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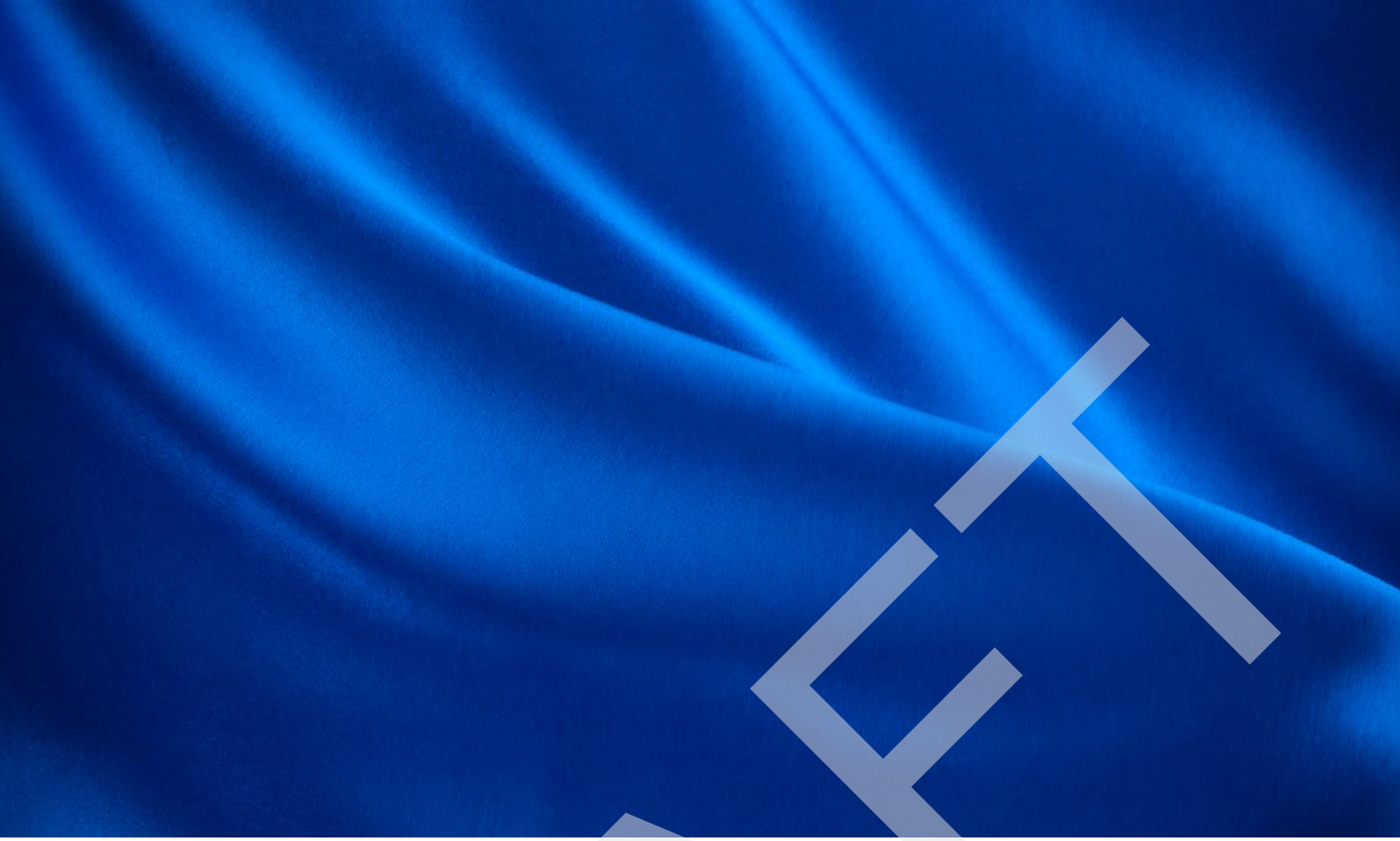
Technical Report

A clinical practice guideline for deprescribing in older people

THE UNIVERSITY OF WESTERN AUSTRALIA

WESTERN AUSTRALIAN CENTRE FOR HEALTH AGEING

Centre for Optimisation of Medicines



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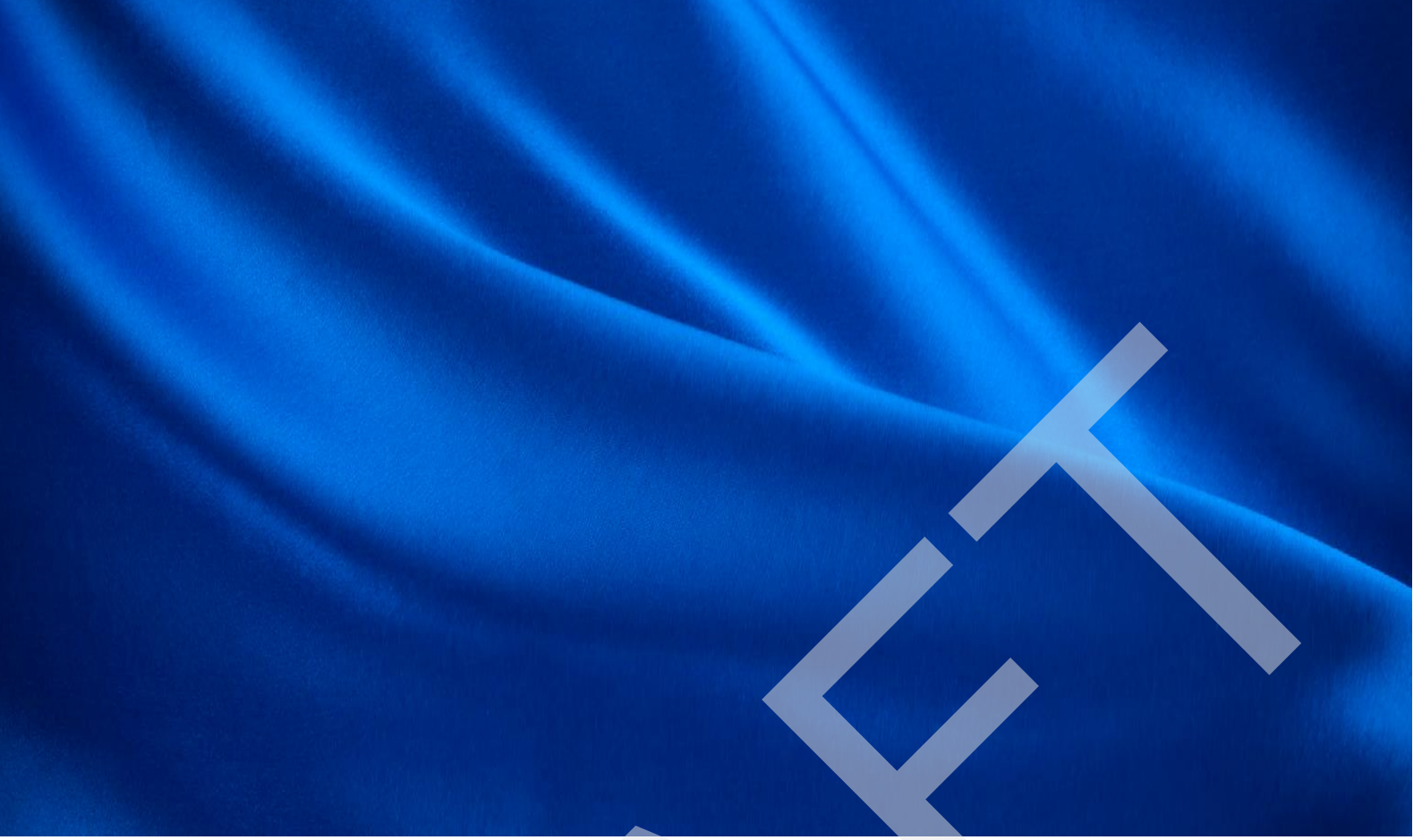

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All funders had no role in the formulation of recommendations, data interpretation, or the final content of this guideline. All decisions were made independently by the guideline development group in accordance with best practices for evidence-based guideline development.

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List of Abbreviations

Abbreviation	Full Name
ACE	Angiotensin-Converting Enzyme
ADAPTE	Guideline adaptation (framework)
ADL	Activities of Daily Living
ADS	Anticholinergic Drug Scale
ADWE	Adverse Drug Withdrawal Event
AGREE II	Appraisal of Guidelines for Research and Evaluation II
AIMS	Abnormal Involuntary Movement Scale (AIMS)
ARB	Angiotensin Receptor Blocker
ARMOR	Assess, Review, Minimise, Optimise, Reassess
ASPREE	ASPirin in Reducing Events in the Elderly
ATC	Anatomical Therapeutic Chemical (Classification System)
BMD	Bone Mineral Density
BP	Blood Pressure
BPH	Benign Prostatic Hyperplasia
BPRS	Brief Psychiatric Rating Scale
BPSD	Behavioural and Psychological Symptoms of Dementia
BWSQ	Benzodiazepine Withdrawal Symptom Questionnaire
CBR	Consensus-Based Recommendations
CBT	Cognitive Behavioural Therapy
CGIC	Clinical Global Impression of Change
CI	Confidence Interval
CINAHL	Cumulative Index of Nursing and Allied Health Literature
COPD	Chronic Obstructive Pulmonary Disease
COX-2	Cyclooxygenase-2
DBI	Drug Burden Index
DCM	Dementia Care Mapping
DISCUS	Dyskinesia Identification System Condensed User Scale
EBR	Evidence-Based Recommendations
FRAT	Falls Risk Assessment Tool
FRT	Functional Reach Test
GDG	Guideline Development Group
GLP1	Glucagon-like peptide-1
GORD	Gastro-Oesophageal Reflux Disease
GPGP	Good Palliative-Geriatric Practice
GPS	Good Practice Statements
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
HbA1c	Haemoglobin A1C
ICD	International Classification of Diseases
ICS	Inhaled Corticosteroids

INR	International Normalised Ratio
IQR	Interquartile Range
JBI	Joanna Briggs Institute
MAI	Medication Appropriateness Index
MD	Mean Difference
MMSE	Mini-Mental State Examination
NHBPS	Nursing Home Behaviour Problem Scale
NHMRC	National Health and Medical Research Council
NPI	Neuropsychiatric Inventory
NSAIDs	Non-steroidal anti-inflammatory drugs
OR	Odds Ratio
PBS	Pharmaceutical Benefits Scheme
PICO	Population, Intervention, Comparator and Outcomes
PPI	Proton-pump inhibitor
PRN	Pro Re Nata (as needed)
PROMIS	Patient-Reported Outcomes Measurement Information System
PSQI	Pittsburgh Sleep Quality Index
QALY	Quality-Adjusted Life Year
QoL	Quality of Life
QOLAD	Quality of Life in Alzheimer's Disease
QTRIM	Qatar Tool for Reducing Inappropriate Medication
QUALID	Quality of Life in Late-Stage Dementia
QUALIDEM	Quality of Life in Dementia
RACF	Residential Aged Care Facility
RCT	Randomised Controlled Trial
RoB	Risk of Bias
SD	Standard Deviation
SGLT2	Sodium-Glucose Cotransporter-2
SMD	Standardised Mean Difference
SoF	Summary of Finding
SSRI	Selective Serotonin Reuptake Inhibitor
STALD	Sheffield Test for Acquired Language Disorders
START	Screening Tool to Alert to Right Treatment
STOPP	Screening Tool of Older Persons' Prescriptions
TCA	Tricyclic Antidepressants
TRIM	Tool for Reducing Inappropriate Medications
TSH	Thyroid-Stimulating Hormone
TURP	Transurethral Resection of the Prostate
UPDRS	Unified Parkinson's Disease Rating Scale
WHO	World Health Organisation

1. Background

Inappropriate use of medicines is a longstanding public health issue that continues to have important safety and cost implications. Several initiatives have been introduced to optimise medication use, particularly for older people who are most at risk of any negative consequences from inappropriate use of medicines. Deprescribing is proposed as a patient-centred process of tapering, stopping, discontinuing, or withdrawing one or more medicines considered inappropriate or no longer beneficial to achieve improved outcomes. Current literature consistently shows that clinicians often regard deprescribing as a complex process with many unknowns involved in the process [2-4]. Guidance on when and how to taper or discontinue a medicine is also sparse. Several explicit criteria have been developed to highlight situations where medicines may be considered appropriate to deprescribe, particularly in the context of older people. For instance, the Australian list of potentially inappropriate medicines (PIMs) [5], Beers criteria [6], and STOPPFrail [7]. Several drug-class-specific evidence-based deprescribing clinical practice guidelines [8-13] have also been developed for medicines for which expert clinicians felt priorities should be given for developing guidance for deprescribing [14]. Acknowledging the lack of evidence-based guidance for deprescribing in older people with multimorbidity, our goal is to provide broad guidance for medicines commonly encountered in practice, complementing more detailed drug-specific clinical practice guidelines and a patient-centred approach.

2. Target audience

Health practitioners involved in the care of older people (≥ 65 years), particularly medical practitioners, nurse practitioners, pharmacists, and other non-medical prescribers such as dental practitioners, podiatrists, and optometrists.

3. Target population

Older people (≥ 65 years) taking at least one long-term medicine.

4. Purpose of the guideline

Please refer to the main guideline document.

5. Scope of the guideline

Please refer to the main guideline document.

6. Part A: Initial work

The development of this clinical practice guideline follows the National Health and Medical Research Council (NHMRC) Guideline Development Methodology and the Appraisal of Guidelines for Research & Evaluation (AGREE) II Instrument and User's Manual [15, 16].

This guideline project was initially registered with the NHMRC in 2016. A guideline committee, including external experts, supported the genesis and initial development of the guideline development plan. The initial guideline committee met on 19 April 2016 to determine the initial proposal of the guideline, including the purpose and scope of the guideline.

In 2019, the project was supported by a University of Western Australia Faculty of Health and Medical Sciences Research Scheme Grant bequeathed by Dr Athelstan John Henton Saw OBE MLC. This grant supported research assistants for evidence synthesis and drafting recommendations using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach. Unfortunately, the progress stalled (and registration with the NHMRC lapsed) initially due to significant medical issues affecting one of the key steering committee members, and then the impacts of the COVID-19 pandemic. Despite these setbacks, considerable work has resumed since 2022.

For a detailed description of funding throughout the guideline development process, please refer to the administrative report.

7. Part B: Systematic evidence review

From 2022 to 2024, we updated a 2016 systematic review and meta-analysis to include new evidence since the original search to inform the development of recommendations for this guideline. The systematic review protocol was prospectively published and registered with Joanna Briggs Institute (JBI) Evidence Synthesis [17]. The 2016 and updated 2024 systematic reviews and meta-analyses have been published elsewhere [18, 19]. The methodology for evidence review is described in the publications below.

To ensure the systematic review remains current when the draft guideline is released for public consultation, an additional updated search was conducted on 15th March 2025 using the same search strategy to identify new evidence (refer to Section 7.4).

A copy of the study protocol for the guideline development submitted to a peer-reviewed journal is attached to this technical report under Appendix C (currently under review).

7.1 Clinical question

The clinical question used for the systematic review and meta-analysis was *"In older people, what are the effects of deprescribing (i.e. dose reduction or complete discontinuation) long-term medicines on mortality, adverse drug withdrawal events, health-related outcomes, cognitive function, and quality of life, and medicine regimen?"*

7.2 Population, Intervention, Comparator and Outcomes (PICO), inclusion & exclusion criteria

The PICO framework guiding the evidence review is outlined in Table **1**. The systematic review and meta-analysis were designed to be broad without restrictions on specific drugs or drug classes, provided that studies met all inclusion criteria and none of the exclusion criteria. Both experimental (randomised or non-randomised controlled trials) and observational studies with or without concurrent control groups (before-and-after, case-control or cohort studies) were considered.

In the literature review, we distinguished deprescribing from broader concepts such as medication optimisation. Deprescribing refers to an intervention explicitly aiming to withdraw or reduce the dose of medicine(s) [20], whereas optimisation may include actions such as initiating new treatments or addressing underprescribing. As such, we excluded studies focused solely on medication optimisation or general prescribing quality improvement, where it was not possible to determine whether outcomes were attributable to deprescribing. Similarly, we excluded studies involving temporary withholding (e.g. drug holidays) or short-term medicines not intended for ongoing use to maintain alignment with the definition.

Table 1. PICO for evidence review

	Description	Inclusion Criteria	Exclusion Criteria
Population	Adults aged 65 years and over with no limitation placed on setting, cognitive function, or comorbidities	• Aged 65 years and over, defined as studies where one of the following applies: • Mean participant age is ≥ 65 years • Greater than 75% of participants are aged ≥ 65 years • Data from people aged ≥ 65 years can be extracted	Unclear age or studies including only moribund, terminal, or palliative participants
Intervention	Deprescribing of medicine(s)	Medicine(s) intended for regular use	Medicine(s) intended for short-term, intermittent, as required, or acute use only
Comparator	Continuation of the medicine(s) or no comparator	• Continuation of the medicine(s) • No comparison • Non-pharmacological intervention	Substitution with an alternative medicine(s)
Outcomes	• Mortality • Adverse drug withdrawal events • Cognitive function • Quality of life • Other health-related outcomes • Effect on medicine regimen	Clinically relevant health outcomes, significant events or surrogate endpoints	Outcomes of uncertain or limited clinical relevance

7.3 Limitations

The inclusion and exclusion criteria for studies specific to the PICO criteria are detailed above. The searches were limited to the English language, and study designs were limited to experimental (randomised or non-randomised controlled trials) and observational studies with or without concurrent control groups (before-and-after, case-control or cohort studies). No limitations were placed on study settings or targeted drug classes as long as the studies met all inclusion criteria and none of the exclusion criteria.

7.4 Systematic searching and screening

The search terms were tailored for each specific search platform (see Appendix A). Individual drug names or drug classes were included in the search strategy in addition to generic terms such as “medicines” and “prescription drugs”. Boolean operators and wildcards were used as applicable to take into account the terms with variant spellings.

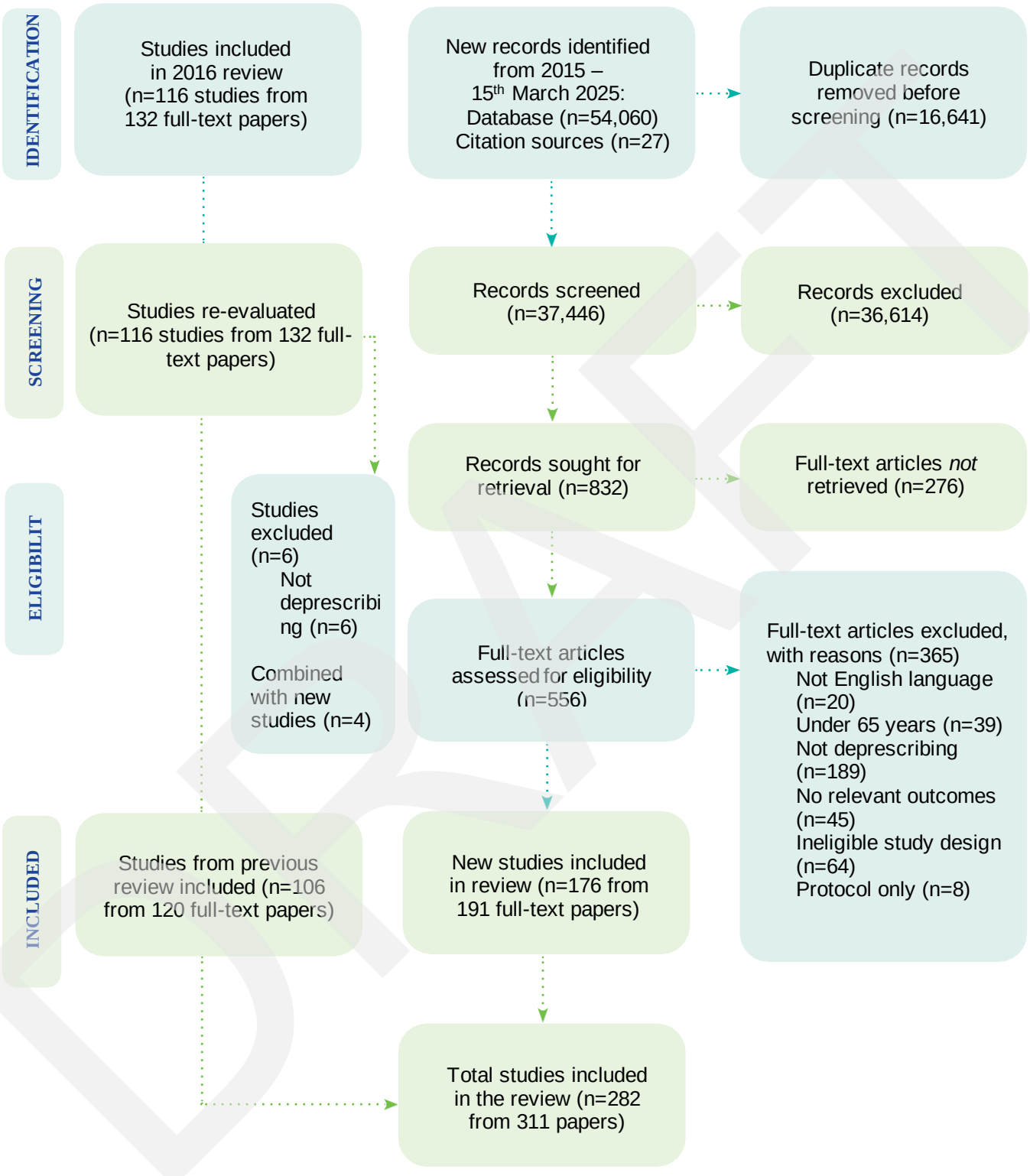
The original search was conducted in February 2015 with an updated search on 26th April 2024. The following databases were searched: CINAHL, Medline, Embase, Scopus, Web of Science, and ProQuest (Dissertations and Theses Global). Figure 1 shows the PRISMA flow diagram for the number of studies identified. The 2016 and updated systematic reviews and meta-analyses have been published elsewhere [18, 19].

To ensure the systematic review remains current when the draft guideline is released for public consultation, an additional updated search was conducted on 15th March 2025 using the same search strategy to identify new evidence. From 26th April 2024 to 15th March 2025, 4788 new studies were identified across all search platforms. Among these records, 1559 duplicates were identified, and 3229 studies were screened for titles and abstracts. Of the 3229 studies, 100 full-text studies were assessed for eligibility. Finally, 25 new studies were included in the guideline as part of the evidence review. Among the 75 studies excluded, 33 studies were not deprescribing, the full text was unavailable for 18 papers, nine studies had ineligible study design, five studies did not report relevant outcomes six studies were conducted in people under the age of 65 years, three papers were not in the English language, and one study had ineligible population.

The studies identified from all databases were imported into a web-based tool (Covidence) following which any duplications were automatically removed [21]. Screening of studies was conducted in two phases. During the first phase, titles and abstracts were screened independently by two researchers, with any disagreements resolved by a third reviewer. All studies that passed the first phase progressed into the second phase where the full-text articles were obtained and screened for eligibility by two researchers. Similarly, any disagreements were resolved by a third reviewer to reach a final consensus for inclusion or exclusion.

Overall, the studies in this guideline covered eligible publications from inception to 15th March 2025.

Figure 1. PRISMA flow diagram



7.5 Critical appraisal of studies for risks of bias

Two researchers independently appraised the studies for risks of bias using the Cochrane Collaboration's Risk of Bias (RoB) tool [22] for randomised controlled trials (RCTs), and combinations of the Cochrane Risk of Bias tool with the Newcastle-Ottawa tool for risk of bias assessments for non-RCTs or single-arm studies [22, 23]. Each study was assessed for potential selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases. More detailed reporting of the RoB is included in the systematic review and meta-analysis publication and its supplementary material [19].

7.6 Data extraction

A standard data extraction template was developed to consistently extract key information from each included study. The form comprised of the following characteristics: study design, number of groups, sample size, participants' age, sex, presence of dementia, inclusion and exclusion criteria, number of concomitant medications, country of origin, study setting, medication targeted, intervention descriptions, withdrawal schedule, comparator, the tool used to identify target medications, reported study outcomes, study dates, follow-up duration and source of funding. A brief summary of each study (grouped by drug class) is presented in Appendix B. Additionally, the complete summary of each included study along with the individual risk of bias assessment were included as supplementary materials in the 2016 and 2024 systematic reviews and meta-analyses (see eResults 1) [18, 19].

7.7 Data analysis

The complete methodology for data analysis was reported in the 2016 systematic review and meta-analysis and applied consistently in the 2024 updated publication (see data collection and analysis) [18, 19]. The methodology is briefly summarised below.

Reported outcomes were categorised into mortality, adverse drug withdrawal events, cognitive function, quality of life, and other health-related outcomes as well as effects on the medicine regimen. Studies reporting each outcome were classified by polypharmacy/multiple drug classes (defined as three or more medicines or classes being deprescribed) or their drug classes. Within each classification, outcomes were further grouped by their study designs (RCTs or non-randomised studies with or without concurrent control groups).

Effect measures were reported as odds ratio (OR) for dichotomous data and mean difference (MD) for continuous data, each accompanied by 95% confidence intervals (CI). An OR of less than 1 for the outcome of interest favoured the deprescribing group, while an OR greater than 1 favoured the control group. For continuous data, when reverse scales were used (where higher values represented better outcomes), the outcome values were multiplied by -1 to ensure consistent directional reporting across all measures in the meta-analysis. An MD of less than zero favoured the deprescribing group, whereas an MD greater than 0 favoured the control group.

For single-arm studies, unless otherwise stated, effect measures were reported as the proportion of individuals with the outcome of interest, endpoint values as mean ± standard deviation, baseline and endpoint values as mean ± standard deviation, or the mean differences with corresponding p-values (if stated in the study).

7.8 Subgroup analyses

Subgroup analyses based on intervention type and participants' age were only conducted if ten or more studies were reporting the same outcome. As a result, subgroup analyses were undertaken only for the effects of deprescribing on mortality, falls, and unplanned hospital admissions for polypharmacy/multiple drug classes studies (refer to Figure 2, eFigure 5, eFigure 6 in the 2024 systematic review and meta-analysis publication) [19].

7.9 Characteristics of studies

The characteristics of included studies, grouped by deprescribing targets, were presented in the 2024 systematic review and meta-analysis (see Table 1 in the publication for polypharmacy and Table 2 in the publication for individual targets in the 2024 systematic review and meta-analysis publication) [19].

7.9 Updating the guidelines

The guideline will be updated within five years of publication to ensure continued relevance to clinical practice. The guideline steering committee will be responsible for this process, including periodic monitoring for emerging evidence and determining when an update is warranted. The update will involve re-running the systematic literature search using the same search strategy on databases, reassessing the quality and certainty of any new evidence, and revising recommendations as needed.

8. Part C: Identifying targeted medicines

8.1 Common medicines

We analysed the Australian Pharmaceutical Benefits Scheme (PBS) data to identify common medicines dispensed to people over the age of 65 in the year 2023. The PBS data was supplied by Services Australia. A limitation of using the PBS data to estimate common medicines is the data does not include medicines available without a prescription, such as over-the-counter and complementary medicines, or medicines dispensed on private prescriptions.

We identified the top 100 ranked medicines with unique Anatomical Therapeutic Chemical (ATC) codes, by 1) prescription dispensing volume and 2) the number of unique persons dispensed. The volume-based metric represents the total number of dispensing in a calendar year, while the person-based metric refers to the number of people who received the medicine in a calendar year. The person-based metric is included to account for medicines with less frequent dosing. Combination products with a unique ATC code were counted separately independent of their active ingredients. Following that, medicines or combination products typically not prescribed for long-term use were excluded. These medicines were amoxicillin, amoxicillin/clavulanic acid, cefalexin, doxycycline, enoxaparin sodium, flucloxacillin, metoclopramide, roxithromycin, trimethoprim, metronidazole, molnupiravir, and nirmatrelvir/ritonavir. As a result, the full list of the top 100 PBS medicines was greater than 100 active ingredients (Table **2**).

