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SHORT COMMUNICATION

Revisiting systematic reviews on deprescribing trials to better inform future practice and research

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Abstract

Deprescribing aims to address the problem of medication overuse in older adults. There has been an increasing number of systematic reviews of 'deprescribing'. We aimed to describe the categories of trials included in recent systematic reviews, and to make recommendations for future research. We categorized 122 trials included in eight recent deprescribing systematic reviews into: discontinuation, deprescribing implementation, medication optimisation (including medication initiation) and non-initiation trials. We identified heterogeneity and inconsistency in the categories of trials included in deprescribing systematic reviews. For example, 39 trials (32.0%) involved medication initiation in addition to the deprescribing component. It is now time for international researchers to develop and validate terminology used for trials involving discontinuation/deprescribing of medications, and to provide recommendations for evidence synthesis that will better inform future research, and translation into practice and policy.

KEYWORDS
deprescribing, deprescriptions (MeSH), medication overuse, systematic review

1 | INTRODUCTION

Medication overuse refers to the use of a medication which is not—or no longer—clinically indicated, not effective for the targeted indication, not aligned with the patient's treatment goals and preferences, or which has an unfavourable benefits-to-risks ratio.[1] It is associated with poor health outcomes such as injurious falls, cognitive impairment, hospitalization, and death, and leads to wasteful healthcare expenditure.[2–4] Deprescribing aims to address the global problem of medication overuse. Deprescribing has been defined as the systematic process of identifying and discontinuing or de-intensifying medications in instances in which existing or potential harms outweigh existing or potential benefits within the context of an individual patient's care goals, current level of functioning, life expectancy, values, and preferences.[5] Deprescribing is highly relevant in the context of older adults with multimorbidity, polypharmacy and low adherence to medications. It is estimated that one- to two-thirds of older people are prescribed a medicine with more harm than benefit.[6,7] Deprescribing may improve overall adherence to essential drugs while reducing costs, inconvenience and medication-related harms.[5]

There has been an increasing amount of research around deprescribing in older adults over the last 15 years.[8–10] Different categories of deprescribing trials exist. Trials have emerged that generate evidence on when and how to deprescribe (e.g., randomized controlled trials [RCTs] comparing continuation of a medication to discontinuation on clinical outcomes), as well as on how best to implement deprescribing in clinical practice (e.g., RCTs evaluating a deprescribing tool or education on rate of discontinuation). Trials may also involve 'medication optimisation' (e.g., via a medication review) that includes a component of deprescribing but may also include starting medications.[11]

Synthesizing evidence through systematic reviews and meta-analyses is essential to inform guideline developers, policymakers and other stakeholders on when and how best to deprescribe in clinical practice. Many systematic reviews on deprescribing have been published recently, and protocols registered on PROSPERO indicates that many others are ongoing. Yet so far, most systematic reviews reported heterogeneity and inconclusive findings. One reason for this is that systematic reviews may include various categories of trials (explained above); however, this has not been explicitly examined to date.

We aimed to describe and discuss the types of trials included in recent systematic reviews, and to make recommendations for future systematic reviews.

What is already known about this subject

- Deprescribing trials generate evidence on how and when to deprescribe and on how to implement deprescribing in practice.
- When synthesizing data, distinctions are needed in relation to the categories of trials, their objectives and outcome measures.
- Several recent deprescribing systematic reviews had weak conclusions due to quality and heterogeneity issues.

What this study adds

- There is heterogeneity and inconsistency in the categories of trials included in deprescribing systematic reviews. The inclusion of broader medication optimization trials is frequent, threatening construct validity.
- A validated taxonomy of discontinuation/deprescribing trials is needed to improve quality of deprescribing evidence syntheses that will better inform future practice and research.

2 | METHODS

We performed a review of trials included in recent systematic reviews on deprescribing.

Systematic reviews were identified through searching Pubmed by one author (AS; Deprescri* in Title, Filters: systematic review). The inclusion criteria were the following: deprescribing or deprescription in the title; systematic review of trials performed in older adults in any setting of care; minimum of five trials included; and published between 2018 and 2022 (search performed on 21 April 2022). Systematic reviews of qualitative studies, on attitudes of patients or healthcare professionals, or on barriers and enablers to deprescribing were excluded. We first retained all the systematic reviews which conducted a meta-analysis, as this was felt most relevant to the present work, and then randomly selected an equal number of additional systematic reviews to include. Out of these systematic reviews without a meta-analysis, we ensured that half targeted a specific medication class (e.g., deprescribing of benzodiazepines) and the other half did not. We considered that this approach would lead to a good variety in the focus and methods of the systematic reviews while having a large enough sample to meet our objectives.

