; medicine	Setting	N of studies (N of RCTs); N of participants	Outcomes
Hansen, 2018* [70]	>65 yrs	deprescribing intervention (broad); mostly PIMs	any	25 (25) N=20.812	• Medication use: reduction of existing inappropriate prescribing lowered the number of drugs (mean difference –0.96, 95% CI –1.53 to –0.38) and reduce the use of PIMs (–0.19, 95% CI –0.40 to 0.02). Successful deprescribing is facilitated by the combination of behaviour change techniques involving a range of intervention components.
Shrestha, 2020 [72]	>65 yrs life-limiting illness limited life expectancy	deprescribing intervention (broad); mostly PIMs	any	9 (3) N = 1375	• Mortality: impact unclear. • Quality of life: impact on quality of life and physical and cognitive function unclear. • Medication use: reduction of PIMs. • Falls: impact unclear.
Cardiovascular medicines (overlap of primary studies within the reviews: 5%)					
Hernández-Prats, 2021 [43]	>65 yrs heart failure	deprescribing intervention (broad); medications for heart failure	any	9 (8) N=3323	• Hospitalisation: only those studies where pharmacists evaluated the appropriateness of treatment to specific heart failure guidelines showed significant differences in patients' clinical outcomes (e.g., lower readmission rates).
Reeve, 2020* [42]	>50 yrs	medication cessation; antihypertensives	any	6 (6) N=1073	• Mortality: low or very low certainty of evidence that stopping did not increase the risk of death. In the discontinuation group compared to continuation, the odds for all-cause mortality 2.08 (95% CI 0.79 to 5.46). • Hospitalisation: low or very low certainty of evidence that stopping did not increase the risk of having a heart attack, stroke, or hospitalisation. In the discontinuation group compared to continuation, the odds for myocardial infarction 1.86 (95% CI 0.19 to 17.98), for stroke 1.44 (95% CI 0.25 to 8.35). • Medication use: most of patients in discontinuation group did not need to restart their medicine (10.5% - 33.3% in discontinuation group compared to 9% - 15% in the continuation group experienced clinical criteria that would require restarting of therapy such as poor blood pressure control). • Adverse drug withdrawal events: very low certainty of evidence that stopping did not increase the risk of adverse events and may resolve side effects. Low certainty of evidence that stopping increased blood pressure by a small amount (mean difference - systolic 9.75 mmHg, 95% CI 7.33 to 12.18; diastolic 3.5 mmHg, 95% CI 1.82 to 5.18).
Crisafulli, 2021 [41]	>65 yrs (mostly)	medication cessation; antihypertensives	any	2 (2) N=1636	• Quality of life: evidence points towards non-inferiority of antihypertensive deprescribing (e.g., in terms of quality of life, blood pressure control, frailty and cardiovascular risk) as compared to treatment continuation, but quality of evidence not high. • Adverse drug withdrawal events: no differences in adverse events, quality of evidence not high.
Jongstra, 2016 [11]	>65 yrs dementia	medication cessation; antihypertensives	any	2 (2) N=2490	• Mortality: unlikely to increase mortality (limited evidence). • Adverse drug withdrawal events: withdrawing associated with increased blood pressure, but no short-term increase in heart attacks or strokes.

Author	Population	Deprescribing approach; medicine	Setting	N of studies (N of RCTs); N of participants	Outcomes
Narayan, 2017 [40]	>65 yrs life-limiting illness	medication cessation; cardiovascular medications	any	10 (1) N= 26.854	• Mortality: discontinuation of warfarin may result in higher mortality. • Quality of life: discontinuation of statins may improve quality of life, very limited evidence. • Medication use: limited life expectancy potentially prompted discontinuation, but some individuals continued to receive preventive medicines until they died. No clear guidance on when to discontinue preventive medicines in people with limited life expectancy. Discontinuation of statins may reduce costs, very limited evidence.
Iyer, 2008 [39]	>65 yrs	medication cessation; mostly medications for cardiovascular or mental disorders	any	31 (15) N=8972	• Mortality: after complete withdrawal of antihypertensives, no increase in mortality. • Medication use: complete withdrawal of diuretics maintained in 51–100% of patients and unsuccessful primarily when heart failure was present. • Adverse drug withdrawal events: infrequently encountered. After withdrawal of antihypertensives, 20–85% remained normotensive or not required instatement of therapy for between 6 months and 5 years. Complete withdrawal of psychotropic medicines improved cognition. • Falls: complete withdrawal of psychotropic medicines reduced falls.
Hopper, 2014* [29]	>40 yrs (mostly) heart failure with recovered ejection fraction or stable systolic heart failure	medication cessation; medications for heart failure	any	26 (11) N=5263[a]	• Mortality: renin-angiotensin-aldosterone system inhibitors and beta-blockers withdrawals have untoward effects on cardiac structure, symptoms, and major outcomes. Current evidence discourages discontinuation of those medicines in patients with stable heart failure, regardless of clinical and/or echocardiographic status. MA of 7 studies on digoxin withdrawal without background beta-blocker showed no impact on all-cause mortality (RR 1.00, 95% CI 0.90 to 1.12). • Hospitalisation: MA of 7 studies on digoxin withdrawal without background beta-blocker showed increased hospitalisations (RR 1.30, 95% CI 1.16 to 1.46; p<0.001), but nor reduction in all-cause hospitalisation (RR 1.03, 95% CI 0.98 to 1.09). • Adverse drug withdrawal events: medicine cessation increases risk of late recurrence of heart failure.
Antibiotics (overlap of primary studies within the reviews: 44%)					
Soni, 2013* [52]	>18 yrs (mostly) and/or paediatric patients known or suspected infection	medication cessation; antibiotics	inpatient	18 (18) N=6457	• Mortality: procalcitonin-guided initiation, intensification, or discontinuation of antibiotic therapy compared to clinically guided therapy had no effect on morbidity or mortality in adult patients in intensive care unit and adult patients with respiratory tract infections. • Medication use: discontinuation in adult patients in intensive care unit reduced antibiotic duration by 2.05 days (95% CI 22.59 to 21.52). Discontinuation in adult patients with respiratory tract infections reduced antibiotic duration by 2.35 days (95% CI: 24.38 to 20.33), reduced antibiotic prescription rate by 22% (95% CI: 241% to 24%), reduced total antibiotic exposure. • Adverse drug withdrawal events: discontinuation safe in adult intensive care unit patients and adult patients with respiratory tract infections. Limited evidence in paediatric patients (1 trial).

