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SYSTEMATIC REVIEW

The feasibility and effect of deprescribing in older adults on mortality and health: a systematic review and meta-analysis

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AIMS

Deprescribing is a suggested intervention to reverse the potential iatrogenic harms of inappropriate polypharmacy. The review aimed to determine whether or not deprescribing is a safe, effective and feasible intervention to modify mortality and health outcomes in older adults.

METHODS

Specified databases were searched from inception to February 2015. Two researchers independently screened all retrieved articles for inclusion, assessed study quality and extracted data. Data were pooled using RevMan v5.3. Eligible studies included those where older adults had at least one medication deprescribed. The primary outcome was mortality. Secondary outcomes were adverse drug withdrawal events, psychological and physical health outcomes, quality of life, and medication usage (e.g. successful deprescribing, number of medications prescribed, potentially inappropriate medication use).

RESULTS

A total of 132 papers met the inclusion criteria, which included 34 143 participants aged 73.8 ± 5.4 years. In nonrandomized studies, deprescribing polypharmacy was shown to significantly decrease mortality (OR 0.32, 95% CI: 0.17–0.60). However, this was not statistically significant in the randomized studies (OR 0.82, 95% CI 0.61–1.11). Subgroup analysis revealed patient-specific interventions to deprescribe demonstrated a significant reduction in mortality (OR 0.62, 95% CI 0.43–0.88). However, generalized educational programmes did not change mortality (OR 1.21, 95% CI 0.86–1.69).

CONCLUSIONS

Although nonrandomized data suggested that deprescribing reduces mortality, deprescribing was not shown to alter mortality in randomized studies. Mortality was significantly reduced when applying patient-specific interventions to deprescribe in randomized studies.

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Polypharmacy in older adults is correlated to poor health outcomes.
- Deprescribing is one proposed intervention to reduce the harm associated with polypharmacy.
- Limited evidence is available to support deprescribing as an intervention.

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WHAT THIS STUDY ADDS

- Deprescribing appears to be a feasible intervention.
- Deprescribing may not affect mortality.
- Evidence exists to guide deprescribing individual medications in carefully defined scenarios.

Introduction

People are living longer than ever before, but many older adults live with multiple chronic diseases [1]. Efficacious medications modify the risk of future serious events such as myocardial infarction or stroke [2]. Medications alleviate symptoms such as pain, anxiety and reflux. Additionally, there is increased evidence for combination therapies for conditions such as hypertension, diabetes and benign prostatic hypertrophy [3–5]. Consequently, the daily routine of taking many medications is now the norm rather than the exception for many older adults. By age 70, three out of four people take five or more medications every day [6]. The potential problem of polypharmacy continues to grow with the average 70-year-old taking an additional two tablets every day than the average 70-year-old did just ten years ago [7–9]. Therefore, the 'cure' may have become the 'disease'. Polypharmacy among older people is associated with poorer health outcomes such as increased rates of impaired cognition, frailty, falls, morbidity and disability [10–12]. It is independently associated with increased mortality [13]. It remains unclear whether polypharmacy is merely an indicator, or cause, of poorer health outcomes.

To reverse the harms of polypharmacy appears simple. The number of medications older adults use should be reduced by 'deprescribing' [14]. Deprescribing is defined as the 'the process of withdrawal of inappropriate medication, supervised by a health care professional with the goal of managing polypharmacy and improving outcomes' [15]. This process can be applied in practice using a five-step approach: (1) consider all medications currently taken and the indication for each medication, (2) evaluate the overall risk of medication-induced harm in an individual person, (3) assess each medication for its potential to be deprescribed, (4) sort medications by the order of priority to deprescribe, (5) implement and monitor deprescribing regimen [14]. A useful mnemonic for this process is CEASE [16]. Yet the evidence base to support deprescribing interventions remains relatively scant, and it is unknown if deprescribing can ameliorate the correlated harms of polypharmacy. Recent systematic reviews have investigated the barriers and enablers for both consumers and prescribers, as well as the definition of deprescribing [15, 17, 18]. Existing systematic reviews have explored deprescribing specific classes (including cardiovascular, psychotropic and hypnotic medications) [19–21] as well as specific scenarios, such as oncology, palliative care and deprescribing to prevent or modify the risk of falls [22, 23]. This systematic review is the first to compile evidence for deprescribing in older adults across all settings and medications. The review aims to determine whether deprescribing is a safe, effective and feasible intervention to modify mortality and health outcomes in older adults. More specifically, the primary aim is to establish the safety of deprescribing by assessing its effects on mortality. The secondary aims include exploring the safety of deprescribing by investigating adverse drug withdrawal events. Further, we explore the efficacy of deprescribing interventions by investigating health outcomes and quality of life. Additionally, we review whether deprescribing interventions are achievable.

Methods

The protocol was prospectively published and registered with Prospero Database of Systematic Reviews (CRD42014009887) [24, 25]. This review was conducted and reported in adherence to the PRISMA statement of quality for reporting systematic reviews and meta-analyses [26].

Selection criteria

The selection criteria were described in detail previously and are briefly described here [24].

Types of participants. This review considered studies that included people aged 65 years and older who were prescribed one or more regular medications at the beginning of the study. Studies that included only moribund, terminal or palliative participants were excluded. No limitation was placed on the setting.

Types of interventions. This review considered studies that evaluated deprescribing by a health care professional of one or more regular prescription medications. Studies were included where the stated aim or effect was to deprescribe one or more medications.

For the study to be eligible for inclusion, the deprescribing intervention needed to target a medication available in 2015 in at least one of the following countries: Australia, New Zealand, United Kingdom, Canada or the United States. This focused the review on medications currently available today, rather than those withdrawn from the market.

These could be compared to either no comparator or usual care, namely the continuation of the prescribed medication.

Types of outcome measures. Outcomes were included where reported as either an outcome or an effect of the intervention in the original paper. Mortality was the primary outcome measure for this review. Secondary outcome measures considered were any reported adverse drug withdrawal events. Health outcomes were considered where there were clinically-relevant physical health, cognitive function and psychological health parameters or events.

Quality of life measured using any standardized tool was considered. The effect on the medication regimen was included if reported using a standard measure, such as any

implicit or explicit prescribing tools, success of deprescribing or total number of medications.

Types of studies. This review considered for inclusion both experimental and observational studies of deprescribing of one or more prescription medications in older people. These were defined as studies where the stated aim or effect of the intervention was to reduce medication. The review included experimental study designs (randomized controlled studies (RCTs), quasi-randomized controlled studies, and nonrandomized controlled studies) as well as observational study designs with concurrent controls (prospective and retrospective cohort studies, case-control studies), and observational studies without concurrent controls (historical cohort studies, two or more single arm studies, and before and after studies).

Studies available in English at any time up to the commencement of the search on 11 February 2015 were considered for inclusion in this review.

Search strategy

The search strategy aimed to identify both published and unpublished studies, and has previously been described in detail [24]. Briefly, databases were searched from inception to February 2015. EbscoHost (CINAHL Plus, Health Source: Nursing/Academic Edition, Academic Search Premier), Ovid (Medline, DARE), Scopus, Web of Science, Elsevier (Embase) and ProQuest (Dissertations and Theses Global) were searched to identify published papers and grey literature. National Institutes of Health Trials Register, Australian New Zealand Clinical Trials Registry and European Union Clinical Trials Register were searched for ongoing trials. The search terms used were:

1. prescribing, prescription, drug, medication, polypharmacy, individual generic drug names, drug classes and therapeutic classes
2. deprescrib*, inappropriate, reduc*, stop*, withdraw*, cessation, ceas*,discontinu*
3. aged OR ageing OR 65 years OR geriatric OR older adult OR older OR elderly OR veteran
4. 1 AND 2 AND 3

The detailed Medline database search is available in the supplementary file. The reference lists of all identified papers were scanned for relevant studies.

Data collection and analysis

Selection of studies. Two researchers independently screened the titles and abstracts of all records retrieved. Full texts of all articles were retrieved that appeared to meet the selection criteria and for those that could not be adequately assessed from the information given. Two researchers independently assessed the full-text articles for eligibility. They resolved any differences through consensus, and where consensus was not achieved, a third researcher made the final decision.

Data extraction and management. An electronic data extraction form was designed using DistillerSR online application [27]. One researcher independently extracted details of included articles, which were verified by a second researcher. Information extracted included the study design and size, intervention dates, setting, participants' age, sex, whether participants were living with dementia, the inclusion and exclusion criteria, medication targeted for deprescribing, withdrawal schedule, reported outcomes, follow-up duration and funding source.

For studies where the stated aim or effect of the intervention was to deprescribe polypharmacy, we extracted additional information about the method used to identify target medication. We extracted data on whether the intervention was patient-specific or educational. Deprescribing interventions were defined as patient-specific when (i) the investigators identified target medications to deprescribe and implemented the process (investigator-led interventions), and (ii) the investigators undertook medication reviews to identify target medications to deprescribe, and then recommended to the prescribing doctors that they deprescribe the medications (medication reviews). Education interventions were defined as those where health care professionals were provided with education sessions with the intention to reduce medication use through modified behaviours.

Missing data. The original authors were contacted to obtain missing information or clarify unclear data. Where this was not successful, we conducted the analysis with only the available data.

Assessment of risk of bias. Two reviewers independently assessed the risk of bias [27]. The second reviewer was blinded to author, year and place of publication. The Cochrane Collaboration's 'Risk of Bias' tool was used to assess the risk of bias for each included RCT [28, 29]. For studies other than RCTs, we modified the standard tool using the recommendations from the Cochrane Handbook and combined it with the Newcastle-Ottawa tool [29].

Assessment of reporting biases. Risk of reporting bias was assessed using funnel plot asymmetry, where data from more than ten similar studies were pooled [29].

Unit-of-analysis issues. Included studies reported in two or more papers were combined into a single study. We extracted data from each report separately, and then combined information across the multiple data collection forms.

For multi-arm studies, the authors used their judgement to identify the most relevant intervention and control group to enter into the meta-analysis. If three or more groups were relevant to the review, then we combined the groups from multiple arms studies into a single group in RevMan v5.3 [30]. This was done to avoid the possibility of introducing bias caused by using one control group for multiple statistical comparisons. Where studies reported an outcome at multiple time points, we used the data from the last time point [29].

For crossover studies and factorial study designs, the analysis techniques used intended to avoid potential unit-of-analysis issues. For crossover studies, we used only data from the first phase of crossover studies. For studies that used a factorial design, the group that received only the deprescribing intervention were selected and compared to the group that received neither intervention.

Data synthesis. Where possible, quantitative data from studies were pooled for statistical meta-analysis using RevMan v5.3 [30]. Data were pooled based on the medication(s) deprescribed regardless of the intervention technique. Studies were pooled as 'polypharmacy' where the stated aim or effect of the intervention was to reduce medications across three or more medications or classes. Data from RCTs were not combined with data from other study designs. We further separated comparative studies with and without concurrent control groups.

Forest plots were produced where three or more studies were included in a meta-analysis.

Data in tables are presented in order of polypharmacy and then by therapeutic class based on the Anatomical Therapeutic Classification (ATC) codes.

Randomized studies. The Mantel-Haenszel method using the fixed effects model was used to pool RCTs. If heterogeneity was detected, we chose the random effects model. Where one or more of the original studies used a cluster-randomization method, we used the generic inverse-variance method rather than the Mantel-Haenszel method.

Nonrandomized studies with concurrent control groups. The generic inverse-variance method with a fixed effects model was used to pool data [29]. If heterogeneity was detected, we chose the random effects model.