For each systematic review, we extracted PICO (patient, intervention, control, outcome) data, number of trials included and authors' conclusion. For each trial included in the systematic reviews, we extracted data on the trial's objectives and description of the intervention and then categorized each study in relation to the category of trial and to the medication target. First, three categories of trials were a priori defined, based on the objectives and intervention evaluated: (1) medication discontinuation trials, that is, trials that aim to evaluate the benefits and harms of discontinuing one specific (or class of) medication; (2) deprescribing implementation trials, that is, trials that evaluate the effect of one or several implementation strategies (e.g., educational intervention, audit and feedback, computerized decision support) to enhance deprescribing of one or several medications in clinical practice, on implementation, efficacy and/or safety outcomes; and (3) medication optimization trials that involve but are not restricted to deprescribing. These trials aim to evaluate implementation strategies to optimize medication use (the whole medication regimen, or a specific set of potentially inappropriate medications) in clinical practice. In addition to stopping or adapting medications, these approaches can also involve starting medications, to address situations of underuse. For trials in this third category, we specifically recorded whether medication initiation was explicitly mentioned by the authors as part of the intervention. During the review process, we added a fourth category, namely non-initiation trials, that is, trials evaluating a strategy that aimed to prevent initiation of inappropriate medications. In some cases, a trial could be considered to be a deprescribing as well as a non-initiation trial, if the strategy targeted both aspects. Figure 1 summarizes the four categories of trials used in the present work. Second, three categories were defined in relation to the medication(s) targeted in the trial: a single and specific medication or medication class, a specific group of medications (e.g., medications from the STOPP list, anticholinergic medications), or any medication taken by the patient.

Data extraction from original manuscripts of trials included in the systematic reviews was first performed by two researchers (AS, WT) independently on a first set of 40 trials, then discrepancies were discussed and definitions adjusted and/or clarified. The rest of the trials had data extracted and were categorized by one researcher with verification performed by a second researcher (AS, WT, ER).

Analysis was descriptive and involved describing the categories of trials and medication targets for each systematic review as well as overall for all systematic reviews included.

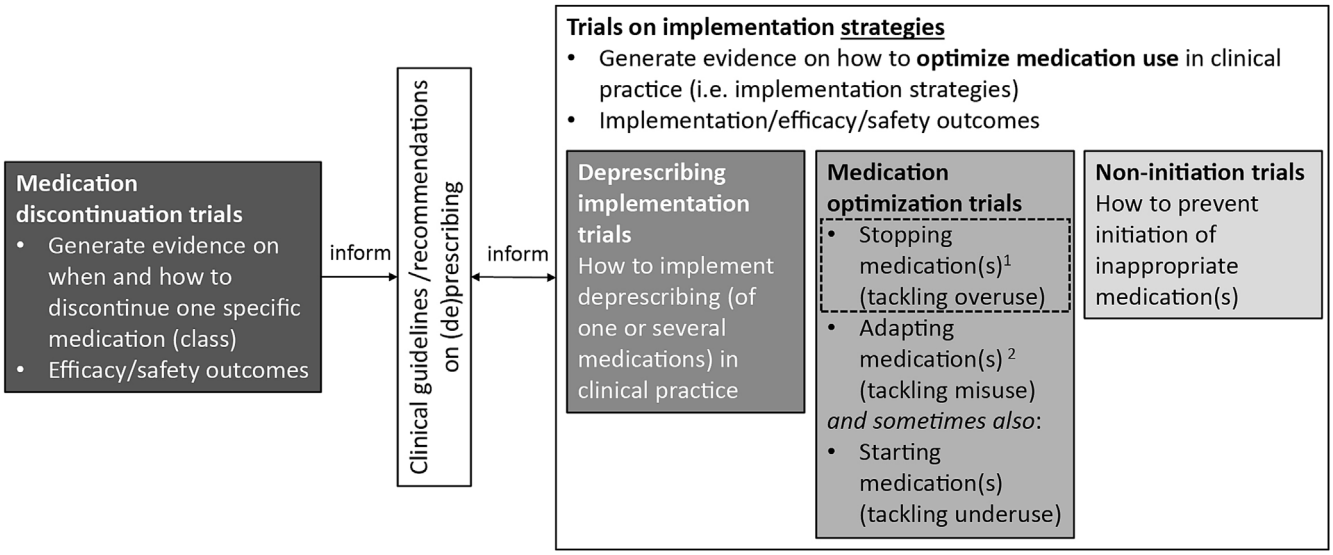

FIGURE 1 Categories of trials included in deprescribing systematic reviews. Legend: [1]This sometimes includes substitution (i.e., stopping a medication and starting another—safer—medication to treat/prevent a specific disease or condition; [2]examples include: adapt dosage to renal function, switch medication to decrease the risk of drug–drug interaction; change formulation to ease administration; provide support to patient to improve adherence.