Author	Population	Deprescribing approach; medicine	Setting	N of studies (N of RCTs); N of participants	Outcomes
Arulkumaran, 2020* [44]	>16 yrs infection or sepsis	medication cessation; antibiotics	inpatient	22 (22) N=6046	• Mortality: neither procalcitonin-guided antibiotic treatment (RR 0.91, CI 0.82 to 1.01), clinical algorithm-guided antibiotic treatment (RR 0.67, CI 0.30 to 1.54), nor fixed-duration antibiotics (RR 1.21, CI 0.90 to 1.63) were associated with reduction in mortality. • Hospitalisation: despite shorter antibiotic duration, neither procalcitonin-guided therapy (RR 0.93, CI 0.84 to 1.03) nor fixed-duration antibiotic therapy (RR 1.06, CI 0.74 to 1.53) was associated with treatment failure. • Medication use: procalcitonin (-1.23 days, CI -1.61 to -0.85), but not clinical algorithm-guided antibiotic therapy (-7.41 days, CI -18.18 to 3.37), was associated with shorter duration of antibiotic therapy.
Lam, 2018* [47]	>18 yrs critically ill	medication cessation; antibiotics	inpatient	15 (15) N=6035[a]	• Mortality: procalcitonin-guided initiation, cessation, and mixed strategies resulted in no difference in short-term mortality (pooled risk ratios 1.00, 95% CI 0.86 to 1.15; p = 0.91; 0.87, 95% CI 0.77 to 0.98; p = 0.02; and 1.01 95% CI, 0.80 to 1.29; p = 0.93, respectively). However, when only examining procalcitonin-guided cessation, mortality was lower. • Hospitalisation: no differences in hospital and intensive care unit length of stay. • Medication use: procalcitonin for cessation and mixed strategies associated with decrease antibiotics duration (–1.26 days, p<0.00 and –3.10 days, p =0.04, respectively). • Adverse drug withdrawal events: no difference in recurrent infections (pooled risk ratios 1.19, 95% CI 0.86 to 1.65).
Schuetz, 2017* [51]	>18 yrs acute respiratory infections	medication cessation; antibiotics	inpatient	26 (26) N=6708	• Mortality: procalcitonin algorithm lowered mortality (adjusted OR 0.83, 95% CI 0.70 to 0.99). • Hospitalisation: treatment failure (e.g., death, rehospitalisation, recurrent infection) not significantly with procalcitonin algorithm (23.0% vs 24.9% in the control group, adjusted OR 0.90, 95% CI 0.80 to 1.01). Results similar among subgroups by clinical setting and type of respiratory infection. • Medication use: procalcitonin algorithm lowered antibiotic consumption for 2.4-day (5.7 vs 8.1 days, 95% CI -2.71 to -2.15). • Adverse drug withdrawal events: procalcitonin algorithm lowered risk for antibiotic-related side effects (16.3% vs 22.1%, adjusted OR 0.68, 95% CI 0.57 to 0.82).
Antidiabetics (overlap of primary studies within the reviews: 23%)					
Abdelhafiz, 2018 [67]	>65 yrs (mostly) type two diabetes	deprescribing intervention; antidiabetics	any	10 (0) N=236.147[a]	• Medication use: patients' characteristics to deintensify inappropriately prescribed hypoglycaemics: dementia, renal impairment, over 80 years, numerous comorbidities, tight glycaemic control (HbA1c < 7%), end of life phase, significant weight loss indicating frailty, inappropriate medicines, frequent hypoglycaemia, diabetes over 20 years duration. • Adverse drug withdrawal events: deintensification in overtreated patients appears to be feasible without deterioration of glycaemic control.
Black, 2017 [25]	>18 yrs type two diabetes	medication cessation; antidiabetics	any	2 (0) N=6352	• Mortality: deprescribing compared to continuing antidiabetic had no difference in the risk of all-cause mortality (limited evidence). • Adverse drug withdrawal events: no significant difference in HbA1C levels, in the rates of hypoglycaemia post-intervention (limited evidence).
Seidu, 2019 [73]	>65 yrs type two diabetes	medication cessation; antidiabetics	any	10 (0) N=26.558	• Mortality: no differences in the majority of studies after deintensification. • Hospitalisation: no deterioration after deintensification. • Medication use: rates of deintensification approaches ranged from 13.4% to 75%. • Adverse drug withdrawal events: no deterioration in HbA1c levels, or hypoglycaemic episodes, after deintensification. No differences observed in adverse events in the majority of studies. • Falls: no deterioration after deintensification.

Author	Population	Deprescribing approach; medicine	Setting	N of studies (N of RCTs); N of participants	Outcomes
Analgesics (overlap of primary studies within the reviews: 14%)					
Mathieson, 2020 [31]	>18 yrs chronic pain	deprescribing intervention; opioids	inpatient	12 (12) N=1126	• Medication use: patient-focused interventions did not reduce opioid use or increase the number of participants who ceased their dose. One clinician intervention of education plus decision tools vs decision tools alone reduced the number of opioid prescriptions and use in the long-term. • Adverse drug withdrawal events: patient-focused interventions did not increase the risk of serious adverse events or adverse events. No recommendation of deprescribing strategies in patients with chronic pain could be given.
White, 2021 [33]	>18 yrs chronic noncancer pain	deprescribing intervention; opioids	any	11 (2) N=2230[a]	• Medication use: consent rates for behavioral interventions ranged from 27% to 98% (% of patients willing to enrol) and completion rates from 6.6% to 100% (% of enrolled patients who adhered to the deprescribing intervention). • Adverse drug withdrawal events: willingness of patients reliant on opioids to declare readiness for tapering is likely to be highly variable. Patients who do engage with behavioral treatment tend to find these approaches acceptable.
Ecclestone, 2017 [27]	>18 yrs chronic noncancer pain	deprescribing intervention; opioids	any	5 (5) N=278	• Medication use: mixed findings, there were reductions in opioid consumption after intervention, and often in control groups too. • Adverse drug withdrawal events: 3 studies reported adverse events related to opioid reduction. Mixed findings for pain intensity and physical functioning.
Zorrilla-Vaca, 2021* [34]	>18 yrs underwent surgery	deprescribing intervention; opioids	inpatient	11 (11) N= 1604	• Medication use: after 15 days, the education group consumed a lower number of opioid pills than control group (weighted mean difference −3.39 pills, 95% CI −6.40 to −0.37) with no significant difference in overall opioid cessation (OR 0.25, 95% CI, 0.04 to 1.56). Perioperative opioid education did not have significant effects on opioid cessation at 6 weeks (OR 0.69, 95% CI, 0.45 to 1.05) and 3 months (OR 0.59, 95% CI 0.17 to 2.01) after surgery, neither reduced the need for opioid refills at 15 days (OR 0.57, 95% CI 0.28 to 1.15) and 6 weeks (OR 1.08, 95% CI 0.59 to 1.98). Type of educational intervention showed a statistical reduction of opioid consumption at 15 days when implementing audiovisual strategies, but no reduction when using only paper-based strategies.
Sørensen, 2019 [14]	>65 yrs dementia	medication cessation; opioids, nonsteroidal anti-inflammatory drugs, paracetamol	any	2 (1) N=355	• Adverse drug withdrawal events: analgesics may be withdrawn (immediate or taper) without clinically significant worsening in pain (limited evidence). Deprescribing of analgesics may precipitate behavioural symptoms and aggravation in pain in some.
Biologic therapy (overlap of primary studies within the reviews: 6%)					