The PBS medicines identified were categorised into drug classes using the World Health Organisation ATC classification system [24]. Evidence identified from the systematic review and meta-analysis was mapped to the relevant drug class section. If a study targeted three or more drug classes or addressed general polypharmacy without clearly distinguishing outcomes related to a specific drug class, the reported outcomes were categorised under “polypharmacy/multiple drug classes”. Depending on the available evidence, this guideline may not address all medicines in the same drug class as the common PBS medicines.

For drug classes where no evidence was identified despite a systematic literature search, a different procedure was followed for formulating recommendations. In these cases, a Delphi process was used to formulate the consensus-based recommendations or guideline practice statements following a narrative review of the potential benefits and harms of both continuing and discontinuing the medicine (See Section 10.2 & 10.3).

8.2 Less common medicines with evidence

In this guideline, we also included less commonly used medicines where there was evidence available to inform deprescribing in people aged over 65 years. These medicines were potassium supplementation, bisphosphonates, urinary antimuscarinic (oxybutynin, solifenacin, tolterodine, trospium, fesoterodine), teriparatide, anticholinesterases, and levodopa (either alone or with carbidopa and bromocriptine).

Table 2. Top 100 medicines dispensed under the Australian Pharmaceutical Benefits Scheme for people aged over 65 years (based on dispensing volume and the number of unique recipients in 2023), categorised according to the World Health Organisation Anatomical Therapeutic Chemical (ATC) Classification System [24]

ATC therapeutic class first level	ATC therapeutic class 2nd/3rd/4th level	**Top 100 dispensed** PBS medicines/ combination products*
ALIMENTARY TRACT AND METABOLISM (A)	Proton-pump inhibitors (A02BC)	Esomeprazole Omeprazole Pantoprazole Rabeprazole
	Other antiemetics (A04AD)	Prochlorperazine# (PBS classification)
	Osmotically acting laxatives (A06AD)	Macrogol laxatives
	Drugs used in diabetes (A10)	Dapagliflozin Empagliflozin Empagliflozin + metformin Gliclazide Insulin glargine# Linagliptin Metformin Semaglutide Sitagliptin Sitagliptin + metformin
BLOOD AND BLOOD FORMING ORGANS (B)	Antithrombotic agents (B01A)	Apixaban Clopidogrel Rivaroxaban Warfarin
	Anti-anaemic preparations (B03)	Ferric carboxymaltose# Hydroxocobalamin#
CARDIOVASCULAR SYSTEM (C)	Digitalis glycosides (C01AA)	Digoxin#
	Organic nitrates (C01D)	Glyceryl trinitrate# Isosorbide mononitrate
	Antiadrenergic agents, centrally acting (C02A)	Moxonidine

ATC therapeutic class first level	ATC therapeutic class 2nd/3rd/4th level	**Top 100 dispensed** PBS medicines/ combination products*
CARDIOVASCULAR SYSTEM (C)	Antiadrenergic agents, peripherally acting (C02C)	Prazosin
	Diuretics (C03)	Furosemide Spironolactone
	Beta-blocking agents (C07)	Atenolol Bisoprolol Metoprolol tartrate Nebivolol Sotalol
	Calcium channel blockers (C08)	Amlodipine Diltiazem Felodipine Lercanidipine Verapamil
	Agents acting on the renin-angiotensin system (C09)	Amlodipine + valsartan + hydrochlorothiazide Amlodipine + valsartan Amlodipine + atorvastatin Candesartan Candesartan + hydrochlorothiazide Irbesartan Irbesartan + hydrochlorothiazide Olmesartan Perindopril Perindopril + indapamide Perindopril + amlodipine Ramipril Sacubitril + valsartan Telmisartan Telmisartan + hydrochlorothiazide Telmisartan + amlodipine
	Lipid-modifying agents (C10)	Atorvastatin Atorvastatin + amlodipine Ezetimibe Ezetimibe + atorvastatin Ezetimibe + rosuvastatin Ezetimibe + simvastatin Fenofibrate Pravastatin Rosuvastatin Simvastatin
DERMATOLOGICALS (D)	Corticosteroids, plain (D07A)	Betamethasone dipropionate Methylprednisolone# Mometasone# Triamcinolone#

ATC therapeutic class first level	ATC therapeutic class 2nd/3rd/4th level	**Top 100 dispensed** PBS medicines/ combination products*
GENITO URINARY SYSTEM AND SEX HORMONES (G)	Estrogens (G03C)	Estradiol Estriol#
	Drugs used in benign prostatic hypertrophy (G04C)	Dutasteride + tamsulosin
SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS (H)	Glucocorticoids (H02AB)	Prednisolone Prednisone#
	Thyroid hormones (H03AA)	Levothyroxine
MUSCULOSKELETAL SYSTEM (M)	Anti-inflammatory and antirheumatic products, non-steroids (M01A)	Celecoxib Meloxicam
	Antigout preparations (M04A)	Allopurinol Colchicine#
	Drugs affecting bone structure and mineralisation (M05B)	Denosumab Risedronate
NERVOUS SYSTEM (N)	Analgesics (N02)	Buprenorphine Oxycodone Oxycodone + naloxone Paracetamol + codeine Tapentadol Tramadol Paracetamol Pregabalin
	Dopaminergic agents (N04B)	Levodopa + carbidopa
	Anxiolytics (N05B)	Diazepam
	Hypnotics and sedatives (N05C)	Temazepam
	Antidepressants (N06A)	Amitriptyline Citalopram Desvenlafaxine Duloxetine Escitalopram Mirtazapine Sertraline Venlafaxine
	Anti-dementia drugs (N06D)	Donepezil

ATC therapeutic class first level	ATC therapeutic class 2nd/3rd/4th level	**Top 100 dispensed** PBS medicines/ combination products*
RESPIRATORY SYSTEM (R)	Drugs for chronic obstructive airway diseases (R03)	Budesonide + formoterol Fluticasone furoate + umeclidinium + vilanterol Fluticasone propionate + salmeterol Tiotropium
SENSORY ORGANS (S)	Corticosteroids, plain (S01BA)	Dexamethasone# Fluorometholone#
	Antiglaucoma preparations and miotics (S01E)	Latanoprost Bimatoprost + timolol
	Other ophthalmologicals (S01X)	Liquid paraffin + glycerol + tyloxapol + poloxamer-188 + trometamol hydrochloride + trometamol + cetalkonium chloride

Medicines intended for short-term, intermittent, as required, or acute use only (e.g. systemic or topical antibacterial, salbutamol) are not within the scope of this guideline.
** Common medicines are based on the Pharmaceutical Benefits Scheme (PBS) prescription dispensing volume unless otherwise stated. Plain products refer to products containing only one active ingredient.*
 # indicates common PBS medicines by the number of unique persons dispensed in a calendar year

9. Part D: Grading of Recommendations, Assessment, Development and Evaluations (GRADE) Framework

For drug classes where evidence was identified from evidence review, the GRADE framework was used to develop and present evidence summaries for formulating guideline recommendations [25].

9.1 Organising outcomes

Each outcome reported in the studies identified from the systematic review and meta-analysis was grouped based on the drug class of the medicine(s) deprescribed. The classification of the medicines was based on the ATC classification system, as shown in Table **2**. If a study targeted multiple drug classes or addressed general polypharmacy without clearly distinguishing outcomes for specific drug classes, the reported outcomes were classified under "polypharmacy/multiple drug classes". All outcomes were then organised into five categories: 1) Mortality, 2) Adverse drug withdrawal events, 3) Health outcomes, 4) Cognitive function, and 5) Quality of life. We further separated the outcome within each category based on the study design (randomised controlled trial, non-randomised controlled trial, or non-controlled trial).

9.2 Rating the importance of outcomes

The importance of each outcome in each study was initially independently rated by three members of the guideline steering committee (HWQ, AP, CEB) using a numerical scale from 1 to 9, where 1 to 3 indicated limited importance, 4 to 6 represented important but not critical outcomes, and 7 to 9 indicated outcomes critical for decision-making [26]. Any disagreements in ratings were resolved through team discussions until consensus was achieved. Based on initial feedback from the guideline development group (GDG), a formal survey was distributed to all GDG members (including the consumer advisory group) to gather input on the importance ratings for each outcome. The final ratings shown in this guideline were determined by a majority vote from GDG members who participated in the rating.

9.3 Assessing outcomes

Each outcome that was rated as important or critical for decision-making (4 to 9) was included in a GRADE Evidence Profile table [27]. The certainty of each outcome was then independently appraised by two GDG members (HWQ and HA or AP) trained in GRADE methodology, with disagreements resolved through discussions until a consensus was reached. GRADE certainty assessment was conducted at the outcome level, evaluating all studies included in the systematic review and meta-analysis that reported a specific outcome. The study design was an important factor in assessing the certainty of the evidence. The ratings for randomised controlled trials had a starting level of high certainty. In contrast, non-randomised studies (e.g. quasi-randomised controlled trials, cohort studies, before-and-after studies, case-control studies) and single-arm studies started at a low-certainty level by default. Non-randomised trials were automatically downgraded for limitations in risk of bias

such as lack of allocation concealment and potential for selection bias inherent to the study design.

9.4 Decreasing levels of certainty

During the GRADE assessment, the following five factors could reduce the certainty of the evidence: risk of bias (study design), inconsistency (variability in results across studies), indirectness (relevance of the evidence considering the PICO), imprecision (certainty around the effect estimates), and other considerations including publication bias [28]. Reviewers had the option of reducing the level of certainty by one level or by two levels if there were serious concerns about the study bias or limitations based on the five factors mentioned above. Non-randomised studies were not downgraded twice for the same issue in risk of bias, unless there were additional concerns not inherent to the study design including but not limited to attrition bias, reporting bias, confounding bias, comparability bias or outcome bias.

9.5 Increasing levels of certainty

The final level of certainty was increased when 1) there was a large effect size, 2) there was a clear and proportionate dose-response gradient, 3) all possible residual confounders would reduce the magnitude of the observed effect, or 4) possible residual confounders expected to reduce the observed effect or to increase the effect but no effect was observed.

9.6 Allocating final ratings

Finally, the four possible ratings for each outcome were high, moderate, low, or very low (Table 3).

Table 3. GRADE certainty of evidence ratings

GRADE ratings	Definitions
High 	We are very confident that the true effect is close to the estimated effect.
Moderate 	We are moderately confident in the estimated effect. The true effect is probably close to the estimated effect, but there is a possibility that it is substantially different.
Low 	We have limited confidence in the estimated effect. The true effect may be substantially different from the estimated effect.
Very low 	We have very little confidence in the estimated effect. The true effect is likely to be substantially different from the estimated effect.

9.7 Presenting evidence and certainty of evidence

A Summary of Findings (SoF) table was prepared for each drug class and included in the main guideline to provide key information underlying a recommendation [27]. The SoF tables serve as a concise and accessible summary for each of the included outcomes along with the final rating for certainty of evidence.

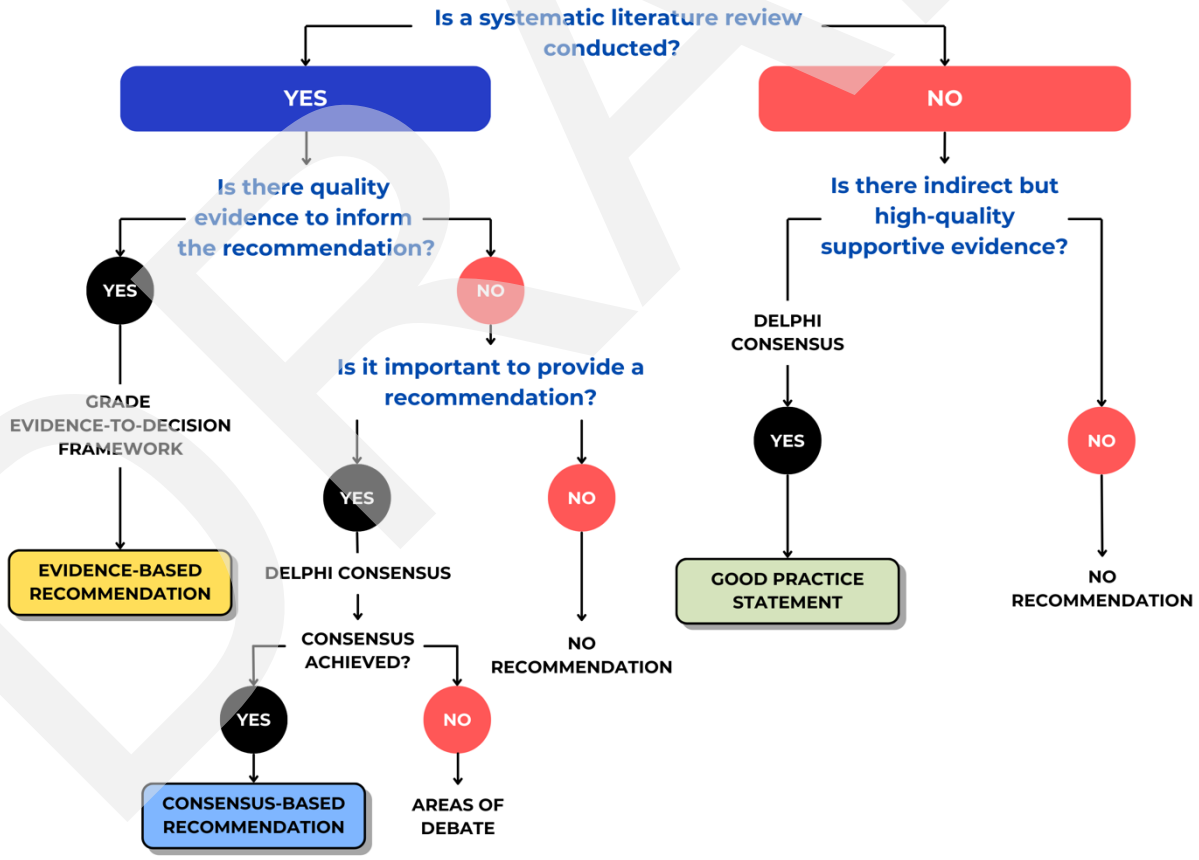
For data presentation, see Section 7.7 Data analysis.

10. Part E: Types of recommendations

Each recommendation was classified as one of three possible types: evidence-based recommendation (EBR), consensus-based recommendation (CBR), or good practice statements (GPS). This section and Figure 2 provide further details to differentiate the three types of recommendations.

The guideline steering committee initially drafted the wording of the recommendations following the GRADE Evidence-to-Recommendations framework [29]. A detailed description of the committee's composition and role is available in the Administrative Report. The GRADE framework was followed to ensure an explicit link between the recommendations and the evidence identified. Critical outcomes (rated 7-9) were weighed when formulating a recommendation, which influenced the overall quality of evidence supporting a recommendation. The resulting recommendations were based on considerations of the following factors using the GRADE approach: the balance between the benefits and risks of medicine continuation and medicine discontinuation, individual's values and preferences (with input from consumer representatives), resource use, costs, acceptability, the feasibility of implementation, and health equity indicators (see Appendix B).

Figure 2. Types of guideline recommendations



10.1 Evidence-based recommendations (EBRs)

If sufficient quality evidence is available to support the recommendations, they are classified as EBRs. These EBRs are assigned a rating and strength based on the GRADE framework (see Table **3** and Table **4**) and worded to indicate the direction of the recommendation – either for or against deprescribing [30]. Strong EBRs are based on high or moderate quality evidence generally, implying that the implementation of deprescribing is strongly recommended by most if not all people. However, it is important to note that the strength of a recommendation is not based solely on the certainty of the evidence, but also dependent on other important GRADE elements listed above (balance and trade-off, values and preferences, resources, acceptability, and feasibility). Recommendations are more likely to be conditional rather than strong when:

1. the certainty in the evidence is low;
2. there is a close balance between desirable and undesirable effects; or
3. there is substantial variability in individual circumstances, values and preferences [25].

The wording "we recommend…" was used to represent a strong evidence-based recommendation. For conditional evidence-based recommendations, "we suggest…" was used. This was decided in accordance with the GRADE framework for clarity. This difference in wording characterises the two categories of strength for the recommendations in this guideline.

Table 4. GRADE strength of evidence-based recommendations

GRADE strength	Definitions
Strong	The guideline development group is confident that most or all people will be best served by the recommended course of action.
Conditional	The guideline development group is confident that not all people will be best served by the recommended course of action. There is a need to consider more carefully than usual the individual's circumstances, values, and preferences.

The wording "**we recommend…**" was used to represent a strong evidence-based recommendation. For conditional evidence-based recommendations, "**we suggest…**" was used. This was decided in accordance with the GRADE framework for clarity. This difference in wording characterises the two categories of strength for the recommendations in this guideline.

10.2 Consensus-based recommendations (CBRs)

CBRs are developed when there is either a lack of evidence or insufficient quality of evidence for deprescribing (i.e. low or very low certainty of outcomes) on which to base a recommendation following a systematic search, but the GDG still considers it important to provide a recommendation. When drafting the CBRs, relevant evidence identified from the systematic literature review related to the benefits and harms of deprescribing was considered, along with other existing resources (e.g. Therapeutic Guidelines, Australian Medicines Handbook, clinical practice guidelines, position statements, and expert consensus documents) for deprescribing or prescribing where appropriate. The resulting recommendations using this process were ungraded and labelled as CBRs. CBRs can be given for or against deprescribing. Although the recommendations are labelled as 'consensus-based', these recommendations are developed rigorously with consideration of any available evidence following a systematic review of the literature for deprescribing. For the purpose of this guideline, the term 'consensus' was chosen for clarity of language, to distinguish these recommendations from EBRs, which are guided by quality evidence. CBRs are developed following a structured Delphi consensus process.

All consensus-based recommendations were phrased as "we suggest...".

All consensus-based recommendations were phrased as "**we suggest...**".

10.3 Good practice statements (GPS)

GPS are also not graded and developed following a structured Delphi consensus process. GPS are an actionable statement developed by the GDG to support recommendations, or to guide deprescribing processes when there is indirect but high-quality supportive evidence and other criteria for GPS development are met (see Table 5). GPS are developed when the GDG deems implementing a course of action clearly doing more good than harm; while conducting a formal evidence review would not be a good use of resources.

The wording "we recommend" for strong EBRs and "we suggest" for conditional EBRs or CBRs are not used for GPS. Instead, the statement "**ungraded good practice statement**" is used in parenthesis after each GPS. This was decided to clarify that GPS are not graded and a formal evidence review was not conducted [1].

Table 5. Five criteria for developing good practice statements

Criteria	Descriptions
1	The statement is clear and actionable
2	The message is necessary regarding healthcare practice
3	The implementation of the statement is likely to result in large net positive consequences
4	The summarisation of evidence would be a poor use of the guideline panel's time
5	The rationale connecting the indirect evidence used to support the statement is clear and explicit

The statement "**ungraded good practice statement**" is used in parenthesis after each GPS. This was decided to clarify that GPS are not graded and a formal evidence review was not conducted [1].

11. Part F: Process of drafting recommendations

The guideline steering committee drafted the initial recommendations and for EBRs, assigned a preliminary strength and certainty of evidence. These initial recommendations were labelled as either EBRs or CBRs (see Figure 2). A detailed description of the committee's composition and role is available in the Administrative Report

11.1 First round

In the first round of review, all GDG members were presented with the full draft guideline, evidence profile, as well as the SoF. A SoF table was prepared for each drug class and included in the main guideline document to provide key information underlying a recommendation [27]. The SoF tables serve as a concise and accessible summary for each of the included outcomes along with the final rating for certainty of evidence. Each drug class section also included a detailed narrative summary. This summary aimed to provide a comprehensive overview of the evidence base. Each narrative summary covered an introduction to the drug class, key characteristics of each included study, a summary of key results, and a summary of withdrawal schedules. While the narrative evidence summary supporting the draft recommendations was provided, the full text of all studies identified were also provided for members to review the evidence in-depth.

All members were explicitly requested to review, provide feedback and approve the purpose, scope, and overall structure of the draft guideline. In addition, they were requested to review the initial draft EBRs based on the GRADE approach and review the draft CBRs. Their comments and suggestions were added to a Qualtrics survey link or added directly to the draft documents as revisions or comments. During the review, all members had the opportunity to revise the draft recommendations and adjust the types of recommendations, ratings, or strengths as applicable.

The first round of review and revisions following the qualitative feedback ran from 9th September 2024 to 2nd March 2025. During this period, the guideline steering committee refined the guideline draft and recommendations, as well as the categories of recommendations based on the initial feedback from the GDG. If there was sufficient quality evidence to support a recommendation, the recommendation was labelled as EBR. If there was no quality evidence for deprescribing from the systematic literature review to underpin recommendations, recommendations previously labelled as EBR were revised to CBR. Following feedback from the GDG, several GPS were also drafted based on the decision algorithm shown in Figure 2.

The guideline steering committee also recruited additional specialists and clinical experts relevant to therapeutic areas included in the guideline following feedback from the GDG. Several online meetings were held throughout the review process to address members' concerns, revise recommendations, and review evidence. Four drop-in sessions were also led by the guideline steering committee in December 2024 to provide an opportunity for live discussion instead of email exchanges. Several other online meetings were also conducted with specialists or clinical experts recruited to discuss the progress of the guidelines and draft recommendations. Many GDG members were not involved in any of the early stages

of planning the guideline in 2016, which may differ from the recommended approach to developing a clinical practice guideline. However, we've made every effort to ensure the guideline meets the standards given the circumstances.

11.2 Subsequent round (Delphi survey rounds)

The recommendations currently presented in this guideline were finalised through two rounds of Delphi consensus rounds. In the final guideline, no recommendations were classified as EBRs. The consensus process for CBRs and GPS followed a Delphi method and was single-blinded, with only the guideline steering committee having knowledge of the vote for each GDG member.

The first Delphi survey was distributed on 3rd March 2025 and closed on 28th March 2025. The survey was originally planned to run for 16 days until 18th March 2025 (taking into consideration two public holidays). However, individual extensions were offered for several members. At the conclusion of the first Delphi round, all but four statements achieved consensus (defined *a priori* as ≥ 75% agreement). Apart from the five guideline steering committee members, all GDG (including consumer advisory group members) had voting rights. In Round 1, 66 out of 67 GDG members (99%), excluding members of the guideline steering committee, completed the survey. A consumer member was not able to complete the survey on time due to personal circumstances.

Following the conclusion of Delphi round 1, some wording adjustments were made to the draft recommendation as needed following qualitative feedback from members. These were made as tracked changes in the guideline draft for review by members.

The second Delphi survey was distributed to all members on 7th April 2025 and closed on 16th April 2025. Explicit endorsements were sought for the three non-consensus statements and the major tracked changes presented in the draft guideline. In Round 2, 58 out of 67 (87%) GDG members completed the survey. Consensus was obtained for all statements presented in the second survey round.

12. Other resources

There are other more detailed drug-specific clinical practice guidelines, expert opinions, position paper recommendations, guidance or resources for a number of drug classes in deprescribing. Our goal for the current guideline is to provide broad guidance for deprescribing medicines commonly encountered in practice, complementing more detailed drug-specific clinical practice guidelines.

These resources will be referenced as additional resources.

A guideline adaptation (ADAPTE) method for adapting recommendations from other guidelines was not used in the current guideline due to the vast difference in the target populations.

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Appendix A. Search terms

CINAHL

Lines	Search terms
S110	S4 AND S104 AND S109
S109	S105 OR S106 OR S107 OR S108
S108	(MM “Inappropriate Prescribing”)
S107	(MM “Deprescribing”)
S106	AB (deprescrib* OR withdraw* OR ceas* OR cessation OR withh#ld OR discontinu* OR deintensify)
S105	TI (deprescrib* OR withdraw* OR ceas* OR cessation OR withh#ld OR discontinu* OR deintensify)
S104	S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 OR S55 OR S56 OR S57 OR S58 OR S59 OR S60 OR S61 OR S62 OR S63 OR S64 OR S65 OR S66 OR S67 OR S68 OR S69 OR S70 OR S71 OR S72 OR S73 OR S74 OR S75 OR S76 OR S77 OR S78 OR S79 OR S80 OR S81 OR S82 OR S83 OR S84 OR S85 OR S86 OR S87 OR S88 OR S89 OR S90 OR S91 OR S92 OR S93 OR S94 OR S95 OR S96 OR S97 OR S98 OR S99 OR S100 OR S101 OR S102 OR S103
S103	(MH “Analgesics, Nonnarcotic+”) OR (MH “Analgesics, Opioid+”)
S102	(MH “Fentanyl+”)
S101	(MH “Morphine+”)
S100	(MM “Oxycodone”)
S99	(MH “Analgesics, Opioid+”)
S98	(MM “Mesalamine”)
S97	(MM “Pravastatin”)
S96	(MH “Atorvastatin+”)
S95	(MM “Ramipril”)
S94	(MM “Perindopril”)
S93	(MH “Lisinopril+”)

S92	(MH “Enalapril+”)
S91	(MH “Dipeptidyl Peptidase 4 Inhibitors+”)
S90	(MH “Telmisartan+”)
S89	(MH “Irbesartan+”)
S88	(MH “Angiotensin II Type I Receptor Blockers+”)
S87	(MM “Prazosin”)
S86	(MH “Carvedilol”)
S85	(MM “Sotalol”)
S84	(MH “Bisoprolol Fumarate+”)
S83	(MM “Atenolol”)
S82	(MM “Metoprolol”)
S81	(MH “Adrenergic Beta-Antagonists+”)
S80	(MH “Antihypertensive Agents+”)
S79	(MM “Desvenlafaxine Succinate”)
S78	(MH “Venlafaxine+”)
S77	(MM “Amitriptyline”)
S76	(MH “Antidepressive Agents, Tricyclic+”)
S75	(MM “Mirtazapine”)
S74	(MM “Fluvoxamine Maleate”)
S73	(MM “Sertraline Hydrochloride”)
S72	(MM “Paroxetine”)
S71	(MM “Citalopram”)
S70	(MH “Fluoxetine+”)
S69	(MH “Serotonin Uptake Inhibitors+”)
S68	(MH “Antianxiety Agents+”)
S67	(MH “Antidepressive Agents+”)
S66	(MM “Digoxin”)
S65	(MH “Antiarrhythmia Agents+”)
S64	(MM “Indapamide”)
S63	(MH “Spironolactone+”)
S62	(MM “Furosemide”)

S61	(MH “Diuretics+”)
S60	(MM “Pregabalin”)
S59	(MM “Valproic Acid”)
S58	(MH “Anticonvulsants+”)
S57	(MM “Sitagliptin”)
S56	(MH “Dipeptidyl Peptidase 4 Inhibitors+”)
S55	(MH “Insulin+”)
S54	(MM “Metformin”)
S53	(MH “Thyroxine+”)
S52	(MM “Allopurinol”)
S51	(MM “Colchicine”)
S50	(MH “Antiinflammatory Agents+”)
S49	(MM “Cox-2 Inhibitors”)
S48	(MH “Antiinflammatory Agents, Non-Steroidal+”)
S47	(MM “Clopidogrel Bisulfate”)
S46	(MM “Aspirin”)
S45	(MH “Fibrinolytic Agents+”)
S44	(MM “Zoledronic Acid”)
S43	(MM “Donepezil”)
S42	(MH “Cholinesterase Inhibitors+”)
S41	(MH “Neuromuscular Nondepolarizing Agents+”)
S40	(MM “Temazepam”)
S39	(MM “Oxazepam”)
S38	(MH “Alprazolam”)
S37	(MH “Hypnotics and Sedatives+”)
S36	(MM “Risperidone”)
S35	(MM “Quetiapine”)
S34	(MH “Olanzapine+”)
S33	(MM “Nitroglycerin”)
S32	(MM “Nifedipine”)
S31	(MM “Felodipine”)