3 | RESULTS

Twelve systematic reviews were identified for potential inclusion. Four systematic reviews with meta-analysis were identified and 2 medication specific and 2 non-medication specific systematic reviews (without meta-analysis) were randomly selected from the remaining eligible systematic reviews without meta-analysis identified by our search. The eight systematic reviews included a total of 122 unique trials (range of 5–41 trials per systematic review; 23 trials [18,9%] were included in more than one systematic review).[12–19] Table 1 and Figure 2 summarize the characteristics of each systematic review and the categories of trials included. In total, 16 trials (13.1%) were discontinuation trials, 32 (26.2%) were deprescribing implementation trials, and 68 (55.7%) were medication optimization trials, among which 39 (32.0%) involved a medication initiation component. Six trials (4.9%) were non-initiation trials—three of these also had a deprescribing implementation component—and three trials could not be categorized because they fitted none of the categories or because of missing information. Trials targeted a single medication or class of medication in 24 studies (19.7%—antipsychotics in 9 studies, benzodiazepines in 8 studies, and other in 7 studies), a group of medications in 41 studies (33.6%—the two most frequent were explicit list of potentially inappropriate medications in 12 studies [STOPP/START, Beers, FORTA, STOPPFrail] and fall-risk increasing drugs in 7 studies), and any medication in 54 studies (44.3%). The three studies which could not be categorized by trial type did not have their medication target categorized.

4 | DISCUSSION

In this review of eight recent deprescribing systematic reviews and their 122 unique included studies, we found heterogeneity and inconsistency in trial and medication types. For example, more than half of the trials included in the systematic reviews were medication optimisation trials which include but are not limited to deprescribing. For five of the systematic reviews we identified, 21% to 67% of the trials in the systematic review involved starting a medication. These findings raise concerns around construct validity, as these 'deprescribing systematic reviews' include outcomes of medication changes other than just deprescribing. Similarly, combining the results of the discontinuation and deprescribing implementation trials, or combining the results of single medication trials and trials on discontinuation of any overused medication, may lead to inaccurate results and conclusions. This likely contributed to the generally weak conclusions of the reviews and impedes translation of deprescribing research into practice. The quality of individual trials also influences the strength of the conclusions but this was not evaluated in the present work. Below, we argue why we believe there is a potential for systematic reviews to answer more precise and focused research questions, and this could maximize value of information for policymakers.

We believe that systematic reviews should only include certain categories of trials. If systematic reviews include several categories of trials, then pre-specified subgroup analysis is needed. This is highly relevant when evaluating and interpreting the effect on medication outcomes and clinical outcomes. For example, if a deprescribing systematic review finds no change in the number of medications but

TABLE 1 Systematic reviews included in the analysis: characteristics and categories of trials included.