Author	Population	Deprescribing approach; medicine	Setting	N of studies (N of RCTs); N of participants	Outcomes
Boyapati, 2018* [26]	>18 yrs Crohn's disease in remission	medication cessation; immunosuppressant or biologic drugs	any	6 (6) N=326	• Hospitalisation: discontinuation of azathioprine monotherapy - no differences in serious adverse events (RR 3.29, 95% CI 0.35 to 30.80). Discontinuation of azathioprine in combination therapy - no differences in serious adverse events (RR 1.00, 95% CI 0.21 to 4.66), evidence very low to low. • Medication use: discontinuation of azathioprine monotherapy - clinical relapse in 13% of patients who continued compared to 32% who discontinued (RR 0.42, 95% CI 0.24 to 0.72). Discontinuation of azathioprine in combination therapy - clinical relapse in 48% of patients who continued combination azathioprine and infliximab, compared to 49% of patients who discontinued azathioprine but remained on infliximab (RR 1.02, 95% CI 0.68 to 1.52), evidence low. • Adverse drug withdrawal events: discontinuation of azathioprine monotherapy - no differences in Crohn's disease-related complications (RR 0.34, 95% CI 0.06 to 2.08), adverse events (RR 0.88, 95% CI 0.67 to 1.17), withdrawal due to adverse events (RR 2.59, 95% CI 0.35 to 19.04). Discontinuation of azathioprine in combination therapy - no differences in adverse events (RR 1.11, 95% CI 0.44 to 2.81), evidence low.
Edwards, 2017 [28]	>18 yrs rheumatic disease	medication cessation; biologic therapies	any	52 (13) N>9000[b]	• Adverse drug withdrawal events: after discontinuation (dose tapering) dose remission is not typically sustained, reported rates of relapse and flare across early rheumatoid arthritis (48-54%), established rheumatoid arthritis (2-84%), axial spondyloarthritis (11-53%) and psoriatic arthritis (44.9%). An acceptable disease activity can be regained upon retreatment.
Verhoef, 2019 [32]	>40 yrs rheumatoid arthritis with low disease activity	medication cessation; anti-TNF agents (mostly adalimumab, etanercept)	any	14 (13) N= 3315	• Adverse drug withdrawal events: anti-TNF dose reduction may cause little or no difference in serious adverse events, withdrawals due to adverse events and proportion of participants with persistent remission (low-certainty evidence). Uncertain whether anti-TNF discontinuation or anti-TNF disease activity-guided dose tapering influences the number of serious adverse events. Discontinuation (also without disease activity–guided adaptation) is probably inferior to continuation of treatment with respect to disease activity, the proportion of participants with persistent remission, function, and minimal radiographic damage.
Anticholinergics (overlap of primary studies within the reviews: 16%)					
Salahudeen, 2022 [102]	>65 yrs	deprescribing intervention (broad); anticholinergics	any	23 (7) N>65.000[b]	• Medication use: interventions reduced the anticholinergic burden. Healthcare practitioner-oriented interventions have the potential to reduce the occurrence of anticholinergic prescribing errors in older people.
Nakham, 2019 [104]	>65 yrs polypharmacy	deprescribing intervention (broad); anticholinergics	any	8 (4) N=991[a]	• Medication use: interventions reduced anticholinergic burden in all but two RCTs. No study reported cost outcome. • Adverse drug withdrawal events: only one RCT reported no difference in cognitive function between intervention and control group.
Antiepileptics					
Ayuga Loro, 2022 [37]	<18 yrs epilepsy with seizure freedom at least two years	medication cessation; antiepileptic medications	any	2 (2) N=206	• Adverse drug withdrawal events: no difference in the proportion of participants remaining seizure-free between the rapid (tapering three months or less) and the slow (tapering more than three months) tapering groups at different time points. No data for other measures such as status epilepticus (a long seizure), or illness relating to seizures. Evidence very limited.
Bisphosphonates					

Author	Population	Deprescribing approach; medicine	Setting	N of studies (N of RCTs); N of participants	Outcomes
Lamarre, 2021* [30]	>60 yrs	medication cessation; bisphosphonates	any	18 (9) N=138.536[a]	• Medication use: bisphosphonates successfully discontinued low overall fracture risk after at least 3 years of use. • Adverse drug withdrawal events: observed reduction in bone mineral density after discontinuation. • Falls: results on fracture risk after discontinuation are mitigated as five RCTs showed no increase in the risk of any fracture after deprescribing. However, MA showed an increased odds ratio of vertebral fractures of 2.04 (95% CI, 1.39–2.99) among discontinuers.
Montelukast					
Dixon, 2022 [38]	<18 yrs asthma	medication cessation; montelukast	any	5 (3) N=155	• Adverse drug withdrawal events: regarding asthma symptoms and control, no differences between the test groups and placebo following montelukast withdrawal; but some significant differences between comparator points in test groups. No data on long-term adverse effects.
Urate-lowering medicines					
Beslon, 2017 [74]	>18 yrs	medication cessation; urate-lowering medications	any	8 (0) N=608	• Adverse drug withdrawal events: relapse rates of discontinuation (taper or immediate stop) were high in gout (36%-81%) and lower in urolithiasis (15%). Relapses occurred 1 to 4.5 years after urate-lowering therapy discontinuation. Relapse of gout is common although delayed after discontinuation (limited evidence).

Deprescribing intervention: reviews that mostly included deprescribing intervention trials (with specific deprescribing intervention or broad treatment optimization intervention with deprescribing and also prescribing components).

Medication cessation: reviews that mostly included medication cessation trials.

*RCT: randomized controlled clinical trial; MA: meta-analysis; NR: not reported; PIMs: potentially inappropriate medications; CI: confidence interval; RR: risk ratio; OR: odds ration; N: total number of participants included in a systematic review; CDSS: clinical decision support system. * meta-analysis performed.*

*** meta-analysis performed only for specific outcomes with a smaller number of studies included in a systematic review.*

[a] calculated using data from a systematic review; [b]calculated using data from a systematic review but data not provided for all studies

Supplementary Table 2 – Characteristics of reviews reporting attitudes, facilitators or barriers to deprescribing approaches.

Author	Population (patients/ others)	Medicine	Setting	N of studies; N of participants	Outcomes
Any medicine (overlap of primary studies within the reviews: 34%)					
Chock, 2021 [75]	>18 yrs/ caregivers	any	any	29 N=11.049	• Attitudes towards deprescribing: 88% patients (95% CI 83.3 to 91.4%) and 75% caregivers (95% CI 49.8% to 93.8%) willing to deprescribe irrespective of participants' characteristics or study setting. Tools used were PATD, rPATD, or PPoD.
Weir, 2021 [76]	>18 yrs/ caregivers	any	any	40 N=10.816	• Attitudes towards deprescribing: 84% patients (95% CI 81%–88%) and 80% caregivers (95% CI 74%–86%) willing to deprescribe. Tools used were PATD, rPATD, or modifications.
Oktora, 2022 [77]	>65 yrs	any	any	16 N=NR	• Attitudes towards deprescribing: percentages of patients willing to stop medicine significantly lower in low-middle-income countries (<70%) compared to high-income countries (>85%). No differences in willingness between global region or healthcare settings, although the highest willingness (>95%) seen in inpatient setting (2 studies). Higher mean age at study level associated with a higher willingness to stop medicine. At individual level, associations between patient characteristics and attitudes toward deprescribing showed inconsistent results. Tool used was rPATD.
Seewoo dharry, 2022 [78]	>65 yrs/ caregivers	any	any	35 N=7071[a]	• Attitudes towards deprescribing: most older adults and caregivers willing to have medicine deprescribed if told to do so by a healthcare professional. Tools used were PATD or rPATD. • Facilitators: trust in the healthcare professional, side effects, inconvenience from medicines, prospect of follow-up and monitoring. • Barriers: perceived effectiveness, unawareness of lack of benefit, negative expectations of ageing, fear.
Burghle, 2020 [79]	>65 yrs limited life expectancy/ caregivers or healthcare professionals	any	any	7 N=623[a]	• Attitudes towards deprescribing (four themes): the well-being of older adults with limited life expectancy, involvement of older adults and their relatives in deprescribing, the role of healthcare professionals in deprescribing, medicine-related factors affecting deprescribing. • Facilitators: medicine administration burden, weaning off medicines, ceasing medicines one at a time, desire and willingness to deprescribe, explanation of risks and benefits. • Barriers: hope for future benefits, fear of missing out on future benefits, unfamiliar staff, shortage of resources, inadequate cooperation between healthcare professionals.
Lundby, 2019 [88]	healthcare professionals of patients >65 yrs with limited life expectancy	any	any	8 N=140[a]	• Facilitators or barriers (four themes): patient and relative involvement, the importance of teamwork, healthcare professionals' self-assurance and skills, the impact of organizational factors.
Doherty, 2020 [80]	>18 yrs multimorbidity polypharmacy / caregivers or healthcare professionals	any	outpatient	40 N=5516	• Facilitators: prudent prescribing, greater availability and acceptability of non-pharmacological alternatives, resources, improved communication, collaboration, knowledge, patient-centred care, shared decision-making. • Barriers*: Cultural and organisational barriers* - a culture of diagnosing and prescribing, evidence-based guidance focused on single diseases, a lack of evidence-based guidance for the care of older people with multimorbidities, a lack of shared communication, decision-making systems, tools, and resources. *Interpersonal and individual barriers* - professional etiquette, fragmented care, prescribers' and patients' uncertainties, gaps in tailored support.