S30	(MM “Diltiazem”)
S29	(MH “Amlodipine+”)
S28	(MH “Calcium Channel Blockers+”) OR (MH “Calcium Channel Agonists”)
S27	(MH “Prednisolone+”) OR (MM”Prednisone”)
S26	(MH “Glucocorticoids+”)
S25	(MM “Fenofibrate”)
S24	(MM “Ranitidine”)
S23	(MH “Histamine H2 Antagonists+”)
S22	(MM “Rabeprazole Sodium”)
S21	(MH “Lansoprazole+”)
S20	(MM “Esomeprazole”)
S19	(MH “Omeprazole+”)
S18	(MM “Pantoprazole Sodium”)
S17	(MH “Antiulcer Agents+”)
S16	(MH “Proton Pump Inhibitors+”)
S15	(MM “Potassium”)
S14	(MM “Rivaroxaban”)
S13	(MH “Fibrin+”)
S12	(MH “Anticoagulants+”)
S11	(MM “Warfarin”)
S10	(MH “Testosterone+”) OR (MH”Testosterone ReplacementTherapy”)
S9	(MH “Progestational Hormones, Synthetic+”)
S8	(MH “Prescriptions, Drug+”) OR (MH “Drugs, Prescription+”)
S7	(MH “Polypharmacy+”)
S6	AB (medication* OR medicin* OR prescription* OR prescrib* OR polypharmac* OR “prescription drug*” OR “hormone replacement therapy” OR #estrogen OR #estradiol OR #estriol OR testosterone OR “direct thrombin inhibitor” OR dabigatran OR warfarin OR anticoagula* OR factor XA inhibitor* OR antithrombin* OR apixaban * OR rivaroxaban OR potassium OR “proton pump inhibitor” OR “antiulcer agent*” OR “acid suppression” OR PPI OR pantopra zole OR omeprazole OR esomeprazole OR lansoprazole OR rabeprazole OR antacid OR “histamine h2 antagonist#” OR ranitidine OR fenofibrate OR fibrate OR ezetimibe OR “adrenal cortex hormone#” OR corticosteroid# OR

glucocorticoid# OR steroid OR prednisolone OR prednisone OR dihyropyridine# OR “calcium channel blocker$” OR amlodipine OR diltiazem OR felodipine OR lercanidipine OR nifedipine OR verapamil OR nitrate$ OR nitroglycerin OR trinitrate OR isosorbide OR mononitrate ORantipsychotic OR “antipsychotic agent$” OR olanzapine OR quetiapine OR risperidone OR benzodiazepine$ OR alprazolam OR oxazepam OR temazepam OR diazepam OR hypnotic OR sedative OR anticholinergic$ OR “muscarinic antagonist$” OR oxybutynin OR anticholinesterase OR cholinesterase inhibitor$ OR donepezil OR bisphosphonate$ OR risedronate OR zoledronic acid OR denosumab OR antiplatelet$ OR “platelet aggregation inhibitor$” OR aspirin OR clopidogrel OR NSAID OR non-steroidal antiinflammator$ OR antiinflammatory agent$ OR cyclooxygenase 2 inhibitor$ OR COX-2 inhibitor$ OR celecoxib OR diclofenac OR meloxicam OR naproxen OR colchicine OR allopurinol OR levothyroxine OR thyroxine OR antihyperglycaemi$ OR “hypoglycaemic agent$” OR biguanide OR metformin OR sulphonylurea OR gliclazide OR glimepiride OR insulin OR “dipeptidyl-peptidase IV inhibitor$” OR Sitagliptin OR antiepilep$ OR anticonvulsant$ OR valproate OR “valproic acid” OR carbamazepine OR pregabalin OR Levetiracetam OR diuretic$ OR frusemide OR furosemide OR indapamide OR spironolactone OR “antiarrhythmia agent$” OR digoxin OR antidepressant$ OR “antidepressive agent$” OR “anti-anxiety agent$” OR SSRI OR “selective serotonin reuptake inhibitor$” OR “serotonin uptake inhibitor$” OR fluoxetine OR citalopram OR paroxetine OR sertraline OR escitalopram OR fluvoxamine OR mirtazapine OR TCA OR “tricyclic antidepressant$” OR amitriptyline OR SNRI OR “serotonin and noradrenaline reuptake inhibitor$” OR venlafaxine OR duloxetine OR desvenlafaxine OR “antihypertensive agent$” OR antihypertensive$ OR “beta blocker” OR metoprolol OR atenolol OR bisoprolol OR carvedilol OR sotalol OR “alpha blocker$” OR prazosin OR “angiotensin II receptor antagonist” OR “angiotensin II type 1 receptor blocker$” OR sartan OR irbesartan OR candesartan OR telmisartan OR olmesartan OR ACEI OR enalapril OR lisinopril OR perindopril OR ramipril OR statin.ti,ab. OR “HmGCoA Reductase Inhibitor$” OR “hydroxymethylglutaryl-CoA reductase inhibitor$” OR atorvastatin OR rosuvastatin OR simvastatin OR pravastatin OR “aminosalicylic acid$” OR amino salicylate$ OR sulfasalazine OR mesalazine OR moxonidine OR opioid$ OR oxycodone OR tramadol OR morphine OR fentanyl OR paracetamol OR acetaminophen)

S5	TI (medication* OR medicin* OR prescription* OR prescrib* OR polypharmac* OR "prescription drug*" OR "hormone replacement therapy" OR #estrogen OR #estradiol OR #estriol OR testosterone OR "direct thrombin inhibitor" OR dabigatran OR warfarin OR anticoagula* OR factor XA inhibitor* OR antithrombin* OR apixaban * OR rivaroxaban OR potassium OR "proton pump inhibitor" OR "antiulcer agent*" OR "acid suppression" OR PPI OR pantoprazole OR omeprazole OR esomeprazole OR lansoprazole OR rabeprazole OR antacid OR "histamine h2 antagonist#" OR ranitidine OR fenofibrate OR fibrate OR ezetimibe OR "adrenal cortex hormone#" OR corticosteroid# OR glucocorticoid# OR steroid OR prednisolone OR prednisone OR dihyropyridine# OR "calcium channel blocker$" OR amlodipine OR diltiazem OR felodipine OR lercanidipine OR nifedipine OR verapamil OR nitrate$ OR nitroglycerin OR trinitrate OR isosorbide OR mononitrate OR antipsychotic OR "antipsychotic agent$" OR olanzapine OR quetiapine OR risperidone OR benzodiazepine$ OR alprazolam OR oxazepam OR temazepam OR diazepam OR hypnotic OR sedative OR anticholinergic$ OR "muscarinic antagonist$" OR oxybutynin OR anticholinesterase OR cholinesterase inhibitor$ OR donepezil OR bisphosphonate$ OR risedronate OR zoledronic acid OR denosumab OR antiplatelet$ OR "platelet aggregation inhibitor$" OR aspirin OR clopidogrel OR NSAID OR non-steroidal antiinflammator$ OR antiinflammatory agent$ OR cyclooxygenase 2 inhibitor$ OR COX-2 inhibitor$ OR celecoxib OR diclofenac OR meloxicam OR naproxen OR colchicine OR allopurinol OR levothyroxine OR thyroxine OR antihyperglycaemi$ OR "hypoglycaemic agent$" OR biguanide OR metformin OR sulphonylurea OR gliclazide OR glimepiride OR insulin OR "dipeptidyl-peptidase IV inhibitor$" OR Sitagliptin OR antiepilep$ OR anticonvulsant$ OR valproate OR "valproic acid" OR carbamazepine OR pregabalin OR Levetiracetam OR diuretic$ OR frusemide OR furosemide OR indapamide OR spironolactone OR "antiarrhythmia agent$" OR digoxin OR antidepressant$ OR "antidepressive agent$" OR "anti-anxiety agent$" OR SSRI OR "selective serotonin reuptake inhibitor$" OR "serotonin uptake inhibitor$" OR fluoxetine OR citalopram OR paroxetine OR sertraline OR escitalopram OR fluvoxamine OR mirtazapine OR TCA OR "tricyclic antidepressant$" OR amitriptyline OR SNRI OR "serotonin and noradrenaline reuptake inhibitor$" OR venlafaxine OR duloxetine OR desvenlafaxine OR "antihypertensive agent$" OR antihypertensive$ OR "beta blocker" OR metoprolol OR atenolol OR bisoprolol OR carvedilol OR sotalol OR "alpha blocker$" OR prazosin OR "angiotensin II receptor antagonist" OR "angiotensin II type 1 receptor blocker$" OR sartan OR irbesartan OR candesartan OR telmisartan OR olmesartan OR ACEI OR enalapril OR lisinopril OR perindopril OR ramipril OR statin.ti,ab. OR "HmG CoA Reductase Inhibitor$" OR "hydroxymethylglutaryl-CoA reductase inhibitor$" OR atorvastatin OR rosuvastatin OR simvastatin OR pravastatin OR "aminosalicylic acid$" OR aminosalicylate$ OR sulfasalazine OR mesalazine OR moxonidine OR opioid$
S4	S1 OR S2 OR S3

S3	TX (elder* or geriatric* or veteran*)
S2	TX (“late life” or “old age” orseniors or geriatric#)
S1	TX ((old or older or ag#ing orsenior) n3 (person# or people# oradult# or patient# or consumer#))

Medline

Lines	Search terms
1	((old or older or ag?ing or senior) adj3 (person? or people? or adult? or patient? or consumer?)).ti,ab,kw.
2	(late life or old age or seniors or geriatric?).ti,ab,kw.
3	(elder* or geriatric* or veteran*).mp.
4	1 or 2 or 3
5	medication$.ti,ab.
6	medicin$.ti,ab.
7	prescription$.ti,ab.
8	prescrib$.ti,ab.
9	polypharmac$.ti,ab.
10	prescription drug$.ti,ab.
11	hormone replacement therapy.ti,ab.
12	?estrogen.ti,ab.
13	?estradiol.ti,ab.
14	?estriol.ti,ab.
15	testosterone.ti,ab.
16	direct thrombin inhibitor.ti,ab.
17	dabigatran.ti,ab.
18	warfarin.ti,ab.
19	anticoagula$.ti,ab.
20	factor XA inhibitor$.ti,ab.
21	antithrombin$.ti,ab.
22	apixaban.ti,ab.
23	rivaroxaban.ti,ab.
24	rivaroxaban/
25	potassium.ti,ab.
26	proton pump inhibitor.ti,ab.
27	anti-ulcer agent$.ti,ab.
28	acid suppression.ti,ab.

29	PPI.ti,ab.
30	pantoprazole.ti,ab.
31	omeprazole.ti,ab.
32	esomeprazole.ti,ab.
33	lansoprazole.ti,ab.
34	rabeprazole.ti,ab.
35	antacid.ti,ab.
36	histamine h2 antagonist$.ti,ab.
37	ranitidine.ti,ab.
38	fenofibrate.ti,ab.
39	fibrate.ti,ab.
40	ezetimibe.ti,ab.
41	adrenal cortex hormone$.ti,ab.
42	corticosteroid$.ti,ab.
43	glucocorticoid$.ti,ab.
44	steroid.ti,ab.
45	prednisolone.ti,ab.
46	prednisolone/
47	prednisone.ti,ab.
48	dihyropyridine$.ti,ab.
49	calcium channel blocker$.ti,ab.
50	amlodipine.ti,ab.
51	diltiazem.ti,ab.
52	felodipine.ti,ab.
53	lercanidipine.ti,ab.
54	nifedipine.ti,ab.
55	verapamil.ti,ab.
56	nitrate$.ti,ab.
57	nitroglycerin.ti,ab.
58	trinitrate.ti,ab.
59	isosorbide.ti,ab.

60	mononitrate.ti,ab.
61	antipsychotic.ti,ab.
62	antipsychotic agent$.ti,ab.
63	olanzapine.ti,ab.
64	quetiapine.ti,ab.
65	risperidone.ti,ab.
66	benzodiazepine$.ti,ab.
67	alprazolam.ti,ab.
68	oxazepam.ti,ab.
69	temazepam.ti,ab.
70	diazepam.ti,ab.
71	hypnotic.ti,ab.
72	sedative.ti,ab.
73	anticholinergic$.ti,ab.
74	muscarinic antagonist$.ti,ab.
75	oxybutynin.ti,ab.
76	anticholinesterase.ti,ab.
77	cholinesterase inhibitor$.ti,ab.
78	donepezil.ti,ab.
79	bisphosphonate$.ti,ab.
80	risedronate.ti,ab.
81	zoledronic acid.ti,ab.
82	denosumab.ti,ab.
83	antiplatelet$.ti,ab.
84	platelet aggregation inhibitor$.ti,ab.
85	aspirin.ti,ab.
86	clopidogrel.ti,ab.
87	NSAID.ti,ab.
88	non-steroidal anti-inflammator$.ti,ab.
89	anti-inflammatory agent$.ti,ab.
90	cyclooxygenase 2 inhibitor$.ti,ab.

91	COX-2 inhibitor$.ti,ab.
92	celecoxib.ti,ab.
93	diclofenac.ti,ab.
94	meloxicam.ti,ab.
95	naproxen.ti,ab.
96	colchicine.ti,ab.
97	allopurinol.ti,ab.
98	levothyroxine.ti,ab.
99	thyroxine.ti,ab.
100	antihyperglycaemi$.ti,ab.
101	hypoglycaemic agent$.ti,ab.
102	biguanide.ti,ab.
103	metformin.ti,ab.
104	sulphonylurea.ti,ab.
105	gliclazide.ti,ab.
106	glimepiride.ti,ab.
107	insulin.ti,ab.
108	dipeptidyl-peptidase IV inhibitor$.ti,ab.
109	Sitagliptin.ti,ab.
110	antiepilep$.ti,ab.
111	anticonvulsant$.ti,ab.
112	valproate.ti,ab.
113	valproic acid.ti,ab.
114	carbamazepine.ti,ab.
115	pregabalin.ti,ab.
116	levetiracetam.ti,ab.
117	diuretic$.ti,ab.
118	frusemide.ti,ab.
119	furosemide.ti,ab.
120	indapamide.ti,ab.
121	spironolactone.ti,ab.

122	anti-arrhythmia agent$.ti,ab.
123	digoxin.ti,ab.
124	antidepressant$.ti,ab.
125	antidepressive agent$.ti,ab.
126	anti-anxiety agent$.ti,ab.
127	SSRI.ti,ab.
128	selective serotonin reuptake inhibitor$.ti,ab.
129	serotonin uptake inhibitor$.ti,ab.
130	fluoxetine.ti,ab.
131	citalopram.ti,ab.
132	paroxetine.ti,ab.
133	sertraline.ti,ab.
134	escitalopram.ti,ab.
135	fluvoxamine.ti,ab.
136	mirtazapine.ti,ab.
137	TCA.ti,ab.
138	tricyclic antidepressant$.ti,ab.
139	amitriptyline.ti,ab.
140	SNRI.ti,ab.
141	(serotonin and noradrenaline reuptake inhibitor$).ti,ab.
142	venlafaxine.ti,ab.
143	duloxetine.ti,ab.
144	desvenlafaxine.ti,ab.
145	antihypertensive agent$.ti,ab.
146	antihypertensive$.ti,ab.
147	beta blocker.ti,ab.
148	metoprolol.ti,ab.
149	atenolol.ti,ab.
150	bisoprolol.ti,ab.
151	carvedilol.ti,ab.
152	sotalol.ti,ab.

153	alpha blocker$.ti,ab.
154	prazosin.ti,ab.
155	angiotensin II receptor antagonist.ti,ab.
156	angiotensin II type 1 receptor blocker$.ti,ab.
157	sartan.ti,ab.
158	irbesartan.ti,ab.
159	candesartan.ti,ab.
160	telmisartan.ti,ab.
161	olmesartan.ti,ab.
162	ACEI.ti,ab.
163	enalapril.ti,ab.
164	lisinopril.ti,ab.
165	perindopril.ti,ab.
166	ramipril.ti,ab.
167	statin.ti,ab.
168	HmG CoA Reductase Inhibitor$.ti,ab.
169	hydroxymethylglutaryl-CoA reductase inhibitor$.ti,ab.
170	atorvastatin.ti,ab.
171	rosuvastatin.ti,ab.
172	simvastatin.ti,ab.
173	pravastatin.ti,ab.
174	aminosalicylic acid$.ti,ab.
175	aminosalicylate$.ti,ab.
176	sulfasalazine.ti,ab.
177	mesalazine.ti,ab.
178	moxonidine.ti,ab.
179	opioid$.ti,ab.
180	oxycodone.ti,ab.
181	tramadol.ti,ab.
182	morphine.ti,ab.
183	fentanyl.ti,ab.

184	paracetamol.ti,ab.
185	acetaminophen.ti,ab.
186	polypharmacy/
187	prescription drugs/
188	hormone replacement therapy/
189	estrogens/
190	testosterone propionate/
191	dabigatran/
192	warfarin/
193	anticoagulants/
194	antithrombins/
195	rivaroxaban/
196	potassium/
197	proton pump inhibitors/
198	anti-ulcer agents/
199	pantoprazole/
200	omeprazole/
201	esomeprazole/
202	lansoprazole/
203	rabeprazole/
204	histamine h2 antagonists/
205	ranitidine/
206	fenofibrate/
207	ezetimibe/
208	adrenal cortex hormones/
209	glucocorticoids/
210	prednisolone/
211	prednisone/
212	dihydropyridines/
213	calcium channel blockers/
214	amlodipine/

215	diltiazem/
216	felodipine/
217	nifedipine/
218	verapamil/
219	nitroglycerin/
220	antipsychotic agents/
221	olanzapine/
222	quetiapine/
223	risperidone/
224	benzodiazepines/
225	“Hypnotics and Sedatives”/
226	alprazolam/
227	oxazepam/
228	temazepam/
229	diazepam/
230	muscarinic antagonists/
231	cholinesterase inhibitors/
232	donepezil/
233	bone density conservation agents/
234	risedronic acid/
235	zoledronic acid/
236	denosumab/
237	platelet aggregation inhibitors/
238	aspirin/
239	clopidogrel/
240	anti-inflammatory agents/
241	anti-inflammatory agents, non-steroidal/
242	cyclooxygenase 2 inhibitors/
243	celecoxib/
244	diclofenac/
245	meloxicam/

246	naproxen/
247	gout suppressants/
248	colchicine/
249	allopurinol/
250	thyroxine/
251	metformin/
252	gliclazide/
253	insulin/
254	dipeptidyl-peptidase IV inhibitors/
255	anticonvulsants/
256	sitagliptin phosphate/
257	valproic acid/
258	carbamazepine/
259	pregabalin/
260	levetiracetam/
261	diuretics/
262	furosemide/
263	spironolactone/
264	indapamide/
265	anti-arrhythmia agents/
266	digoxin/
267	antidepressive agents/
268	anti-anxiety agents/
269	serotonin uptake inhibitors/
270	fluoxetine/
271	citalopram/
272	paroxetine/
273	sertraline/
274	escitalopram/
275	fluvoxamine/
276	mirtazapine/

277	antidepressive agents, tricyclic/
278	amitriptyline/
279	venlafaxine hydrochloride/
280	duloxetine hydrochloride/
281	desvenlafaxine succinate/
282	antihypertensive agents/
283	adrenergic beta-1 receptor antagonists/
284	metoprolol/
285	atenolol/
286	bisoprolol/
287	sotalol/
288	carvedilol/
289	prazosin/
290	angiotensin II type 1 receptor blockers/
291	irbesartan/
292	telmisartan/
293	angiotensin-converting enzyme inhibitors/
294	enalapril/
295	lisinopril/
296	perindopril/
297	ramipril/
298	anticholesteremic agents/
299	hydroxymethylglutaryl-CoA reductase inhibitors/
300	atorvastatin/
301	rosuvastatin calcium/
302	simvastatin/
303	pravastatin/
304	aminosalicyclic acids/
305	sulfasalazine/
306	mesalamine/
307	analgesics, opioid/

308	oxycodone/
309	tramadol/
310	morphine/
311	fentanyl/
312	analgesics, non-narcotic/
313	acetaminophen/
314	Pharmaceutical Preparations/
315	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129 or 130 or 131 or 132 or 133 or 134 or 135 or 136 or 137 or 138 or 139 or 140 or 141 or 142 or 143 or 144 or 145 or 146 or 147 or 148 or 149 or 150 or 151 or 152 or 153 or 154 or 155 or 156 or 157 or 158 or 159 or 160 or 161 or 162 or 163 or 164 or 165 or 166 or 167 or 168 or 169 or 170 or 171 or 172 or 173 or 174 or 175 or 176 or 177 or 178 or 179 or 180 or 181 or 182 or 183 or 184 or 185 or 186 or 187 or 188 or 189 or 190 or 191 or 192 or 193 or 194 or 195 or 196 or 197 or 198 or 199 or 200 or 201 or 202 or 203 or 204 or 205 or 206 or 207 or 208 or 209 or 210 or 211 or 212 or 213 or 214 or 215 or 216 or 217 or 218 or 219 or 220 or 221 or 222 or 223 or 224 or 225 or 226 or 227 or 228 or 229 or 230 or 231 or 232 or 233 or 234 or 235 or 236 or 237 or 238 or 239 or 240 or 241 or 242 or 243 or 244 or 245 or 246 or 247 or 248 or 249 or 250 or 251 or 252 or 253 or 254 or 255 or 256 or 257 or 258 or 259 or 260 or 261 or 262 or 263 or 264 or 265 or 266 or 267 or 268 or 269 or 270 or 271 or 272 or 273 or 274 or 275 or 276 or 277 or 278 or 279 or 280 or 281 or 282 or 283 or 284 or 285 or 286 or 287 or 288 or 289 or 290 or 291 or 292 or 293 or 294 or 295 or 296 or 297 or 298 or 299 or 300 or 301 or 302 or 303 or 304 or 305 or 306 or 307 or 308 or 309 or 310 or 311 or 312 or 313 or 314
316	deprescrib$.ti,ab.
317	withdraw$.ti,ab.
318	ceas$.ti,ab.
319	cessation.ti,ab.
320	withh?ld.ti,ab.
321	discontinu$.ti,ab.

322	de-intensify.ti,ab.
323	deprescriptions/
324	inappropriate prescribing/
325	316 or 317 or 318 or 319 or 320 or 321 or 322 or 323 or 324
326	4 and 315 and 325

Embase

Lines	Search terms
1	((old or older or ag?ing or senior) adj3 (person? or people? or adult? or patient? or consumer?)).ti,ab,kw.
2	(late life or old age or seniors or geriatric?).ti,ab,kw.
3	(elder* or geriatric* or veteran*).mp.
4	1 or 2 or 3
5	medication$.ti,ab.
6	medicin$.ti,ab.
7	prescription$.ti,ab.
8	prescrib$.ti,ab.
9	polypharmac$.ti,ab.
10	prescription drug$.ti,ab.
11	hormone replacement therapy.ti,ab.
12	?estrogen.ti,ab.
13	?estradiol.ti,ab.
14	?estriol.ti,ab.
15	testosterone.ti,ab.
16	direct thrombin inhibitor.ti,ab.
17	dabigatran.ti,ab.
18	warfarin.ti,ab.
19	anticoagula$.ti,ab.
20	factor XA inhibitor$.ti,ab.
21	antithrombin$.ti,ab.
22	apixaban.ti,ab.
23	rivaroxaban.ti,ab.
24	potassium.ti,ab.
25	proton pump inhibitor.ti,ab.
26	anti-ulcer agent$.ti,ab.
27	acid suppression.ti,ab.
28	PPI.ti,ab.

29	pantoprazole.ti,ab.
30	omeprazole.ti,ab.
31	esomeprazole.ti,ab.
32	lansoprazole.ti,ab.
33	rabeprazole.ti,ab.
34	antacid.ti,ab.
35	histamine h2 antagonist$.ti,ab.
36	ranitidine.ti,ab.
37	fenofibrate.ti,ab.
38	fibrate.ti,ab.
39	ezetimibe.ti,ab.
40	adrenal cortex hormone$.ti,ab.
41	corticosteroid$.ti,ab.
42	glucocorticoid$.ti,ab.
43	steroid.ti,ab.
44	prednisolone.ti,ab.
45	prednisone.ti,ab.
46	dihyropyridine$.ti,ab.
47	calcium channel blocker$.ti,ab.
48	amlodipine.ti,ab.
49	diltiazem.ti,ab.
50	felodipine.ti,ab.
51	lercanidipine.ti,ab.
52	nifedipine.ti,ab.
53	verapamil.ti,ab.
54	nitrate$.ti,ab.
55	nitroglycerin.ti,ab.
56	trinitrate.ti,ab.
57	isosorbide.ti,ab.
58	mononitrate.ti,ab.
59	antipsychotic.ti,ab.

60	antipsychotic agent$.ti,ab.
61	olanzapine.ti,ab.
62	quetiapine.ti,ab.
63	risperidone.ti,ab.
64	benzodiazepine$.ti,ab.
65	alprazolam.ti,ab.
66	oxazepam.ti,ab.
67	temazepam.ti,ab.
68	diazepam.ti,ab.
69	hypnotic.ti,ab.
70	sedative.ti,ab.
71	anticholinergic$.ti,ab.
72	muscarinic antagonist$.ti,ab.
73	oxybutynin.ti,ab.
74	anticholinesterase.ti,ab.
75	cholinesterase inhibitor$.ti,ab.
76	donepezil.ti,ab.
77	bisphosphonate$.ti,ab.
78	risedronate.ti,ab.
79	zoledronic acid.ti,ab.
80	denosumab.ti,ab.
81	antiplatelet$.ti,ab.
82	platelet aggregation inhibitor$.ti,ab.
83	aspirin.ti,ab.
84	clopidogrel.ti,ab.
85	NSAID.ti,ab.
86	non-steroidal anti-inflammator$.ti,ab.
87	anti-inflammatory agent$.ti,ab.
88	cyclooxygenase 2 inhibitor$.ti,ab.
89	COX-2 inhibitor$.ti,ab.
90	celecoxib.ti,ab.

91	diclofenac.ti,ab.
92	meloxicam.ti,ab.
93	naproxen.ti,ab.
94	colchicine.ti,ab.
95	allopurinol.ti,ab.
96	levothyroxine.ti,ab.
97	thyroxine.ti,ab.
98	antihyperglycaemi$.ti,ab.
99	hypoglycaemic agent$.ti,ab.
100	biguanide.ti,ab.
101	metformin.ti,ab.
102	sulphonylurea.ti,ab.
103	gliclazide.ti,ab.
104	glimepiride.ti,ab.
105	insulin.ti,ab.
106	dipeptidyl-peptidase IV inhibitor$.ti,ab.
107	Sitagliptin.ti,ab.
108	antiepilep$.ti,ab.
109	anticonvulsant$.ti,ab.
110	valproate.ti,ab.
111	valproic acid.ti,ab.
112	carbamazepine.ti,ab.
113	pregabalin.ti,ab.
114	levetiracetam.ti,ab.
115	diuretic$.ti,ab.
116	frusemide.ti,ab.
117	furosemide.ti,ab.
118	indapamide.ti,ab.
119	spironolactone.ti,ab.
120	anti-arrhythmia agent$.ti,ab.
121	digoxin.ti,ab.

122	antidepressant$.ti,ab.
123	antidepressive agent$.ti,ab.
124	anti-anxiety agent$.ti,ab.
125	SSRI.ti,ab.
126	selective serotonin reuptake inhibitor$.ti,ab.
127	serotonin uptake inhibitor$.ti,ab.
128	fluoxetine.ti,ab.
129	citalopram.ti,ab.
130	paroxetine.ti,ab.
131	sertraline.ti,ab.
132	escitalopram.ti,ab.
133	fluvoxamine.ti,ab.
134	mirtazapine.ti,ab.
135	TCA.ti,ab.
136	tricyclic antidepressant$.ti,ab.
137	amitriptyline.ti,ab.
138	SNRI.ti,ab.
139	(serotonin and noradrenaline reuptake inhibitor$).ti,ab.
140	venlafaxine.ti,ab.
141	duloxetine.ti,ab.
142	desvenlafaxine.ti,ab.
143	antihypertensive agent$.ti,ab.
144	antihypertensive$.ti,ab.
145	beta blocker.ti,ab.
146	metoprolol.ti,ab.
147	atenolol.ti,ab.
148	bisoprolol.ti,ab.
149	carvedilol.ti,ab.
150	sotalol.ti,ab.
151	alpha blocker$.ti,ab.
152	prazosin.ti,ab.