Reference, title	PICO (patients, intervention, control, main outcomes)	Authors' conclusion	Trials (number and categories)
Hansen 2018[12] Identification of behaviour change techniques in **deprescribing interventions**: a systematic review and meta-analysis	P: patients ≥65 years or a HCP with prescribing, dispensing or administration authority; any setting of care I: interventions encouraging the deprescribing of existing drugs or the reduction of existing inappropriate prescribing C: active interventions or inactivity O: number of total and inappropriate prescriptions and/or drugs; proportion of participants with a reduction in number of total and inappropriate prescriptions and/or drugs; and implementation of recommendations.	In general, deprescribing interventions effectively reduce medication use and inappropriate prescribing in older people. Successful deprescribing is facilitated by the combination of behaviour change techniques involving a range of intervention components	25 trials Discontinuation: 0 (0%) Deprescribing intervention: 4 (16%) Medication optimization: 21 (80%), including 13 (52%) with a START component Non-initiation: 1 (4%) All medication: 16 (64%) Group of medications: 8 (32%) Single medication: 1 (4%)
Thillainadesan 2018[13] Impact of **Deprescribing Interventions** in Older Hospitalised Patients on Prescribing and Clinical Outcomes: A Systematic Review of Randomised Trials	P: older population, median age ≥ 65 years, in the hospital setting I: any intervention aimed at reduction of PIMs including electronic and non-electronic deprescribing interventions, pharmacist-led medication reviews, physician-led interventions, prescriber education programmes, multidisciplinary interventions and clinical decision support systems C: usual care O: reduction in PIMs; clinical outcomes	Deprescribing interventions in hospital are feasible, generally effective at reducing PIMs and safe. However, the current evidence is limited, of low quality and the impact on clinical outcomes is unclear.	9 trials Discontinuation: 0 (0%) Deprescribing: 2 (22%) Medication optimization: 7 (80%), including 6 (67%) with a START component Non-initiation: 0 (0%) All medication: 3 (33%) Group of medications: 6 (67%) Single medication: 0 (0%)
Kua 2019[14] Health Outcomes of **Deprescribing Interventions** Among Older Residents in Nursing Homes: A Systematic Review and Meta-analysis	P: participants ≥60 years in a nursing home setting I: deprescribing in a nursing home setting by a health care professional C: not specified O: any reported health outcomes (including falls, inappropriate medications, all-cause mortality, and hospitalization rates)	Compared to other deprescribing interventions, medication review-directed deprescribing had significant benefits on older residents in nursing homes	41 trials Discontinuation: 13 (32%) Deprescribing: 8 (20%) Medication optimization: 15 (37%), including 9 (22%) with a START component Non-initiation: 3 (7%) All medication: 11 (27%) Group of medications: 11 (27%) Single medication: 16 (39%)
Bloomfield 2020[15] **Deprescribing** for Community-Dwelling Older Adults: a Systematic Review and Meta-analysis	P: community-dwelling adults aged ≥ 65 years I: any deprescribing intervention (categorized as comprehensive medication review, educational initiatives, and computerized decision support) C: usual care or another intervention O: all-cause mortality, hospitalizations, health-related quality of life, and falls	In community-dwelling people aged 65 years and older, medication deprescribing interventions may provide small reductions in mortality and use of potentially inappropriate medications	38 trials Discontinuation: 0 (0%) Deprescribing: 8 (21%) Medication optimization: 29 (76%), including 16 (42%) with a START component Non-initiation: 2 (5%) All medication: 25 (66%) Group of medications: 11 (29%) Single medication: 2 (5%)

TABLE 1 (Continued)

Reference, title	PICO (patients, intervention, control, main outcomes)	Authors' conclusion	Trials (number and categories)
Romano 2021[16] **Deprescribing Interventions** among Community-Dwelling Older Adults: A Systematic Review of Economic Evaluations	P: community-dwelling adults aged ≥ 65 years I: any intervention conducted in the community or primary care settings that includes deprescribing inappropriate medicines, C: usual care O: economic impact of the intervention from any perspective, converted into 2019 US Dollars	Although results varied across setting, time horizon and intervention, most were cost effective according to the World Health Organization threshold. Deprescribing interventions are promising from an economic viewpoint, but more studies are needed.	14 trials Discontinuation: 0 (0%) Deprescribing: 4 (29%) Medication optimization: 10 (71%), including 3 (21%) with a START component Non-initiation: 0 (0%) All medications: 9 (64%) Group of medications: 4 (29%) Single medication: 1 (7%)
Shrestha 2021[17] Impact of **deprescribing** dual-purpose medications on patient-related outcomes for older adults near end-of-life: a systematic review and meta-analysis	P: patients in any setting, average age ≥65 years, at the end-of-life due to any life-limiting illnesses, prescribed with ≥1 potentially inappropriate dual-purpose medication I: any type of strategy to deprescribe such medications C: control group O: any clinical or patient-reported measures	There were insufficient numbers of high-quality studies powered to confirm whether deprescribing of dual-purpose medication reduces adverse events, health service use, or improves the quality of life or functioning in older adults near the end of life	5 trials Discontinuation: 1 (20%) Deprescribing: 4 (80%) Medication optimization: 0 (0%) Non-initiation: 0 (0%) All medications: 1 (20%) Group of medications: 2 (40%) Single medication: 1 (20%)
Systematic reviews targeting a specific medication class			
Ribeiro 2021[18] Benzodiazepine **deprescription strategies** in chronic users: a systematic review	P: Chronic benzodiazepine users I: Combined or multidisciplinary deprescription strategies (groups, cognitive behavioural therapy, campaigns …) C: Individual approach in health care O: Benzodiazepine deprescription	Although the comparison of different strategies was impaired by the high risk of bias in some studies, patient education focused interventions presented good results.	11 trials Discontinuation: 1 (9%) Deprescribing: 9 (82%) Medication optimization: 1 (9%), including 0 (0%) with a START component Non-initiation: 1 (9%) All medications: 2 Group of medications: 3 Single medication: 6
Lee 2021[19] **Deprescribing** fall-risk increasing drugs (FRIDs) for the prevention of falls and fall-related complications: a systematic review and meta-analysis	P: adults aged ≥65 years from all settings I: FRID deprescribing or withdrawal with the intent of reducing falls C: usual care or a control intervention O: primary: rate of fall and incidence of falls; secondary: fall- related fractures, fall-related injuries, fall- related hospitalization, adverse effects related to the withdrawal intervention (e.g., disease relapse, symptomatic withdrawal)	There is a paucity of robust high-quality evidence to support or refute that a FRID deprescribing strategy alone is effective at preventing falls or fall-related injury in older adults. Although there may be other reasons to deprescribe FRIDs, our systematic review found that it may result in little to no difference in the rate or risk of falls as a sole falls reduction strategy.	5 trials Discontinuation: 2 (40%) Deprescribing: 3 (60%) Medication optimization: 0 (0%), including 0 (0%) with a START component Non-initiation: 0 (0%) All medications: 0 (0%) Group of medications: 5 (100%) Single medication: 0 (0%)