Nonrandomized studies without a concurrent control group. The data were reported narratively for these studies [29].

Dichotomous data. Effect sizes and their 95% confidence intervals were expressed as odds ratios (OR). Where a study reported zero events in both arms, the study was excluded from the meta-analysis [29].

Continuous data. Effect sizes and their 95% confidence intervals were expressed as weighted mean differences (MD). Where studies reported the mean but not the standard deviation, we have looked for other reports of variance for continuous data. If other measures of variance have been given, such as standard error or 95% confidence interval and *P*-values, we have entered these data into RevMan 5.3 to calculate the standard deviation [30]. We chose the larger of the two values where the significant decimal places in a measure of variance had been rounded and resulted in an uneven spread. We sought the standard deviation from the study author where insufficient detail of variance was provided in the paper to calculate the standard deviation. Where the detail of variance was still unavailable, the study was excluded from the meta-analysis.

Assessment of heterogeneity. Heterogeneity was assessed visually with forest plots where applicable. Heterogeneity was quantitatively assessed using the standard Chi-square and defined as either $I^2 \leq 50\%$ or $P > 0.1$ [29].

Subgroup analysis. Subgroup analyses were undertaken when ten or more studies investigating the same deprescribing target medication(s) reported an outcome. The subgroup analyses were based on age (participants aged under 80 years and those aged 80 years and over), cognitive function (participants living with dementia and cognitively intact participants) and intervention method (patient-specific interventions and educational programmes). The subgroups based on age and cognitive function, which were prespecified in the protocol as the old-old and people living with dementia, are demographic groups where there is often sparse clinical evidence to support medication use, and often have greater or specific health care needs.

Results

Description of studies

Results of the search. The initial search identified 27 086 records, and 1378 were identified through other methods (Figure 1). A total of 497 full papers were retrieved for further examination, and 132 papers reported 116 studies that met the inclusion criteria (Figure 1) [31–162]. Additional information was sought from the authors of 18 studies [41, 43, 48–50, 57, 59, 65, 77, 84, 88, 92, 99, 104, 105, 109, 119, 160]. Five authors responded to this request for further information [84, 88, 92, 99, 109].

Included studies

A detailed summary of all included studies is presented in Table 1 for deprescribing polypharmacy (three or more medications or classes) and Table 2 for deprescribing individual targets, and a description of each included study is presented in Results S1. These included studies are summarized in tables based on study design and sorted by deprescribing target (Table 3, Tables S2 and S3).

Study design

Included studies were RCTs (participants = 17 428; studies = 56) [32, 36–38, 40–43, 45–50, 53, 55, 57–59, 62, 63, 68, 76–78, 81, 82, 84, 86, 88, 90, 92, 99, 102, 106, 112, 116, 118–120, 123, 129, 135, 142–145, 147, 149, 152, 157, 159, 161], comparative studies with a concurrent control group (participants = 14 522; studies = 22) [31, 33, 34, 39, 44, 51, 52, 54, 56, 60, 64, 66, 69–75, 79–81, 83, 87–89, 91, 93–98, 101, 104, 105, 107–109, 111, 113, 114, 117, 122, 124–126, 132–134, 137, 139–141, 146, 148, 150, 156, 158, 160, 162], and comparative studies without a concurrent control group (participants = 2207; studies = 37) [33, 34, 39, 44, 51, 56, 64, 66, 69, 71–75, 79, 83, 87–89, 91, 93–96, 98, 104, 105, 107–109, 113, 117, 124, 126, 134, 140, 141, 148, 156, 160]. Follow-up was for a weighted mean (SD) of 15.5 ± 17.4 months.

Participants

The 34 143 participants had a mean age of 73.8 ± 5.4 years, and 51.8% were male. The mean age was over 80 years in 38 studies (4833 participants) [33–35, 37–40, 44–46, 50, 62, 74, 78–80, 84, 86, 94, 108–110, 112, 119, 120, 123]. Thirty-three studies included people living with dementia (6090 participants) [34, 36, 37, 40, 45, 50, 62, 63, 77–81, 94, 102, 107, 109, 110, 112, 120, 123, 131, 133], and another six studies were unclear whether they included participants living with dementia (429 participants) [38, 55, 74, 145, 150, 160].

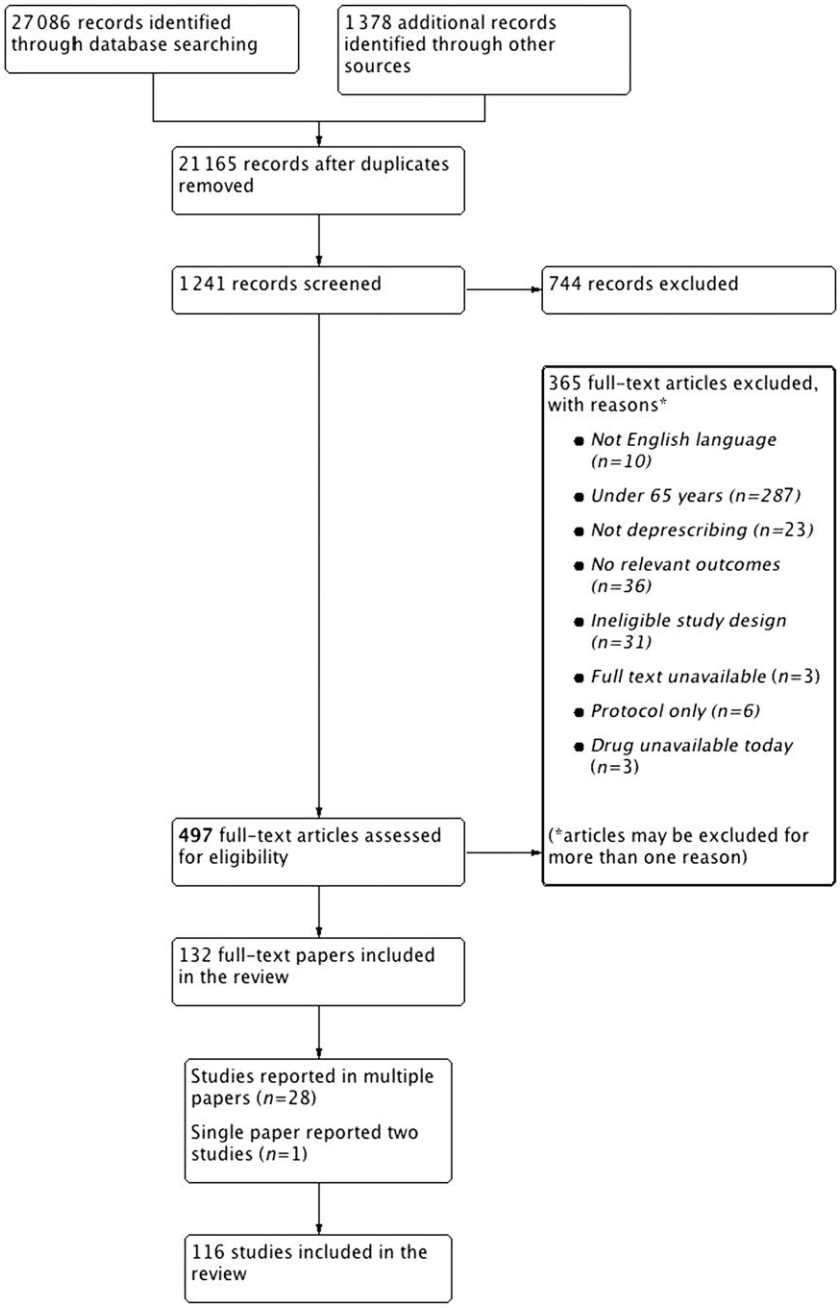

Figure 1
Selection process for included papers

Setting. Fourteen studies were set in hospital [34, 46, 55, 60, 64, 77, 80, 94, 99, 101, 111, 119, 145], 29 in residential aged care facilities [36, 37, 39, 40, 44, 45, 50, 51, 74, 78, 83, 86, 93, 107, 108, 112, 120, 123, 131, 133, 137, 139, 146, 147, 149, 155, 160, 162], and 73 were community based, which included outpatient facilities, general practice and retirement villages [31–33, 41–43, 47–49, 52–54, 56–59, 62, 63, 65, 66, 68–73, 76, 79, 81, 82, 84, 87–92, 95–98, 102, 104–106, 109, 110, 113, 114, 116–118, 122, 124–126, 129, 132, 134, 135, 140–144, 150, 152, 156–159, 161]. One study included participants based in the community and residential aged care [38], and another was based in community and hospital [75].

Interventions

Deprescribing single medications was the most common type of intervention investigated. These included deprescribing (i) a single medication (e.g. atenolol) [31, 41, 42, 49, 51, 54, 56, 60, 62–65, 69–71, 74, 81, 90, 92, 104, 106, 108, 109, 117, 118, 129, 134, 135, 140, 144, 147, 158, 160, 161]; (ii) a single pharmacological class (e.g. beta-blockers) [52, 53, 59, 82,

Table 1

Characteristics of included studies deprescribing polypharmacy (three or more drugs or drug classes). Presented in order of study design (highest level of evidence to lower levels of evidence) and then chronological order

Reference	Intervention type	Tool to identify targets	Study design	Country	Setting	Follow-up duration (months)	Number of participants enrolled	Gender male (Percentage)	Mean age of participants in years	Includes participants with dementia	Outcomes
Potter *et al.* [123]	Investigator-initiated deprescribing – doctor led (patient-specific)	Modified Good Palliation-Good Practice tool	Randomized controlled study	Australia	Residential care	12	95	48	84.3	Yes	Median number of regular medicines Cognitive function Independence in activities of daily living Falls Fractures Sleep quality Bowel function Quality of life Mortality
Dalleur *et al.* [55]	Medication-review by multidisciplinary team to recommend deprescribing targets (patient-specific)	STOPP criteria	Randomized controlled study	Belgium	Hospital	12	158	34	Not stated - median: 84 years	Unclear - 26 participants are described as having a 'cognitive disorder'	Proportion of potentially inappropriate medicines ceased between hospital admission and discharge Characteristics associated with discontinuation of potentially inappropriate medicines at discharge Proportion of potentially inappropriate medicines that were still discontinued 1 year after discharge Clinical significance of the STOPP-related recommendations Mortality
García-Gollarte *et al.* [78]	Education to nursing home physicians	STOPP/START criteria	Randomized controlled study	Spain	Residential care	6	1018	73	84.4	Yes, 1010 (99%)	STOPP/START criteria – participants with at least one item Falls

(continues)

Table 1
(Continued)

Reference	Intervention type	Tool to identify targets	Study design	Country	Setting	Follow-up duration (months)	Number of participants enrolled	Gender male (Percentage)	Mean age of participants in years	Includes participants with dementia	Outcomes
											Delirium, number of episodes Mortality Physician visits Emergency department visits Hospital in-patient days
Pitkala *et al.* [120]	Education to nursing staff at aged care facilities	Beers Criteria	Randomized controlled study	Finland	Residential care	12	227	29	82.9	Yes	Proportion of persons using inappropriate, anticholinergic or more than two psychotropic drugs Change in the mean number of inappropriate, anticholinergic and psychotropic drugs Number of hospitalizations Ambulatory service utilization 15D HRQOL measure Mortality
Beer *et al.* [38]	Investigator-initiated deprescribing – doctor led (patient-specific)	Pre-specified list of target medications	Randomized controlled study	Australia	Residential care Community	3	44	32	81	Unclear – mean MMSE 27 ± 2 so may include participants with mild dementia	Short-form 36 health survey EuroQol 5-D visual analog scale Sleep quality MMSE Medication Adherence Mortality
Gallagher *et al.* [77]	Medication-review by doctors to recommend deprescribing targets (patient-specific)	STOPP/START criteria	Randomized controlled study	Ireland	Hospital	6	400	45	Unstated (median 74.5)	Yes	Medicine Appropriateness Index Assessment of Underutilization indexSTOPP/START criteria – participants with