Author	Population (patients/ others)	Medicine	Setting	N of studies; N of participants	Outcomes
Bloomfield, 2019 [81]	>65 yrs/ prescribers	any	any	9 N>280[b]	• Barriers: patient (e.g., concern about safety of alternative medicine regimens, reluctance to give up medicines), prescriber (e.g., lack of knowledge, not believing in need for comprehensive medication review), system factors (e.g., lack of institutional support, resources, time).
Paque, 2019 [82]	all ages life-limiting illness/ caregivers or healthcare professionals	any	any	5 N=1187[a]	• Facilitators: organizational, professional and patient (family)-related. The most prominent were organizational support (e.g. for standardized medication review), involvement of multidisciplinary teams in medication review and the perception of the importance of coming to a joint decision regarding deprescribing. • Barriers: the most important were shortages in staff and the perceived difficulty or resistance of the nursing home resident's family or the resident himself.
Group of potentially inappropriate medications (overlap of primary studies within the reviews: 0%)					
Anderson, 2014 [89]	prescribers	PIMs	any	21 N=540[a]	• Facilitators or barriers (four themes): problem awareness; inertia secondary to lower perceived value proposition for ceasing vs continuing PIMs; self-efficacy in regard to personal ability to alter prescribing; and feasibility of altering prescribing in routine care environments given external constraints. The 1-3 themes are intrinsic to the prescriber (e.g., beliefs, attitudes, knowledge, skills, behaviour) and the 4 is extrinsic (e.g., patient, work setting, health system and cultural factors).
Bourne, 2022 [45]	healthcare professionals of intensive care unit patients >18 yrs in transition to a hospital ward	PIMs	inpatient	14 N>10.000 [b]	• Facilitators: intensive care unit clinical pharmacist availability and participation in multiprofessional ward rounds, staff education, medicines reconciliation, medication reviews, and deprescribing. • Barriers: increased workload associated with the discharge intervention process.
Medicines for mental disorders (overlap of primary studies within the reviews: 2%)					
Rasmussen, 2021 [83]	>65 yrs/ caregivers or healthcare professionals	benzodiazepines and Z-drugs	any	10 N=323	• Attitudes towards deprescribing: patients willing to deprescribe, while doctors consider patients will resist. • Facilitators: education a shared facilitator among stakeholders. Other shared facilitators were improving cooperation between healthcare personnel (by physician and nurses), patient motivation (by patients and physicians) and awareness of side effects (by patients and caregivers). • Barriers: shared barrier was lack of knowledge (by patients and nurses) and lack of time (by physician and nurses).
Reeve, 2013 [84]	all ages/ caregivers	mostly for mental disorders	any	21 N=1310	• Facilitators: agreement with appropriateness of cessation, presence of a process for cessation, positive influences to cease medicine, dislike of medicines. • Barriers: disagreement with appropriateness of cessation, absence of a process for cessation, negative influences to cease medicine, fear of cessation.
Moth, 2021 [90]	general practitioners, nursing home physicians or nursing home staff	psychotropic medications	long-term care	14 N=1056[a]	• Facilitators or barriers or both (five themes): Operationality and routines; Lack of resources and qualifications; Patient-related outcomes, which points to a strong belief in negative patient-related outcomes of discontinuation and a downplay of side effects of the medicine; Policies, including support and buy-in from nursing home leadership; and Collaboration between physicians and nursing home staff. Themes 1 and 4 consist of facilitators. Theme 2 consists of barriers. Theme 3 and 5 consist of both facilitators and barriers.

Author	Population (patients/ others)	Medicine	Setting	N of studies; N of participants	Outcomes
Anticholinergics					
Stewart, 2021 [85]	>18 yrs/ caregivers or healthcare professionals	anticholinergics	any	2 N=48	No studies involved patients or caregivers. • Facilitators of healthcare providers: good communication and relationships with patients, caregivers and other healthcare professionals, having a named person for prescribing decisions, clear role boundaries. • Barriers of healthcare providers: poor motivation to reduce anticholinergic use, low confidence, system resources and organisation of care.
Cancer therapy (overlap of primary studies within the reviews: 0%)					
Clarke, 2015 [86]	>18 yrs advanced solid tumours/ caregivers or public health professionals	cancer therapy (molecular targeted agents)	inpatient	42 N>400.000[b]	• Attitudes towards deprescribing *How are decisions made?* Decision-making shared and ongoing, including stopping, starting and trying different treatments. Oncologists often experienced 'professional role dissonance' between their self-perception as 'treaters', and talking about end of life care. *Why are decisions made?* Clinical factors: disease progression, worsening functional status, treatment side-effects. Non-clinical factors: physicians' personal experience, values, emotions. Some patients continued treatment to maintain 'hope', of ten reflecting limited understanding of palliative goals. *When are decisions made?* Limited evidence reveals patients 'decisions based upon quality of life benefits. Clinicians found timing withdrawal particularly challenging. *Who makes the decisions?* Decisions were based within physician-patient interaction.
Valdez-Martinez, 2014 [87]	<20 yrs not curative cancer/ parents or healthcare professionals	cancer treatment	inpatient	18 N>300 [b]	• Attitudes towards deprescribing: doctors generally shared information so that parents alone could decide. When parents received information, and personalized interest in their child, they more likely achieved shared trust and clearer transition to palliation. Although under-represented in research studies, young people's perspectives showed some differences to those of parents and professionals (e.g., young people preferred to be informed even when prognosis was poor, and had desire to help others by participating in research).

CI: confidence interval; N: total number of participants included in a systematic review; PATD: the patients' attitudes towards deprescribing questionnaire; rPATD: the revised patients' attitudes towards deprescribing; PPoD: the patient perceptions of deprescribing questionnaire; PIMs: potentially inappropriate medications.
[a] calculated using data from a systematic review; [b] calculated using data from a systematic review but data not provided for all studies

Supplementary Table 3 – Characteristics of reviews focused on tools for deprescribing approaches.