Abbreviation: PIM, potentially inappropriate medication.

included trials with a medication initiation component, then the outcome is not appropriate in relation to impact on deprescribing. Subgroup analysis was performed in only one of the systematic reviews evaluated,[14] with differing results between categories.

Effectiveness research and implementation research pursue different objectives. Using the simple language of G.M. Curran[20] adapted to deprescribing, effectiveness research looks at whether discontinuing a medication works, while implementation research looks at how to help

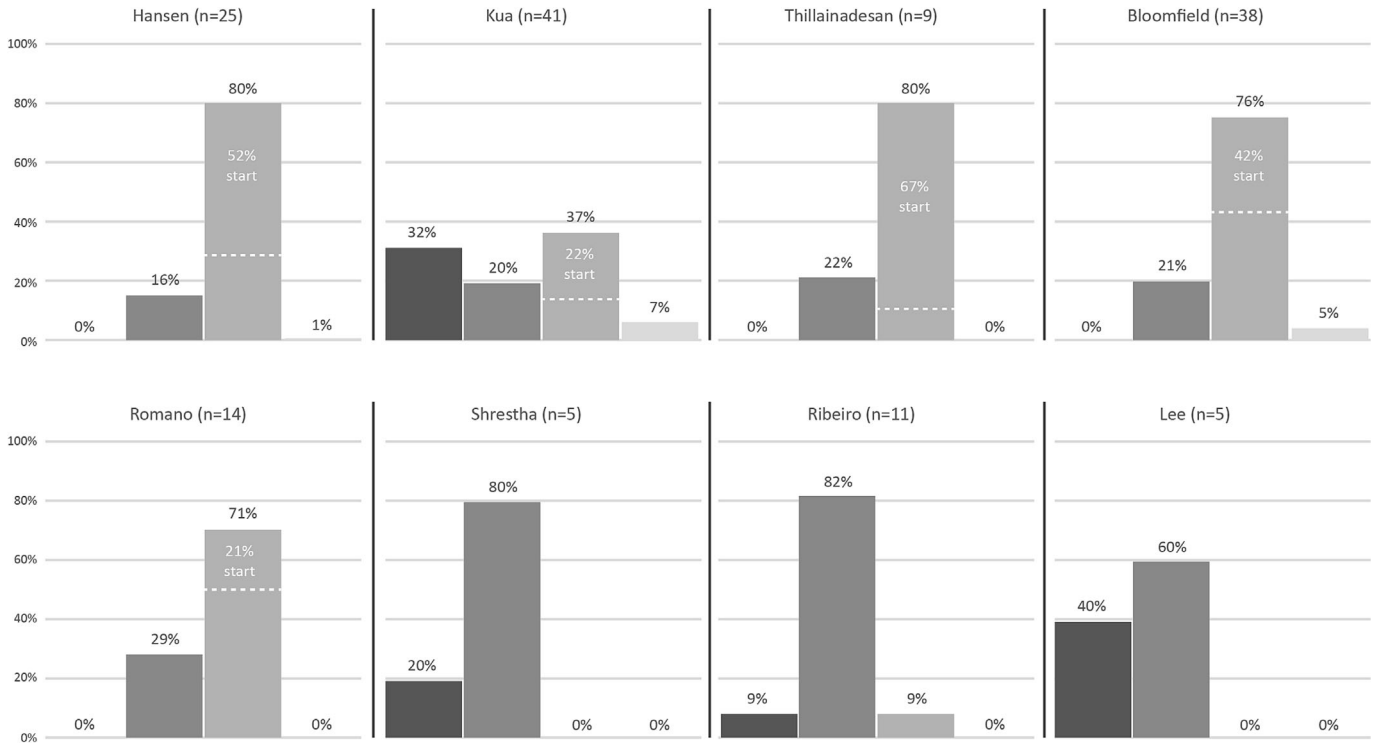

FIGURE 2 Categories of trials included in each systematic review. Legend: The four categories of trials represented on the figure are, from left to right: discontinuation trials (black bars); deprescribing implementation trials (dark grey bars); medication optimization trials, with upper part referring to trials for which a 'starting drug' component was included (medium grey bars); non-initiation trials (light grey bars).

people discontinue medications (i.e what strategies or interventions to use). Systematic reviews should clearly specify if their objective is to review effectiveness or implementation research or both (e.g., hybrid trials), and the language used should be unequivocal. This was not always the case in the systematic reviews reviewed here. For example, Kua et al.[14] aimed to evaluate *the impact of deprescribing interventions*, yet they included both effectiveness (i.e., discontinuation) trials and implementation trials. Lee et al.[19] aimed to determine *the efficacy of deprescribing* fall-risk increasing drugs, and their meta-analysis included both effectiveness and implementation trials. This demonstrates how the term deprescribing trial is used in various ways and this can be misleading. Given that deprescribing has been an emerging research field, these reviews may have wished to maximize inclusion to gain the most information possible to inform practice and research. They may also have been limited by how the original trials were described, as implementation science has only recently been used to inform deprescribing research, with this terminology not yet widespread.