(continues)

Table 1
(Continued)

Reference	Intervention type	Tool to identify targets	Study design	Country	Setting	Follow-up duration (months)	Number of participants enrolled	Gender male (Percentage)	Mean age of participants in years	Includes participants with dementia	Outcomes
											at least one item Falls All cause mortality Duration of initial hospital stay Hospital readmission General practitioner visits
Gnjidic *et al.* [84]	Medication-review to recommend deprescribing targets (patient-specific)	Drug Burden Index	Randomized controlled study	Australia	Community	3	115	73	80.4	No	Frequency of use of Drug Burden Index regularly scheduled and/or as-needed drugs across different drug classes at baseline and prescribing change at follow-up Impact of study intervention on prescribing change Barriers to reducing regularly scheduled Drug Burden Index drugs Mortality
Weber *et al.* [159]	Medication-review by pharmacist or doctor to recommend deprescribing targets (patient-specific)	No identification method tool specified	Randomized controlled study	USA	Community	15	620	21	76.9	Yes	Medication use Falls, percentage of participants who reported at least one fall Mortality
Allard *et al.* [32]	Medication-review to recommend deprescribing targets (patient-specific)	List of potentially inappropriate medications list developed by the Quebec Committee on Drug Use	Randomized controlled study	Canada	Community	12	503	17	80.4	No	Total number of potentially inappropriate medicines per person Total number of medicines

(continues)

Table 1
(Continued)

Reference	Intervention type	Tool to identify targets	Study design	Country	Setting	Follow-up duration (months)	Number of participants enrolled	Gender male (Percentage)	Mean age of participants in years	Includes participants with dementia	Outcomes
		in the Elderly									prescribed per person Number of subjects with at least one potentially inappropriate medicine Mortality
Campbell *et al.* [47]	General Practitioner to identify participants, investigator-led intervention – doctor led (patient-specific)	Pre-specified list of target medications (benzodiazepine, any other hypnotic or any antidepressant or major tranquilizer)	Randomized controlled study	New Zealand	Community	10	93	24	74.6	No	Falls
Tabloski *et al.* [142]	Investigator-initiated deprescribing – nurse-led (patient-specific)	Pre-specified list of target medications (sedative-hypnotic medications)	Randomized controlled study	USA	Community	1.25	20	0	77.5	No	Sleep complaints Time in bed (minutes) Sleep latency (minutes) Total sleep time (minutes) Sleep (minutes) Sleep efficiency (score) Longest Sleep Period (minutes) Number of wakes Wake After Sleep Onset (minutes)
Hanlon *et al.* [88]	Investigator-initiated deprescribing – pharmacist led (patient-specific)	Medicines Appropriateness Index	Randomized controlled studyAND Before-and-after study (2 papers)	USA	Community	12	207	61	Unstated (median 69 years)	No	Medicine Appropriateness Index Health-related quality of life using Short-form 36 health survey Adverse drug reactions

(continues)

Table 1
(Continued)

Reference	Intervention type	Tool to identify targets	Study design	Country	Setting	Follow-up duration (months)	Number of participants enrolled	Gender male (Percentage)	Mean age of participants in years	Includes participants with dementia	Outcomes
											Patient medication compliance and knowledge Adverse drug withdrawal effects Medicines associated with adverse drug withdrawal effects Predictive factors of adverse drug withdrawal effects Mortality
Pitkala *et al.* [122]	Investigator-initiated deprescribing – doctor-led (patient-specific)	Health professional judgment (no list, criteria, or tool used)	Pseudo-Randomized controlled study	Finland	Community	Unstated	174	34	77	Yes	Drug utilization
Salonoja *et al.* [132]	Investigator-initiated deprescribing – doctor-led (patient-specific)	Three pre-specified lists of target medications based on falls-risk increasing medications and psychotropic medications	Nonrandomized controlled study	Finland	Community	48	591	11	Unstated (minimum age 65)	No	Number of falls in total (i.e. one person may have had one or more falls, so can contribute more than once) Number of people falling (i.e. just if the person has fallen at least once) Risk of a fall that required medical treatment (regression – deprescribing group is reference group)
Muir *et al.* [111]	Medication-review by doctor after provided with medication reconciliation and medicine list (patient-specific)	Health professional judgment (no list, criteria, or tool used)	Nonrandomized controlled study	USA	Hospital	1.25 to 1.75	836	99	65.2	No	Change in medications and doses Number of admission and

(continues)

Table 1
(Continued)

Reference	Intervention type	Tool to identify targets	Study design	Country	Setting	Follow-up duration (months)	Number of participants enrolled	Gender male (Percentage)	Mean age of participants in years	Includes participants with dementia	Outcomes
											discharge medications by drug class Proportions of patients taking individual medications
Van Der Velde *et al.* [150, 151]	Investigator-initiated deprescribing – doctor-led (patient-specific)	Pre-specified list of target medications (falls-risk increasing medications)	Case-control Study	The Netherlands	Community	2	141	26	78.4	Unclear	Risk of a fall during follow-up Mobility testing
Yeh *et al.* [162]	Education to primary care physicians at nursing homes via mail (education)	Clinician-Rated Anticholinergic Score (CR-ACHS) and pre-specified list of target medications (Beta-blockers, benzodiazepines, antidepressants, atypical antipsychotics)	Prospective cohort study	Taiwan	Residential care	3	67	100	83.4	Yes	Clinician-Rated Anticholinergic Score MMSE Modified Bartel Index Hospital admissions Mortality
Garfinkel *et al.* [80]	Investigator-initiated deprescribing – doctor led (patient-specific)	Good Palliation-Good Practice tool	Prospective cohort study	Israel	Hospital	12	190	31	81.2	Yes	Successful deprescribing Mortality Admitted to acute care facility Medicine cost
Kroenke *et al.* [101]	Medication-review by doctors to recommend deprescribing targets (patient-specific)	Health professional judgment (no list, criteria, or tool used)	Prospective cohort study	USA	Hospital	6	79	59	72.3	No	Mean number of medicines Daily dose
Garfinkel *et al.* [79]	Investigator-initiated deprescribing – doctor led (patient-specific)	Good Palliation-Good Practice tool	Before-and-after study	Israel	Community	19.2	70	39	82.8	Yes	Symptom recurrence after discontinuation Successful deprescribing rate Global assessment scale Cognitive function - MMSE Hospital admission

(continues)

Table 1
(Continued)

Reference	Intervention type	Tool to identify targets	Study design	Country	Setting	Follow-up duration (months)	Number of participants enrolled	Gender male (Percentage)	Mean age of participants in years	Includes participants with dementia	Outcomes
											Commenced recommended new medicine
Gerety *et al.* [83]	Medication review by pharmacists to recommend deprescribing targets (patient-specific)	Health professional judgment (no list, criteria, or tool used)	Before-and-after study	USA	Residential care	6	132	Unstated	70.1	No	Incidence and severity of adverse drug events Incidence and severity of adverse drug withdrawal events Demographic factors associated with risk of adverse drug events and adverse drug withdrawal events. Change in medicine use

Table 2

Characteristics of included studies for individual deprescribing targets (one or two drug or therapeutic classes). Presented in order of drug class (by Anatomical Therapeutic Classification codes), then by study design (highest level of evidence to lower levels of evidence), *and then in chronological order*

Reference	Deprescribing target	Study design	Country	Setting	Follow-up duration (months)	Number of participants enrolled	Gender male (percentage)	Mean age of participants in years	Includes participants with dementia	Outcomes
Reeve *et al.* [126]	Proton pump inhibitors	Before-and-after study	Australia	Community	6	6	33	70	No	Proton pump inhibitor use Adverse drug withdrawal effects
Sjöblom *et al.* [137]	Insulin, oral antiglycaemic	Prospective cohort study	Sweden	Residential care	6	98	42	84.4	No	Glycaemic control HbA1C Clinical outcomes All cause mortality
Henschke *et al.* [93]	Potassium supplementation	Before-and-after study	Canada	Residential care	3	33	100	70	No	Potassium levels Distributions of erythrocyte K values
Yedidya *et al.* [161]	Clopidogrel	Randomized controlled study	Israel	Community	24	20.00	75	65.9	No	Hematological endpoints (surrogate endpoints) e.g. platelet aggregation Clinical events (bleeding or Ischemic)
Sambu *et al.* [134]	Clopidogrel	Before-and-after study	England	Community	1	38	82	65.9	No	Clinical events Concomitant medical treatment and platelet reactivityThromboxane B2 levelsAdenosine diphosphate (ADP)-induced platelet aggregation Arachidonic acid-induced platelet aggregation Inflammatory biomarkers
Derogar *et al.* [60]	Aspirin	Retrospective cohort study	Sweden	Hospital	24	118	60	unstated (median 79)	No	Death Acute cardiovascular events Hospitalization due to endoscopically verified Recurrent peptic ulcer bleeding
Patel *et al.* [118]	Rivaroxaban	Randomized controlled study	International	Community	0.1 to 1	5882	unstated	Unstated (median 73)	No	Stroke, noncentral nervous system, embolism, myocardial infarction, or vascular death Major bleeding
Dawson *et al.* [57]	Cilostazol, pentoxifylline	Randomized controlled study	USA	Community	7	60	65	66.4	No	Maximal walking distance Pain-free walking distance Resting Doppler limb pressures Safety and tolerability of the study medications were assessed for all subjects with clinical laboratory monitoring, electrocardiography, physical examination,

(continues)

Table 2
(Continued)

Reference	Deprescribing target	Study design	Country	Setting	Follow-up duration (months)	Number of participants enrolled	Gender male (percentage)	Mean age of participants in years	Includes participants with dementia	Outcomes
										vital signs, and adverse event reporting
Moonen *et al.* [110]	Antihypertensives	Randomized controlled study	Netherlands	Community	4	385	46	81.1	Yes	Systolic blood pressure Diastolic blood pressure Cognition Depression Functional status Quality of life
Jondeau *et al.* [99]	Antihypertensives (Beta-blocker)	Randomized controlled study	France	Hospital	3	169	57	72.3	No	Dyspnea and general well-being BNP plasma levels Duration of hospitalizations Re-hospitalization rate Death rate Successful deprescribing
Hearing *et al.* [92]	Antihypertensives (atenolol)	Randomized controlled study	England	Community	0.5	37	38	72.3	No	Cognitive Drug Research Computerized Cognitive Assessment System
Espeland *et al.* [68]; **Kostis *et al.*** [100]	Antihypertensive	Randomized controlled study	USA	Community	26.7	975	48	65.8	No	Predictors of successful deprescribing Cardiovascular events Reported rates of cardiovascular events The probability of remaining normotensive without receiving antihypertensive medication
Nelson *et al.* [114]	Antihypertensive	Case-control study AND Before-and-after study (2 papers)	Australia	Community	12	6833	44	71.9	No	Remaining normotensive Characteristics predictive of remaining normotensive
Lernfelt *et al.* [105]	Antihypertensive	Historical cohort study	Sweden	Community	48	25	40	Unstated (inclusion criteria mean that participants were all over 70 years)	No	Blood pressure Successful deprescribing Left ventricular function and other surrogate measures
Hajjar *et al.* [87]	Antihypertensive	Before-and-after study	USA	Community	0.75	53	36	71	No	Adverse drug withdrawal effects Blood pressure (systolic and diastolic)
Jimenez-Candil *et al.* [98]	Antihypertensive (ACEI)	Before-and-after study	Spain	Community	3	22	59	71.6	No	Exercise-induced blood pressure response (fall or failure to rise) Exercise duration Haemodynamic response
Alsop *et al.* [33]	Antihypertensive	Before-and-after study	England	Community	30	338	25	80	No	Symptom improvement Successful deprescribing