153	angiotensin II receptor antagonist.ti,ab.
154	angiotensin II type 1 receptor blocker$.ti,ab.
155	sartan.ti,ab.
156	irbesartan.ti,ab.
157	candesartan.ti,ab.
158	telmisartan.ti,ab.
159	olmesartan.ti,ab.
160	ACEI.ti,ab.
161	enalapril.ti,ab.
162	lisinopril.ti,ab.
163	perindopril.ti,ab.
164	ramipril.ti,ab.
165	statin.ti,ab.
166	HmG CoA Reductase Inhibitor$.ti,ab.
167	hydroxymethylglutaryl-CoA reductase inhibitor$.ti,ab.
168	atorvastatin.ti,ab.
169	rosuvastatin.ti,ab.
170	simvastatin.ti,ab.
171	pravastatin.ti,ab.
172	aminosalicylic acid$.ti,ab.
173	aminosalicylate$.ti,ab.
174	sulfasalazine.ti,ab.
175	mesalazine.ti,ab.
176	moxonidine.ti,ab.
177	opioid$.ti,ab.
178	oxycodone.ti,ab.
179	tramadol.ti,ab.
180	morphine.ti,ab.
181	fentanyl.ti,ab.
182	paracetamol.ti,ab.
183	acetaminophen.ti,ab.

184	exp polypharmacy/
185	exp prescription drug/
186	exp hormone substitution/
187	exp estrogen/
188	exp testosterone propionate/
189	exp dabigatran/
190	exp warfarin/
191	exp anticoagulant agent/
192	exp antithrombin/
193	exp rivaroxaban/
194	exp potassium/
195	exp proton pump inhibitor/
196	exp antiulcer agent/
197	exp pantoprazole/
198	exp omeprazole/
199	exp esomeprazole/
200	exp lansoprazole/
201	exp rabeprazole/
202	exp histamine H2 receptor antagonist/
203	exp ranitidine/
204	exp fenofibrate/
205	exp ezetimibe/
206	exp corticosteroid/
207	exp glucocorticoid/
208	exp prednisolone/
209	exp prednisone/
210	exp dihydropyridine derivative/
211	exp calcium channel blocking agent/
212	exp amlodipine/
213	exp diltiazem/
214	exp felodipine/

215	exp nifedipine/
216	exp verapamil/
217	exp glyceryl trinitrate/
218	exp neuroleptic agent/
219	exp olanzapine/
220	exp quetiapine/
221	exp risperidone/
222	exp benzodiazepine/
223	exp hypnotic sedative agent/
224	exp alprazolam/
225	exp oxazepam/
226	exp temazepam/
227	exp diazepam/
228	exp muscarinic receptor blocking agent/
229	exp cholinesterase inhibitor/
230	exp donepezil/
231	exp bone density conservation agent/
232	exp risedronic acid/
233	exp zoledronic acid/
234	exp denosumab/
235	exp antithrombocytic agent/
236	exp acetylsalicylic acid/
237	exp clopidogrel/
238	exp antiinflammatory agent/
239	exp cyclooxygenase 2 inhibitor/
240	exp celecoxib/
241	exp diclofenac/
242	exp meloxicam/
243	exp naproxen/
244	exp antigout agent/
245	exp colchicine/

246	exp *allopurinol/
247	exp thyroxine/
248	exp metformin/
249	exp insulin/
250	exp dipeptidyl peptidase IV inhibitor/
251	exp anticonvulsive agent/
252	exp sitagliptin/
253	exp valproic acid/
254	exp carbamazepine/
255	exp nonsteroid antiinflammatory agent/
256	exp pregabalin/
257	exp levetiracetam/
258	exp diuretic agent/
259	exp furosemide/
260	exp spironolactone/
261	exp indapamide/
262	exp antiarrhythmic agent/
263	exp digoxin/
264	exp antidepressant agent/
265	exp anxiolytic agent/
266	exp serotonin uptake inhibitor/
267	exp fluoxetine/
268	exp citalopram/
269	exp paroxetine/
270	exp sertraline/
271	exp escitalopram/
272	exp fluvoxamine/
273	exp mirtazapine/
274	exp tricyclic antidepressant agent/
275	exp amitriptyline/

276	exp venlafaxine/
277	exp duloxetine/
278	exp desvenlafaxine/
279	exp antihypertensive agent/
280	exp beta 1 adrenergic receptor blocking agent/
281	exp metoprolol/
282	exp atenolol/
283	exp bisoprolol/
284	exp sotalol/
285	exp carvedilol/
286	exp prazosin/
287	exp angiotensin 1 receptor antagonist/
288	exp irbesartan/
289	exp telmisartan/
290	exp dipeptidyl carboxypeptidase inhibitor/
291	exp enalapril/
292	exp lisinopril/
293	exp perindopril/
294	exp ramipril/
295	exp hypocholesterolemic agent/
296	exp hydroxymethylglutaryl coenzyme A reductase inhibitor/
297	exp atorvastatin/
298	exp rosuvastatin/
299	exp simvastatin/
300	exp pravastatin/
301	exp aminosalicylic acid/
302	exp salazosulfapyridine/
303	exp salazosulfapyridine/
304	exp mesalazine/
305	exp narcotic analgesic agent/
306	exp oxycodone/

307	exp tramadol/
308	exp morphine/
309	exp fentanyl/
310	exp analgesic agent/
311	exp paracetamol/
312	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129 or 130 or 131 or 132 or 133 or 134 or 135 or 136 or 137 or 138 or 139 or 140 or 141 or 142 or 143 or 144 or 145 or 146 or 147 or 148 or 149 or 150 or 151 or 152 or 153 or 154 or 155 or 156 or 157 or 158 or 159 or 160 or 161 or 162 or 163 or 164 or 165 or 166 or 167 or 168 or 169 or 170 or 171 or 172 or 173 or 174 or 175 or 176 or 177 or 178 or 179 or 180 or 181 or 182 or 183 or 184 or 185 or 186 or 187 or 188 or 189 or 190 or 191 or 192 or 193 or 194 or 195 or 196 or 197 or 198 or 199 or 200 or 201 or 202 or 203 or 204 or 205 or 206 or 207 or 208 or 209 or 210 or 211 or 212 or 213 or 214 or 215 or 216 or 217 or 218 or 219 or 220 or 221 or 222 or 223 or 224 or 225 or 226 or 227 or 228 or 229 or 230 or 231 or 232 or 233 or 234 or 235 or 236 or 237 or 238 or 239 or 240 or 241 or 242 or 243 or 244 or 245 or 246 or 247 or 248 or 249 or 250 or 251 or 252 or 253 or 254 or 255 or 256 or 257 or 258 or 259 or 260 or 261 or 262 or 263 or 264 or 265 or 266 or 267 or 268 or 269 or 270 or 271 or 272 or 273 or 274 or 275 or 276 or 277 or 278 or 279 or 280 or 281 or 282 or 283 or 284 or 285 or 286 or 287 or 288 or 289 or 290 or 291 or 292 or 293 or 294 or 295 or 296 or 297 or 298 or 299 or 300 or 301 or 302 or 303 or 304 or 305 or 306 or 307 or 308 or 309 or 310 or 311
313	deprescrib$.ti,ab.
314	withdraw$.ti,ab.
315	ceas$.ti,ab.
316	cessation.ti,ab.
317	withh?ld.ti,ab.
318	discontinu$.ti,ab.
319	de-intensify.ti,ab.
320	exp deprescription/

321	exp inappropriate prescribing/
322	313 or 314 or 315 or 316 or 317 or 318 or 319 or 320 or 321
323	4 and 312 and 322

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(((medication* OR prescrib* OR polypharmac* OR "prescription drug*") OR ("hormone replacement therapy" OR estrogen OR estradiol OR estriol OR testosterone) OR ("direct thrombin inhibitor" OR dabigatran OR warfarin OR anticoagula* OR "factor XA inhibitor*") OR (antithrombin* OR "apixaban*" OR rivaroxaban OR potassium OR "proton pump inhibitor") OR ("anti-ulcer agent*" OR "acid suppression" OR PPI OR pantoprazole OR omeprazole) OR (esomeprazole OR lansoprazole OR rabeprazole OR antacid OR "histamine h2 antagonist?") OR noft(ranitidine OR fenofibrate OR fibrate OR ezetimibe OR "adrenal cortex hormone?") OR noft(corticosteroid? OR glucocorticoid? OR steroid OR prednisolone OR prednisone) OR noft(dihyropyridine? OR "calcium channel blocker*" OR amlodipine OR diltiazem OR felodipine)) OR ((lercanidipine OR nifedipine OR verapamil OR nitrate* OR nitroglycerin OR trinitrate OR isosorbide) OR (mononitrate OR antipsychotic OR "antipsychotic agent*" OR olanzapine OR quetiapine) OR (risperidone OR benzodiazepine* OR alprazolam OR oxazepam OR temazepam OR diazepam) OR (hypnotic OR sedative OR anticholinergic* OR "muscarinic antagonist*" OR oxybutynin) OR (anticholinesterase OR "cholinesterase inhibitor*" OR donepezil OR bisphosphonate*) OR (risedronate OR "zoledronic acid" OR denosumab OR antiplatelet*) OR ("platelet aggregation inhibitor*" OR aspirin OR clopidogrel OR NSAID) OR ("non-steroidal anti-inflammator*" OR "anti-inflammatory agent*") OR ("cyclooxygenase 2 inhibitor*" OR "COX-2 inhibitor*" OR celecoxib OR diclofenac OR meloxicam) OR (naproxen OR colchicine OR allopurinol OR levothyroxine OR thyroxine OR antihyperglycaemi*)) OR (("hypoglycaemic agent*" OR biguanide OR metformin OR sulphonylurea OR gliclazide OR glimepiride OR insulin OR "dipeptidyl-peptidase IV inhibitor*" OR Sitagliptin OR antiepilep* OR anticonvulsant* OR valproate OR "valproic acid" OR carbamazepine OR pregabalin) OR (Levetiracetam OR diuretic* OR frusemide OR furosemide OR indapamide OR spironolactone OR "anti-arrhythmia agent*" OR digoxin OR antidepressant* OR "antidepressive agent*" OR "anti-anxiety agent*" OR SSRI OR "selective serotonin reuptake inhibitor*" OR "serotonin uptake inhibitor*" OR fluoxetine OR citalopram OR paroxetine OR sertraline) OR (escitalopram OR fluvoxamine OR mirtazapine OR TCA OR "tricyclic antidepressant*" OR amitriptyline OR SNRI OR "serotonin and noradrenaline reuptake inhibitor*" OR venlafaxine OR duloxetine OR desvenlafaxine OR "antihypertensive agent*" OR antihypertensive* OR "beta blocker" OR metoprolol OR atenolol OR bisoprolol OR carvedilol OR sotalol OR "alpha blocker*" OR prazosin OR "angiotensin II receptor antagonist") OR ("angiotensin II type 1 receptor blocker*" OR sartan OR irbesartan OR candesartan OR telmisartan OR olmesartan OR ACEI OR enalapril OR lisinopril OR perindopril OR ramipril OR statin OR "HmG CoA Reductase Inhibitor*" OR "hydroxymethylglutaryl-CoA reductase inhibitor*" OR atorvastatin OR rosuvastatin OR simvastatin OR pravastatin OR "aminosalicylic acid*" OR aminosalicylate* OR sulfasalazine OR mesalazine OR moxonidine OR opioid* OR oxycodone OR tramadol OR morphine OR fentanyl OR paracetamol OR

acetaminophen)) OR (MAINSUBJECT.EXACT("Polypharmacy") OR MAINSUBJECT.EXACT("Prescription drugs") OR MAINSUBJECT.EXACT("Hormone replacement therapy") OR MAINSUBJECT.EXACT("Estrogen") OR MAINSUBJECT.EXACT("Anticoagulants") OR MAINSUBJECT.EXACT("Nonsteroidal anti-inflammatory drugs") OR MAINSUBJECT.EXACT("Insulin") OR MAINSUBJECT.EXACT("Antihypertensives") OR MAINSUBJECT.EXACT("Analgesics")) OR ((polypharmacy OR "prescription drug" OR "hormone substitution" OR estrogen OR "testosterone propionate" OR dabigatran OR warfarin OR agent OR antithrombin OR rivaroxaban OR potassium OR "proton pump inhibitor" OR "antiulcer agent" OR pantoprazole OR omeprazole OR esomeprazole OR lansoprazole OR rabeprazole OR "histamine H2 receptor antagonist" OR ranitidine OR fenofibrate OR ezetimibe OR corticosteroid OR glucocorticoid OR prednisolone OR prednisone OR "dihydropyridine derivative" OR "channel blocking agent" OR amlodipine OR diltiazem OR felodipine OR nifedipine OR verapamil OR "glyceryl trinitrate" OR "neuroleptic agent" OR olanzapine OR quetiapine OR risperidone OR benzodiazepine OR "hypnotic sedative agent" OR alprazolam OR oxazepam OR temazepam OR diazepam) OR ("muscarinic receptor blocking agent" OR "cholinesterase inhibitor" OR donepezil OR "bone density conservation agent" OR "risedronic acid" OR "zoledronic acid" OR denosumab OR "antithrombocytic agent" OR "acetylsalicylic acid" OR clopidogrel OR "antiinflammatory agent" OR "nonsteroid antiinflammatory agent" OR "cyclooxygenase 2 inhibitor" OR celecoxib OR diclofenac OR meloxicam OR naproxen OR "antigout agent" OR colchicine OR allopurinol OR thyroxine OR metformin OR insulin OR "dipeptidyl peptidase IV inhibitor") OR ("anticonvulsive agent" OR sitagliptin OR "valproic acid" OR carbamazepine OR pregabalin OR levetiracetam OR "diuretic agent" OR furosemide OR spironolactone OR indapamide OR "antiarrhythmic agent" OR digoxin OR "antidepressant agent" OR "anxiolytic agent" OR "serotonin uptake inhibitor" OR fluoxetine OR citalopram OR paroxetine OR sertraline OR escitalopram OR fluvoxamine OR mirtazapine OR "tricyclic antidepressant agent" OR amitriptyline OR venlafaxine OR duloxetine OR desvenlafaxine OR "antihypertensive agent" OR "beta 1 adrenergic receptor blocking agent" OR metoprolol OR atenolol OR bisoprolol OR sotalol) OR (carvedilol OR prazosin OR "angiotensin 1 receptor antagonist" OR irbesartan OR telmisartan OR "dipeptidyl carboxypeptidase inhibitor" OR enalapril OR lisinopril OR perindopril OR ramipril OR "hypocholesterolemic agent" OR "hydroxymethylglutaryl coenzyme A reductase inhibitor" OR atorvastatin OR rosuvastatin OR simvastatin OR pravastatin OR "aminosalicylic acid" OR salazosulfapyridine OR salazosulfapyridine OR mesalazine OR "narcotic analgesic agent" OR oxycodone OR tramadol OR morphine OR fentanyl OR "analgesic agent" OR paracetamol))) AND (((old OR older OR ag?ing OR senior) NEAR/3 (person? OR people? OR adult? OR patient? OR consumer?)) OR ("late life" OR "old age" OR seniors OR geriatric?) OR (elder* OR geriatric* OR veteran*)) AND (deprescrib* OR withdraw* OR ceas* OR cessation OR with?ld OR discontinu* OR de-intensify OR deprescription OR "inappropriate prescribing")

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KEY (deprescrib* OR withdraw* OR ceas* OR cessation OR with?ld OR discont
inu* OR de-intensify OR deprescription OR “inappropriate
prescribing” ((AND)) TITLE-ABS-
KEY) medication* OR prescrib* OR polypharmac* ((OR) TITLE) polypharmacy
OR “prescription drug” OR “hormone substitution” OR estrogen OR “testosterone
propionate” OR dabigatran OR warfarin OR agent OR antithrombin OR rivaroxa
ban OR potassium OR “proton pump inhibitor” OR “antiulcer
agent” OR pantoprazole OR omeprazole OR esomeprazole OR lansoprazole OR
rabeprazole OR “histamine H2 receptor
antagonist” OR ranitidine OR fenofibrate OR ezetimibe OR corticosteroid OR glu
cocorticoid OR prednisolone OR prednisone OR “dihydropyridine
derivative” OR “channel blocking
agent” OR amlodipine OR diltiazem OR felodipine OR nifedipine OR verapamil
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agent” OR olanzapine OR quetiapine OR risperidone OR benzodiazepine OR “h
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density conservation agent” OR “risedronic acid” OR “zoledronic
acid” OR denosumab OR “antithrombocytic agent” OR “acetylsalicylic
acid” OR clopidogrel OR “antiinflammatory agent” OR “nonsteroid antiinflammatory
agent” OR “cyclooxygenase 2
inhibitor” OR celecoxib OR diclofenac OR meloxicam OR naproxen OR “antigout
agent” OR colchicine OR allopurinol OR thyroxine OR metformin OR insulin OR
“dipeptidyl peptidase IV inhibitor” OR “anticonvulsive
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agent” OR digoxin OR “antidepressant agent” OR “anxiolytic agent” OR “serotonin
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agent” OR amitriptyline OR venlafaxine OR duloxetine OR desvenlafaxine OR “a
ntihypertensive agent” OR “beta 1 adrenergic receptor blocking
agent” OR metoprolol OR atenolol OR bisoprolol OR sotalol OR carvedilol OR
prazosin OR “angiotensin 1 receptor
antagonist” OR irbesartan OR telmisartan OR “dipeptidyl carboxypeptidase
inhibitor” OR enalapril OR lisinopril OR perindopril OR ramipril OR “hypocholeste
rolemic agent” OR “hydroxymethylglutaryl coenzyme A reductase
inhibitor” OR atorvastatin OR rosuvastatin OR simvastatin OR pravastatin OR “a

minosalicylic
acid" OR salazosulfapyridine OR salazosulfapyridine OR mesalazine OR "narcotic analgesic
agent" OR oxycodone OR tramadol OR morphine OR fentanyl OR "analgesic agent" OR paracetamol (((AND) TITLE-ABS-
KEY)) old OR older OR ag?ing OR senior (W/3) person? OR people? OR ad ult? OR patient? OR consumer? (OR ("late life" OR "old
age" OR seniors OR geriatric? (OR (elder* OR geriatric* OR veteran*)))

Web of Science

Lines	Search terms
1	TS=((old or older or ag?ing or senior)n3(person? or people? or adult? or patient? or consumer?))
2	TS=(“late life” or “old age” or seniors or geriatric?)
3	TS=(elder* or geriatric* or veteran*)
4	#1 OR #2 OR #3
5	TS=(medication* OR medicin* OR prescription* OR prescrib* OR polypharmac* OR“prescription drug*” OR “hormone replacement therapy” OR ?estrogen OR ?estradiol OR ?estriol OR testosterone OR ”direct thrombin inhibitor” OR dabigatran OR warfarin OR anticoagula* OR factor XA inhibitor* OR antithrombin* OR apixaban * OR rivaroxaban OR potassium OR “proton pump inhibitor” OR “anti-ulcer agent*” OR “acid suppression” OR PPI OR pantoprazole OR omeprazole OR esomeprazole OR lansoprazole OR rabeprazole OR antacid OR “histamine h2 antagonist?” OR ranitidine OR fenofibrate OR fibrate OR ezetimibe OR “adrenal cortex hormone?” OR corticosteroid? OR glucocorticoid? OR steroid OR prednisolone OR prednisone OR dihyropyridine? OR “calcium channel blocker*” OR amlodipine OR diltiazem OR felodipine OR lercanidipine OR nifedipine OR verapamil OR nitrate* OR nitroglycerin OR trinitrate OR isosorbide OR mononitrate OR antipsychotic OR “antipsychotic agent*” OR olanzapine OR quetiapine OR risperidone OR benzodiazepine* OR alprazolam OR oxazepam OR temazepam OR diazepam OR hypnotic OR sedative OR anticholinergic* OR “muscarinic antagonist*” OR oxybutynin OR anticholinesterase OR cholinesterase inhibitor* OR donepezil OR bisphosphonate* OR risedronate OR zoledronic acid OR denosumab OR antiplatelet* OR “platelet aggregation inhibitor*” OR aspirin OR clopidogrel OR NSAID OR non-steroidal anti-inflammator* OR anti-inflammatory agent* OR cyclooxygenase 2 inhibitor* OR COX-2 inhibitor* OR celecoxib OR diclofenac OR meloxicam OR naproxen OR colchicine OR allopurinol OR levothyroxine OR thyroxine OR antihyperglycaemi* OR “hypoglycaemic agent*” OR biguanide OR metformin OR sulphonylurea OR gliclazide OR glimepiride OR insulin OR “dipeptidyl-peptidase IV inhibitor*” OR Sitagliptin OR antiepilep* OR anticonvulsant* OR valproate OR “valproic acid” OR carbamazepine OR pregabalin OR Levetiracetam OR diuretic* OR frusemide OR furosemide OR indapamide OR spironolactone OR “anti-arrhythmia agent*” OR digoxin OR antidepressant* OR “antidepressive agent*” OR “anti-anxiety agent*” OR SSRI OR “selective serotonin reuptake inhibitor*” OR

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6	TS=(polypharmacy OR prescription drug OR “hormone substitution” OR estrogen OR testosterone propionate OR dabigatran OR warfarin OR agent OR antithrombin OR rivaroxaban OR potassium OR “proton pump inhibitor” OR “antiulcer agent” OR pantoprazole OR omeprazole OR esomeprazole OR lansoprazole OR rabeprazole OR “histamine H2 receptor antagonist” OR ranitidine OR fenofibrate OR ezetimibe OR corticosteroid OR glucocorticoid OR prednisolone OR prednisone OR “dihydropyridine derivative” OR “channel blocking agent” OR amlodipine OR diltiazem OR felodipine OR nifedipine OR verapamil OR “glyceryl trinitrate” OR “neuroleptic agent” OR olanzapine OR quetiapine OR risperidone OR benzodiazepine OR “hypnotic sedative agent” OR alprazolam OR oxazepam OR temazepam OR diazepam OR “muscarinic receptor blocking agent” OR “cholinesterase inhibitor” OR donepezil OR “bone density conservation agent” OR risedronic acid OR “zoledronic acid” OR denosumab OR “antithrombocytic agent” OR “acetylsalicylic acid” OR clopidogrel OR “antiinflammatory agent” OR “nonsteroid antiinflammatory agent” OR “cyclooxygenase 2 inhibitor” OR celecoxib OR diclofenac OR meloxicam OR naproxen OR “antigout agent” OR colchicine OR allopurinol OR thyroxine OR metformin OR insulin OR “dipeptidyl peptidase IV inhibitor” OR “anticonvulsive agent” OR sitagliptin OR “valproic acid” OR carbamazepine OR pregabalin OR levetiracetam OR “diuretic agent” OR furosemide OR spironolactone OR indapamide OR “antiarrhythmic agent” OR digoxin OR “antidepressant agent” OR “anxiolytic agent” OR “serotonin uptake inhibitor” OR fluoxetine OR citalopram OR paroxetine OR sertraline OR escitalopram OR fluvoxamine OR mirtazapine OR “tricyclic antidepressant agent” OR amitriptyline OR venlafaxine OR duloxetine OR desvenlafaxine OR “antihypertensive agent” OR “beta 1 adrenergic receptor blocking agent” OR metoprolol OR atenolol OR

	bisoprolol OR sotalol OR carvedilol OR prazosin OR “angiotensin 1 receptor antagonist” OR irbesartan OR telmisartan OR “dipeptidyl carboxypeptidase inhibitor” OR enalapril OR lisinopril OR perindopril OR ramipril OR “hypocholesterolemic agent” OR “hydroxymethylglutaryl coenzyme A reductase inhibitor” OR atorvastatin OR rosuvastatin OR simvastatin OR pravastatin OR aminosalicylic acid OR salazosulfapyridine OR salazosulfapyridine OR mesalazine OR “narcotic analgesic agent” OR oxycodone OR tramadol OR morphine OR fentanyl OR “analgesic agent” OR paracetamol)
7	#5 OR #6
8	TS=(deprescrib* OR withdraw* OR ceas* OR cessation OR with?ld OR discontinu* OR de-intensify OR deprescription OR “inappropriate prescribing”)
9	#8 AND #7 AND #4

Appendix B. GRADE: Presentation of evidence and Evidence-to-Decision using the GRADE Framework, by drug class

1. Polypharmacy/ Multiple Drug Classes

1.1 Overview of studies

Article	Target drugs	Tool to identify target drugs	Study design	Sample size	Follow-up (months)	Withdrawal schedule
8 2021 [1]	Potentially inappropriate medications (PIMs)	STOPP and the Danish Deprescribing list	Randomised controlled trial (RCT)	67	12+ (median 18)	Individualised
Cateau 2021 (IDeI) [2]	PIMs	STOPP/START second version, 2015	RCT	58	4	Not described
Cossette 2017 [3]	PIMs	Geriatric explicit criteria developed using Beers and STOPP/START criteria	RCT	231	1	Dose cessation or dose reduction
Etherton-Beer 2023 [4]	PIMs	Study-specific protocol	RCT	303	12	Abrupt discontinuation or tapered gradually by halving at fortnightly intervals until a dose of half the lowest dose form was reached, following which the medication was ceased
Lenander 2017 [5]	PIMs	Indicators described by the Swedish National Board of Health and Welfare	RCT	Not reported, 32566 prescriptions for PIMs	6	Not described

Potter 2016 [6]	PIMs	Modified Good Palliative-Geriatric Practice tool	RCT	95	12	Individualised
Vasilevskis 2023, Lee 2024 [7, 8]	PIMs	Beers Criteria, STOPP Criteria and the RASP (Rationalization of Home Medication by an Adjusted STOPP in Older Patients) List	RCT	372 (n= 283 in Lee 2024)	3	Not described
Bayliss 2022 [9]	PIMs	Beers criteria	Cluster RCT	3012	6	Not described
Cateau 2021 (QC-Demo) [10]	PIMs	Beers' list and the Norwegian General Practice Nursing Home criteria (NORGEP-NH)	Cluster RCT	56 nursing homes	12	Not described
Clyne 2015 [11]	PIMs	Prescribing Criteria/Prescribing Indicator developed as part of the study protocol	Cluster RCT	196	12	Individualised
Edey 2019 [12]	PIMs	Study-specific deprescribing guide	Cluster RCT	358	1	Not described
Fournier 2020 [13]	PIMs	STOPPFrail criteria	Cluster RCT	306	15	Not described
McCarthy 2022, Gillespie 2024 [14, 15]	PIMs	Study-specific list developed based predominantly on the STOPP/START version 2 criteria	Cluster RCT	404 (n=229 in Gillespie 2024)	6	Individualised
Rudolf 2021 [16]	PIMs	German PRISCUS list	Cluster RCT	1138	12	Not described
Wouters 2017 [17]	PIMs	STOPP/START and Beers Criteria 2012	Cluster RCT	426	4.7	Not described
Ammerman 2019 [18]	PIMs	Beers Criteria plus aspirin 325 mg	Retrospective cohort study	568	Not stated	Not described

Caffiero 2017 [19]	PIMs	Institutional pre-specified list of drugs to avoid in the elderly	Retrospective cohort study	9059	3.3	Not described
Cossette 2016 [20]	PIMs	Beers Criteria	Before and after study	8622	24	Slowly tapered or replaced
Fried 2017 [21]	PIMs	Study-specific Tool to Reduce Inappropriate Medications (TRIM)	Before and after study (Pseudo-RCT)	128	3	Discontinuation or dosage changes for inappropriate medications
Seto 2022 [22]	PIMs	Study-specific deprescribing protocol	Retrospective cohort study	184	6	Not described
Silva-Almodovar 2020 [23]	PIMs	Beers Criteria	Before and after study	17933	4	Not described
Gibert 2018 [24]	PIMs	STOPP criteria, Medication Appropriateness Index	Before and after study	172	2	Not described
Jovevski 2023 [25]	PIMs	Beers Criteria	Before and after study	298	2	Not described
Kimura 2022 [26]	PIMs	STOPP-v2 with STOPP-Japanese	Before and after study	544	3	Not described
Leguelinel-Blache 2020 [27]	PIMs	Beers, STOPP, Laroche criteria	Before and after study	49	6	Individualised
Mudge 2016 [28]	PIMs	STOPP criteria	Before and after study	17	3	Individualised
Sanz-Tamargo 2019 [29]	PIMs	Study-specific computerized prescription system of the PS 'La Florida'	Before and after study	234	12	Individualised
Schapira 2021 [30]	PIMs	Beers Criteria	Before and after study	879	18	Drug-specific
Alyazeedi 2024 [31]	PIMs	Qatar Tool for Reducing Inappropriate Medication (QTRIM) developed by an expert consensus panel using the Beers Criteria	Cohort study	337	15	Not described