Author	Tool investigated	Conclusion
Michiels-Corsten, 2020 [91]	Tools designed to evaluate medicine and provide an advice on discontinuation	16 generic instruments for drug discontinuation guidance for patients with polypharmacy identified. Instruments included the stages of deprescribing, i.e. preparation, medicine evaluation, decision making and implementation. 3 types of instruments: general frameworks, detailed medicine assessment tools and comprehensive discontinuation guidelines.
Thompson, 2019 [92]	Deprescribing tools for frail older persons or with limited life expectancy excluding palliative cancer patients	15 tools identified: 2 described a model or framework for approaching deprescribing, 9 outlined a deprescribing approach for the entire medicine list, 4 provided medicine specific advice. The development methodology varied, the methods used to synthesize the tools not well described. Most tools based on expert opinion. Only 4 tested in clinical practice.
Van Merendonk, 2022 [93]	Tools for palliative care patients specifically designed for cancer patients or not	9 tools or guidelines identified (OncPal, 6-Step method, Steps to deprescribe, Futility criteria, Preventative medications, Medications for chronic diseases, Beers criteria, STOPP criteria, Medication appropriateness index). One tool externally validated and applied in several studies and settings. Tools developed for geriatric patients contain information on inappropriate medications in the palliative cancer care. Tools developed for cancer patients are more suitable and can be applied in combination with stepwise methods to individualize deprescribing per patient.
Fajardo, 2019 [97]	Education materials on deprescribing one or more medicines, able to be printed or read online	48 patient education materials identified, most commonly addressing deprescribing of medicines for symptom control (81%). Preventative medicines rarely addressed and material (39%) focused on older people. Only 37% provided information about both potential benefits and harms of deprescribing, while 40% focussed on benefits only. Most materials pitched above average reading levels making them inaccessible for low health literacy populations.
Clough, 2018 [98]	N-of-1 trial method to determine the effects of deprescribing long-term medicines in adults >50 yrs	6 studies with N-of-1 trial method identified (N=106). N-of-1 method safely tolerated in older adults. Feasibility of the N-of-1 method to determine the effects of deprescribing medicines on short-term outcomes is not yet assessed.
Renn, 2018 [94]	Guidelines addressing treatment recommendations for dementia, or Alzheimer's disease specifically	16 guidelines identified. No consensus in guidelines about discontinuation of cholinesterase inhibitors. Limited empirical investigation of discontinuation, considerable variability across practice guidelines and recommendations, and the absence of any definitive guideline or recommendation, all argue against the use of a formulaic approach to cholinesterase inhibitors discontinuation.
Van der Ploeg, 2020 [95]	International guidelines for cardiovascular disease prevention and statins discontinuation in older adults	18 guidelines applicable to older adults identified, however provide little specific guidance for physicians on statin discontinuation in the context of declining health status and short life expectancy.
Darr-Foit, 2019 [96]	Dermatological guidelines with specific indications for treatment discontinuation	16 guidelines reviewed. None addressed all of the systemic therapies recommended with indications for discontinuation of treatment. Many guidelines contained either no or only sketchy information on deprescribing.

N-of-1 trial method: single patient, randomized, double blind, placebo-controlled crossover studies

Supplementary Table 4 - Quality assessment of reviews on clinical and humanistic outcomes of deprescribing approaches using the PRISMA 2020 checklist.

	PRISMA 2020 checklist item																									
Study	1 Title	3 Rationale	4 Objectives	5 Eligibility criteria	6 Information sources	7 Search strategy	8 Selection process	9 Data collection process	10 Data items	11 Study risk of bias assessment	12 Effect measures	13 Synthesis methods	14 Reporting bias assessment	15 Certainty assessment	16 Study selection	17 Study characteristics	18 Risk of bias in studies	19 Results of individual studies	20 Results of syntheses	21 Reporting biases	22 Certainty of evidence	23 Discussion	24 Registration and protocol	25 Support	26 Competing interests	27 Availability of data, code and other materials	Score proportion
Pruskowski, 2019 [68]	1	1	1	1	1	0	1	1	1	1	0	1	0	0	0	1	1	1	1	0	0	1	1	1	1	0	0.69
Shrestha, 2021 [66]	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	0.96
Ostini, 2011 [65]	1	1	1	1	1	1	1	1	0	1	1	1	0	0	0	0	1	1	1	0	0	1	0	0	0	0	0.58
Page, 2016 [64]	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1.00
Bužančić, 2021 [56]	1	1	1	1	1	1	1	1	1	1	0	1	0	0	1	1	1	1	1	0	0	1	1	1	1	1	0.81
Dills, 2018 [58]	1	1	1	1	1	1	1	1	1	1	0	1	1	0	1	0	1	1	1	0	0	1	0	0	0	0	0.65
Kua, 2019* [62]	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	0	0.92
Christopher, 2021 [57]	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	0.96
Romano, 2022 [59]	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	0	1	0	1	1	1	0.88
Johansson, 2016 [100]	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	0.96
Bloomfield, 2020 [55]	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	0	0.92
Ulley, 2019 [61]	1	1	1	1	1	1	1	1	1	1	0	1	0	0	0	1	1	1	1	0	0	1	1	1	1	1	0.77
Ali, 2020 [54]	0	1	0	1	1	0	0	0	1	1	1	1	0	1	1	0	1	1	1	1	1	1	1	1	1	0	0.69
Ibrahim, 2021 [101]	1	1	1	1	1	1	1	1	1	1	0	1	0	0	1	1	1	1	1	0	0	1	1	1	1	1	0.81
Lee, 2021 [49]	1	1	1	1	1	1	1	1	1	1	0	1	0	0	1	1	1	1	1	0	0	1	0	1	1	0	0.73
Thio, 2018 [60]	1	1	1	1	1	0	1	1	1	1	0	0	0	0	1	0	1	1	1	0	0	1	0	1	1	1	0.65
Wilsdon, 2017 [7]	1	1	1	1	1	1	1	1	1	1	0	1	0	0	1	0	1	1	1	0	0	1	1	1	1	0	0.73
Boghossian, 2017 [5]	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1.00
Haastrup, 2014 [6]	1	1	1	1	1	0	1	1	0	0	0	0	0	0	1	0	1	1	0	0	0	1	0	1	1	0	0.50
Mugunthan, 2011 [21]	1	1	1	1	1	1	0	1	1	0	1	1	0	0	1	1	1	1	1	0	0	1	0	1	1	0	0.69
Reeve, 2017 [13]	1	1	1	1	1	1	1	1	1	1	0	0	0	0	1	1	1	1	1	0	0	1	0	1	1	0	0.69