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Table 2
(Continued)

Reference	Deprescribing target	Study design	Country	Setting	Follow-up duration (months)	Number of participants enrolled	Gender male (percentage)	Mean age of participants in years	Includes participants with dementia	Outcomes
Ekbom *et al.* [66]	Antihypertensive	Before-and-after study	Sweden	Community	60	333	32	75.2	No	Probability of restarting antihypertensive therapy Total mortality Cardiovascular events Comparison of death hazard between the three states and that of the normal Swedish population, matched for age and sex Major reasons for restarting treatment
Fotherby *et al.* [75]	Antihypertensive	Before-and-after study	England	Community Hospital	12	78	63	76	No	Successful deprescribing
Nadal *et al.* [113]	Antihypertensive	Before-and-after study	Sweden	Community	36	86	38	74	No	Reverted to hypertensive during the one month washout period Successful deprescribing from one month to 36 months Differences in those that restarted and those who were deprescribed successfully Serious adverse events
Hansen *et al.* [89]	Antihypertensive	Before-and-after study	Denmark	Community	12	169	unstated	75	No	Successful deprescribing Screening normotensive
Fair [71]	Digoxin	Before-and-after study	Scotland	Community	4- 11	32	28	74.2	No	Successful deprescribing Adverse drug withdrawal events Digoxin dose when reinstated
Macarthur [108]	Digoxin	Before-and-after study	Canada	Residential care	16	14	0	82.5	No	Successful deprescribing Clinical outcomes
Wilkins [160]	Digoxin	Before-and-after study	USA	Residential care	Unstated	19	16	84.9	Unclear	Clinical outcomes after deprescribing Pulse Weight
Daly and Edwards [56]	Digoxin	Before-and-after study	Scotland	Community	1	15	40	74.7	No	Successful deprescribing New incidences of heart failure New or increase prescription of diuretics
Sommers *et al.* [140]	Digoxin	Before-and-after study	South Africa	Community	15	20	30	73	No	Clinical evaluation Successful deprescribing
Fonrose *et al.* [74]	Digoxin	Before-and-after study	USA	Residential care	Unstated	31	10	83	Unclear	Successful deprescribing Adverse events Death

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Reference	Deprescribing target	Study design	Country	Setting	Follow-up duration (months)	Number of participants enrolled	Gender male (percentage)	Mean age of participants in years	Includes participants with dementia	Outcomes
van Kraaij *et al.* [152]	Diuretic	Randomized controlled study	The Netherlands	Community	Unstated	32	47	75	No	Successful deprescribing Changes at three months Blood pressure Temporary difference
Walma *et al.* [157]	Diuretic	Randomized controlled study	The Netherlands	Community	6	202	25	76	No	Successful deprescribing Changes in systolic and diastolic blood pressures
De Jonge *et al.* [59]	Diuretic	Randomized controlled study	The Netherlands	Community	1.5	63	13	unstated (minimum age 65)	No	Ankle oedema Successful deprescribing Determinants of oedema after deprescribing
Myers *et al.* [112]	Diuretic	Randomized controlled study	Canada	Residential care	12	77	78	Females: 84.5 Males: 79.1	Yes	Hypertension Congestive heart failure Biochemical abnormalities Weight Ankle oedema Events
Burr *et al.* [46]	Diuretics & potassium supplementation	Randomized controlled study	USA	Hospital	3	106	12	80.5	No	Blood pressure and pulse Distribution of plasma potassium levels Distribution of plasma urea levels Changes in ankle oedema
Straand *et al.* [141]	Diuretic	Before-and-after study	Norway	Community	6	33	24	82	No	Successful deprescribing
Walma *et al.* [156]	Diuretic	Before-and-after study	The Netherlands	Community	6	15	27	78	No	Successful deprescribing Blood pressure Heart failure score Weight Ankle circumference
George *et al.* [82]	Nitrates	Randomized controlled study	Israel	Community	3	120	55	65.5	No	Successful deprescribing Relapse Characteristics of participants who relapsed Cardiovascular events Death
Jackson *et al.* [95]	Nitrates	Before-and-after study	England	Community	3	55	unstated	65.2	No	Successful deprescribing Exacerbation of angina Five-item Sexual Health Inventory for Men
Kutner *et al.* [102]	Statin	Randomized controlled study	USA	Community	12	381	55	74.8	Yes	Survival at 60 days Time to death Time to first cardiovascular-related event Cost savings Quality of life Symptoms

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Reference	Deprescribing target	Study design	Country	Setting	Follow-up duration (months)	Number of participants enrolled	Gender male (percentage)	Mean age of participants in years	Includes participants with dementia	Outcomes
										Number of nonstatin medications Likelihood to receive the recommended care
Lin *et al.* [106]	Benign prostatic hypertrophy treatment (alpha-blocker and 5-alpha–reductase inhibitor therapy)	Randomized controlled study	Taiwan	Community	12	240	0	78.3 and 74.3	No	Successful deprescribing Progression of benign prostatic hypertrophy symptoms Progression of lower urinary tract symptoms Maximum flow rate (Q_{max}) Volume International Prostate Symptom Score –Storage subscore International Prostate Symptom Score – Voiding subscore International Prostate Symptom Score – Total score Quality of life Postvoid residual urine Total prostate volume Transition zone index Serum prostate-specific antigen
Coll and Abourizk [51]	Levothyroxine	Before-and-after study	USA	Residential care	3	22	9	78	No	Successful deprescribing Adverse effects
Cibere *et al.* [49]	Glucosamine	Randomized controlled study	Canada	Community	6	137	44	65	No	Disease flare Function measured using Western Ontario and McMaster Universities Osteoarthritis Index Quality of life measured using EuroQol 5-D utility and visual analog scale
Esselinckx *et al.* [69]	Prednisolone	Before-and-after study	England	Community	Unstated	18	39	69	No	Successful deprescribing after abrupt discontinuation Laboratory results after gradual discontinuation Laboratory outcomes after abrupt discontinuation Successful deprescribing after titrated withdrawal Adverse effects
Black *et al.* [41]	Bisphosphonates (zoledronic acid)	Randomized controlled study	International	Community	60	1099	0	73.7	No	Bone mass density in femoral neck – percentage

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Reference	Deprescribing target	Study design	Country	Setting	Follow-up duration (months)	Number of participants enrolled	Gender male (percentage)	Mean age of participants in years	Includes participants with dementia	Outcomes
										changebone mass density of spine and total hip Changes from pretreatment levels over 6 years (baseline to 6 years) Biochemical bone turnover markers Fractures (clinical, nonvertebral, clinical spine, and morphometric vertebral) Adverse events
Black *et al.* [42]	Bisphosphonates (alendronate)	Randomized controlled study	USA	Community	36	1233	0	75.5	No	Change in bone mineral density for duration of deprescribing Biochemical markers of bone turnover Incidence of fracture Histomorphometry/ Micro–computed tomography Histomorphometric findings from iliac crest biopsies Adverse events Antifracture efficacy of continued alendronate in subgroups defined by femoral neck T-score and vertebral fracture status
Watts *et al.* [158]	Bisphosphonate (risedronate)	Nonrandomized controlled study	USA	Community	12	759	0	68.5	No	Bone mass density of the femoral neck Bone mass density of the lumbar spine Urine NTX Serum bone-specific alkaline phosphatase New vertebral fractures New nonvertebral fractures
da Silva *et al.* [54]	Bisphosphonates (alendronate)	Prospective cohort study	Brazil	Community	12	90	0	71.0	No	Bone mass density Fractures Bone turnover markers Parathyroid and calcium and vitamin D levels
Eastell *et al.* [65]	Bisphosphonates (risedronate)	Prospective cohort study	80 European and Australian centers	Community	12	61	0	66.9	No	Adverse events Bone mass density change from baseline Bone markers change from baseline

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Reference	Deprescribing target	Study design	Country	Setting	Follow-up duration (months)	Number of participants enrolled	Gender male (percentage)	Mean age of participants in years	Includes participants with dementia	Outcomes
OrrWalker *et al.* [117]	Bisphosphonates (Pamidronate)	Before-and-after study	New Zealand	Community	48	22	0	65.9	No	Change in bone mass density
Leder *et al.* [104]	Teriparatide	Two single arm studies (without concurrent control group)	USA	Community	42	65	54	65	No	Bone mass density (PA spine, femoral neck, total hip, and trabecular spine) Biochemical markers of bone turnover
Radford *et al.* [125]	Calcium supplement	Nonrandomized controlled study	New Zealand	Community	60	1408	100	74.1	No	Death Any fracture Osteoporotic fracture Forearm fracture Vertebral fracture Hip fracture Myocardial infarction Stroke Bone mass density
Dawson-Hughes *et al.* [58]	Calcium, vitamin D	Randomized controlled study	USA	Community	60	325	39	74	No	Vertebral fractures Nonvertebral fracturesbone mass density testing Laboratory measurements
Gallagher *et al.* [76]	Calcitriol and/or hormone replacement therapy	Randomized controlled study	USA	Community	6	489	0	71.8	No	Mean bone mass density for spine, total body, total femur, total hip, trochanter Urinary N-telopeptides Serum osteocalcin Serum parathyroid hormone Serum 25OHOD levels
Tariot *et al.* [144]	Carbamazepine	Randomized controlled study	USA	Community	0.75	51	unstated	86	Yes	Brief Psychiatric Rating Scale Physical Self-Maintenance Scale Clinical Global Impressions scale MMSE Adverse effects
Drimer *et al.* [64]	Anticholinergic medicine (biperiden)	Before-and-after study	Israel	Hospital	0.3	27	48	65.7	No	Adverse drug withdrawal effects Mental status Alzheimer's disease Assessment scale – cognitive sub-scale results
Tse *et al.* [147]	Levodopa	Randomized controlled study	USA	Residential care	1	11	36	82	Yes	MMSE Unified Parkinson's Disease Rating Scale Nursing assistant Behavioural detection form Hoehn and Yahr staging scale Motor and behavioural deterioration as assessed by the blinded floor physician