Hanlon 1996 [32]	Polypharmacy	Medicines Appropriateness Index	RCT AND Before and after study (2 papers)	208	12	Not described
Herrinton 2023 [33]	Polypharmacy	CEASE (confirm, estimate, assess, sort, and eliminate) deprescribing framework, detailed operational playbook, a Hyperpolypharmacy Program Tool, drug-specific deprescribing protocols	RCT	2470	6	Drug-specific
Beer 2011 [34]	Polypharmacy	Pre-specified list of target medications	RCT	44	3	Dose reduced at approximately two-weekly intervals
Curtin 2020 [35]	Polypharmacy	STOPPFrail criteria	RCT	130	3	Individualised
Dalleur 2014 [36]	Polypharmacy	STOPP criteria	RCT	158	12	Not described
Wong 2021 [37]	Polypharmacy	Beers Criteria	RCT	253	1	Not described
Anderson 2020 [38]	Polypharmacy	CEASE deprescribing framework	Before and after study	145	4.1	Not described
Pitkala 2014 [39]	Polypharmacy	Beers Criteria	Cluster RCT	227	12	Not described
Mortsiefer 2023 [40]	Polypharmacy	European Union list of the number of potentially inappropriate medications	Cluster RCT	521	12	Not described
Vaughan 2023 [41]	Polypharmacy	Beers criteria	Cluster RCT	83988	12	Not described
Allard 2001 [42]	Polypharmacy	List of potentially inappropriate medications list developed by the Quebec Committee on Drug Use in the Elderly	Cluster RCT	266	12	Not described

Husebo 2019 [43]	Polypharmacy including psychotropic medicines	Norwegian Medical Agency's guidelines for medication reviews, START/STOPP criteria, Duran et al.'s list of drugs with anticholinergic profiles available in Norway	Cluster RCT	545	9	Not described
Mahlknecht 2021 [44]	Polypharmacy	Beers Criteria (Italian Version) and Lexicomp/UpToDate® for drug-drug interactions	Cluster RCT	579	24	Not described
Rieckert 2020 [45]	Polypharmacy	Study-specific electronic tool	Cluster RCT	3904	24	Not described
Schafer 2018 [46]	Polypharmacy	No identification method tool specified	Cluster RCT	604	12	Not described
Zechmann 2020 [47]	Polypharmacy	Study-specific deprescribing tool based on Good Palliative-Geriatric Practice algorithm	Cluster RCT	334	12	Individualised
Bilek 2019 (Study 1) [48]	Polypharmacy	Good Palliative-Geriatric Practice (GPGP) method	Before and after study	200	Until hospital discharge	Not described
Bilek 2019 (Study 2) [48]	Polypharmacy	GPGP method	Before and after study	200	6	Not described
Muir 2001 [49]	Polypharmacy	Health professional judgment (no list, criteria, or tool used)	Before and after study	836	1.25 to 1.75	Not described
Pitkala 2001 [50]	Polypharmacy	Health professional judgment (no list, criteria, or tool used)	Before and after study	174	Not stated	Not described
Reus 2022 [51]	Polypharmacy	LESS-CHRON criteria plus a study-specific tool – CheckTheMeds	Before and after study	168	12	Not described
Blenke 2018 [52]	Polypharmacy	STOPP/START criteria	Before and after study	45	3	One drug ceased at a time until the 60-day mark

Chan 2022 [53]	Polypharmacy	Beers Criteria	Retrospective cohort study	142	4	Not described
Komagamine 2017 [54]	Polypharmacy	Beers Criteria	Retrospective cohort study	164	8	Not described
Kose 2023 [55]	Polypharmacy	Beers criteria	Retrospective cohort study	153	Until hospital discharge	Not described
Matsumoto 2022 [56]	Polypharmacy	Beers Criteria	Retrospective cohort study	91	Until hospital discharge	Not described
Garfinkel 2007 [57]	Polypharmacy	GPGP method	Prospective cohort study	190	12	Not described
Kroenke 1990 [58]	Polypharmacy	Health professional judgment (no list, criteria, or tool used)	Prospective cohort study	79	6	Not described
Russell 2021 [59]	Polypharmacy	Beers Criteria	Prospective cohort study	239	12	Not described
Garfinkel 2010 [60]	Polypharmacy	Good Palliation-Good Practice tool	Before and after study	70	19.2	Not described
Garfinkel 2018 [61]	Polypharmacy	GPGP method	Before and after study	193	36	Individualised
Gerety 1993 [62]	Polypharmacy	Health professional judgment (no list, criteria, or tool used)	Before and after study	132	6	Not described
Horii 2020 [63]	Polypharmacy	No identification method tool specified	Before and after study	53	Until hospital discharge	Not described
Houlind 2020 [64]	Polypharmacy	STOPP criteria	Before and after study	39	1	Individualised
Balsom 2020 [65]	Polypharmacy	Beers & STOPP criteria	RCT	45	6	Abrupt discontinuation, tapering medication, or switching to a more appropriate medication
Meaney 2024 [66]	PIMs/ polypharmacy	Beers & STOPP criteria	Retrospective cohort study	128	Until hospital	Not described

					discharge	
Sakran 2024 [67]	PIMs/ polypharmacy	Beers & STOPP criteria	Retrospective cohort study	392	Until hospital discharge	Not described
Selman 2024 [68]	PIMs/ polypharmacy	STEADI-Rx (Stopping Elderly Accidents, Deaths and Injuries) algorithm and Beers criteria	Prospective cohort study	309	12	Abrupt discontinuation or taper for medications with dependency or withdrawal risk
Garfinkel 2024 [69]	PIMs/ polypharmacy	GPGP method	Before and after study	307	57 (mean)	Not described
Hurley 2024 [70]	PIMs/ polypharmacy	STOPPFrail	Before-and-after study	99	6	Individualised
Velani 2024 [71]	PIMs/ polypharmacy	STOPPFrail	Before-and-after study	27	2	Not described
Etherton-Beer 2024 [72]	PIMs/ polypharmacy	Taper MD	RCT	98	12	Not described
Van Der Meer 2018 [73]	Polypharmacy including at least one psycholeptic or psychoanaleptic medicine	Dutch guideline	RCT	157	3	Individualised
Kua 2021 [74]	PIMs/ polypharmacy	Beers and STOPP criteria	Cluster RCT	295	12	Individualised
McDonald 2022 [75]	PIMs/ polypharmacy	Study-specific tool - MedSafer	Cluster RCT	5698	1	Individualised, tapering instructions where indicated
Van der Linden 2017 [76]	PIMs/ polypharmacy	RASP list (Rationalization of Home Medication by an Adjusted STOPP in Older Patients)	Before and after study	172	3	Not described
Kaminaga 2021 [77]	PIMs/ polypharmacy	STOPP/START criteria	Before and after study	121	Until hospital	Not described

					discharge	
Gareri 2024 [78]	PIMs/ polypharmacy	Beers and STOPP&START criteria	Before and after study	205	12	Not described
Hopkins 2023 [79]	PIMs/ polypharmacy	Unstated	Before and after study	35	6	Not described
Mejias-Trueba 2023 [80]	PIMs/ polypharmacy	LESS-CHRON criteria	Before and after study	95	6	Individualised
Rea 2024 [81]	PIMs/ polypharmacy	VIONE tool (vital, important, optional, not indicated, and every medication has an indication)	Before and after study	63	Unstated	Not described
Junius-Walker 2021 [82]	PIMs/ polypharmacy	Study-specific electronic tool	Before and after study	41	1	Individualised
Liu 2019 [83]	PIMs/ polypharmacy	Modified Beers Criteria according to common practice and culture in Taiwan	Before and after study	911	Until hospital discharge	Not described
Andrew 2018 [84]	PIMs/ polypharmacy	Beers Criteria	Before and after study	529	36	Not described
McCarthy 2017 [15]	PIMs/ polypharmacy	Study-specific SPPiRE software	Before and after study	10	Not specified	Individualised
McDonald 2019 [85]	PIMs/ polypharmacy	MedSafer incorporates Beers' criteria, STOPP criteria and Choosing Wisely list.	Before and after study	873	1	Ceased or tapered
McKean 2016 [86]	PIMs/ polypharmacy	Decision support tool based on a five-step CEASE deprescribing protocol	Before and after study	50	Reported in median (IQR)	Individualised
Molist-Brunet 2020 [87]	PIMs/ polypharmacy	Study-specific list	Before and after study	103	6	Individualised
Weber	Polypharmacy	No identification method tool	Cluster RCT	620	15	Not described

2008 [88]	and psychoactive medications	specified				
Petersen 2018 [89]	PIMs and medications associated with geriatric syndromes	Study-specific list including a combination of Beers Criteria 2015 and START	Before and after study	40	Until hospital discharge	Dose reduction or discontinuation
Ye 2021 [90]	Polypharmacy and high-risk medicines	No identification method tool specified	Case-control study	136	Until hospital discharge	Discontinuation, dose reduction or frequency reduction
Stuckey 2018 [91]	High-risk medicines	Beers Criteria	Before and after study	34	3	Individualised
Boye 2017 [92]	Fall-risk-increasing-drugs	Study-specific list of fall-risk-increasing-drugs	RCT	612	12	Discontinued when considered redundant, reduced in dose over a one-month period, if safely possible, or substituted for potentially safer drugs if necessary and available.
Mott 2016 [93]	Fall-risk-increasing-drugs	Study-specific list of fall-risk-increasing-drugs	Cluster RCT	80	6	Individualised
Salonoja 2012 [94]	Fall-risk-increasing-drugs	Three pre-specified lists of target medications	Retrospective cohort study	591	48	Geriatrician provided plans to users to gradually reduce these medicines as a stepwise procedure over some months
Marvin 2017 [95]	Fall-risk-increasing-drugs	'STOPIT' tool developed from the STOPP criteria	Before and after study	100	Until hospital discharge	Not described
Van Der Velde 2007a, b [96, 97]	Fall-risk-increasing-drugs	Pre-specified list of target medications (fall-risk-increasing-drugs)	Case-control study	141	2	Abrupt discontinuation, if safe, else reduced dose over 1-month to a lower dose or to complete withdrawal
Foster 2022 [98]	Fall-risk-increasing-drugs	ASCP-NCOA Falls Risk Reduction Toolkit	Before and after study	113	3	Not described
Pavon 2024 [99]	Fall-risk-increasing-drugs	Unstated	Before and after study	472	12	Not described

Campbell 2021 [100]	Anticholinergic medications	Focus on tricyclic antidepressants and urinary antispasmodics	Cluster RCT	552	12	Individualised
Moga 2017 [101]	Anticholinergic medications	Medication Appropriateness Index (MAI) and Anticholinergic Drug Scale (ADS)	RCT	50	2	Not described
Rojo-Sanchis 2017 [102]	Anticholinergic medications	STOPP/START validation criteria, Anticholinergic Cognitive Burden Scale, Anticholinergic Drug Scale, Anticholinergic Risk Scale	Before and after study	67	Until hospital discharge	Not described
Yeh 2013 [103]	Anticholinergic medications	Clinician-Rated Anticholinergic Score (CR-ACHS) and prespecified list of target medications (Beta-blockers, benzodiazepines, antidepressants, atypical antipsychotics)	Prospective cohort study	67	3	Slowly tapered off or switched to alternatives with lower anticholinergic burden according to the recommendations from the research team.
Wehran 2024 [104]	Anticholinergic medications	Study-specific list based on published evidence and expert opinion (85 anticholinergic drugs)	Cohort study	9	0.5	Individualised based on 21 study-specific algorithms for reducing anticholinergic load
Gnjidic 2010 [105]	Anticholinergic and sedative medications	Drug Burden Index	Cluster RCT	115	3	Not described
Jamieson 2023 [106]	Anticholinergic and sedative medicines	Drug Burden Index	RCT	363	6	Not described
Kouladjian O'Donnell 2021 [107]	Anticholinergic and sedative medications	Goal-directed Medication Review Electronic Decision Support System (G-MEDSS)	Cluster RCT	159	3	Not described
Ailabouni 2019 [108]	Anticholinergics and sedative medicines	Drug Burden Index	Before and after study	46	6	Individualised

Masnoon 2023 [109]	Anticholinergic and sedative medications	Drug Burden Index	Before and after study	256	Not specified	Initial dose reduction in the hospital, then GP continue weaning the dose after discharge.
Cossette 2025 [110]	Anticholinergic and sedative medications	Drug Burden Index adapted for Canadian context	Before and after study	5	5	Individualised
Martin 2018 [111]	Sedative hypnotics, first-generation antihistamines, glyburide, or NSAIDs	Beers Criteria	Cluster RCT	489	6	Individualised
Haque & Zakia 2019 [112]	Psychotropic drugs	Assess, Review, Minimize, Optimize, Reassess (ARMOR) protocol	Before and after study	1013	12	Not described
Massot Mesquida 2019 [113]	Psychotropic drugs	No identification method tool specified	Before and after study	240	6	Individualised
Pasina 2016 [114]	Psychotropic drugs	Beers Criteria	Before and after study	272	9	Not described
Pellicano 2018 [115]	Psychotropic drugs	Local clinical guideline	Before and after study	116	Until hospital discharge	Cease abruptly/ weaning plan/ dose reduction/ continue with the regimen
Kose 2024 [116]	Psychotropic drugs	Unstated	Retrospective cohort study	128	Until hospital discharge	Not described
Campbell 1999 [117]	Anti-anxiolytics, antipsychotics, antidepressants, benzodiazepines	Pre-specified list of target medications (benzodiazepine, any other hypnotic or any antidepressant or major tranquillizer)	RCT	93	10	Not described

Cossette 2020 [118]	Antipsychotics, benzodiazepines, antidepressants	Study-specific provincial guidelines	Before and after study	464	9	Not described
Cossette 2022 [119]	Antipsychotics, benzodiazepines, antidepressants	Study-specific provincial guidelines	Before and after study	10601	9	Not described
Adeola 2018 [120]	Delirium-associated medicines	Study pre-defined list	Before and after study	Not specified (49,305 admissions)	Not stated	Not described
Phelan 2024 [121]	Centrally nervous system active medications (opioids, benzodiazepines, Z-drugs, muscle relaxants, tricyclic antidepressants, antihistamines)	Study pre-defined list	Cluster RCT	2367	12	Tapering
Crutzen 2023 [122]	Cardiometabolic medication (i.e., glucose-lowering medication, antihypertensives and HMG CoA reductase inhibitors)	Conversation aid, agreement card for patients, and summary of the deprescribing guidelines	Before and after study	197	3	Not described
Bawazeer 2022 [123]	Five classes - NSAIDs, PPIs, TCAs, and antihyperglycemics (insulin, sulfonylurea)	Deprescribing algorithm developed by Potter et al. (2016), Beers Criteria	Before and after study	80	12	Individualised

Morley 2022 [124]	Eight classes - diuretics, opioids, antipsychotics, anticoagulants, antianxiety, antibiotics, hypnotics, and antidepressants	Beers Criteria and rules issued by Centers for Medicare & Medicaid Services	Before and after study	12144	Not stated	Not described

1.2 Evidence for general deprescribing of polypharmacy/ multiple drug classes

Study	Specific outcome	Odds ratio (95% CI)	Mean difference (95% CI)
1. Mortality			
Allard 2001	Death at 12 months	0.38 (0.14, 1.03)	
Balsom 2020	Death at 6 months	1.48 (0.29, 7.54)	
Bawazeer 2022	Death at 12 months	0.33 (0.01, 8.22)	
Bayliss 2022	Death at 6 months	1.05 (0.78, 1.41)	
Beer 2011	Death at 3 months	3.77 (0.15, 97.75)	
Cateau 2021 (IDeI)	Death at 4 months	0.52 (0.11, 2.38)	
Cossette 2017	In-hospital death	0.53 (0.19, 1.48)	
Curtin 2020	Death at 3 months	0.59 (0.26, 1.35)	
Dalleur 2014	Death at 12 months	1.06 (0.38, 2.97)	
Etherton-Beer 2023	Death at 12 months	0.98 (0.49, 1.95)	
Garfinkel 2007	Death at 12 months	0.32 (0.17, 0.62)	
Gnjidic 2010	Death at 3 months	0.14 (0.01, 2.73)	
Hanlon 1996	Death at 12 months	0.66 (0.24, 1.82)	
Jamieson 2023	Death at 6 months	0.77 (0.30, 1.99)	
Komagamine 2017	Death at 8 months	1.31 (0.40, 4.32)	
Kouladjian 2021	Death at 3 months	0.25 (0.03, 2.16)	
Kua 2021	Death at 3 months	0.74 (0.19, 2.80)	
Mahlknecht 2021	Death at 24 months	1.32 (0.75, 2.35)	
Pitkala 2014	Death at 12 months	1.75 (0.97, 3.17)	
Potter 2016	Death at 12 months	0.57 (0.24, 1.38)	
Rieckert 2020	Death at 24 months	1.05 (0.89, 1.23)	
Rudolf 2021	Death at 12 months	0.64 (0.34, 1.22)	
Russell 2021	Death at 12 months	2.11 (1.10, 4.05)	
Van der Linden 2017	Death at 6 months	1.02 (0.35, 2.95)	
Van der Meer 2018	Death at 3 months	1.05 (0.06, 17.09)	
Vasilevskis 2023	Death at 3 months	0.90 (0.37, 2.18)	
Weber 2008	Death at 15 months	0.59 (0.29, 1.23)	

Wong 2021	Death at 1-month post-discharge	5.08 (0.24, 106.81)	
Yeh 2013	Death at 3 months	0.22 (0.01 to 5.56)	
Zechmann 2020	Death at 12 months	0.86 (0.33, 2.21)	
Phelan 2024	Death at 18 months	0.95 (0.69, 1.32)	
2. Adverse drug withdrawal events (ADWEs)			
Hanlon 1996	ADWEs	118.07 (7.13, 1954.32)	
Vasilevskis 2023	ADWEs	0.77 (0.41, 1.46)	
Wong 2021	ADWEs	1.63 (1.11, 2.41)	
Phelan 2024	ADWEs	2.84 (0.89, 9.10)	
Cateau 2021 (IDeI)	Exacerbation of underlying condition	6.75 (0.33, 136.91)	
3. Health outcomes			
Adverse drug events			
Hanlon 1998	At least one adverse drug event	0.66 (0.35, 1.24)	
McDonald 2022	At least one adverse drug event	0.98 (0.76, 1.27)	
Zechmann 2020	At least one adverse drug event	1.97 (1.24, 3.12)	
Komagamine 2017	At least one adverse drug event	0.20 (0.03, 1.59)	
Rieckert 2020	Number of adverse drug events		-0.30 (-0.48, -0.12)
Etherton-Beer 2023	Frequency of Medication Side Effects, measured using the Beliefs About Medicines Questionnaire		-0.40 (-1.23, 0.43)
McDonald 2022	Adverse events within 30 days of discharge, number of participants	0.92 (0.82, 1.04)	
Etherton-Beer 2024	Change in the number of adverse drug events		0.11 (-0.23, 0.45)
Falls			
Campbell 1999	At least one fall	0.08 (0.02, 0.35)	
Cateau 2021 (Idel)	At least one fall	0.82 (0.27, 2.49)	
Curtin 2020	At least one fall	0.87 (0.36, 2.08)	
Kouladjian 2021	At least one fall	1.34 (0.43, 4.18)	
Kua 2021	At least one fall	1.37 (0.73, 2.57)	
Mahlknecht 2021	At least one fall	0.66 (0.44, 0.97)	
McDonald 2022	At least one fall	0.76 (0.57, 1.01)	

Mott 2016	At least one fall	1.22 (0.45, 3.30)	
Potter 2016	At least one fall	0.69 (0.30, 1.58)	
Van Der Meer 2018	At least one fall	1.81 (0.82, 4.00)	
Weber 2008	At least one fall	1.06 (0.66, 1.71)	
Pavon 2024	At least one fall	0.55 (0.28, 1.06)	
Salonoja 2012	At least one fall	0.84 (0.51, 1.40)	
Seto 2022	At least one fall	0.59 (0.14, 2.53)	
Van der Linden 2017	At least one fall	1.06 (0.52, 2.13)	
Van der Velde 2007	At least one fall	0.64 (0.30, 1.37)	
Cateau 2021 (IDeI)	Number of falls		-0.03 (-0.46, 0.40)
Etherton-Beer 2023	Number of falls		0.00 (-0.55, 0.55)
Rieckert 2020	Number of falls		-0.01 (-0.09, 0.07)
Van der Velde 2007	Number of falls		-2.30 (-4.94, 0.34)
Cateau 2021 (IDeI)	Number of falls in participants who fell at least once		0.20 (-0.24, 0.64)
Kua 2021	Fall risk score, measured using the Falls Risk Assessment Tool (FRAT)		-0.22 (-0.53, 0.09)
Van der Velde 2007	Fall risk		0.48 (0.23, 1.00)
Selman 2024	Falls led to emergency department visits at 12 months	0.87 (0.52, 1.46)	
Health service use			
Cateau 2021 (IDeI)	Hospital days		3.00 (-2.67, 8.67)
McCarthy 2022	Hospital days		-0.64 (-2.25, 0.97)
Bayliss 2022	Unplanned hospitalisation	0.91 (0.74, 1.12)	
Cateau 2021 (IDeI)	Unplanned hospitalisation	2.79 (0.27, 28.50)	
Curtin 2020	Unplanned hospitalisation	1.93 (0.61, 6.10)	
Jamieson 2023	Unplanned hospitalisation	1.02 (0.66, 1.57)	
Kua 2021	Unplanned hospitalisation	0.55 (0.38, 0.78)	
Mahlknecht 2021	Unplanned hospitalisation	1.61 (1.11, 2.32)	
Potter 2016	Unplanned hospitalisation	1.05 (0.46, 2.36)	
Rieckert 2020	Unplanned hospitalisation	0.91 (0.80, 1.03)	
Rudolf 2021	Unplanned hospitalisation	1.46 (1.14, 1.87)	

Van Der Meer 2018	Unplanned hospitalisation	0.40 (0.10, 1.57)	
Vasilevskis 2023	Unplanned hospitalisation	0.61 (0.40, 0.92)	
Wong 2021	Unplanned hospitalisation	0.87 (0.46, 1.62)	
Zechmann 2020	Unplanned hospitalisation	1.42 (0.88, 2.30)	
Anderson 2020	Unplanned hospitalisation	0.45 (0.17, 1.23)	
Bawazeer 2022	Unplanned hospitalisation	0.23 (0.02, 2.16)	
Komagamine 2017	Unplanned hospitalisation	1.20 (0.47, 3.08)	
Russell 2022	Unplanned hospitalisation	0.67 (0.36, 1.25)	
Seto 2022	Unplanned hospitalisation	1.89 (0.61, 5.86)	
Van der Linden 2017	Unplanned hospitalisation	0.81 (0.43, 1.53)	
Ye 2021	Unplanned hospitalisation	0.64 (0.27, 1.52)	
Lee 2024	Percentage of difference in the time to first 90-day unplanned emergency department visit/hospital readmission/death		-0.15 (-0.40, 0.10)
Herrinton 2023	Number of hospital outpatient visits		0.40 (-0.31, 1.11)
Mortsiefer 2023	Hospitalisations, average per participant		-0.01 (-0.29, 0.27)
Kose 2023	Rate of discharge to home (indication of successful rehabilitation)	0.82 (0.42, 1.59)	
Jamieson 2023	Institutionalisation	0.80 (0.35, 1.84)	
Kouladjian 2021	Institutionalisation	1.27 (0.55, 2.93)	
Vasilevskis 2023	ICU transfer	0.75 (0.16, 3.38)	
McCarthy 2022	Emergency room presentation		0.13 (-0.11, 0.37)
Cossette 2017	Emergency room presentation or readmission	1.02 (0.56, 1.86)	
Curtin 2020	Emergency room presentation or readmission	0.58 (0.13, 2.54)	
Edey 2019	Emergency room presentation or readmission	0.39 (0.17, 0.87)	
Jamieson 2023	Emergency room presentation or readmission	1.08 (0.70, 1.66)	
Vasilevskis 2023	Emergency room presentation or readmission	0.67 (0.40, 1.12)	
Seto 2022	Emergency room presentation or	1.43 (0.55, 3.73)	

	readmission		
Van der Linden 2017	Emergency room presentation or readmission	0.62 (0.33, 1.19)	
Van der Linden 2017	Readmission risk	0.81 (0.43, 1.53)	
Sleep			
Beer 2011	Sleep quality, measured using the Pittsburgh Sleep Quality Index (PSQI)		1.00 (-1.02, 3.02)
Potter 2016	Change in PSQI		1.00 (-1.99, 3.99)
Fractures			
Etherton-Beer 2023	Fractures	0.46 (0.16, 1.27)	
Mahlknecht 2021	Fractures	1.83 (0.92, 3.66)	
Komagamine 2017	Fractures	0.81 (0.22, 2.97)	
Curtin 2020	Fractures, non-vertebral	0.67 (0.36, 1.27)	
Potter 2016	Fractures, non-vertebral	0.58 (0.13, 2.54)	
Rieckert 2020	Fractures, non-vertebral	0.39 (0.17, 0.87)	
Blood pressure			
Chan 2022	Blood pressure, diastolic		4.01 (0.13, 7.89)
Chan 2022	Blood pressure, systolic		8.97 (2.36, 15.58)
Delirium			
Komagamine 2017	Delirium	0.66 (0.30, 1.45)	
Seto 2022	Delirium	1.00 (0.52, 1.93)	
Van der Linden 2017	Delirium	0.97 (0.40, 2.33)	
Morbidity			
Kouladjian 2021	Morbidity, measured using the Functional Comorbidity Index		1.20 (0.50, 1.90)
McCarthy 2022	Global multimorbidity treatment burden questionnaire score		-4.72 (-8.63, -0.81)
Physical function			
Husebo 2019	Change in dependency in activities of daily living, measured using Physical Self-Maintenance Scale		-1.50 (-2.81, -0.19)
Etherton-Beer 2024	Change in activities of daily living measured using modified Barthel Index		2.20 (-8.13, 12.53)

Etherton-Beer 2023	Activity of daily living, measured using the modified Barthel Index		9.00 (-0.10, 18.10)
Yeh 2013	Activity of daily living, measured using the modified Barthel Index		3.80 (-2.59, 10.19)
Potter 2016	Change in modified Barthel Index		1.00 (-6.84, 8.84)
Kouladjian 2021	Physical function, measured using the short physical performance battery		0.50 (-0.60, 1.60)
Etherton-Beer 2024	Change in frailty measured using Frailty Scale		0.60 (-0.07, 1.27)
Behavioural and psychological symptoms			
Husebo 2019	Change in Neuropsychiatric Inventory-Nursing Home (NPI-NH)		-1.50 (-3.26, 0.26)
Potter 2016	Change in NPI-NH		0.10 (-1.83, 2.03)
Etherton-Beer 2023	NPI-NH		2.00 (-2.51, 6.51)
Adverse events/ serious adverse events/ cardiovascular events			
Komagamine 2017	Cardiovascular events	0.15 (0.01, 2.57)	
Clinical Global Impressions of Change (CGIC)			
Husebo 2019	Change in Clinical Global Impressions of Change (CGIC)		-0.20 (-0.41, 0.01)
Others			
Komagamine 2017	In-hospital infections	1.56 (0.56, 4.34)	
Ye 2021	Incidence of Clostridium difficile infections	0.46 (0.24, 0.90)	
Potter 2016	Change in bowel motions		-1.50 (-4.01, 1.01)
Van der Velde 2007	Mobility test, measured by 10m walk		-4.70 (-7.17, -2.23)
Van der Velde 2007	Functional Reach Test (FRT)		-3.50 (-6.52, -0.48)
Van der Velde 2007	Test of balance (Timed “Up and Go”)		-4.60 (-7.42, -1.78)
Van der Velde 2007	Body sway (cm) measured by recording involuntary body sway for one minute		-9.90 (-16.20, -3.60)
Van der Velde 2007	Quadriceps strength		34.0 8.86, 59.14)
4. Cognitive function			