	PRISMA 2020 checklist item																									
Study	1 Title	3 Rationale	4 Objectives	5 Eligibility criteria	6 Information sources	7 Search strategy	8 Selection process	9 Data collection process	10 Data items	11 Study risk of bias assessment	12 Effect measures	13 Synthesis methods	14 Reporting bias assessment	15 Certainty assessment	16 Study selection	17 Study characteristics	18 Risk of bias in studies	19 Results of individual studies	20 Results of syntheses	21 Reporting biases	22 Certainty of evidence	23 Discussion	24 Registration and protocol	25 Support	26 Competing interests	27 Availability of data, code and other materials	Score proportion
Van Leeuwen, 2021 [24]	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1.00
Maund, 2019 [19]	1	1	1	1	1	1	1	1	1	1	1	1	0	0	1	0	1	0	1	0	0	1	1	1	1	0.73
Parr, 2008 [22]	1	1	1	1	1	1	1	0	1	1	1	1	0	0	1	0	1	1	1	0	0	1	0	0	1	0.65
Ribeiro, 2021 [23]	1	1	1	1	1	1	1	0	1	1	0	0	0	0	1	0	1	1	1	0	0	1	1	1	1	0.65
Paquin, 2014 [16]	0	1	1	1	1	1	1	1	1	0	1	1	0	0	1	1	0	1	1	0	0	1	0	1	1	0.65
Matsui, 2019 [18]	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	0.92
Monahan, 2021 [20]	1	1	0	1	1	1	1	0	0	1	0	1	0	0	1	1	1	1	1	0	0	1	1	1	1	0.65
Van Leeuwen, 2018 [15]	0	0	1	1	1	0	0	0	1	1	0	1	0	1	1	1	0	1	1	0	1	1	1	1	1	0.62
Van de Loo-Neus, 2011 [36]	0	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	1	1	0.27
Lohr, 2021 [35]	0	1	1	1	1	0	1	0	1	0	0	0	0	0	1	1	0	1	1	0	0	1	0	0	1	0.46
Davies, 2019 [17]	1	1	1	1	1	1	1	0	1	0	0	0	0	0	1	0	0	1	1	0	0	1	0	0	1	0.50
Parsons, 2021 [12]	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1.00
Lee, 2021 [48]	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1.00
Lindsay, 2013 [103]	0	1	1	1	1	0	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0	1	0	0	1	0.31
Monteiro, 2019 [71]	1	1	1	1	1	0	1	1	1	1	0	1	0	0	1	1	1	1	1	0	0	1	1	1	1	0.73
Cardona, 2021 [46]	1	1	0	1	1	1	1	0	1	1	0	1	0	0	1	1	1	1	1	0	0	1	1	1	1	0.69
Saeed, 2022 [50]	1	1	1	1	1	1	1	1	1	1	0	0	0	0	1	1	1	1	1	0	0	1	1	1	1	0.77
Thillainadesan, 2018 [53]	1	1	1	1	1	1	1	1	1	1	0	1	0	0	1	1	1	1	1	0	0	1	1	1	1	0.81
Bourne, 2022 [45]	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	0.96
Hansen, 2018 [70]	1	1	1	1	1	1	1	1	1	1	1	1	0	0	1	1	1	1	1	0	0	1	1	1	1	0.85
Shrestha, 2020 [72]	1	1	1	1	1	1	1	1	1	1	0	1	0	0	1	1	1	1	1	0	0	1	1	0	1	0.77
Hernández-Prats, 2021 [43]	1	1	1	1	1	1	1	1	1	1	0	0	0	0	1	1	1	1	1	0	0	1	0	1	1	0.73

	PRISMA 2020 checklist item																									
Study	1 Title	3 Rationale	4 Objectives	5 Eligibility criteria	6 Information sources	7 Search strategy	8 Selection process	9 Data collection process	10 Data items	11 Study risk of bias assessment	12 Effect measures	13 Synthesis methods	14 Reporting bias assessment	15 Certainty assessment	16 Study selection	17 Study characteristics	18 Risk of bias in studies	19 Results of individual studies	20 Results of syntheses	21 Reporting biases	22 Certainty of evidence	23 Discussion	24 Registration and protocol	25 Support	26 Competing interests	27 Availability of data, code and other materials	Score proportion
Reeve, 2020 [42]	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1.00
Crisafulli, 2021 [41]	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	0	1	1	0	1	1	0.88
Jongstra, 2016 [11]	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1.00
Narayan, 2017 [40]	1	1	1	1	1	1	1	1	1	1	1	1	0	0	1	1	1	1	0	0	0	1	0	1	1	0.77
Iyer, 2008 [39]	1	1	1	1	1	0	1	1	1	0	0	1	0	0	0	1	0	1	0	0	0	1	0	1	1	0.54
Hopper, 2014 [29]	1	1	1	1	1	0	0	1	1	0	1	1	1	0	1	1	0	1	1	1	0	1	0	1	1	0.73
Soni, 2013 [52]	1	1	1	1	1	1	1	1	1	1	0	1	0	1	1	1	0	1	1	0	0	1	0	1	1	0.73
Arulkumaran, 2020 [44]	1	1	1	1	1	1	1	1	1	1	1	1	0	0	1	1	1	1	1	0	0	1	0	1	1	0.81
Lam, 2018 [47]	1	1	1	1	1	0	1	1	1	1	1	1	1	0	1	1	1	1	1	1	0	1	0	1	1	0.85
Schuetz, 2017 [51]	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1.00
Abdelhafiz, 2018 [67]	1	1	1	0	1	0	1	1	1	0	0	0	0	0	1	1	0	1	1	0	0	1	0	0	0	0.46
Black, 2017 [25]	1	1	1	1	1	1	1	1	1	1	0	1	0	1	1	1	1	1	1	0	1	1	1	1	1	0.88
Seidu, 2019 [73]	1	1	1	1	1	1	1	1	1	1	0	1	0	0	1	1	1	1	1	0	0	1	1	1	1	0.81
Mathieson, 2020 [31]	1	1	1	1	1	1	1	1	1	1	0	0	0	0	1	1	1	1	1	0	0	1	1	1	1	0.77
White, 2021 [33]	1	1	1	1	1	1	1	1	1	1	0	1	0	0	1	1	1	1	1	0	0	1	0	1	1	0.73
Eccleston, 2017 [27]	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1.00
Zorrilla-Vaca, 2021 [34]	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0.96
Sørensen, 2019 [14]	1	1	1	1	1	0	1	1	0	0	0	0	0	0	1	1	0	1	1	0	0	1	0	0	1	0.50
Boyapati, 2018 [26]	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1.00
Edwards, 2017 [28]	1	1	0	1	1	1	1	1	1	1	0	1	0	0	1	0	0	1	1	0	0	1	0	1	1	0.62
Verhoef, 2019 [32]	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1.00
Salahudeen, 2022 [102]	1	1	1	1	1	1	1	1	1	1	0	0	0	0	1	0	1	1	0	0	0	1	0	1	1	0.65

	PRISMA 2020 checklist item																									
Study	1 Title	3 Rationale	4 Objectives	5 Eligibility criteria	6 Information sources	7 Search strategy	8 Selection process	9 Data collection process	10 Data items	11 Study risk of bias assessment	12 Effect measures	13 Synthesis methods	14 Reporting bias assessment	15 Certainty assessment	16 Study selection	17 Study characteristics	18 Risk of bias in studies	19 Results of individual studies	20 Results of syntheses	21 Reporting biases	22 Certainty of evidence	23 Discussion	24 Registration and protocol	25 Support	26 Competing interests	27 Availability of data, code and other materials	Score proportion
Nakham, 2019 [104]	1	1	1	1	1	1	1	0	0	1	0	0	0	0	1	0	1	1	1	0	0	1	1	1	1	0.62
Ayuga Loro, 2022 [37]	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1.00
Lamarre, 2021 [30]	1	1	0	1	1	0	1	0	1	1	1	1	1	1	1	0	1	1	1	0	1	1	1	1	1	0.77
Dixon, 2022 [38]	1	1	1	1	1	1	1	1	0	1	0	1	0	0	1	1	1	1	1	0	0	1	1	1	1	0.77
Beslon, 2017 [74]	1	1	1	1	1	1	1	1	1	1	0	1	0	0	1	1	1	1	1	0	0	1	1	0	1	0.73
Score proportion	0.91	0.99	0.93	0.99	1.00	0.79	0.91	0.83	0.89	0.84	0.49	0.79	0.36	0.36	0.90	0.76	0.83	0.97	0.93	0.34	0.36	0.99	0.59	0.84	0.96	0.51	

1 (green) = checklist item fulfilled.; 0 (red) = checklist item not fulfilled. Checklist item 2: Abstract is presented in Supplementary Table 5.

Supplementary Table 5 - Quality assessment of abstract (item 2) in reviews on clinical and humanistic outcomes of deprescribing approaches using the PRISMA 2020 checklist.