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Reference	Deprescribing target	Study design	Country	Setting	Follow-up duration (months)	Number of participants enrolled	Gender male (percentage)	Mean age of participants in years	Includes participants with dementia	Outcomes
Cunnington *et al.* [52]	Dopamine agonist	Case-control study	Scotland	Community	Unstated	46	67	70	No	Presence of dopamine agonist withdrawal syndrome
Hauser *et al.* [91]	Levodopa/carbidopa and bromocriptine	Before-and-after study	USA	Community	0.5	31	unstated	69.2	No	Adverse drug withdrawal effects Unified Parkinson's disease rating scale
Hardy *et al.* [90]	Lithium	Randomized controlled study	Canada	Community	24	12	17	79	No	Serum creatinine Serum thyroid-stimulating hormone Mean composite side effect symptom scores Depression
Fahy and Lawlor [70]	Lithium	Case-control study	Ireland	Community	19.5	21	5	77.6	No	Time to relapse or follow-up time Response to reintroduction of therapy
Flint and Rifat [73]	Lithium, antidepressants	Before-and-after study	Canada	Community	24	21	unstated	74.4	No	Depression recurrence Predictors of recurrence Response to reintroduction of therapy
Bergh *et al.* [40]	Antidepressants	Randomized controlled study	Norway	Residential care	6	128	25	85.3	Yes	Cornell scale Neuropsychiatric Index Quality of life – Alzheimer's disease scale Unified Parkinson's disease rating scale Severe impairment battery Lawton and Brody's physical self-maintenance scale Weight Change in number of psychotropic drugs taken Oxazepam (mg)/day in last 21 days Change in number of falls per day in the last 21 days Clinical dementia rating Death
Ulfvarson *et al.* [149]	Antidepressants	Randomized controlled study	Sweden	Residential care	12	70	33	84.1	No	Montgomery Asberg depression rating scale Global assessment of functioning Health index Symptom assessment form Symptoms of side effects of Selective Serotonin Reuptake Inhibitor (SSRI) drug treatment Death at one year

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Reference	Deprescribing target	Study design	Country	Setting	Follow-up duration (months)	Number of participants enrolled	Gender male (percentage)	Mean age of participants in years	Includes participants with dementia	Outcomes
Bergh and Engedal [39]	Antipsychotics and antidepressants	Before-and-after study	Norway	Residential care	6	23	8	84.1	No	Neuropsychiatric Index Cornell's Depression Score Severe impairment battery Unified Parkinson Disease Rating Scale
Lindström *et al.* [107]	Antidepressants	Before-and-after study	Sweden	Residential care	Unclear, perhaps up to 28 weeks	119	unstated	Unstated (age group 65–74 years: 9 participants; age group 75–84 years: 45 participants; age group 85 years and over: 65 participants)	Yes	Successful deprescribing Predictors of successful deprescribing assessed using the Montgomery Asberg Depression Rating Scale
Devanand *et al.* [62]	Antipsychotic (risperidone)	Randomized controlled study	USA	Community and Residential care	11	110	40	80.3	Yes	Adverse events Relapse Simpson–Angus Abnormal Involuntary Movement Scale Treatment Emergent Symptoms Scale Alzheimer's Disease Assessment Scale – cognitive Physical Self-Maintenance Scale MMSE scores Increases in body weight
Devanand *et al.* [63]	Typical antipsychotic	Randomized controlled study	USA	Community	10	44	43	75.0	Yes	Relapse measured by Clinical Global Impression-Change Behavior measured by MMSE, modified Blessed Functional Activity Scale Death Brief Psychiatric Rating Scale Unified Parkinson's Disease Rating Scale
Ballard *et al.* [35, 36]	Antipsychotics	Randomized controlled study	England and Scotland	Residential care	3	100	19	83.6	Yes	Survival Successful deprescribing Total Severe Impairment Battery score (change from baseline to 6 mo) Standardized MMSE FAS test of Verbal Fluency Bristol Activities of Daily Living Scale Sheffield Test for Acquired Language Disorders Neuropsychiatric Index Modified Unified Parkinson's Disease Rating Scale

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Reference	Deprescribing target	Study design	Country	Setting	Follow-up duration (months)	Number of participants enrolled	Gender male (percentage)	Mean age of participants in years	Includes participants with dementia	Outcomes
										Clinician's Global Impression of Change Post-Hoc Additional Exploratory Sensitivity Analysis
Ballard *et al.* [37]	Antipsychotics	Randomized controlled study	England	Residential care	12	165	24	84.8	Yes	Quality of life (measured as differences in change in behavioral symptoms) Change in Neuropsychiatric Inventory
Ruths *et al.* [131]	Antipsychotic	Randomized controlled study	Norway	Residential care	1	30	20	83.4	Yes	Medication useSleep/wake activity Neuropsychiatric inventory Successful deprescribing Deaths
Van Reekum *et al.* [155]	Antipsychotic	Randomized controlled study	Canada	Residential care	6	34	50	84.4	Yes	Behaviour assessed by the Behavioral Pathology in Alzheimer's Disease Rating Scale, Neuropsychiatric Inventory, Retrospective Overt Aggression Scale Cognitive Function assessed by the MMSE and Mattis Dementia Rating Scale Functional level assessed by the Blessed Dementia Scale – activities of daily living and motivational behavior sub-scale Extrapyramidal symptoms assessed by the Extrapyramidal Symptom Rating Scale Clinical global impression scale Behavioural deteriorations leading to study withdrawal Lorazepam use as required
Bridges-Parlet *et al.* [45]	Antipsychotic	Randomized controlled study	USA	Residential care	1	36	19	81.7	Yes	Episodes of physically aggressive behaviour Adverse drug withdrawal events
Somani [139]	Typical antipsychotic	Nonrandomized controlled study	USA	Residential care	8	57	25	85	Yes	Presence of dyskinesias Severity withdrawal dyskinesias Reversible of withdrawal dyskinesias Behavioural relapse Falls

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Reference	Deprescribing target	Study design	Country	Setting	Follow-up duration (months)	Number of participants enrolled	Gender male (percentage)	Mean age of participants in years	Includes participants with dementia	Outcomes
										Adverse drug withdrawal events Successful deprescribing
Thapa *et al.* [146]	Typical antipsychotic	Nonrandomized controlled study	USA	Residential care	6	334	22	82.6	Yes	Psychotropic medicine use Behavioural problems assessed using the nursing home Behaviour Problem Scale Psychiatric symptoms assessed using the Brief Psychiatric Rating Scale Function Activities of Daily Living assessed using Lawton's Physical Self-Maintenance Scale Cognition assessed using MMSE Geriatric Depression Scale Abnormal Involuntary Movement Scale
Horwitz *et al.* [94]	Typical antipsychotic	Comparative study with two single arms	USA	Hospital	12	53	17	82.7	Yes	Discontinued antipsychotic MMSE Sandoz Clinical Assessment Geriatric scale Overt Aggression Scale Functional status measured by the Minimum Data Set Plus of the New York State Department of Health Psychotic symptoms as judged by a psychiatric nurse-specialist Quantified Neurological Exam Abnormal Involuntary Movement Scale
Azermai *et al.* [34]	Antipsychotics	Before-and-after study	Belgium	Hospital	1	40	53	84	Yes	Successful deprescribing Neuropsychiatric Index Possible adverse drug withdrawal effects
Fernandez *et al.* [72]	Atypical antipsychotic	Before-and-after study	USA	Community	Unstated	6	67	78	No	Relapse
Cohen-Mansfield *et al.* [50]	Benzodiazepine, typical antipsychotics	Randomized controlled study	USA	Residential care	5	58	26	86	Yes	Brief Psychiatric Rating Scale Mansfield Agitation Inventory FunctionAdverse effects Global Impression Accuracy of staff prediction as to whether the withdrawal would be successful

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Reference	Deprescribing target	Study design	Country	Setting	Follow-up duration (months)	Number of participants enrolled	Gender male (percentage)	Mean age of participants in years	Includes participants with dementia	Outcomes
Tannenbaum *et al.* [143]	Benzodiazepine	Randomized controlled study	Canada	Community	6	303	31	75.0	No	Successful deprescribing Adverse drug withdrawal effects
Curran *et al.* [53]	Benzodiazepine	Randomized controlled study	England	Community	12	138	29	77	No	Successfully deprescribing Cognitive and psychomotor tests Benzodiazepine withdrawal scale visual analog scalesGeriatric Depression Scale Mood factors Health-related quality of life - sub-scales of the Medical Outcomes Study Short-form 36 questionnaire
Petrovic *et al.* [119]	Benzodiazepine	Randomized controlled study	Belgium	Hospital	12	40	33	81	No	Successful deprescribing Pittsburgh Sleep Quality Index score Benzodiazepine Withdrawal Symptom Questionnaire
Habraken *et al.* [86]	Benzodiazepine	Randomized controlled study	Belgium	Residential care	12	55	18	84	No	Level of daily functioning Adverse drug withdrawal effects
Tham *et al.* [145]	Benzodiazepine	Randomized controlled study	Ireland	Hospital	Unstated	36	14	81.7	Unclear	Hours of sleep Number of times awake
Salzman *et al.* [133]	Benzodiazepine	Prospective cohort study	USA	Residential care	12	25	20	83	Yes	Memory Dementia Mood Assessment Scale to measure changes in sleep and affect (depression and anxiety) Successful deprescribing
Puustinen *et al.* [124]	Benzodiazepine	Historical cohort study	Finland	Community	6	89	34	66.7	No	Cognitive performance using the computerized test battery of attention, vigilance and controlled psychomotor processing
Tsunoda *et al.* [148]	Benzodiazepine	Before-and-after study	Japan	Residential care	2	30	57	79.1	Yes	Stability of body Neuropsychological status Critical Flicker Fusion Test Leeds Sleep Evaluation Questionnaire
Gaudig *et al.* [81]	Anticholinesterase inhibitors (Galantamine)	Randomized controlled study	USA	Community	1.5	798	11	77.9	Yes	Alzheimer's Disease Assessment Scale using the 11-item cognitive sub-scale Safety and tolerability assessments included adverse event monitoring Physical examinations and laboratory testing

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Reference	Deprescribing target	Study design	Country	Setting	Follow-up duration (months)	Number of participants enrolled	Gender male (percentage)	Mean age of participants in years	Includes participants with dementia	Outcomes
Scarpini *et al.* [135]	Anticholinesterase inhibitors (galantamine)	Randomized controlled study	Italy	Community	36	139	40	74.5	Yes	Drop outs Adverse drug events
Minett *et al.* [109]	Anticholinesterase inhibitors (donepezil)	Comparative study with two single arms	England	Community	7.5	24	unstated	81.0	Yes	Clinical outcomes
Rice *et al.* [129]	Prednisolone	Randomized controlled study	USA	Community	6	38	100	72	No	Average number of chronic obstructive pulmonary disease exacerbations Average daily systemic corticosteroid dose Dyspnea index Health-related quality of life Spirometric results Changes in body weight Adverse drug withdrawal effects - symptoms of steroid withdrawal
Adams *et al.* [31]	Tiotropium, inhaled	Nonrandomized controlled study	International	Community	12	921	65	65	No	Medicine use at three weeks after deprescribing Dyspnea Peak Expiratory Flow Rate (morning and evening) Health-related quality of life measured using the St George's Respiratory Questionnaire
Borrill *et al.* [43]	Fluticasone and salmeterol, inhaled	Randomized controlled study	England	Community	1.5	14	unstated	65.0	No	Exacerbations causing dropouts Forced expiratory volume in one second Sputum neutrophil percentage
Choudhury *et al.* [48]	Inhaled corticosteroids	Randomized controlled study	England	Community	12	260	52	67.6	No	chronic obstructive pulmonary disease exacerbation frequency Time to first exacerbation Reported symptoms Peak expiratory flow rate Reliever inhaler use Return to usual steroid inhaler Lung function Health-related quality of life– St George's respiratory questionnaire– EuroQol 5-D total and visual analog scale Adverse effects
O'Brien *et al.* [116]	Inhaled corticosteroids	Randomized controlled study	USA	Community	3	24	100	66.9	No	Exacerbations Chronic Respiratory Disease Questionnaire