Beer 2011	Mini-Mental State Examination (MMSE)		0.00 (-1.34, 1.34)
Etherton-Beer 2023	MMSE		4.40 (1.54, 7.26)
Kouladjian 2021	Mini-Cog		-0.50 (-0.88, -0.12)
Potter 2016	MMSE		1.00 (-1.21, 3.21)
Mahlknecht 2021	Participants with cognitive impairment, score ≥ 8 points on 6-Item Cognitive Impairment Test	0.98 (0.65, 1.47)	
Yeh 2013	Cognition, measured using the Mini-Mental State Examination		-0.40 (-1.39, 0.59)
Anderson 2020	Worsened score in EQ-5D-5L depression/anxiety domain	0.37 (0.15, 0.93)	
Wehran 2023	Neuropsychiatric symptoms measured using the Neuropsychological Assessment Battery, memory		7.00 (-0.20, 14.20)
Wehran 2023	Neuropsychiatric symptoms measured using the Neuropsychological Assessment Battery, attention		2.00 (-1.92, 5.92)
Etherton-Beer 2024	Change in cognition measured using standardised Mini-Mental State Examination		0.20 (-1.27, 1.67)
5. Quality of life			
Boye 2017	Change in EQ-5D utility score		-0.05 (-0.09, -0.01)
Potter 2016	Change in EQ-5D utility score		18.00 (6.71, 29.29)
Etherton-Beer 2024	Change in EQ-5D-5L score		0.12 (-0.04, 0.28)
Etherton-Beer 2023	EQ-5D-5L		0.07 (-0.01, 0.15)
Gillespie 2024	EQ-5D-5L		0.07 (-0.03, 0.16)
Russell 2021	EQ-5D index		-0.07 (-0.17, 0.03)
Russell 2021	VAS score		-2.90 (-9.58, 3.78)
Husebo 2019	Change in EQ-VAS		0.30 (-5.43, 6.03)
Beer 2011	EQ-5D VAS		-9.00 (-26.03, 8.03)
Curtin 2020	Change in Quality of Life for People with Dementia (QUALIDEM)		-0.42 (-2.52, 1.68)

Husebo 2019	Change in QUALIDEM		0.30 (-1.65, 2.25)
Curtin 2020	Change in ICEpop CAPability measure for Older people (ICECAP-O)		0.09 (-0.11, 0.29)
Potter 2016	Change in Quality of life in Alzheimer's Dementia (QOLAD)		0.00 (-2.98, 2.98)
Husebo 2019	Change in Quality of Life in Late Stage of Dementia score (QUALID)		-0.60 (-2.37, 1.17)
Boye 2017	Change in Short Form-12 mental component		0.10 (-1.54, 1.74)
Boye 2017	Change in Short Form-12 physical component		-1.30 (-2.73, 0.13)
Pitkala 2014	15-dimension instrument of health-related quality of life		-0.03 (-0.06, -0.01)
Beer 2011	Short Form-36		5.00 (-8.59, 18.59)
Hanlon 1996	Short Form-36		-2.20 (-2.69, -1.71)
Moga 2017	Short Form-36		3.40 (-6.57, 13.37)
6. Effect on medication regimen			
Aharaz 2021	Deprescribing successful	0.13 (0.04, 0.47)	
Cossette 2017	Deprescribing successful	0.40 (0.20, 0.82)	
Edey 2019	Deprescribing successful	0.25 (0.11, 0.55)	
Martin 2018	Deprescribing successful	0.71 (0.40, 1.25)	
Wouters 2017	Deprescribing successful	0.65 (0.44, 0.98)	
Caffiero 2017	Deprescribing successful	0.14 (0.08, 0.23)	
Ye 2021	Deprescribing successful	1.25 (0.59, 2.65)	
Aharaz 2021	Change in total medicines prescribed		-0.90 (-1.74, -0.06)
Allard 2001	Change in total medicines prescribed		-0.11 (-0.59, 0.37)
Balsom 2020	Change in total medicines prescribed		-2.88 (-4.54, -1.22)
Curtin 2020	Change in total medicines prescribed		-2.25 (-3.30, -1.20)
Herrinton 2023	Change in total medicines prescribed		0.00 (-0.28, 0.28)
Husebo 2019	Change in total medicines prescribed		-0.70 (-1.30, -0.10)
Potter 2016	Change in total medicines prescribed		-2.00 (-3.82, -0.18)
Rieckert 2020	Change in total medicines prescribed		-0.48 (-0.61, -0.35)

Zechmann 2020	Change in total medicines prescribed		-0.01 (-0.05, 0.04)
Chan 2022	Change in total medicines prescribed		-1.44 (-2.42, -0.46)
Kroenke 1990	Change in total medicines prescribed		-0.31 (-0.76, 0.13)
Muir 2001	Change in total medicines prescribed		-2.55 (-2.64, -2.46)
Pitkala 2001	Change in total medicines prescribed		-0.13 (-0.67, 0.41)
Seto 2022	Change in total medicines prescribed		-1.60 (-2.20, -1.00)
Etherton-Beer 2024	Change in total medicines prescribed		-1.00 (-2.84, 0.84)
Bayliss 2022	Total medicines prescribed		-0.10 (-0.24, 0.04)
Etherton-Beer 2023	Total medicines prescribed		-2.80 (-4.04, -1.56)
Kouladjian 2021	Total medicines prescribed		0.40 (-0.86, 1.66)
Kua 2021	Total medicines prescribed		-0.04 (-0.57, 0.49)
McCarthy 2022	Total medicines prescribed		-1.53 (-2.31, -0.75)
Mortsiefer 2023	Total medicines prescribed		-0.19 (-0.44, 0.06)
Rieckert 2020	Total medicines prescribed		-0.40 (-0.59, -0.21)
Schafer 2018	Total medicines prescribed		0.50 (-0.05, 1.05)
Vasilevskis 2023	Total medicines prescribed		-0.85 (-0.92, -0.78)
Bilek 2019	Total medicines prescribed		-1.17 (-1.88, -0.46)
Fried 2017	Total medicines prescribed		-0.50 (-2.65, 1.65)
Komagamine 2017	Total medicines prescribed		-2.30 (-3.29, -1.31)
Allard 2001	Change in PIM		-0.09 (-0.24, 0.06)
Pitkala 2014	Change in PIM		-0.54 (-0.88, -0.20)
Etherton-Beer 2024	Change in PIM		-0.10 (-0.42, 0.22)
Allard 2001	Reduced PIM	0.82 (0.43, 1.55)	
McCarthy 2022	Reduced PIM	0.78 (0.51, 1.18)	
Vaughan 2023	Reduced PIM	1.15 (1.09, 1.22)	
Kose 2024	Benzodiazepines discontinuation	0.05 (0.01, 0.24)	
Kose 2024	Hypnotics discontinuation	0.21 (0.07, 0.59)	
Allard 2001	Total PIM prescribed		0.09 (-0.06, 0.24)
Clyne 2015	Total PIM prescribed		-0.48 (-0.51, -0.45)
McCarthy 2022	Total PIM prescribed		-0.19 (-0.47, 0.09)
Mortsiefer 2023	Total PIM prescribed		-0.19 (-0.44, 0.06)

Vasilevskis 2023	Total PIM prescribed		-0.88 (-0.97, -0.79)
Bawazeer 2022	Total PIM prescribed		-0.60 (0.32, 0.88)
Komagamine 2017	Total PIM prescribed		-0.30 (-0.63, 0.03)
Seto 2022	Total PIM prescribed		-0.60 (-0.85, -0.35)
Sanz-Tamargo 2019	Number of PIM identified per participant		-1.58 (-3.89, 0.73)
Russell 2022	Beer score		0.30 (-0.13, 0.73)
Fournier 2020	At least one PIM	1.08 (0.63, 1.85)	
Bayliss 2022	At least one PIM	0.82 (0.68, 0.98)	
McCarthy 2022	At least one PIM	0.64 (0.34, 1.21)	
Rudolf 2021	At least one PIM	1.09 (0.82, 1.45)	
McCarthy 2022	At least one high-risk potentially inappropriate prescriptions	0.83 (0.56, 1.24)	
Martin 2018	No longer filled prescriptions for inappropriate medicines	5.45 (3.43, 8.66)	
Etherton-Beer 2023	Drug ceased		-2.40 (-3.52, -1.28)
McCarthy 2022	Drug ceased		-1.05 (-1.67, -0.43)
Anderson 2020	Drug ceased or reduced		-0.56 (-0.90, -0.22)
Petersen 2018	Drug ceased or reduced		-2.50 (-4.65, -0.35)
McCarthy 2022	Drug commenced		0.35 (-0.23, 0.93)
Anderson 2020	Drug commenced		-0.06 (-0.28, 0.16)
McCarthy 2022	15 or more medicines prescribed	0.38 (0.24, 0.60)	
Rudolf 2021	At least one undesirable drug-drug interaction	1.29 (0.92, 1.79)	
Etherton-Beer 2023	Total pro re nata (PRN) medicines prescribed		0.40 (-0.40, 1.20)
Curtin 2020	Unscheduled medical reviews	1.28 (0.64, 2.57)	
Campbell 2021	Anticholinergic medicine use	0.68 (0.55, 0.83)	
Moga 2017	Change in Medicine Appropriate Index		-2.60 (-3.16, -2.04)
Moga 2017	Anticholinergic Drug Scale		-0.80 (-0.97, -0.63)

Cateau 2021 (IDeI)	Use of physical restraints, number of days		0.50 (-19.67, 20.67)
Crutzen 2023	Cardiometabolic medicines		0.00 (-0.50, 0.50)
Mott 2016	fall-risk-increasing-drugs discontinued	0.12 (0.02, 0.60)	
Komagamine 2017	Total fall-risk-increasing-drugs prescribed		-0.70 (-1.19, -0.21)
Martin 2018	Discontinued inappropriate NSAID	4.89 (1.46, 16.34)	
Etherton-Beer 2023	Drug Burden Index (DBI)		-0.10 (-0.32, 0.12)
Vasilevskis 2023	DBI		-0.34 (-0.63, -0.05)
Wouters 2017	DBI		0.17 (-0.06, 0.40)
Pavon 2024	Drug Burden Index	0.37 (0.21, 0.66)	
Pavon 2024	Drug Burden Index increased by at least 0.5	0.34 (0.14, 0.54)	
Gnjidic 2010	Improved DBI	0.43 (0.15, 1.25)	
Kouladjian 2021	Improved DBI	0.61 (0.25, 1.51)	
Jamieson 2023	DBI reduced by at least 0.5	1.03 (0.54, 1.97)	
Van Der Meer 2018	DBI reduced by at least 0.5	0.86 (0.36, 2.03)	
Petersen 2018	Change in DBI		-0.50 (-1.06, 0.06)
Pavon 2024	Change in DBI		-0.04 (-0.16, 0.08)
Kouladjian 2021	Medication Adherence, measured using the Morisky Green Levine scale		0.17 (-0.06, 0.40)
Hanlon 1996	Change in Medicine Appropriate Index		-3.90 (-4.09, -3.71)
Yeh 2013	Clinician-rated anticholinergic score		-0.60 (-1.08, -0.12)

1.3 Evidence for general deprescribing of polypharmacy/ multiple drug classes (non-controlled outcomes)

Study	Specific outcome	Result
1. Mortality		
Gerety 1993	Mortality at 6 months	19%
Garfinkel 2010	Mortality at 21 months	14%
Garfinkel 2018	Mortality (follow-up until death was 24-32 months)	38%
Garfinkel 2024	Mortality at 36 months follow up	27%
Jovevski 2023	Mortality at 2 months	1%
Hurley 2024	Mortality at 6 months	0%
2. Adverse drug withdrawal events (ADWEs)		
Gerety 1993	ADWEs	47%
Garfinkel 2010	Return of original condition	2%
3. Health outcomes		
Health service use		
Adeola 2018	Change in hospital admissions	-14%
Leguelinel-Blache 2020	At least one hospital admission	10%
Jovevski 2023	Hospitalised within 30 days	9%
Jovevski 2023	Emergency department visit within 30 days	18%
Hopkins 2023	Outpatient hospital visit following deprescribing	32.5%
Hopkins 2023	Hospitalisation following deprescribing	10%
Hopkins 2023	Emergency room visit following deprescribing	2.5%
Garfinkel 2024	Hospitalisation	49%
Hurley 2024	Nonelective hospitalisations in the preceding 6 months per patient	Mean difference and p-value -0.01, p=0.78
Hurley 2024	Emergency department visits in the preceding 6 months per patient	Mean difference and p-value +0.03, p=0.26
Falls		
Leguelinel-Blache 2020	Change in the proportion of patients having at least one fall	7%
Haque & Zakia 2019	Change in falls	Mean difference and p-value +1.09, p=0.77
Adverse drug events		
McDonald 2019	Adverse drug events	5%

Physical function		
Ailabouni 2019	Frailty	Endpoint mean -1.35 ± 2.93
Garfinkel 2018	Function status worsened	45%
Garfinkel 2024	Function status improved	18%
Haque & Zakia 2019	Increased need for activities of daily living	Mean difference and p-value -4.60, p=0.09
Cossette 2025	10-meter walk test normal pace, gait speed (meters/second)	Baseline to endpoint 0.95 ± 0.20 to 1.13 ± 0.26, p-value unstated
Cossette 2025	Short Physical Performance Battery (balance, gait speed, and chair stand, each scoring up to four points for a total score of 12; where a higher score indicates a better lower extremity Function)	Baseline to endpoint 8.8 ± 2.4 to 11.0 ± 1.0, p-value unstated
Cossette 2025	mini-BESTest (anticipatory postural adjustments, reactive postural control, sensory orientation, and dynamic gait with a maximum score of 28 and a higher score indicating better balance)	Baseline to endpoint 18.2 ± 7.0 to 20.6 ± 1.9, p-value unstated
Sleep		
Garfinkel 2018	Night-time sleep quality worsened	13%
Garfinkel 2024	Night-time sleep quality improved	31%
Garfinkel 2018	Daytime wakefulness worsened	10%
Garfinkel 2024	Daytime wakefulness improved	18%
Mental status		
Garfinkel 2018	Mental status worsened	14%
Garfinkel 2024	Mental status improved	41%
Haque & Zakia 2019	Depression	Mean difference and p-value -0.78, p=0.65
Others		
Garfinkel 2018	Urine continence worsened	20%
Garfinkel 2024	Urine continence improved	3%
Garfinkel 2018	Appetite decreased	12%
Garfinkel 2024	Appetite improved	21%
Garfinkel 2018	Vascular complications	17%
Haque & Zakia 2019	Pain	Mean difference and p-value

		+3.08, p=0.24
Garfinkel 2024	Pain improved	7%
Haque & Zakia 2019	Disruptive behaviours	Mean difference and p-value -6.85, p=0.02
Hopkins 2023	Improved or cleared dermatitis over more than 1 visit	18%
4. Cognitive function		
Garfinkel 2018	Cognitive status worsened	32%
Garfinkel 2024	Cognitive status improved	8%
5. Quality of life		
Garfinkel 2010	Overall improvement in the global assessment of perceived general health pertaining to mood and functional and cognitive capacity	88%
Garfinkel 2010	Overall significant worsening in the global assessment of perceived general health considering mood and functional and cognitive capacity	0%
Garfinkel 2010	Improvements in absolute MMSE score	4%
Hurley 2024	Mean EQ-5D-5L Summary	Mean difference and p-value -0.024, p=0.18
Hurley 2024	Mean EQ-5D-5L VAS score	Mean difference and p-value 1.53, p=0.45
6. Effect on medication regimen		
Ailabouni 2019	Reduction in the mean number of medicines	Endpoint mean - 2.13 ± 3.86
Garfinkel 2010	Reduction in the mean number of medicines	Endpoint mean -1.1 ± 1.6
Gerety 1993	Reduction in the mean number of medicines	Baseline to endpoint 7.0 ± 3.4 to 5.9 ± 2.8 (p<0.001)
Rea 2024	Reduction in the mean number of medicines	5.6 ± 2.7
Hanlon 1996	Reduction in the mean number of medicines	Endpoint mean -1.92 ±1.32
Horii 2020	Reduction in the mean number of medicines	Mean difference and p-value -2, p<0.001
Sakran 2024	Reduction in the mean number of medicines	Mean difference and standard deviation -1.3 ± 1.14
Velani 2024	Reduction in the mean number of medicines	Mean 3 (range 1-8)

Alyazeedi 2024	Reduction in the prescription rate of potentially inappropriate medications per 1000 orders	Baseline to endpoint 1.2 ± 0.7 to 0.8 ± 0.2 (p=0.26)
Stuckey 2018	Reduction of high-risk medications	-33%, p=0.0005
Garfinkel 2010	Successfully deprescribed after 19 months	81%
Jovevski 2023	Successfully deprescribed after 2 months	57%
Lee 2017	Successfully deprescribed after 2 months	70%
Foster 2022	Successfully deprescribed after 3 months	8%
Silva-Almodovar 2020	Successfully deprescribed after 4 months	45%
Meaney 2024	Successfully deprescribed at hospital discharge	53%
Gibert 2018 Junius-Walker 2021	Successfully withdrawn	45-57%
Marvin 2017	Successfully withdrawn completely or dose reduced	38%
McKean 2016	Unsuccessful deprescribing (i.e. medicine reinstated)	6%
Scuderi 2022	Unsuccessful deprescribing (i.e. medicine reinstated)	11%
Andrew 2018	Change in the proportion of individuals taking >10 medications	-7%
Andrew 2018	Medications used per individual	Baseline to endpoint 16.7 ± 5.6 to 15.5 ± 6.2
Fried 2017	Number of medicines at 3-month	Baseline to endpoint 13.4 ± 5.2 to 13.3 (SD not reported)
Kaminaga 2021	Number of medicines	Baseline to endpoint 9.1 ± 2.6 to 4.7 ± 2.5
Liu 2019	Number of medicines	Baseline to endpoint 12.5 ± 2.7 to 6.9 ± 3.0
McCarthy 2017	Number of medicines	Baseline to endpoint 17.5 ± 3.41 to 16.8 ± 3.94
Molist-Brunet 2020	Number of medicines	Baseline to endpoint 6.63 ± 2.93 to 4.97 ± 2.88
Mudge 2016	Number of medicines	Baseline to endpoint 14.3 ± 6.1 to 11.2 ± 5.1
Pasina 2016	Number of medicines	Baseline to endpoint 7.0 ± 2.9 to 5.9 ± 2.6
Hurley 2024	Number of medicines (regular and pro re nata (PRN))	Mean difference and p-value -0.6, p=0.031

Hurley 2024	Number of regular medicines	Mean difference and p-value -1.3*, p < .001)
Hurley 2024	Number of pro re nata (PRN)	Mean difference and p-value +0.5, p = 0.01)
Mudge 2016	Mean tablet load	Baseline to endpoint 20.5 ± 9.1 to 16.9 ± 7.7
Morley 2022	Number of medication classes per individual	Endpoint 1.74 (SD not reported)
Kaminaga 2021	Number of potentially inappropriate medicines	Baseline to endpoint 1.2 ± 1.1 to 0.6 ± 0.8
Kaminaga 2021	Potential prescribing omissions	Baseline to endpoint 0.5 ± 0.5 to 2.1 ± 1.6
Andrew 2018	Medications used per individual with dementia	Baseline to endpoint 15.9 ± 5.4 to 14.4 ± 6.0
Gareri 2024	Mean percentage home patients drugs	-0.2%, p=0.04
Gareri 2024	Mean percentage outpatient drugs	-0.4%
Andrew 2018	Change in the proportion of individuals with inappropriate medication use	-5%
Leguelinel-Blache 2020	Change in the proportion of individuals with inappropriate medication use	-22%
Cossette 2016	Change in individuals with inappropriate medication use, patient days	Mean difference and p-value -2.6 ± 143.3, p=0.12
McDonald 2019	Proportion of participants with one or more potentially inappropriate medicines deprescribed at discharge	55%
Massot Mesquida 2019	Change in psychotropic drugs prescribed per participant after 1 month	Mean difference and p-value 0.8, p < 0.001
Massot Mesquida 2019	Change in psychotropic drugs prescribed per participant after 6 months	Mean difference and p-value 0.7, p < 0.001
Morley 2022	Antipsychotic use	-2.4%, p=0.010
Haque & Zakia 2019	Antipsychotic use	-3.58, p=0.15
Pasina 2016	Use of psychotropic drugs	70%
Morley 2022	Diuretic use	-4.2%, p=0.001
Haque & Zakia 2019	Antianxiety use	-0.26, p=0.93
Morley 2022	Opioid use	-3.8%, p=0.001
Gibert 2018	Medication Appropriateness Index (MAI) score for all medicines	-5.7, p<0.001
Hurley 2024	Modified MAI score	Mean difference and p-value

		-0.10, p < .001
Houlind 2020	Reduction in MAI score	87%
Horii 2020	Polypharmacy rate	-14.3%, p<0.0001
Molist-Brunet 2020	Polypharmacy rate	53%
Molist-Brunet 2020	Excessive polypharmacy rate	6%
Liu 2019	Proportions of major polypharmacy	-14.4%, p<0.001
Kimura 2022	Reduced number of medicines	57%
Marvin 2017	Participants taking one or more fall-risk-increasing-drugs at discharge	60%
Masnoon 2023	Deprescribing attempted out of all patients reviewed	31%
Schapira 2021	Prevalence of benzodiazepines	-31%, p<0.001
Schapira 2021	Prevalence of non-steroidal anti-inflammatory drugs	-73%, p<0.001
Schapira 2021	Prevalence of tricyclic antidepressants	-49%, p<0.001
Schapira 2021	Prevalence of histamine 1 receptor antagonist	-60%, p<0.001
Schapira 2021	Prevalence of anti-hypertensives	-48%, p=0.002
Schapira 2021	Prevalence of opioids	-42%, p=0.013
Schapira 2021	Prevalence of oxybutynin	-38%, p=0.008
Schapira 2021	Prevalence of muscle relaxants	-56%, p<0.001
Rojo-Sanchis 2017	Reduction in anticholinergic burden, as measured using the Anticholinergic Cognitive Burden Scale	-22.2%, p=0.047
Rojo-Sanchis 2017	Reduction in anticholinergic burden, as measured using the Anticholinergic Drug Scale	-14.3%, p=0.087
Rojo-Sanchis 2017	Reduction in anticholinergic burden, as measured using the Anticholinergic Risk Scale	-44.4%, p=0.001
Rojo-Sanchis 2017	Reduction in anticholinergic drugs	-5.3%, p=0.151
Hurley 2024	Anticholinergic cognitive burden score	Mean difference and p-value -0.34, p=0.032
Cossette 2020	Successfully withdrawn completely or dose reduced	188/220 (85%)
Cossette 2022	Successfully withdrawn completely or dose reduced	1082/1404 (77%)
Pasina 2016	Severe drug–drug interactions	-21.3%, p<0.0001
Rea 2024	Patients referred for disease state management by pharmacists	25%

1.4 GRADE evidence profile (critical or important but not critical outcomes only)

Question: In older people, what are the effects of deprescribing (i.e. dose reduction or complete discontinuation) long-term medicines on mortality, adverse drug withdrawal events, health-related outcomes, cognitive function, and quality of life?

Certainty assessment							Number of participants		Effect	Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Deprescribing	Continuation			
1. Mortality											
25 [2, 3, 6, 8, 9, 16, 32, 34-37, 39, 42, 44, 45, 47, 65, 73, 74, 88, 105, 107, 121, 125, 126]	Randomised controlled trials (RCTs)	Serious [1]	Not serious	Not serious	Serious [2]	Not serious	7618	7756	OR 0.97 (0.87, 1.08)		8
6 [54, 57, 59, 76, 103, 123]	Non-randomised studies	Serious [3]	Not serious	Serious [4]	Serious [5]	Not serious	440	413	OR 0.70 (0.36, 1.38)		8
6 [25, 60-62, 69, 70]	Non-controlled studies	Serious [6,49]	Not serious	Serious [7]	Serious [8]	Not serious	1139	N/A	19% [62] 14% [60] 38% [61] 1% [25] 27% [69] 0% [70]		8
2. Adverse drug withdrawal events (ADWEs)											
ADWEs											
4 [8, 32, 37, 121]	RCTs	Serious [9]	Serious [10]	Not serious	Not serious	Not serious	1535	1561	OR 1.98 (1.48, 2.66)		6
1 [62]	Non-controlled study	Serious [11]	Not serious	Serious [12]	Serious [13]	Not serious	132	N/A	47%		6
Exacerbation /return of underlying condition											

1 [2]	RCT	Serious [14,15]	Not serious	Not serious	Serious [16]	Not serious	31	27	OR 6.75 (0.33, 136.91)	6
1 [60]	Non-controlled study	Serious [17]	Not serious	Serious [18]	Serious [19]	Not serious	70	N/A	2%	6
3. Health outcomes										
Adverse drug events										
6 [32, 45, 47, 72, 75, 125]	RCTs	Serious [17,50]	Serious [10]	Not serious	Serious [8]	Not serious	4153	4798	The number of participants who experienced at least one adverse drug event did not differ significantly between the deprescribing and continuation groups (OR 1.11, 95% CI 0.64, 1.91, studies = 3, n = 5492) [32, 47, 75]. In one cluster RCT, deprescribing was associated with a significantly fewer number of adverse drug events (MD -0.30, 95% CI -0.48, -0.12, study = 1, n = 3185) [45]. Deprescribing was not associated with a significant difference in the frequency of medication side effects (MD -0.40, 95% CI -1.23, 0.43, study = 1, n = 202) [4], the number of participants with adverse events within 30 days of discharge (OR 0.92, 95% CI 0.82, 1.04, study = 1, n = 4988) [75], or the change in the number of adverse drug events (MD 0.11, 95% CI -0.23, 0.45, study = 1, n = 72) [72].	5
1 [54]	Non-randomised study	Serious [20]	Not serious	Not serious	Serious [21]	Not serious	32	132	OR 0.20 (0.03, 1.59)	5
1 [85]	Non-controlled study	Serious [22]	Not serious	Not serious	Serious [23]	Not serious	873	N/A	5%	5
Falls										
14 [2, 6, 35, 44, 45, 68, 73-75, 88, 107, 117, 125, 127]	RCTs	Serious [24,51]	Serious [10]	Not serious	Serious [25]	Not serious	5972	6538	Deprescribing was not associated with a significant difference in the number of participants who had at least one fall (OR 0.88, 95% CI 0.66, 1.17, studies = 11, n = 8416) [2, 6, 35, 44, 73-75, 88, 107, 117, 127]. The mean number of falls did not differ significantly between the deprescribing and continuation groups (MD -0.01, 95% CI -0.09, 0.07, studies = 3, n = 3843) [2, 45, 125].	5