One possibility to decrease confusion would be, to use the terms 'deprescribing strategies' or 'deprescribing interventions' when referring to implementation trials. This would align with core aspects of the definition of deprescribing, that is, a systematic and patient-centred process coordinated by a healthcare professional.[5,21] The term 'discontinuation' could be used for efficacy/effectiveness trials. The term discontinuation is indeed more widely used to refer to trials where the target medication is discontinued in all patients from the intervention group and none of the patients from the control group.

The present work has some limitations. First, we included a sample of eight systematic reviews and did not perform an umbrella review of all deprescribing systematic reviews. However, our pragmatic approach aligned with our main objective to explore current status, highlight the issues, and generate ideas for further discussion and development. Second, it was sometimes difficult to categorize the type of trial due to unclear or missing information. Better reporting of interventions has been widely promoted over the last 10 years and is essential for adequate evidence synthesis.[22]

In line with previous calls to better describe, define and categorize deprescribing trials,[10,23] with the recent Cochrane Library Special Collection that provides an overview of Cochrane Reviews on deprescribing of unnecessary medications,[9] and with recent guidance on implementation trials,[24] we believe it is now the right time for international deprescribing researchers to develop and validate a taxonomy of trials related to the discontinuation/deprescribing of medications, and to provide recommendations for evidence synthesis that will better inform future research, practice and policy. Active members of existing deprescribing research networks worldwide can join their forces to make this happen.

AUTHOR CONTRIBUTIONS

Anne Spinewine drafted the study protocol, which was discussed with and amended by Emily Reeve and Wade Thompson. All authors performed data extraction. Anne Spinewine performed data analysis. Interpretation occurred through discussion among all authors. Anne Spinewine wrote the first draft of the manuscript, which was then revised and amended by all authors. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

ER is supported by a United States National Institutes of Health (NIH) grant and has received royalties for co-authoring a chapter on deprescribing in UpToDate and honorarium from the Society of Hospital Pharmacists of Australia (leading workshops on deprescribing). The authors have no other conflict of interest to disclose in relation to this work.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in OSF https://doi.org/10.17605/OSF.IO/U8TSY.

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