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Reference	Deprescribing target	Study design	Country	Setting	Follow-up duration (months)	Number of participants enrolled	Gender male (percentage)	Mean age of participants in years	Includes participants with dementia	Outcomes
Jarad *et al.* [97]	Inhaled corticosteroids	Prospective cohort study	England	Community	2	272	15	66	No	Exacerbations
Jampel *et al.* [96]	Intraocular pressure-lowering medicine	Nonrandomized study	USA	Community	0.2 to 1	603	55	70.3	No	Intraocular pressure percentage increase Intraocular pressure percentage decrease

Table 3
Included study characteristics by deprescribing target (randomized studies)

References	Deprescribing target	Setting	Follow-up duration in months (weighted mean ± standard deviation (SD))	Number of participants randomized	Gender	Age of participants in years (weighted mean ± SD)	Participants with dementia	Withdrawal schedule
Allard *et al.* [32]; **Beer *et al.*** [38]; **Campbell *et al.*** [47]; **Dalleur *et al.*** [55]; **Gallagher *et al.*** [77]; **García-Gollarte *et al.*** [78]; **Gnjidic *et al.*** [84]; **Hanlon *et al.*** [88]; **Pitkala *et al.*** [120]; **Potter *et al.*** [123]; **Tabloski *et al.*** [142]; **Weber *et al.*** [159].	Polypharmacy	Hospital (participants = 558, studies = 2) Community (participants = 1568, studies = 7) Residential aged care (participants = 1365; studies = 4)	9.6 ± 3.8	3500	1961 female, 1539 male	80.3 ± 3.1	Yes (Participants; = 1535; studies = 6)	One study described dose reductions occurring at approximately two-weekly intervals (participants = 95; studies = 1). The withdrawal schedule in two studies as dose reduction at approximately two-weekly intervals (participants = 44; studies = 1) Half dose of psychotropic medicines for one week before ceasing the medicine (participants = 20; studies = 1)STD-Tabloski-1998 Not described (participants = 3341; studies = 9)

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Table 3
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References	Deprescribing target	Setting	Follow-up duration in months (weighted mean ± standard deviation (SD))	Number of participants randomized	Gender	Age of participants in years (weighted mean ± SD)	Participants with dementia	Withdrawal schedule
Yedidya *et al.* [161]	Clopidogrel	Community	24	20	5 female, 15 male	65.9 ± 5.0	No	Abrupt cessation in one group was compared with tapered withdrawal where the dose was changed to 75mg alternate days for four weeks before it was ceased
Patel *et al.* [118]	Rivaroxaban	Community	Not given (range 3 to 30 days)	14,143	5590 female, 8553 male	Not given (Median age of 73)	No	Not described
Dawson *et al.* [57]	Cilostazol 100mg twice-daily and pentoxifylline 400mg three times daily	Community	1.5	60	6 female, 39 male	66.4 ± 7.3	No	Not described
Hearing *et al.* [92] **Jondeau *et al.*** [99]	Beta-blockers	Community (participants = 37; studies = 1) Hospital (participants = 169; studies = 1)	2.6 ± 1.0	206	88 female, 110 male, 8 not stated	72.3 ± 0.0	No	Titrated over one week (participants = 37; studies = 1), Abruptly ceased the beta-blocker (participants = 169; studies = 1).
Moonen *et al.* [110]	Antihypertensive	Community	4	385	208 female, 177 male	81.1 ± 4.3	Yes	Tapered over six weeks until a maximum increase of 20mm Hg in systolic blood pressure
Burr *et al.* [46]; **Myers *et al.*** [112]; **van Kraaij *et al.*** [152]; **Walma *et al.*** [157] **De Jonge *et al.*** [59]	Diuretics	Community (participants = 297; studies = 3) Hospital (participants =1 06; studies = 1) Residential aged care (participants = 77; studies = 1)	5.7 ± 3.3	480	425 female, 147 male	77.6 ± 2.1	Yes (participants = 77; studies = 1)	Dose halved for one week then placebo, though in one study participants who were on 80mg frusemide had the daily dose halved for two weeks (participants 234 =; studies = 2) Not described (participants = 246; studies = 3)
George *et al.* [82]	Nitrates	Community	3	102	54 female, 66 male	65.5 ± 11	No	Not described
Kutner *et al.* [102]	Statins	Community	12	381	171 female, 210 male	74.8	Yes (participants =84)	Not described
Lin *et al.* [106]	Alpha-blocker (doxazosin 4 mg) and 5-Alphaereductase Inhibitor Therapy (dutasteride 0.5 mg)	Community	12	240	0 female, 240 male	78.3 ± 8.19	No	Not described
Cibere *et al.* [49]	Glucosamine	Community	6	137	77 female, 60 male	65	No	Not described

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Table 3
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References	Deprescribing target	Setting	Follow-up duration in months (weighted mean ± standard deviation (SD))	Number of participants randomized	Gender	Age of participants in years (weighted mean ± SD)	Participants with dementia	Withdrawal schedule
Black *et al.* [41, 42]	Bisphosphonates	Community	47 ± 12	2,332	2,332 female, 0 male	74.7 ± 0.9	No	Not described
Dawson-Hughes *et al.* [58]	Calcium 500mg and vitamin D 17.5 mcg	Community	60	295	167 female, 128 male	74 ± 5	No	Not described
Gallagher *et al.* [76]	Individually and together: Calcitriol 0.25 mcg twice-daily Conjugated equine estrogens 0.625 mg daily (Premarin®) (combined with medroxyprogesterone acetate 2.5 mg daily in the woman had a uterus)	Community	24	487	487 female, 0 male	71.8 ± 0.31	No	Not described
Tariot *et al.* [144]	Carbamazepine	Community	0.75	51	Not stated	86 ± 6.4	Yes severe dementia with a mean (SD) mini-mental-state-examination (MMSE) score of 6 ± 7	Not described
Tse *et al.* [147]	Levodopa	Residential aged care facilities	1	11	7 females, 4 males	82.0 ± 10.1	Yes all 11 participants	Not described
Hardy *et al.* [90]	Lithium	Community	24	12	10 females, 2 males	79 ± 6	No	Titrated by reducing the daily dose by 150mg each week in the withdrawal group until completely replaced with a placebo
Bergh *et al.* [40]	Antidepressants	Residential aged care facilities	6	198	143 female, 55 male	85.3 ± 8.2	Yes (participants = 128; studies = 1)	Not described
Ballard *et al.* [36, 37] **Bridges-Parlet *et al.*** [45] **Devanand *et al.*** [62, 63] **Ruths *et al.*** [131] **Van Reekum *et al.*** [155]	Antipsychotics	Community (participants = 99; studies = 2) Residential aged care facilities (participants = 420; studies = 6)	21.3 ± 22.6	519	367 female, 151 male	82.5 ± 2.8	Yes all 519 participants	Abrupt discontinuation of their antipsychotic (participants = 30; studies = 1) Abrupt only if the dose was less than 50mg daily of chlorpromazine equivalence, and dose equivalent to 50mg chlorpromazine daily or above, the dose was reduced by half in week one and ceased in week two (participants = 36; studies = 1)

(continues)

Table 3
(Continued)

References	Deprescribing target	Setting	Follow-up duration in months (weighted mean ± standard deviation (SD))	Number of participants randomized	Gender	Age of participants in years (weighted mean ± SD)	Participants with dementia	Withdrawal schedule
								titrated over 1 to 3 weeks depending on the original antipsychotic dose (participants = 44; studies = 1) Reduce the regular daily dose by half in week one, a quarter of the regular daily dose in week three and cease in week three (participants = 34; studies = 1) Not described (participants = 375; studies = 3)
Curran *et al.* [53], **Habraken *et al.*** [86] **Petrovic *et al.*** [119] **Tham *et al.*** [145] **Tannenbaum *et al.*** [143]	Benzodiazepine	community (participants = 441; studies = 2) Residential aged care facilities (participants = 55; studies = 1) hospital (participants = 76; studies = 2)	8.6 ± 3.0	572	406 female, 161 male	77.2 ± 3.1	Unclear Mild to moderate confusion (participants = 25; studies = 1)	Individually tailored dose titration schedule with regard to the original dose and specific benzodiazepine (participants = 138; studies = 1) Titrated over five weeks with a 25% reduction weekly for three weeks then 12.5% dose reduction for two weeks before ceasing the benzodiazepine (participants = 55; studies = 1) Titrated using one week of 1mg lormetazepam (which was less than half the average daily benzodiazepine dose in the group) before ceasing the benzodiazepine (participants = 40; studies = 1). Abrupt withdrawal (switched straight to a placebo for 10 days) compared to gradual withdrawal (5mg temazepam for 4 days, 2mg temazepam for 4 days, placebo for

(continues)

Table 3
(Continued)

References	Deprescribing target	Setting	Follow-up duration in months (weighted mean ± standard deviation (SD))	Number of participants randomized	Gender	Age of participants in years (weighted mean ± SD)	Participants with dementia	Withdrawal schedule
								2 days) (participants = 36; studies = 1). Titrated over 21 weeks. Dose reduction from full dose to half a dose to quarter dose before it was ceased (participants = 303; studies = 1). STD-Tannenbaum-2014
Cohen-Mansfield *et al.* [50]	Antipsychotic Benzodiazepines	Residential aged care facilities	5	58	43 female, 15 male	86	Yes Yes - mean MMSE was 7.90	Tapered during a 3-week period, and then ceased
Gaudig *et al.* [81]; **Scarpini *et al.*** [135]	Anticholinesterase inhibitors	Community	14.4 ± 10.5	257	152 female, 105 male	75.4 ± 1.0	Yes All 257 participants	Not described
Rice *et al.* [129]	Prednisolone, oral	Community	6	38	0 female, 38 male	72 ± 6	No	Reduce the daily maintenance dose by 5mg per week
Choudhury *et al.* [48]; **O'Brien *et al.*** [116]	Corticosteroids, inhaled	Community	11.2 ± 2.5	284	124 female, 160 male	67.4 ± 0.2	No	Abrupt (participants = 260, studies = 1) Not described (participants = 24; studies = 1)
Borrill *et al.* [43]	Corticosteroids and beta-2 receptor agonist, inhaled	Community	1.5	14	Gender not stated	65	No	Not described

95]; or (iii) a single therapeutic category (e.g. antihypertensives) [33, 34, 36, 37, 39, 45, 46, 63, 66, 68, 72, 75, 87, 89, 93, 94, 105, 107, 112–114, 131, 137, 139, 146, 149, 155]. Eleven studies investigated withdrawing two medications [39, 43, 44, 50, 57, 58, 73, 76, 91, 97, 106].

Twenty-one studies investigated deprescribing polypharmacy [32, 38, 47, 55, 77–80, 83, 84, 88, 101, 111, 120, 123, 132, 142, 150, 159, 162]. Of these studies, 18 were patient-specific interventions [32, 38, 47, 55, 77, 79, 80, 83, 84, 88, 101, 111, 122, 123, 132, 142, 150, 159]. These patient-specific interventions were led by doctors in 11 studies [38, 47, 77, 79, 80, 101, 111, 122, 123, 132, 150], pharmacists in two studies [83, 88], nurses in one study [142], and multidisciplinary teams in four studies [32, 55, 84, 159]. These were investigator-led deprescribing interventions in 10 studies [38, 47, 79, 80, 88, 122, 123, 132, 142, 150], and used medication reviews with recommendations to the prescriber in eight studies [32, 55, 77, 83, 84, 101, 111, 159]. Three studies were educational programmes delivered at residential aged care facilities to nurses [120] and to the prescribing doctors [78, 162].