									In one study, the risk of experiencing at least one fall did not differ significantly between the deprescribing and continuation groups (OR -0.22, 95% CI -0.53, 0.09, study = 1, n = 885) [74]. In one study, there was no statistically significant difference in fall-related emergency department visits between patients who had modifications to medications following pharmacist reviews and those who had not implemented changes (OR 0.87, 95% CI 0.52, 1.46, n = 309) [68].		
5 [22, 76, 94, 96, 99]	Non-randomised studies	Serious [3]	Not serious	Serious [4]	Serious [26]	Serious [27]	580	741	Deprescribing was not associated with a significant difference in the number of participants who had at least one fall (OR 0.75, 95% CI 0.55, 1.03, studies = 5, n = 1321) [22, 76, 94, 96, 99]. In one study, the mean number of falls did not differ significantly between the deprescribing and continuation groups (MD -2.30, 95% CI -4.94, 0.34, study = 1, n = 141) nor the risk of experiencing at least one fall (OR 0.48, 95% CI 0.23, 1.00, study = 1, n = 141) [96].		5
2 [27, 112]	Non-controlled studies	Serious [28]	Not serious	Serious [29]	Serious [26]	Not serious	1062	N/A	Non-controlled studies reported that deprescribing was associated with a 7% reduction in the proportion of patients who had at least one fall (study = 1, n = 49) [27] and a 1.09% increase in the rate of falls (p=0.77, study = 1, n = 1013) [112].		5
Health service use											
20 [2, 3, 6-9, 12, 15, 16, 33, 35, 37, 40, 44, 45, 47, 73, 74, 107, 126]	RCTs	Serious [1,52]	Serious [10]	Not serious	Not serious	Not serious	7628	7802	Deprescribing was not associated with a significant difference in the number of participants with unplanned hospital admissions (OR 0.99, 95% CI 0.82, 1.21, studies = 13, n = 11157) [2, 6, 8, 9, 16, 35, 37, 44, 45, 47, 73, 74, 106], number of hospital outpatient visit (MD 0.40, 95% -0.31, 1.11, study = 1, n = 2470) [33], the number of hospitalisations (MD -0.01, 95% -0.29, 0.27, study = 1, n = 521) [40], or percentage of difference in the time to first 90-day unplanned emergency department visit/hospital readmission/death (MD -0.15, 95% CI -0.40, 0.10, n = 283) [7]. Deprescribing was not associated with a significant		5

									difference in the length of hospital stay (MD -0.37, 95% CI -1.92, 1.18, studies = 2, n = 462) [2, 128], institutionalisation (OR 1.01, 95% CI 0.56, 1.82, studies = 2, n = 496) [106, 107], intensive care unit transfer (OR 0.75, 95% CI 0.16, 3.38, study = 1, n = 372) [8], number of emergency room presentation (MD 0.13, 95% CI -0.11, 0.37, study = 1, n = 229) [128], and the number of participants with emergency room presentation or readmission (OR 0.85, 95% CI 0.72, 1.01, studies = 6, n = 4287) [3, 8, 9, 12, 35, 106].		
8 [22, 38, 54, 55, 59, 76, 90, 123]	Non-randomised studies	Serious [24]	Not serious	Serious [4]	Serious [26]	Not serious	547	656	Deprescribing was not associated with a significant difference in the number of participants with unplanned hospital admissions (OR 0.81, 95% CI 0.55, 1.18, studies = 6, n = 870) [22, 38, 54, 76, 90, 123]. Deprescribing was not associated with a significant difference in the number of participants with emergency room presentation or readmission (OR 0.81, 95% CI 0.47, 1.38, studies = 2, n = 350) [22, 76] and readmission risk (OR 0.74, 95% CI 0.48, 1.15, studies = 2, n = 346) [59, 76]. Deprescribing was not associated with a significant change in the rate of hospital discharge to home (OR 0.82, 95% CI 0.42, 1.59, study = 1, n = 153) [55].		5
5 [25, 27, 69, 79, 120]	Non-controlled studies	Serious [30,49]	Not serious	Serious [31]	Serious [8]	Not serious	693 (one study not stated)	N/A	Deprescribing was associated with a 14% reduction in hospital admissions (n = not stated) [120], 10% of the participants had at least one hospital admission (n = 49) [27], 9-49% were hospitalised following deprescribing (studies = 3, n = 574) [25, 69, 79], 2.5-18% had emergency department visit following deprescribing (studies = 2, n = 333) [25, 79], and 32.5% had an outpatient hospital visit following deprescribing (n = 35) [79]. There was no significant change in the number of emergency department visits (+0.03, p=0.26, n= 99), non-elective hospitalisations (-0.01, p = 0.78, n = 99) six months after deprescribing [70].		5
Sleep											

2 [6, 34]	RCTs	Serious [32]	Not serious	Not serious	Serious [33]	Not serious	24	23	Deprescribing was not associated with a significant difference in sleep quality (MD 1.00, 95% CI -0.68, 2.68, studies = 2, n = 47) [6, 34].		4
2 [61, 69]	Non-controlled studies	Serious [34,49]	Not serious	Not serious	Serious [35]	Not serious	475	N/A	A non-controlled study reported that 13% of participants had worsened night-time sleep quality and 10% had worsened daytime wakefulness (n = 193) following deprescribing. Another study by the same author reported that 31% of participants had improved night-time sleep quality and 18% had improved daytime wakefulness following deprescribing (n=282) [69].		4
Fractures											
5 [4, 6, 35, 44, 45]	RCTs	Serious [24]	Not serious	Not serious	Serious [36]	Not serious	2446	2421	Deprescribing was not associated with a significant difference in any fractures (OR 0.97, 95% CI 0.60, 1.57, studies = 5, n = 4867) [4, 6, 35, 44, 45] and non-vertebral fractures (OR 0.66, 95% CI 0.37, 1.18, studies = 2, n = 223) [6, 35, 45].		5
1 [54]	Non-randomised study	Serious [20]	Not serious	Not serious	Serious [21]	Not serious	32	132	Deprescribing was not associated with a significant difference in any fractures (OR 0.81, 95% CI 0.22, 2.97, study = 1, n = 164).		5
Mental status											
1 [38]	Non-randomised study	Serious [37]	Not serious	Not serious	Serious [35]	Not serious	73	64	Deprescribing was not associated with a significant change in the number of participants who had worsened scores in the EQ-5D-5L depression and anxiety domain (OR 0.37, 95% CI 0.15, 0.93, study = 1, n = 137).		6
3 [61, 69, 112]	Non-controlled studies	Serious [34,49]	Serious [38]	Not serious	Serious [35]	Not serious	1488	N/A	A non-controlled study [61] reported that 14% had worsened mental status (mood, depression) following deprescribing (n=193) and another study by the same author reported that 41% of participants had improved mental status following deprescribing (n=282) [69]. Another study [112] reported a lower rate of depression (-0.78%, p=0.65, n = 1013).		6
Adverse events/ serious adverse events/ cardiovascular events											
1 [54]	Non-randomised study	Serious [20]	Not serious	Not serious	Serious [21]	Not serious	32	132	<u>Cardiovascular events</u> OR 0.15 (0.01, 2.57)		7
1 [61]	Non-controlled study	Serious [34]	Not serious	Not serious	Serious [35]	Not serious	193	N/A	<u>Vascular complications</u> 17%		7

Delirium											
3 [22, 54, 76]	Non-randomised studies	Serious [30]	Not serious	Serious [4]	Serious [26]	Not serious	215	305	OR 0.87 (0.56, 1.35)		5
Morbidity											
2 [107, 128]	RCTs	Serious [39]	Serious [,38]	Not serious	Serious [16]	Not serious	271	292	Different measures were used for reporting morbidity in two studies. Morbidity, measured using Functional Comorbidity Index, showed deterioration with deprescribing (MD 1.20, 95% CI 0.50, 1.90, study = 1, n = 159) [107] whereas morbidity improved with deprescribing in one study that used Global Multimorbidity Treatment Burden questionnaire (MD -4.72, 95% CI -8.63, -0.81, study = 1, n = 404) [128]. Higher scores represent greater comorbidity in both measures.		5
Behavioural and psychological symptoms											
3 [4, 6, 43]	RCTs	Serious [30]	Not serious	Serious [40]	Serious [41]	Not serious	427	378	Neuropsychiatric symptoms, measured using the Neuropsychiatric Inventory-Nursing Home (NPI-NH) with high scores indicate worse neuropsychiatric symptoms. MD -0.56 (-1.81, 0.69)		6
1 [112]	Non-controlled study	Serious [28]	Not serious	Not serious	Serious [42]	Not serious	1013	N/A	A non-controlled study reported that deprescribing was associated with a significant change in the rate of disruptive behaviours (-6.85%, p = 0.02).		6
Physical function											
5 [6, 43, 72, 107, 125]	RCTs	Serious [30,50]	Not serious	Serious [40]	Serious [41]	Not serious	445	440	Two RCTs measured the dependency in activities of daily living using the modified Barthel Index [4, 6] where a lower score indicates higher dependency and reported no significant difference between the deprescribing and continuation groups (SMD 0.22, 95% CI -0.02, 0.46, studies = 2, n = 266). One study measured the dependency in activities of daily living using the Physical Self-Maintenance Scale where higher scores indicate higher dependency and reported an improvement in dependency following deprescribing (MD -1.50, 95% CI -2.81, -0.19, study = 1, n = 397 [43]. Physical function, measured using the Short Physical Performance Battery MD 0.50 (-0.60, 1.60)		6

									[107]. Change in frailty measured using Frailty Scale (MD 0.60, 95% CI -0.07, 1.27, n = 63) [72] Change in activities of daily living measured using modified Barthel Index (MD 2.20, 95% CI -8.13, 12.53, n = 63) [72]		
1 [103]	Non-randomised study	Serious [43]	Not serious	Not serious	Serious [35]	Not serious	32	21	One study measured the dependency in activities of daily living using the modified Barthel Index where a lower score indicates higher dependency and reported no significant difference between the deprescribing and continuation groups (MD 3.80, 95% CI -2.59, 10.19).		6
5 [61, 69, 110, 112, 120]	Non-controlled studies	Serious [44,49]	Serious [38]	Not serious	Serious [45]	Not serious	1539	N/A	A non-controlled study [61] reported that 45% of participants had worsened functional status following deprescribing (n=193) and another study by the same author reported that 18% of participants had improved functional status following deprescribing (n=282) [69]. A study reported a significant reduction in frailty, assessed using the Edmonton Frailty Scale (MD 1.35, 95%, CI − 2.22, − 0.48, n = 46) [108]. A study reported that deprescribing was associated with a significant change in the rate of increased need for activities of daily living (-4.6%, p = 0.09) [112]. A small pilot study (n=5) reported improvements in [110]: • gait speed measuring using the 10-meter walk test normal pace from 0.95 ± 0.20 to 1.13 ± 0.26 meter/second, p-value unstated • Short Physical Performance Battery (balance, gait speed, and chair stand, each scoring up to four points for a total score of 12; where a higher score indicates a better lower extremity function) from 8.8 ± 2.4 to		6

									• 11.0 ± 1.0, p-value unstated • mini-BESTest (anticipatory postural adjustments, reactive postural control, sensory orientation, and dynamic gait with a maximum score of 28 and a higher score indicating better balance) from 18.2 ± 7.0 to 20.6 ± 1.9, p-value unstated		
Clinical Global Impressions of Change											
1 [43]	RCT	Serious [46]	Not serious	Not serious	Serious [35]	Not serious	214	183	MD -0.20 (-0.41, 0.01)		4
Pain											
2 [69, 112]	Non-controlled studies	Serious [28,49]	Not serious	Not serious	Serious [42]	Not serious	1295	N/A	A non-controlled study (n=1013) reported that deprescribing was not associated with a significant change in the rate of pain (+3.08%, p = 0.24) whereas another study reported that 7% of participants had reduced pain following deprescribing (n=282) [69].		5
4. Cognitive function											
7 [6, 34, 44, 72, 104, 107, 125]	RCTs	Serious [1,50]	Serious [38]	Not serious	Serious [8]	Not serious	498	503	The measures used for reporting cognitive functions were heterogeneous across the studies. Deprescribing was not associated with a significant difference in cognitive functions measured using Mini-Mental State Examination (MD 0.62, 95% CI -0.24, 1.48, studies = 4, n = 353) [6, 34, 72, 125]. In one study, there was a modest but significant decrease in cognitive function measured using Mini-Cog (MD -0.50, 95% CI -0.88, -0.12, study = 1, n = 159) [107]. In two other studies, deprescribing was not associated with a significant difference between the two groups in the number of participants with cognitive impairment (score ≥ 8 points on 6-Item Cognitive Impairment Test) (OR 0.98, 95% CI 0.65, 1.47, study = 1, n = 485) [44], memory (MD 7.00, 95% CI -0.20, 14.20) or cognition (MD 2.00, 95% CI -1.92, 5.92) measured using the Neuropsychological Assessment Battery (study = 1, n = 9) [104].		7
1 [103]	Non-randomised study	Serious [43]	Not serious	Not serious	Serious [35]	Not serious	32	21	Deprescribing was not associated with a significant change in cognitive functions measured using Mini-Mental State Examination (MD -0.40, 95% CI -1.39, 0.59, study = 1, n = 53).		7
2 [61, 69]	Non-controlled studies	Serious [34,49]	Not serious	Serious [47]	Serious [35]	Not serious	352	N/A	Two non-controlled studies reported that 4-8% of participants had improved cognition (n = 352) [61, 69]. One of these studies [61] reported that 32% of		7

									participants had worsened cognitive status (n = 193) following deprescribing.		
5. Quality of life (QoL)											
11 [6, 14, 32, 34, 35, 39, 43, 72, 92, 101, 125]	RCTs	Serious [1,50]	Serious [38]	Not serious	Serious [26]	Not serious	992	919	The measures used for reporting quality of life were heterogeneous across the studies, and some studies adopted multiple measures in one study. Deprescribing was not associated with a significant difference in the quality of life reported using EQ-5D utility score (MD 0.04, 95% CI -0.06, 0.15, studies = 7, n = 1654) [6, 14, 34, 43, 72, 92, 125], Quality of Life for People with Dementia (QUALIDEM) (MD -0.03, 95% CI -1.46, 1.40, studies = 2, n = 620) [35, 43], ICEpop CAPability measure for Older people (ICECAP-O) (MD 0.09, 95% CI -0.11, 0.29, study = 1, n = 50) [35], Quality of life in Alzheimer's Dementia (QOLAD) (MD 0.00, 95% CI -2.98, 2.98, study = 1, n = 37) [6], Quality of Life in Late Stage of Dementia score (QUALID) (MD -0.60, 95% CI -2.37, 1.17, study = 1, n = 545) [43], Short Form-12 mental component (MD 0.10, 95% CI -1.54, 1.74, study = 1, n = 541) [92], and Short Form-12 physical component (MD -1.30, 95% CI -2.73, 0.13, study = 1, n = 541) [92]. Deprescribing was associated with a significant deterioration in the quality of life reported using the 15-dimension instrument of health-related quality of life (MD -0.03, 95% CI -0.06, -0.01, study = 1, n = 189) [39] and Short Form-36 (MD -2.18, 95% CI -2.67, -1.68, studies = 3, n = 257) [32, 34, 101].		7
1 [59]	Non-randomised study	Serious [43]	Not serious	Not serious	Serious [35]	Not serious	118	62	EQ-5D index, MD -0.07 (-0.17, 0.03) VAS score, MD -2.90 (-9.58, 3.78)		7
2 [60, 70]	Non-controlled study	Serious [48]	Not serious	Not serious	Serious [26]	Not serious	169	N/A	88% of the participants reported improvement in perceived general health pertaining to mood and functional and cognitive capacity following deprescribing (n=70) [60]. However, in another study, there was no significant change in the mean EQ-5D-5L summary score (-0.024, p=0.18) or EQ-5D-5L VAS score (1.53, p=0.45) six months after deprescribing (n=99) [70].		7

[1] The pooled risk of bias is rated as serious due to many studies having performance bias due to a lack of blinding or potential selection bias and confounding biases. Follow-up duration was heterogeneous across the studies. In one or more studies, the randomisation method was not clearly described.
[2] Some imprecision exists as many studies had small sample sizes, wide confidence intervals, or lack of statistical significance for some outcomes.
[3] Non-randomised designs and potential for selection bias in the majority of studies.
[4] One study (Van der Linden 2017) involved very old inpatients, potentially limiting the generalisability of the finding.
[5] Small sample size and wide confidence intervals in the estimates of effect.
[6] Single-arm studies with potential for selection, performance, detection, and reporting biases in most studies.
[7] One study (Garfinkel 2010) used indirect outcome measures (subjective health assessments) and one study (Gerety 1993) had limited generalisability to non-veteran-affairs nursing home populations.
[8] Small sample size and/or wide confidence intervals for some studies.
[9] Unblinded studies; however, in the Hanlon 1996 study, assessors were blinded for some outcomes. In the Vasilevskis 2023 study, primary investigators and reviewers for safety measures were blinded to group assignments; however, site staff collecting the data at each follow-up time point were not blinded. In Phelan 2024, clinicians and participants were not blinded to group assignments.
[10] There is considerable heterogeneity in the meta-analysis of the studies.
[11] Retrospective design, potential for selection bias
[12] Limited generalisability as the study was for Veterans Affairs nursing home populations.
[13] Small sample size.
[14] Lack of blinding and potential for performance and detection bias.
[15] Short follow-up duration (4 months)
[16] Wide confidence intervals and small sample size.
[17] Potential for selection and performance bias.
[18] The study used indirect outcome measures (subjective health assessments).
[19] Small sample size and lack of reported confidence intervals.
[20] Potential for selection bias and confounding factors in the observational design.
[21] Small sample size, particularly in the intervention group (n = 32).
[22] Non-controlled study design and potential for selection and performance biases.
[23] Sample size and number of events were likely not enough for a precise effect estimate.
[24] Potential selection bias, lack of blinding, and performance bias in some studies.
[25] The pooled imprecision is rated as serious as some studies had wide confidence intervals, small sample sizes, or were underpowered for certain outcomes.
[26] Small sample sizes and limited precision in some studies.
[27] One or more of the studies were sponsored by pharmaceutical companies, although the authors stated that the sponsors had no further role in the paper.
[28] Lack of a concurrent control group and potential biases in both studies.
[29] One study (Leguelinel-Blache 2020) used surrogate outcomes that may not directly reflect patient-important outcomes.
[30] The pooled risk of bias is rated as serious due to the observational designs, potential for confounding bias, and lack of control groups in the included studies.
[31] Limited generalisability as more than half of the studies involved older people who were hospitalised or admitted to the emergency department during the study.
[32] The pooled risk of bias is rated as serious due to the open-label designs and potential for selection and performance bias in both studies.
[33] The pooled imprecision is rated as serious due to the small sample sizes and lack of precision in effect estimates.
[34] Non-controlled study, potential for selection, performance, detection, and reporting biases.
[35] Small sample size.
[36] All studies had wide confidence intervals or were underpowered for certain outcomes.
[37] Non-randomised design and potential for selection and confounding bias.
[38] High variability in the outcome reported or outcome measures.

[39] Potential selection bias, lack of blinding, and attrition bias in both studies.
[40] The pooled indirectness is rated as serious as one study (Husebo 2019) introduced a multicomponent intervention whereas two other studies focused only on medication reviews.
[41] The studies had imprecise effect estimates or were underpowered for some outcomes.
[42] Although the study showed statistical significance in the outcome reported, the outcome is likely imprecise due to the sample size and number of events.
[43] Potential selection bias, performance bias, and detection bias in the open-label study design.
[44] Non-randomised designs, lack of control groups, and potential for various biases in all studies.
[45] Lack of power for some outcomes, small sample sizes, and lack of reported precision estimates.
[46] Potential performance and detection biases from lack of blinding and use of proxy-rated assessments.
[47] One study (Garfinkel 2010) used indirect outcome measures (subjective health assessments).
[48] Observational study design with potential for selection bias and residual confounding.
[49] In one study (Garfinkel 2024), population was self-selected, with all included patients provided with the intervention.
[50] One study (Etherton-Beer 2024) reported a power of only 0.24 to detect statistical significance due to the low recruitment rate.
[51] One study (Selman 2024) compared the number of falls between patients who received pharmacist recommendations on high-risk medications and made modifications and those who received recommendations but showed no evidence of modification. This could potentially introduce confounding, as factors influencing medication changes may also affect fall risk.
[52] Lee (2024) was a secondary analysis of the Vasilevskis 2023 study; however, in this study 24% of the original 372 participants were excluded due to various reasons which introduce potential bias.

1.5 Evidence-to-Decision table

Question: In older people, what are the effects of deprescribing (i.e. dose reduction or complete discontinuation) long-term medicines on mortality, adverse drug withdrawal events, health-related outcomes, cognitive function, and quality of life?

Decision domain	Summary of reason for decision	Subdomains influencing decision
Certainty of evidence Is there a high or moderate certainty of evidence? Yes ☐ No ☑	The certainty of evidence for the benefits of deprescribing is very low to low. The certainty of evidence for the harms of deprescribing is very low to low.	Key reasons for downgrading: Risk of bias, imprecision Are all critical outcomes measured? Yes ☑ No ☐
Benefits and harms Is there certainty that the benefits of deprescribing outweigh the harms? Yes ☐ No ☑	The effects of deprescribing multiple medications have been comprehensively reported in the systematic review and meta-analysis, as well as tabulated in Appendix B (GRADE evidence profile table) with an overview provided in the guideline document (as a narrative overview and GRADE summary of findings table). Below is a summary according to the study designs. <u>Summary of outcomes:</u> Randomised and non-randomised controlled trials: • No significant difference in mortality, exacerbation or return of the underlying condition, falls, fractures, health service use, sleep quality, mental status, cardiovascular events, delirium, behavioural and psychological symptoms, and clinical global impressions of change • Significantly more adverse drug withdrawal events • Significantly fewer number of adverse drug events in one RCT but no significant difference in the proportion of participants who experienced at least one adverse drug event or change in the number of adverse drug events Inconsistent findings across randomised controlled trials for morbidity, physical function, cognitive function, and quality of life from randomised controlled trials and non-randomised studies (likely due to the different	Is the baseline risk for benefits and harms of deprescribing similar across subgroups? Yes ☐ No ☑ Evidence at this time suggests that the benefits or harms of deprescribing differ based on the age of the person and intervention types. Subgroup analyses from the systematic review and meta-analysis revealed a significant reduction in mortality in the young old (aged 65–79) (OR 0.71, 95% CI 0.51–0.99) and when patient-specific interventions were applied (OR 0.79, 95% CI 0.63–0.99). Should there be separate recommendations for subgroups? Yes ☑ No ☐ The guideline development group acknowledges that certain subgroups may have factors (e.g. disease state, life expectancy, functional status, the indication for use of multiple medications, other

	measures being used). Non-controlled trials: • Reduced disruptive behaviours • Improved mood, functional and cognitive capacity • No significant change in pain severity • Mortality (0-38%) • Adverse drug withdrawal events (47%) • Exacerbation or return of the underlying condition (2%) • 13% of participants had worsened quality of sleep but 31% had improved night-time sleep quality and 18% had improved daytime wakefulness • 14% of participants had worsened mental status (mood, depression) but 41% of participants had improved mental status and another study reported a lower rate of depression • Adverse events (e.g. vascular complications, 17%) Inconsistent findings across studies for falls, physical function, cognitive function, health service use, and quality of life. <u>Summary of withdrawal schedules:</u> No consistency in methods used for deprescribing in the studies and no evidence that any particular method was associated with statistically significant results Randomised controlled trials: Individualised (studies=13, n=11128), Not described (studies=27, n=98648, n unstated in 2 studies), Abrupt discontinuation or taper gradually (studies=3, n=478), Dose reduced at approximately two-weekly intervals (study=1, n=44), Discontinuation, dose reduction or alternative drug (study=1, n=50), Dose reduced over one month (study=1, n=612), Non-randomised controlled trials: Individualised (studies=5, n=546), Not described (studies=19, n=13221), Discontinuation, dose reduction or frequency reduction	comorbidities, medication adherence, medication burden, presence of adverse drug events or evidence of prescribing cascade) that could impact the balance of benefits and risks from deprescribing. However, the available evidence is insufficient to justify distinct evidence-based recommendations.

	(study=1, n=136), Dose reduction or discontinuation (study=1, n=40), Taper slowly (study=1, n=67), Geriatrician provided plans to users to gradually reduce these medicines as a stepwise procedure over some months (study=1, n=591), Abrupt discontinuation or slowly tapered over one month period to a lower dose or to complete discontinuation (study=1, n=141), Abrupt discontinuation or taper for medications with dependency or withdrawal risk (study=1, n=309) Non-controlled trials: Ceased or tapered (study=1, n=873), Individualised (studies=15, n=1926), Not described (studies=26, n=47191, n unstated in one study), One drug ceased at a time up to 60 days (study=1, n=45), Slowly tapered or replaced (study=1, n=8622), Tapered over three days with one-third of the initial dose removed daily (study=1, n=27), Cease abruptly/ weaning plan/ dose reduction/ continue with regimen (study=1, n=116), Initial dose reduction in the hospital, then continue weaning the dose after discharge (study=1, n=256)	
Values and preferences Is there confidence in the estimate of the relative importance of outcomes and individual preferences? Yes ☑ No ☐	Generally, patients see their medications as essential, despite potential side effects. The extent to which these side effects are concerning varies individually, often influenced not only by the severity of side effects but also by the benefits they perceive and the relationship or trust they have with their healthcare providers – an influence that can vary substantially among providers. Patients value highly informed consent in the process of prescribing and deprescribing. To ensure informed consent, patients require comprehensive information from their healthcare providers to make well-informed decisions about their treatment. Deprescribing raises concerns about changes in interactions with other concurrent medications, food or allergens, making it crucial to consider each patient's unique circumstances and preferences. For older people, the cost of medications can be a significant barrier, especially when medications require frequent refills or are dispensed at different times, creating accessibility issues. These financial considerations further highlight the need for careful medication management and coordinated care planning to ensure medications	Perspective taken: The lack of evidence for serious harm as a result of deprescribing and evident benefits related to reduced medication burden and costs. Individual values and preferences determine the deprescribing approaches. Sources of values and preferences: 1) Consultation with patient and carer representatives 2) Non-systematic review of evidence Source of variability, if any: Difficult to determine the extent of variability; high variability for patient preferences. Method for determining values satisfactory for this recommendation?

	remain accessible and aligned with patients' preferences. Many patients express a preference for a holistic approach to care, where physical, mental, social, and emotional health factors are considered in conjunction with their medicine regimens. If deprescribing is to be implemented, patients require timely follow-up monitoring as health situations can change between their appointments with healthcare providers. Effective deprescribing relies on good communication among providers and coordinated care, particularly when medications are prescribed by different providers. The majority of healthcare professionals believe that deprescribing can be beneficial for patients. However, deprescribing is often impeded by barriers such as a lack of time, insufficient knowledge to initiate the plan, unwillingness to discontinue medications prescribed by another doctor or specialist, and competing priorities during a patient consultation. Additionally, the complexity of discussing and implementing deprescribing for patients with multiple morbidities and an increased risk of poor communication between parties involved in a patient's care have also been cited in the literature. When prescribing is directly influenced by patient requests for specific medicines, the resulting patient resistance or refusal to deprescribe medicines may also be a barrier to medication cessation. For healthcare professionals, there are major concerns arising from deprescribing about undertreatment, underdosing, and not complying with the recommendations from existing treatment guidelines, particularly in the absence of clear and consistent high-quality evidence for deprescribing.	Yes ☑ No ☐ Yes, but would be improved with direct patient input.
Resources Are the resources worth the expected net benefit? Yes ☑ No ☐	A comprehensive economic evaluation was outside the scope of the current review. However, potential cost and resource implications related to deprescribing interventions and continuation of medications are discussed below. Cost implications: The inappropriate use of multiple medications led to higher total medication costs and increased costs due to medication errors and medication-related harms. The World Health Organisation estimated that 0.3% of the global healthcare expenditure (US$ 18	Feasibility: Is this intervention generally available? Yes ☑ No ☐ Opportunity cost: Is this intervention and its effects worth withdrawing or not allocating resources from other interventions? Yes ☑ No ☐

	billion) could be avoided by optimising polypharmacy management. An Australian pharmacist-led deprescribing intervention in residential aged care facilities (Opti-Med) estimated discontinuation of inappropriate medication use could potentially save $1 to $16 million per annum for the health system nationally without reducing the quality of life. Physician implications: There is a lack of robust data informing the cost of the intervention and subsequently, cost-effectiveness. Most clinicians believe that deprescribing is a complex process, with barriers to resources commonly reported (e.g. suboptimal deprescribing organisational environment that included competing workloads, staffing issues, and limited financial support).	Economic and preventive benefits for harms: Is there a lot of variability in resource requirements across settings? Yes ☐ No ☑
Equity What would be the impact of deprescribing on health inequities? ☑ Uncertain	The social determinants of health equity are complex and multifaceted. The impact of deprescribing on health equity is inadequately explored in the literature. Older people affected by the inappropriate use of medications are likely to derive substantial benefits in terms of health equity from deprescribing. By reducing medication burdens, lowering costs, and simplifying medicine regimens, deprescribing may enhance access to care and improve health outcomes for this vulnerable population. However, ensuring equitable implementation and addressing potential challenges faced by people with varying health literacy and access disparities is crucial to maximising these benefits. Culturally and linguistically diverse populations, Aboriginal and Torres Strait Islander populations, people with low socioeconomic status, and those living in rural or remote areas may require additional support or considerations when implementing deprescribing intervention, including the ongoing monitoring process.	
Acceptability Is the option of deprescribing acceptable to key stakeholders? ☑ Probably yes	Healthcare practitioners: Deprescribing is likely acceptable to most healthcare practitioners, especially when supported by clinical practice guidelines and a shared decision-making process with patients. The term deprescribing may be new to healthcare practitioners but the concept is not. Healthcare practitioners are very familiar with discontinuing ineffective medications or those causing adverse effects worse than the condition being treated. Patients, their caregivers and family members: Many are open to deprescribing if they understand the potential benefits and risks, especially when given the option to restart medications when necessary. Policymakers and health systems: From a broader perspective, deprescribing can be seen as a way to reduce healthcare costs and improve patient outcomes. However, the short-term impacts on patient care and the resources required to implement effective deprescribing strategies may be a concern.	
Overall judgment	There is a lack of quality evidence for deprescribing to inform evidence-based recommendations.	