	PRISMA 2020 checklist item 2: Abstract												
Study	1 Title	2 Objectives	3 Eligibility criteria	4 Information sources	5 Risk of bias	6 Synthesis of results	7 Included studies	8 Synthesis of results	9 Limitations of evidence	10 Interpretation	11 Funding	12 Registration	Score proportion
Pruskowski, 2019 [68]	1	1	1	1	1	0	1	1	1	1	0	0	0.75
Shrestha, 2021 [66]	1	1	1	1	1	1	1	1	1	1	0	0	0.83
Ostini, 2011 [65]	1	1	0	1	0	0	0	1	1	1	0	0	0.50
Page, 2016 [64]	1	1	0	0	0	1	1	1	0	1	0	0	0.50
Bužančić, 2021 [56]	1	1	0	0	0	1	1	1	1	1	0	0	0.58
Dills, 2018 [58]	1	1	0	1	1	0	0	1	1	1	0	0	0.58
Kua, 2019* [62]	1	1	0	1	0	1	1	1	0	1	0	1	0.67
Christopher, 2021 [57]	1	1	0	1	0	1	1	1	0	1	0	0	0.58
Romano, 2022 [59]	1	1	1	1	1	0	0	1	1	1	0	0	0.67
Johansson, 2016 [100]	1	1	0	0	0	1	1	1	1	1	0	0	0.58
Bloomfield, 2020 [55]	1	1	0	1	1	1	0	1	1	1	0	1	0.75
Ulley, 2019 [61]	1	1	0	0	1	0	0	0	1	1	0	1	0.50
Ali, 2020 [54]	0	1	0	0	0	0	0	0	0	0	0	0	0.08
Ibrahim, 2021 [101]	1	1	0	1	1	1	1	1	0	1	0	1	0.75
Lee, 2021 [49]	1	1	0	1	0	0	0	1	1	1	0	0	0.50
Thio, 2018 [60]	1	1	0	1	0	0	0	1	0	1	0	0	0.42
Wilsdon, 2017 [7]	1	1	0	1	0	0	0	1	1	1	0	0	0.50
Boghossian, 2017 [5]	1	1	1	1	1	1	1	1	1	1	0	0	0.83
Haastrup, 2014 [6]	1	0	1	1	0	0	0	1	0	1	0	0	0.42
Mugunthan, 2011 [21]	1	1	0	1	0	1	1	1	0	1	0	0	0.58
Reeve, 2017 [13]	1	1	0	1	1	0	0	1	0	1	0	0	0.50
Van Leeuwen, 2021 [24]	1	1	1	1	1	1	1	1	1	1	0	0	0.83
Maund, 2019 [19]	1	1	0	0	0	1	0	1	0	1	0	0	0.42

	PRISMA 2020 checklist item 2: Abstract												
Study	1 Title	2 Objectives	3 Eligibility criteria	4 Information sources	5 Risk of bias	6 Synthesis of results	7 Included studies	8 Synthesis of results	9 Limitations of evidence	10 Interpretation	11 Funding	12 Registration	Score proportion
Parr, 2008 [22]	1	1	1	0	0	0	0	1	1	1	0	0	0.50
Ribeiro, 2021 [23]	1	1	0	1	1	0	0	1	1	1	0	0	0.58
Paquin, 2014 [16]	0	0	0	0	0	0	0	1	0	1	0	0	0.17
Matsui, 2019 [18]	1	1	0	1	0	1	1	1	1	1	0	0	0.67
Monahan, 2021 [20]	1	1	1	1	0	0	0	1	1	1	0	0	0.58
Van Leeuwen, 2018 [15]	0	1	0	0	0	1	1	0	1	1	0	1	0.50
Van de Loo-Neus, 2011 [36]	0	1	0	0	1	0	0	1	1	1	0	0	0.42
Lohr, 2021 [35]	0	1	0	1	0	0	0	0	1	1	0	0	0.33
Davies, 2019 [17]	1	0	0	0	0	0	0	1	1	1	0	0	0.33
Parsons, 2021 [12]	1	1	1	1	1	1	1	1	1	1	0	1	0.92
Lee, 2021 [48]	1	1	1	1	1	1	1	1	1	1	0	1	0.92
Lindsay, 2013 [103]	0	1	0	1	0	0	0	1	1	1	0	0	0.42
Monteiro, 2019 [71]	1	1	0	1	0	0	1	1	1	1	0	1	0.67
Cardona, 2021 [46]	1	1	0	0	0	0	0	1	1	1	0	0	0.42
Saeed, 2022 [50]	1	1	0	0	1	0	0	1	1	1	0	0	0.50
Thillainadesan, 2018 [53]	1	1	1	1	1	0	1	1	1	1	0	0	0.75
Bourne, 2022 [45]	1	1	1	0	1	1	0	1	1	1	0	1	0.75
Hansen, 2018 [70]	1	1	1	1	1	1	0	1	1	1	0	0	0.75
Shrestha, 2020 [72]	1	1	0	1	0	1	1	1	0	1	0	0	0.58
Hernández-Prats, 2021 [43]	1	1	0	1	1	0	0	1	0	1	0	0	0.50
Reeve, 2020 [42]	1	1	1	1	0	1	1	1	1	1	0	1	0.83
Crisafulli, 2021 [41]	1	1	0	1	1	1	0	1	1	1	0	0	0.67
Jongstra, 2016 [11]	1	1	1	1	1	1	1	1	1	1	0	1	0.92
Narayan, 2017 [40]	1	1	1	1	1	0	1	1	0	1	0	0	0.67

	PRISMA 2020 checklist item 2: Abstract												
Study	1 Title	2 Objectives	3 Eligibility criteria	4 Information sources	5 Risk of bias	6 Synthesis of results	7 Included studies	8 Synthesis of results	9 Limitations of evidence	10 Interpretation	11 Funding	12 Registration	Score proportion
Iyer, 2008 [39]	1	1	0	0	0	0	1	1	1	0	0	0	0.42
Hopper, 2014 [29]	1	0	0	0	0	1	0	1	0	1	0	0	0.33
Soni, 2013 [52]	1	0	1	1	0	0	0	1	0	1	0	0	0.42
Arulkumaran, 2020 [44]	1	1	1	1	0	1	1	1	0	1	0	0	0.67
Lam, 2018 [47]	1	1	0	1	0	1	0	1	0	1	0	0	0.50
Schuetz, 2017 [51]	1	1	1	1	0	1	1	1	1	1	0	1	0.83
Abdelhafiz, 2018 [67]	1	1	0	1	0	0	0	0	0	1	0	0	0.33
Black, 2017 [25]	1	0	1	1	1	1	0	1	0	1	0	1	0.67
Seidu, 2019 [73]	1	1	0	1	0	1	1	1	0	1	1	0	0.67
Mathieson, 2020 [31]	1	1	1	0	1	1	1	1	1	1	0	1	0.83
White, 2021 [33]	1	1	0	1	1	0	0	1	1	1	0	0	0.58
Eccleston, 2017 [27]	1	1	1	1	1	1	1	1	1	1	0	1	0.92
Zorrilla-Vaca, 2021 [34]	1	1	1	1	0	1	1	1	0	1	0	0	0.67
Sørensen, 2019 [14]	1	1	0	1	0	0	1	1	0	1	0	0	0.50
Boyapati, 2018 [26]	1	1	1	1	1	1	1	1	1	1	0	1	0.92
Edwards, 2017 [28]	1	0	0	0	0	0	0	1	1	1	0	0	0.33
Verhoef, 2019 [32]	1	1	1	1	1	1	1	1	1	1	0	1	0.92
Salahudeen, 2022 [102]	1	1	1	1	0	0	0	1	0	1	0	0	0.50
Nakham, 2019 [104]	1	1	0	1	0	0	0	1	0	1	0	1	0.50
Ayuga Loro, 2022 [37]	1	1	1	1	1	1	1	1	1	1	0	1	0.92
Lamarre, 2021 [30]	1	1	0	0	0	1	0	1	0	1	0	0	0.42
Dixon, 2022 [38]	1	0	0	1	0	1	0	1	1	1	0	1	0.58
Beslon, 2017 [74]	1	1	0	1	1	0	0	1	1	1	0	1	0.67
Score proportion	0.91	0.89	0.39	0.73	0.43	0.51	0.46	0.93	0.63	0.97	0.01	0.30	

1 (green) = checklist item fulfilled.; 0 (red) = checklist item not fulfilled.