Excluded studies

Citations for excluded full-text papers are shown in the supplementary file 2 along with the rationale for exclusion. Only a published protocol or trial registration was found for seven studies (supplementary file 2) [123, 163–167]. Six of these studies were excluded as no results were available [163–166]. Results were available for one unpublished study, so the unpublished data has been included [123]. This paper has since been published.

Risk of bias in included studies

Details of the risk of bias for RCTs are presented in Figure 2. The risk of bias assessment for each study is presented in Results S1. The risk of bias was rated low in at least four of the seven parameters assessed in 32% (18 of the 56) of RCTs [36, 40, 45, 47–49, 53, 62, 77, 90, 102, 110, 112, 116, 123, 129, 131, 135, 143, 157]. The remaining 68% of studies all had unclear or high risk of bias. Industry funded ten studies that were included in this review, which was declared in the paper in each case [31, 41, 42, 57, 66, 81, 97, 114, 118, 135].

Heterogeneity in included studies

Quantitative heterogeneity assessments are presented in Tables S3 and S4. Forest plots are presented in Figures 3–6, and Figures S1–S9.

Effects of interventions for deprescribing: primary outcome (mortality)

Polypharmacy: randomized studies. Ten studies that investigated deprescribing to reduce polypharmacy reported mortality (eTable 3) [32, 38, 55, 77, 78, 84, 88, 120, 123, 159]. The follow-up duration was a weighted mean (SD) of 9.6 ± 3.9 months. They were set in the community [32, 38,

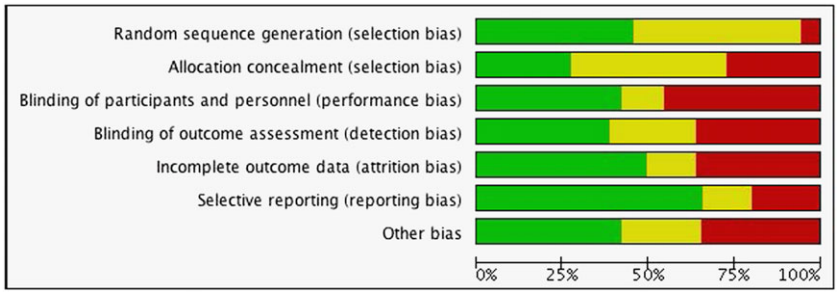

Figure 2

Risk of bias graph for all included randomized studies. Low risk of bias, unclear risk of bias, high risk of bias

Study or Subgroup	log[Odds Ratio]	SE	Experimental Total	Control Total	Weight	Odds Ratio IV, Random, 95% CI
Allard 2001	−0.9612	0.5044	136	130	7.9%	0.38 [0.14, 1.03]
Beer 2011	1.3269	1.661	20	24	0.9%	3.77 [0.15, 97.75]
Dalleur 2014	0.0564	0.5274	77	81	7.3%	1.06 [0.38, 2.97]
Gallagher 2011	−0.3476	0.4273	200	200	10.3%	0.71 [0.31, 1.63]
Garcia-Gollarte 2014	0.2121	0.2108	516	502	25.2%	1.24 [0.82, 1.87]
Gnjidic 2010	−1.9813	1.5235	57	58	1.0%	0.14 [0.01, 2.73]
Hanlon 1996	−0.409	0.5136	105	103	7.7%	0.66 [0.24, 1.82]
Pitkala 2014	0.149	0.2958	118	109	17.4%	1.16 [0.65, 2.07]
Potter 2015	−0.6476	0.4461	47	48	9.6%	0.52 [0.22, 1.25]
Weber 2008	−0.5246	0.3714	413	207	12.7%	0.59 [0.29, 1.23]
Total (95% CI)			**1689**	**1462**	**100.0%**	**0.82 [0.61, 1.11]**

Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 11.64$, df = 9 (P = 0.23); $I^2 = 23\%$
Test for overall effect: Z = 1.27 (P = 0.20)

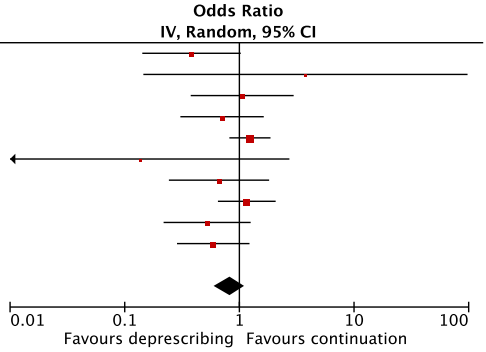

Figure 3

Mortality associated with deprescribing interventions to reduce polypharmacy (randomized studies)

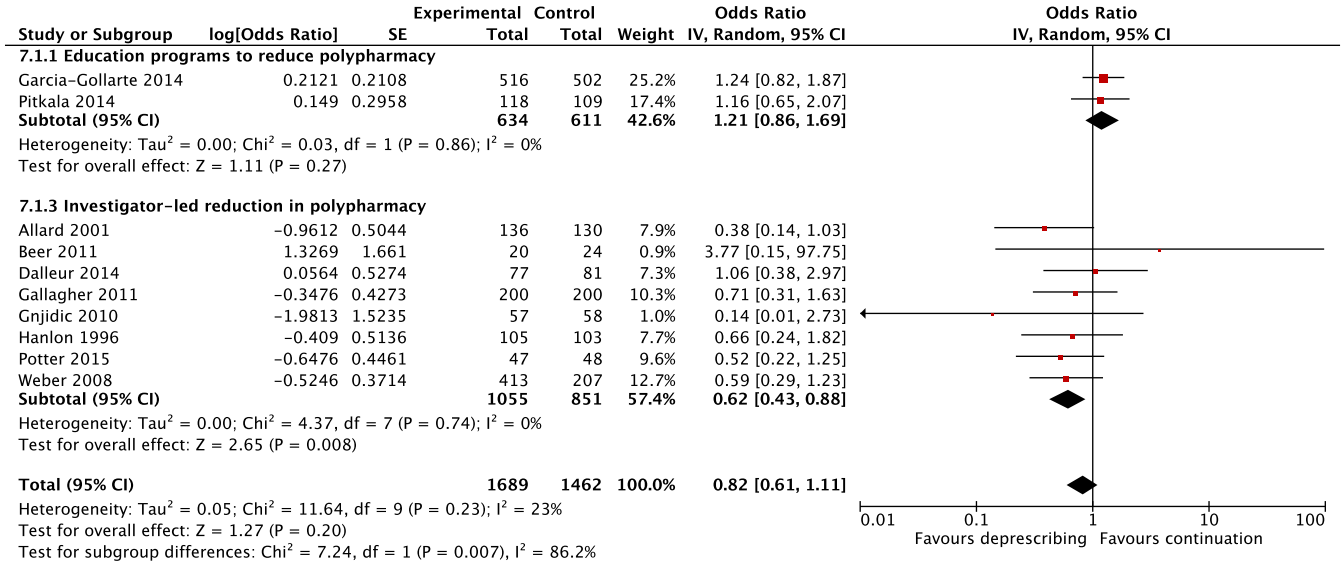

Figure 4

Mortality associated with deprescribing interventions to reduce polypharmacy for subgroup analysis based on intervention technique (randomized studies)

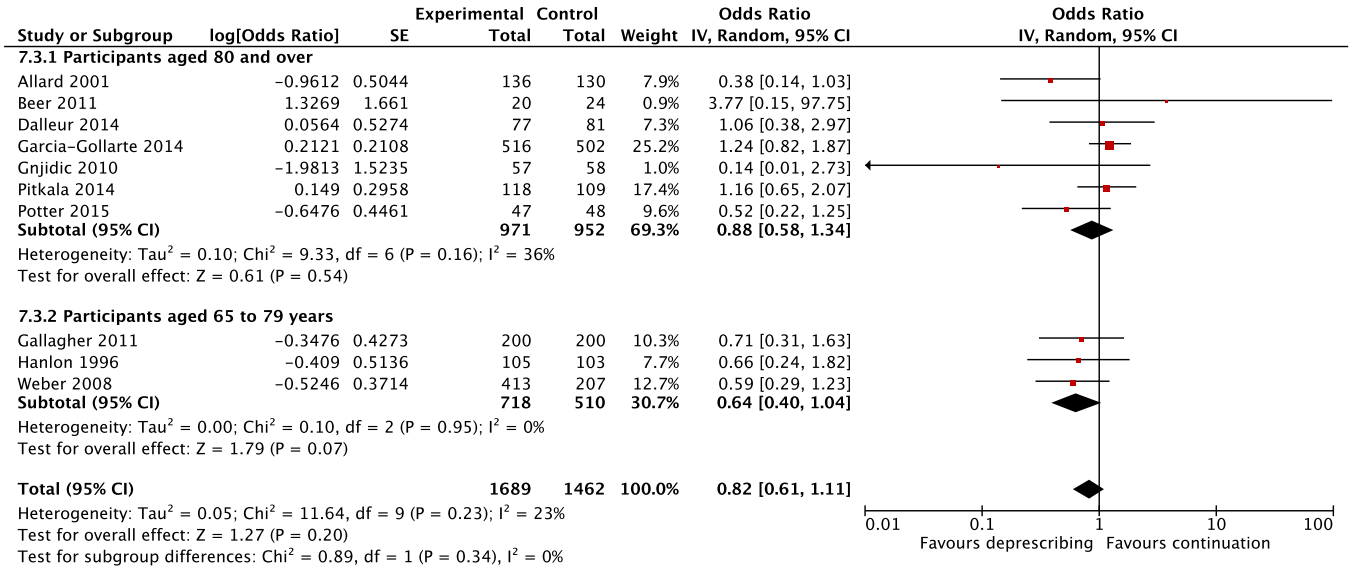

Figure 5

Mortality associated with deprescribing interventions to reduce polypharmacy for subgroup analysis based on age (randomized studies)

84, 123], hospital [55, 77] and residential care [38, 78, 120, 123]. Across these studies, deprescribing did not significantly modify mortality (OR 0.82, 95% CI 0.61–1.11; participants = 3151, studies = 10) (Figure 3) [32, 38, 55, 77, 78, 84, 88, 120, 123, 159].

The sub-group analysis based on intervention technique demonstrated differences in mortality. Mortality was significantly reduced when patient-specific interventions were applied (OR 0.62, 95% CI 0.43–0.88; participants = 1906; studies = 8) (Figure 4) [32, 38, 55, 77, 84, 88, 123, 159]. In contrast, educational programmes demonstrated no change in mortality (OR 1.21, 95% CI 0.86–1.69; participants = 1245; studies = 2) [78, 120].

Participant sub-group analysis: age. The sub-group analysis based on age demonstrated no change in mortality (Figure 5) for people aged over 80 years (OR 0.98, 95% CI 0.74–1.31; participants = 1923; studies = 7) [32, 38, 55, 78, 84, 120, 123]. People aged under 80 years showed a trend to reduced mortality (OR 0.64, 95% CI 0.40–1.04; participants = 1228; studies = 3) [47, 77, 142].

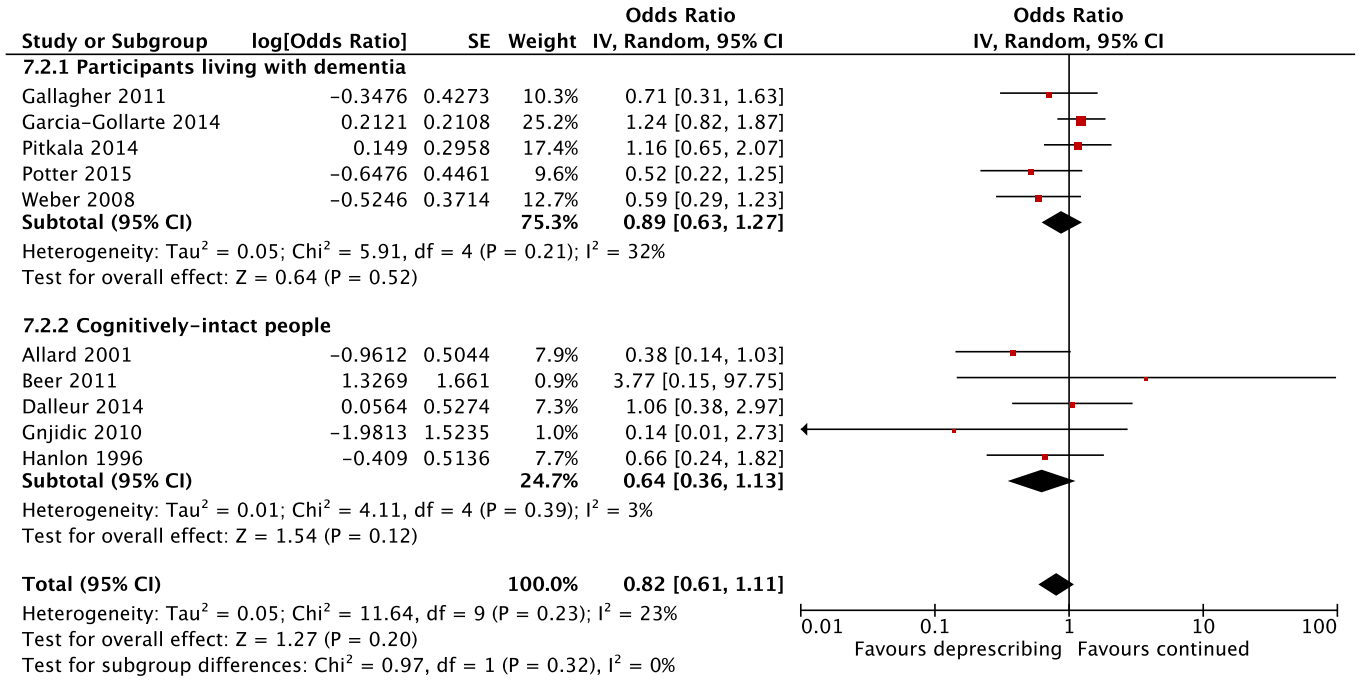

Figure 6

Mortality associated with deprescribing interventions to reduce polypharmacy for subgroup analysis for participants living with dementia and cognitively intact participants (randomized studies)

Participant sub-group analysis: dementia. Subgroup analysis indicated dementia did not show altered mortality outcomes associated with deprescribing (Figure 6) [77, 78, 120, 123, 159].

Polypharmacy: nonrandomized studies. Two studies assessed the effect of deprescribing polypharmacy on mortality (Table S4). They indicated a significant decrease in mortality (OR 0.32, 95% CI 0.17–0.60; participants = 257; studies = 2) [80, 162].

Single medications/classes: randomized studies. Deprescribing of single medications/classes in RCTs (eTable 3) was not associated with a statistically significant difference in mortality. For example, deprescribing antipsychotics did not significantly reduced mortality (OR 0.59, 95% CI 0.33–1.07; participants = 453; studies = 5) (eFigure 1) [35–37, 62, 131, 155].

Single medications/classes: nonrandomized studies. Deprescribing of single medications/classes in nonrandomized studies (eTable 4) was also not associated with a statistically significant difference in mortality [60, 125].

Effects of interventions for deprescribing: secondary outcomes

Deprescribing polypharmacy. Adverse drug withdrawal events, health outcomes, quality of life and the effect on the medication regime in RCTs to reduce polypharmacy are reported in Table S3, Figures S2 and S3. For nonrandomized studies, the results are reported in Tables S4 and S5 and Figure S9. They are briefly summarized below.

Adverse drug withdrawal events. Deprescribing to reduce polypharmacy was not associated with a significant increase in adverse drug withdrawal events [88].

Health outcomes. Deprescribing to reduce polypharmacy did not change the incidence of adverse drug events [88]. Cognitive function did not significantly change (Table S3) [38, 123]. Deprescribing did not significantly improve the risk of experiencing at least one fall (OR 0.65, 95% CI 0.40–1.05; participants = 2173; studies = 5) (Figure S2) [47, 77, 78, 123, 159]. However, participants who did fall had significantly fewer falls overall in the deprescribing group compared to those in the control group (MD −0.11, 95% CI −0.21–−0.02; participants = 844; studies = 3) (Figure S3) [78, 123, 168].

Quality of life. Deprescribing to reduce polypharmacy was not associated with significant changes in quality of life using standardized measures (Table S3). The exception was one study where deprescribing produced a significant yet modest positive finding that it slows the decline in quality of life (MD 0.03, 95% CI 0.01–0.06; participants = 189; studies = 1) [120].

Effect on the medication regime. Deprescribing reduced both the total number of medications (MD −0.99, 95% CI −1.83–−0.14; participants = 451; studies = 2) [78, 123] and number of potentially inappropriate medications taken (MD −0.49, 95% CI −0.70–−0.28; participants = 839; studies = 3) [32, 78, 120].

Deprescribing single medications/classes. The secondary outcomes for studies where a single medication was

deprescribed are reported in Table S3, Figures S4–S8. They are briefly summarized below.

Adverse drug withdrawal effects. Adverse drug withdrawal effects (Tables S3) were most frequently exacerbations of the underlying condition or known withdrawal effects. There was no statistical difference in exacerbations of the underlying condition after deprescribing glucosamine, carbamazepine and corticosteroids [48, 49, 129, 144], or in reported adverse drug withdrawal effects in response to deprescribing benzodiazepines, antipsychotics and antidepressants (Table S3, Figure S4) [45, 53, 62, 131, 149].

Health outcomes. Health outcomes of deprescribing (Table S3; eFigure S5–S7) were related to the signs, symptoms or disease state that the medication(s) were intended to manage, or improvement of suspected adverse effects. For example, the effect of deprescribing antihypertensives on blood pressure control was investigated. This produced an increased systolic (MD 7.40, 95% CI 3.10–11.70; participants = 385 studies = 1) [110] and diastolic blood pressure (MD 2.60, 95% CI 0.24–4.96 participants = 385 studies = 1) [110]. Similar changes in the systolic (MD 9.73, 95% CI 8.13–11.33; participants = 368; studies = 3) [46, 112, 157] and diastolic blood pressure (MD 3.99, 95% CI 3.04–4.94; participants = 367; studies = 3) [46, 112, 157] were observed when diuretics were deprescribed (Figure S6 and S7).

Quality of life. Deprescribing single medications was not associated with significant changes in quality of life using standardized measures (Table S3).

Effect on the medication regime. Effect on the medication regimen varied according to the medication (Table S3; Figure S8).

Discussion

This paper reports the first comprehensive systematic review of deprescribing interventions intended to reduce one or more medications. Deprescribing to reduce polypharmacy was not shown to modify mortality in RCTs although nonrandomized data suggested that it reduced mortality. Mortality was significantly reduced when patient-specific deprescribing interventions were applied in RCTs. Deprescribing appears to be feasible and generally safe.

Deprescribing to reduce polypharmacy appears to have some health benefits. The number of people who fell did not change, but it reduced the number of falls they experienced. This finding is consistent with a previous review on interventions to reduce falls [22]. Deprescribing does not appear to modify mortality in people aged over 80 years despite epidemiological and animal evidence that associates polypharmacy to poorer health outcomes in older adults [10–12]. Nonetheless, a trend to decreased mortality was noted in the 65–80-year-old age group. This hints that the susceptibility to the effects from deprescribing may vary across the lifespan.

The health outcomes from deprescribing varied with the target medication. This is unsurprising as the evidence to support treatment, the risk to benefit profile, and rationale for both prescribing and deprescribing varies between medications. For example, the rationale for deprescribing bisphosphonates after 3–5 years of treatment is that the therapeutic benefit persists after drug withdrawal [169]. In contrast, antihypertensives rapidly cease to exert an effect. Deprescribing antihypertensives resulted in modest increases in blood pressure. The rationale for deprescribing antihypertensives would need to be individualized to consider actual adverse effects experienced, blood pressure controlled too tightly, or to consider the less stringent blood pressure targets that may be appropriate for older adults [14, 170]. Another consideration for these preventative treatments is whether the treatment is appropriate late in life with a limited life expectancy [171]. However, deprescribing single medications did not always significantly alter health outcomes and quality of life. The available data suggests some medications can be deprescribed without adverse changes in the specific health outcomes the medications were intended to treat, which was consistent with the findings of previous systematic reviews that assessed deprescribing of specific medications [19, 20].

Deprescribing is difficult to implement, though this review suggests that deprescribing is feasible [21, 172]. It reinforces the importance of individualized approaches to medication use for older adults. Identifying deprescribing targets is not an exact science, and health care professionals can vary in their assessment on which medications are inappropriate [173, 174]. Evidence of feasibility supports the existing body of research including previous systematic reviews on the intervention techniques, barriers and enablers [17, 18, 175]. These combined works can be integrated to inform the design and implementation of future deprescribing interventions and contribute to the growing discussion about deprescribing [14, 176–178].

There are several limitations to this review. Language bias may have also been introduced as we included only English-language studies though applied no other limits. The review had broad inclusion criteria and a comprehensive search strategy, and we detected many relevant studies for inclusion. Despite this, there may be studies that were not identified, as the area of deprescribing has been poorly indexed historically. The review included many studies that were nonrandomized and many small RCTs of low quality. The limited methodological rigour was signified by an uncertain or high risk of bias assessment for most studies. Many of these studies aimed to assess the feasibility of the deprescribing intervention rather than the health or mortality outcomes, which was reflected in the included studies with limited well-powered RCTs to assess health outcomes. The follow-up durations, settings, age and health status of participants were variable. These limitations make it difficult to generalize the findings broadly in practice, though together they suggest that deprescribing in older adults is a field that warrants further attention.

This review collates the growing body of research in the field of deprescribing for older adults. However, as previously discussed, there are substantial limitations to the available study data. Rigorous large clinical trial data that implement patient-specific deprescribing interventions are needed to confirm the outcomes suggested in this review. Further research is needed to understand which medications should be deprescribed in which patients and at what time.

This study suggests that deprescribing needs to be considered for older people as a routine component of the ongoing medication review process. Clinicians would benefit from

deprescribing guidelines to support the implementation of deprescribing in practice. In the meantime, clinicians can use the data synthesized in this paper to inform decisions about deprescribing in conjunction with practical algorithms such as the CEASE acronym [16].

Conclusion

The available data suggest that patient-specific deprescribing interventions to reduce polypharmacy may improve longevity. Deprescribing is often achieved without adverse changes in quality of life or health outcomes, which is helpful for older adults. Though more research is needed, the current evidence suggests that individualized interventions to reduce inappropriate polypharmacy appear safe and feasible.

Competing Interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: AP had support from a University Postgraduate Award from the University of Western Australia, Australia and KP had support from a National Health and Medical Research Council (NHMRC) Early Career Fellowship for the submitted work. CEB and RC had no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

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