Supplementary Table 6 - Quality assessment of reviews reporting attitudes, facilitators or barriers to deprescribing approaches using the ENTREQ 2012 checklist.

	ENTREQ 2012 checklist																				
Study	1 Aim	2 Synthesis methodology	3 Approach to searching	4 Inclusion criteria	5 Data sources	6 Electronic Search strategy	7 Study screening methods	8 Study characteristics	9 Study selection results	10 Rationale for appraisal	11 Appraisal items	12 Appraisal process	13 Appraisal results	14 Data extraction	15 Software	16 Number of reviewers	17 Coding	18 Study comparison	19 Derivation of themes	20 Quotations	21 Synthesis output	Score proportion
Chock, 2021 [75]	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	0	0	0	0	1	0.76
Weir, 2021 [76]	1	1	1	1	1	0	1	1	1	1	1	1	1	1	0	1	0	1	0	0	1	0.76
Oktora, 2022 [77]	1	1	0	1	0	0	1	1	1	0	0	0	0	1	1	1	0	1	0	0	1	0.52
Seewoodharry, 2022 [78]	1	1	0	1	1	1	1	1	1	1	1	1	1	1	0	1	0	0	0	0	1	0.71
Burghle, 2020 [79]	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	0	1	0.86
Lundby, 2019 [88]	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	0	1	1	0	1	0.86
Doherty, 2020 [80]	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	1	1	1	0.90
Bloomfield, 2019 [81]	1	0	0	1	1	1	1	1	1	0	0	0	0	1	0	1	0	0	0	0	0	0.43
Paque, 2019 [82]	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0	1	0.81
Anderson, 2014 [89]	1	1	0	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	0.90
Bourne, 2022 [45]	1	1	1	1	1	1	1	0	1	0	1	1	1	1	1	1	0	0	0	0	0	0.67
Rasmussen, 2021 [83]	1	1	1	1	1	0	1	1	1	0	1	1	1	1	1	1	1	1	1	0	1	0.86
Reeve, 2013 [84]	1	1	0	1	1	1	1	1	1	1	1	0	1	1	0	1	1	1	1	0	1	0.81
Moth, 2021 [90]	1	1	0	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	0.90
Stewart, 2021 [85]	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	0.95
Clarke, 2015 [86]	1	1	0	1	1	1	1	1	1	0	1	1	1	0	1	1	0	0	0	1	1	0.71
Valdez-Martinez, 2014 [87]	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0.95
Score proportion	1.00	0.94	0.47	1.00	0.94	0.76	1.00	0.94	1.00	0.71	0.88	0.82	0.88	0.94	0.59	1.00	0.41	0.53	0.53	0.29	0.88	

1 (green) = checklist item fulfilled.; 0 (red) = checklist item not fulfilled.

Supplementary Table 7 - Quality assessment of reviews focused on tools for deprescribing approaches using the PRISMA 2020 checklist.

	PRISMA 2020 checklist item																									
Study	1 Title	3 Rationale	4 Objectives	5 Eligibility criteria	6 Information sources	7 Search strategy	8 Selection process	9 Data collection process	10 Data items	11 Study risk of bias assessment	12 Effect measures	13 Synthesis methods	14 Reporting bias assessment	15 Certainty assessment	16 Study selection	17 Study characteristics	18 Risk of bias in studies	19 Results of individual studies	20 Results of syntheses	21 Reporting biases	22 Certainty of evidence	23 Discussion	24 Registration and protocol	25 Support	26 Competing interests	27 Availability of data, code and other materials	Score proportion
Michiels-Corsten, 2020 [91]	1	1	1	1	1	1	1	0	1	0	0	1	0	0	1	1	1	0	1	0	0	1	0	1	1	0	0.62
Thompson, 2019 [92]	1	1	1	1	1	1	1	1	1	0	0	1	0	0	1	1	0	1	1	0	0	1	0	1	1	0	0.65
Van Merendonk, 2022 [93]	1	1	0	1	1	1	1	1	0	0	0	0	0	0	1	1	0	1	1	0	0	1	0	0	1	1	0.54
Fajardo, 2019 [97]	0	1	1	1	1	1	1	1	1	0	1	1	0	0	1	0	0	0	1	0	0	1	0	1	1	1	0.62
Clough, 2018 [98]	1	1	1	1	1	1	1	1	1	1	0	0	0	0	1	1	1	1	1	0	0	1	0	1	1	0	0.69
Renn, 2018 [94]	1	1	1	1	1	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0	0	1	0	1	1	0	0.38
Van der Ploeg, 2020 [95]	1	1	1	1	1	0	1	1	0	1	0	1	0	0	1	0	0	0	1	0	0	1	1	1	1	0	0.58
Darr-Foit, 2019 [96]	1	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1	0	0	1	0	0.23
Score proportion	0.88	0.88	0.75	1.00	1.00	0.63	0.75	0.63	0.50	0.25	0.13	0.50	0.00	0.00	0.88	0.50	0.25	0.38	1.00	0.00	0.00	1.00	0.13	0.75	1.00	0.25	

1 (green) = checklist item fulfilled.; 0 (red) = checklist item not fulfilled. Checklist item 2: Abstract is presented in Supplementary Table 8.

Supplementary Table 8 - Quality assessment of item 2 (Abstract) in reviews focused on tools for deprescribing approaches using the PRISMA 2020 checklist.

Study	**PRISMA 2020 checklist item 2: Abstract**												
	1 Title	2 Objectives	3 Eligibility criteria	4 Information sources	5 Risk of bias	6 Synthesis of results	7 Included studies	8 Synthesis of results	9 Limitations of evidence	10 Interpretation	11 Funding	12 Registration	Score proportion
Michiels-Corsten, 2020 [91]	1	1	0	1	0	1	0	1	0	1	0	0	0.50
Thompson, 2019 [92]	1	1	0	1	0	1	0	1	1	1	0	0	0.58
Van Merendonk, 2022 [93]	1	1	0	1	0	0	0	1	0	1	0	0	0.42
Fajardo, 2019 [97]	0	1	0	1	0	1	0	1	1	1	0	0	0.50
Clough, 2018 [98]	1	0	1	0	1	0	1	1	0	1	0	0	0.50
Renn, 2018 [94]	1	1	0	0	0	1	0	0	1	1	0	0	0.42
Van der Ploeg, 2020 [95]	1	1	1	1	1	1	0	1	1	1	0	0	0.75
Darr-Foit, 2019 [96]	1	1	0	0	0	0	0	1	0	1	0	0	0.33
Score proportion	0.88	0.88	0.25	0.63	0.25	0.63	0.13	0.88	0.50	1.00	0.00	0.00	

1 (green) = checklist item fulfilled.; 0 (red) = checklist item not fulfilled.