2. Proton-pump inhibitors (PPIs)

2.1 Overview of studies targeted proton-pump inhibitors

Article	Drug/Class	Study design	Sample size	Follow-up (months)	Withdrawal schedule
Reeve 2015 [129]	Proton-pump inhibitors	Before and after study	6	6	Halving the dose every two weeks and reduction to as-needed use if the participant remained symptom-free on the low-dose
McDonald 2015 [130]	Proton-pump inhibitors	Before and after study	152	Until hospital discharge	Not described
Bhardwaj 2022 [131]	Proton-pump inhibitors	Before and after study	170	Not specified	Slowly tapered according to a specific protocol
Calvo 2021 [132]	Proton-pump inhibitors	Before and after study	75	6	Sudden cessation, gradual taper, or switching to “on-demand” dosing
Lee 2017 [133]	Proton-pump inhibitors	Before and after study	28	2	Abrupt discontinuation
Leszcynski 2023 [134]	Proton-pump inhibitors	Before and after study	228	Not specified	Dose halved every 2-4 weeks until the lowest dose
Czikk 2022 [135]	Proton-pump inhibitors, H2 blocker	Before and after study	29	2	Ceased over a 2-week period
Tandun 2019 [136]	Proton-pump inhibitors	Before and after study	58	4	Individualised as follows: Abrupt discontinuation with monitoring, tapering the dose, switching to as-needed ranitidine, or switching to as-scheduled ranitidine
Wahking 2018 [137]	Proton-pump inhibitors	Before and after study	220	3	Abrupt discontinuation or dose reduction
Visser 2021 [138]	HMG CoA reductase inhibitors and proton-pump inhibitors	Before and after study	66	6	Individualised
Linsky 2022 [139]	Antidiabetic medicines and proton-pump inhibitors	Before and after study	348	1	Not described
Mati 2024	Proton-pump inhibitors	Before and	53	3	Gradually discontinued every two days for 3 weeks until

[140]		after study			the lowest possible marketed dose is reached

2.2 Evidence for deprescribing of proton-pump inhibitors

Study	Specific outcome	Odds ratio (95% CI)	Mean difference (95% CI)
1. Mortality			
No available evidence			
2. Adverse drug withdrawal events (ADWEs)			
No available evidence			
3. Health outcomes			
No available evidence			
4. Cognitive function			
No available evidence			
5. Quality of life			
No available evidence			
6. Effect on medication regimen			
No available evidence			

2.3 Evidence for deprescribing of proton-pump inhibitors (non-controlled outcomes)

Study	Specific outcome	Result
1. Mortality		
Reeve 2015	Mortality at 6 months	0%
Czikk 2022	Mortality at 2 months	3%
Mati 2024	Mortality at 3 months	11%
2. Adverse drug withdrawal events (ADWEs)		
Reeve 2015	Maintained symptom-free on a reduced dose at six months	33% (1/3)
Czikk 2022	Adverse drug withdrawal events	48% (14/29)
Czikk 2022	Gastrointestinal bleed	10% (3/29)
Mati 2024	Adverse drug withdrawal events	17% (9/53)
3. Health outcomes		
Serum electrolytes levels		
Czikk 2022	Serum calcium, mmol/L	2.34 ± 0.12 to 2.31 ± 0.18
Czikk 2022	Serum phosphate, mmol/L	1.55 ± 0.29 to 1.85 ± 0.34
Czikk 2022	Serum magnesium, mmol/L	1.01 ± 0.16 to 1.06 ± 0.14
4. Cognitive function		
No available evidence		
5. Quality of life		
No available evidence		
6. Effect on medication regimen		
Reeve 2015	Successfully deprescribed and symptom-free at six months	67%
Calvo 2021	Successfully deprescribed after 1-month	81%
Lee 2017	Successfully deprescribed after 2 months	19/27 (70%)
Calvo 2021	Successfully deprescribed after 3 months	75%
Wahking 2018	Successfully deprescribed after 3 months	57%
Tandun 2019	Successfully deprescribed after 4 months	80%
Calvo 2021	Successfully deprescribed after 6 months	72%
Bhardwaj 2022	Successful deprescribing	71%
Wahking 2018	Successfully deprescribed inpatient PPI therapy	211/220 (96%)

Wahking 2018	Maintained dose reduction after 3 months	82%
Visser 2021	Successfully withdrawn completely or dose reduced (HMG CoA reductase inhibitors and proton-pump inhibitors)	52%
McDonald 2015	Remained off PPI therapy 3 months after discharge	17/18 (94%)
Czikk 2022	Unsuccessful deprescribing (i.e. medicine reinstated)	48% (14/29)
Leszcynski 2023	Number of potentially inappropriate medicines	-39.5%, p<0.0001
McDonald 2015	Change in the proportion of proton-pump inhibitors deprescribed at discharge	+10.8%, p=0.03
Wahking 2018	Patients who required PRN acid suppressive therapy	17%
Linsky 2022	Reduced number of medicines (antidiabetic medicines and proton-pump inhibitors)	14%

2.4 GRADE evidence profile (critical or important but not critical outcomes only)

Question: In older people, what are the effects of deprescribing (i.e. dose reduction or complete discontinuation) long-term PPIs on mortality, adverse drug withdrawal events, health-related outcomes, cognitive function, and quality of life?

Certainty assessment							Number of participants		Effect	Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Deprescribing	Continuation			
1. Mortality											
3 [129, 135, 140]	Non-controlled studies	Serious [1,2]	Not serious	Serious [3]	Serious [4]	Not serious	88	N/A	0/6 (0%) [129] 1/29 (3%) [135] 6/53 (11%) [140]	⨁◯◯◯	8
2. Adverse drug withdrawal events (ADWEs)											
Exacerbation/return of underlying condition											
1 [135]	Non-controlled study	Serious [5,6]	Not serious	Serious [3]	Serious [4]	Not serious	29	N/A	10/29 (34%) (10 had a reoccurrence of gastroesophageal reflux disease).	⨁◯◯◯	6
ADWEs											
3 [129, 135, 140]	Non-controlled studies	Serious [1,6]	Not serious	Serious [3]	Serious [4]	Not serious	88	N/A	3/29 (10%) had gastrointestinal bleed (of which one was fatal). 2/3 (67%) of those with dose reduction did not maintain symptom-free at six months. 9/53 (17%) restarted PPI of whom 5/53 (9%) had recurrent gastro-oesophageal reflux disease (GORD) with epigastric pain and 4/53 (8%) had suspected peptic ulcer with acute anaemia.	⨁◯◯◯	6
3. Health outcomes											
No available evidence											
4. Cognitive function											
No available evidence											
5. Quality of life (QoL)											
No available evidence											

[1] Lack of a concurrent control group
[2] Follow-up duration was heterogeneous across the studies, ranging from 2-6 months
[3] One study (Czikk 2022) included only patients with end-stage kidney disease
[4] Small sample size
[5] Lack of a concurrent control group with inadequate follow-up duration of 8 weeks
[6] Potential for confounding bias

2.5 Evidence-to-Decision table

Question: In older people, what are the effects of deprescribing (i.e. dose reduction or complete discontinuation) long-term PPIs on mortality, adverse drug withdrawal events, health-related outcomes, cognitive function, and quality of life?

Decision domain	Summary of reason for decision	Subdomains influencing decision
Certainty of evidence Is there a high or moderate certainty of evidence? Yes ☐ No ☑	The certainty of evidence for the benefits of deprescribing is very low. The certainty of evidence for the harms of deprescribing is very low.	Key reasons for downgrading: Risk of bias, indirectness, imprecision Are all critical outcomes measured? Yes ☐ No ☑ There is a lack of evidence on critical outcomes including health outcomes, cognitive function, and quality of life.
Benefits and harms Is there certainty that the benefits of deprescribing outweigh the harms? Yes ☐ No ☑	The effects of deprescribing PPIs have been tabulated in Appendix B (GRADE evidence profile table) with an overview provided in the guideline document (a narrative overview and GRADE summary of findings table). Below is a summary according to the study designs. <u>Summary of outcomes:</u> Non-controlled trials: • Mortality (0-11%) • Adverse drug withdrawal events (10-67%) • Exacerbation or return of the underlying condition (34%) <u>Summary of withdrawal schedules:</u> Three non-controlled trials reported important/critical outcomes (very low certainty). 1) Reeve 2015 (n=6): The dose was halved every two weeks, and if participants remained symptom-free on the reduced dose, PPIs were changed from a daily dose to as-required administration. 2) Czikk 2022 (n=29): PPI withdrawn over two weeks. Finally, in the study by Mati 2024, PPI was gradually discontinued every two days for 3 weeks until the lowest possible	Is the baseline risk for benefits and harms of deprescribing similar across subgroups? Yes ☐ No ☑ The evidence from our systematic review and meta-analysis at this time suggests some individuals with severe comorbidities (e.g. end-stage kidney disease) could be at risk of developing withdrawal effects or disease exacerbation from PPI withdrawal. Should there be separate recommendations for subgroups? Yes ☑ No ☐ The guideline development group acknowledges that certain subgroups may have factors (e.g. disease state, life expectancy, indication for use of PPIs, other important comorbidities, and previous history of gastrointestinal complications) that could impact the balance of benefits and risks from deprescribing. However, the available evidence is insufficient to justify distinct evidence-based recommendations.

	marketed dose was reached. Other studies: Slowly tapered according to a specific protocol (study=1, n=170), Sudden cessation, gradual taper, or switching to “on-demand” PRN dosing (study=1, n=75), Abrupt cessation (study=1, n=28), Dose halved every 2-4 weeks until the lowest dose (study=1, n=228), Not described (studies=2, n=500), Abrupt discontinuation or dose reduction (study=1, n=220), Individualised (studies=2, n=124).	
Values and preferences Is there confidence in the estimate of the relative importance of outcomes and individual preferences? Yes ☑ No ☐	In a survey of patients using PPIs for GORD, approximately half expressed concerns regarding long-term PPI therapy, and 41-48% were unaware of the intended duration of their treatment. Patients are often not informed about the potential serious side effects associated with prolonged PPI use or about alternative management strategies, such as lifestyle modifications, for managing their condition. Generally, patients are open to discussions about deprescribing PPIs. The most important driver for deprescribing is the initiation of discussion by primary care providers. Symptom control remains a priority for many patients, and most report low tolerance for even minor symptoms. However, one study indicated that approximately 40% of patients would consider deprescribing if recommended by their healthcare provider. Healthcare professionals initiated most deprescribing conversations. Clinicians believe it is relatively easy to discuss deprescribing PPIs with their patients and the topics of discussion are generally around symptom control, tapering plans and monitoring.	Perspective taken: The lack of evidence for serious harm following PPI withdrawal (but there are exceptions based on expert opinions) and the evident benefits related to reduced medication burden and costs. Individual values and preferences determine the deprescribing approaches. Sources of values and preferences: 1) Consultation with patient and carer representatives 2) Non-systematic review of evidence Source of variability, if any: Difficult to determine the extent of variability; high variability for patient preferences. Method for determining values satisfactory for this recommendation? Yes ☑ No ☐ Yes, but would be improved with direct patient input
Resources Are the resources worth the expected net	A comprehensive economic evaluation was outside the scope of the current review. However, potential cost and resource implications related to deprescribing interventions and continuation of medications are discussed below.	Feasibility: Is this intervention generally available? Yes ☑ No ☐ Opportunity cost: Is this intervention and its effects worth

benefit? Yes ☑ No ☐	Cost implications: In Australia, PPIs contributed to the largest potentially inappropriate medication cost in residential aged care facilities (34.4%). A feasibility study showed that PPI deprescribing guidelines successfully led to a modest but significant cost saving per resident. Another study involving discontinuing inappropriate PPIs after cessation of NSAIDs or low-dose aspirin showed an increase in quality-adjusted life years in addition to cost savings. Based on the negative incremental costs, deprescribing of inappropriate PPIs is likely self-sustaining in the following year. Physician implications: The additional time and resources needed for deprescribing considerations are likely less significant than the routine monitoring in people who use PPI long-term. There is a lack of robust data informing the cost of the intervention and subsequently, cost-effectiveness. Most clinicians believe that deprescribing is a complex process, with barriers to resources commonly reported (e.g. suboptimal deprescribing organisational environment that included competing workloads, staffing issues, and limited financial support).	withdrawing or not allocating resources from other interventions? Yes ☑ No ☐ Economic and preventive benefits for harms: Is there a lot of variability in resource requirements across settings? Yes ☐ No ☑
Equity What would be the impact of deprescribing on health inequities? ☑ Uncertain	The social determinants of health equity are complex and multifaceted. The impact of deprescribing on health equity is inadequately explored in the literature. Older people affected by the inappropriate use of PPIs are likely to derive substantial benefits in terms of health equity from deprescribing. By reducing medication burdens, lowering costs, and simplifying medicine regimens, deprescribing may enhance access to care and improve health outcomes for this vulnerable population. However, ensuring equitable implementation and addressing potential challenges faced by people with varying health literacy and access disparities is crucial to maximising these benefits. Culturally and linguistically diverse populations, Aboriginal and Torres Strait Islander populations, people with low socioeconomic status, and those living in rural or remote areas may require additional support or considerations when implementing deprescribing intervention. Patients with limited access to healthcare resources may face barriers in accessing necessary care, including follow-up appointments and laboratory testing, hence finding it challenging to adhere to the deprescribing plan.	
Acceptability Is the option of	Healthcare practitioners: Deprescribing is likely acceptable to most healthcare practitioners, especially when supported by clinical practice guidelines and a shared decision-making process with patients. The term deprescribing may be new	

deprescribing acceptable to key stakeholders? ☑ Probably yes	to healthcare practitioners but the concept is not. Healthcare practitioners are very familiar with discontinuing ineffective medications or those causing adverse effects worse than the condition being treated. Patients, their caregivers and family members: Many are open to deprescribing if they understand the potential benefits and risks, especially when given the option to restart medications when necessary. Policymakers and health systems: From a broader perspective, deprescribing can be seen as a way to reduce healthcare costs and improve patient outcomes. However, the short-term impacts on patient care and the resources required to implement effective deprescribing strategies may be a concern.
Overall judgment	There is a lack of quality evidence for deprescribing to inform evidence-based recommendations.

Abbreviations: GORD gastro-oesophageal reflux disease, NSAIDs non-steroidal anti-inflammatory drugs, PPIs proton-pump inhibitors

3. Prochlorperazine

We were unable to identify a study that assessed deprescribing prochlorperazine from the systematic search.

4. Macrogol laxative

We were unable to identify a study that assessed deprescribing macrogol laxatives from the systematic search.

5. Drugs used in diabetes

5.1 Overview of studies targeted drugs used in diabetes

Article	Drug/Class	Study design	Sample size	Follow-up (months)	Withdrawal schedule
Sjöblom 2008 [141]	Insulin, oral antiglycaemic	Prospective cohort study	32	6	Abrupt cessation except for insulin over 20 units/day for which the dose was halved
Hui 2019 [142]	Antidiabetic medicines	Retrospective cohort study	2740	6	Individualised
Niznik 2022 [143]	Antidiabetic medicines	Retrospective cohort study	2082	2	Not described
Silverii 2020 [144]	Antidiabetic medicines	Before and after study	46	6	Not described
Linsky 2022 [139]	Antidiabetic medicines and proton-pump inhibitors	Before and after study	348	1	Not described

5.2 Evidence for deprescribing of drugs used in diabetes

Study	Specific outcome	Odds ratio (95% CI)	Mean difference (95% CI)
1. Mortality			
Hui 2019	Mortality at 6 months	0.40 (0.24, 0.69)	
Niznik 2022	Mortality at 2 months	1.77 (1.08, 2.89)	
2. Adverse drug withdrawal events (ADWEs)			
Hui 2019	Exacerbation/return of underlying condition	0.43 (0.13, 1.43)	
Sjöblom 2008	Exacerbation/return of underlying condition	21.0 (1.09, 403.01)	
3. Health outcomes			
Adverse drug events			
Hui 2019	Incidence of hypoglycaemic episodes	0.46 (0.24, 0.90)	
Health service use			
Niznik 2022	Visit to the emergency department or acute hospital setting	1.10 (0.89, 1.36)	
4. Cognitive function			
No available evidence			
5. Quality of life			
No available evidence			
6. Effect on medication regimen			
No available evidence			

5.3 Evidence for deprescribing of drugs used in diabetes (non-controlled outcomes)

Study	Specific outcome	Result
1. Mortality		
No available evidence		
2. Adverse drug withdrawal events (ADWEs)		
No available evidence		
3. Health outcomes		
Glycated haemoglobin, Hb_{A1c} levels		
Silverii 2020	Glycated haemoglobin, Hb_{A1c} levels	Baseline to endpoint 6.4 ± 2.6% (46.0 ± 5.3 mmol/mol) to 7 ± 3.3% (53.0 ± 12.5 mmol/mol)
4. Cognitive function		
No available evidence		
5. Quality of life		
No available evidence		
6. Effect on medication regimen		
Linsky 2020	Reduced number of medicines (antidiabetic medicines and proton-pump inhibitors)	14%
Silverii 2020	Successfully withdrawn	22%

5.4 GRADE evidence profile (critical or important but not critical outcomes only)

Question: In older people, what are the effects of deprescribing (i.e. dose reduction or complete discontinuation) drugs used in diabetes on mortality, adverse drug withdrawal events, health-related outcomes, cognitive function, and quality of life?

Certainty assessment							Number of participants		Effect	Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Deprescribing	Continuation			
1. Mortality											
2 [142, 143]	Non-randomised studies	Serious [1]	Serious [2]	Not serious	Not serious	Not serious	1239	3583	OR 0.85 (0.20, 3.60)		8
2. Adverse drug withdrawal events (ADWEs)											
Exacerbation/return of underlying condition											
2 [141, 142]	Non-randomised studies	Serious [3]	Serious [2]	Not serious	Serious [4]	Not serious	717	2121	OR 2.35 (0.05, 103.89)		6
3. Health outcomes											
Health service use											
1 [143]	Non-randomised study	Serious [1]	Not serious	Not serious	Not serious	Not serious	554	1528	OR 1.10 (0.89, 1.36)		5
Adverse drug events											
1 [142]	Non-randomised study	Serious [1]	Not serious	Not serious	Not serious	Not serious	685	2055	Incidence of hypoglycaemic episodes OR 0.46 (0.24, 0.90)		5
Glycated haemoglobin, HbA_{1c} levels											
1 [144]	Non-controlled study	Serious [5]	Not serious	Not serious	Not serious	Not serious	46	N/A	Baseline to endpoint 6.4 ± 2.6% (46.0 ± 5.3 mmol/mol) to 7 ± 3.3% (53.0 ± 12.5 mmol/mol)		4
4. Cognitive function											
No available evidence											
5. Quality of life (QoL)											
No available evidence											

[1] Non-randomised studies with control group propensity score matched. There was an unbalanced number of participants in both groups
[2] There is considerable heterogeneity in the meta-analysis of the studies
[3] In one study (Sjoblom 2008), group allocation was based on the type of diabetes, HbA_{1c} level and diabetic medication which could introduce selection bias
[4] Wide confidence intervals in the estimates of effect
[5] Single-arm study without a concurrent control group with a potential risk of selection, performance, detection, and reporting biases

5.5 Evidence-to-Decision table

Question: In older people, what are the effects of deprescribing (i.e. dose reduction or complete discontinuation) drugs used in diabetes on mortality, adverse drug withdrawal events, health-related outcomes, cognitive function, and quality of life?

Decision domain	Summary of reason for decision	Subdomains influencing decision
Certainty of evidence Is there a high or moderate certainty of evidence? Yes ☐ No ☑	The certainty of evidence for the benefits of deprescribing is very low. The certainty of evidence for the harms of deprescribing is very low.	Key reasons for downgrading: Risk of bias Are all critical outcomes measured? Yes ☐ No ☑ There is a lack of evidence on critical outcomes including cognitive function and quality of life.
Benefits and harms Is there certainty that the benefits of deprescribing outweigh the harms? Yes ☐ No ☑	The effects of deprescribing drugs used in diabetes have been tabulated in Appendix B (GRADE evidence profile table) with an overview provided in the guideline document (a narrative overview and GRADE summary of findings table). Below is a summary according to the study designs. <u>Summary of outcomes</u> Non-randomised controlled trials: • No significant difference in mortality, exacerbation or return of the underlying condition, and health service use • Significant reduction in adverse drug events (i.e. hypoglycaemia) Non-controlled trials: • A modest increase in Hb_{A1c} levels <u>Summary of withdrawal schedules:</u> Three non-randomised controlled trials reported important/critical outcomes (very low certainty): Individualised (study=1, n=2740), Abrupt discontinuation except for insulin over 20 units/day for	Is the baseline risk for benefits and harms of deprescribing similar across subgroups? Yes ☐ No ☑ There is no evidence at this time that the harms of deprescribing differ based on subgroups. However, evidence at this time suggests benefits may be more pronounced in people at a high risk of hypoglycaemia or among patients with advanced dementia or limited life expectancy, although the certainty was very low. Should there be separate recommendations for subgroups? Yes ☑ No ☐ The guideline development group acknowledges that certain subgroups may have factors (e.g. disease state, life expectancy, indication for use of diabetes medicines, other important comorbidities, and established vascular complications) that could impact the balance of benefits and risks from deprescribing. However, the available evidence is insufficient to justify distinct evidence-based recommendations.

	which the dose was halved (study=1, n=32), Not described (studies=2, n=2128). Another study: Not described (study=1, n=348)	
Values and preferences Is there confidence in the estimate of the relative importance of outcomes and individual preferences? Yes ☑ No ☐	Patients emphasise the importance of informed consent and comprehensive education about diabetes, including its management options, associated benefits, and potential risks, when initiating treatment. For some, an understanding of the increased risk of falls due to hypoglycaemia is essential. Adherence to antihyperglycemic medications is often reported as poor, with common barriers including confusion over required monitoring, the long-term impact of uncontrolled diabetes, and the relevance of symptoms to disease progression. Gastrointestinal symptoms are common for some medicines used to manage diabetes. Adherence to antihyperglycaemic medicines in older people with type 2 diabetes is sub-optimal (53%) with medicine side effects among the most commonly cited reasons for non-adherence. Furthermore, patients highlight the importance of understanding the rationale for deprescribing in cases of limited life expectancy. In these situations, discussions around time-to-benefit and guidance on lifestyle interventions can help align treatment decisions with the patient's quality-of-life goals. Educating patients on these factors will facilitate shared decision-making and ensure that treatment aligns with their preferences and values. Most clinicians are familiar with the concept of individualising target glycaemic control and de-escalation of antihyperglycaemic treatment in patients with type 2 diabetes. However, they may have differing opinions on the HbA1c threshold at which a	Perspective taken: We have taken into consideration the treatment satisfaction and quality of life besides therapeutic outcomes. Sources of values and preferences: 1) Consultation with patient and carer representatives 2) Non-systematic review of evidence Source of variability, if any: Difficult to determine the extent of variability; high variability for patient preferences. Method for determining values satisfactory for this recommendation? Yes ☑ No ☐ Yes, but would be improved with direct patient input

	conversation about deprescribing should be initiated. The decision to deprescribe appears to be primarily influenced by the stability of glycaemic control and the perceived risk of hypoglycaemia. In general, Diabetes Australia suggests targeting HbA_{1c} < 7-8% for most people with HbA_{1c} targets successively increased for older people with increasing frailty, functional dependence, or limited life expectancy. Primary Health Tasmania suggests deprescribing is often appropriate when HbA1c is < 7.0% as low HbA1c levels are associated with increased morbidity and mortality in older people with type 2 diabetes.	
Resources Are the resources worth the expected net benefit? Yes ☑ No ☐	A comprehensive economic evaluation was outside the scope of the current review. However, potential cost and resource implications related to deprescribing interventions and continuation of medications are discussed below. Cost implications: There is little evidence about the cost implications and cost-effectiveness analysis of deprescribing antidiabetic medications. However, data from the United States showed that deintensification of glycaemic control reduced healthcare costs by $47.7 billion, with a projected gain of 3.2 million life-years in a lifetime horizon nationwide. While deprescribing of antidiabetic medications can reduce the cost associated with adverse drug events (e.g. hypoglycaemia), potential complications arising from suboptimal glycaemic control incur significant healthcare expenditures (e.g. hospitalisations, medical interventions, long-term management costs). Patients' quality of life and lost productivity also contribute to indirect economic burdens beyond direct healthcare expenses.	Feasibility: Is this intervention generally available? Yes ☑ No ☐ Opportunity cost: Is this intervention and its effects worth withdrawing or not allocating resources from other interventions? Yes ☑ No ☐ Economic and preventive benefits for harms: Is there a lot of variability in resource requirements across settings? Yes ☐ No ☑

	Physician implications: Healthcare providers will need to closely monitor patients to assess the impact of deprescribing on glycaemic control and the ongoing risks-benefit profile. This may involve additional clinic visits, laboratory tests. In this context, collaboration with diabetes educators could be valuable, offering targeted support in managing changes in treatment while helping patients understand lifestyle modifications and ongoing management needs.	
Equity What would be the impact of deprescribing on health inequities? ☑ Varies	The social determinants of health equity are complex and multifaceted. The impact of deprescribing on health equity is inadequately explored in the literature. However, deprescribing of antidiabetic medications significantly reduced the risk of hypoglycaemia associated with antidiabetic medications. This can benefit patients who are more vulnerable to these adverse effects due to socioeconomic factors, such as limited access to emergency care. However, ensuring equitable implementation and addressing potential challenges faced by people with varying health literacy and access disparities is crucial to maximising these benefits. Culturally and linguistically diverse populations, Aboriginal and Torres Strait Islander populations, people with low socioeconomic status, and those living in rural or remote areas may require additional support or considerations when implementing deprescribing intervention. Patients with limited access to healthcare resources may face barriers in accessing necessary care, including follow-up appointments and regular blood glucose monitoring, hence finding it challenging to adhere to the deprescribing plan.	
Acceptability Is the option of deprescribing acceptable to key stakeholders? ☑ Probably yes	Healthcare practitioners: Deprescribing is likely acceptable to most healthcare practitioners, especially when supported by clinical practice guidelines and a shared decision-making process with patients. The term deprescribing may be new to healthcare practitioners but the concept is not. Healthcare practitioners are very familiar with discontinuing ineffective medications or those causing adverse effects worse than the condition being treated. Patients, their caregivers and family members: Many are open to deprescribing if they understand the potential benefits and risks, especially when given the option to restart medications when necessary. Policymakers and health systems: From a broader perspective, deprescribing can be seen as a way to reduce healthcare costs and improve patient outcomes. However, the short-term impacts on patient care and the resources required to implement effective deprescribing strategies may be a concern.	
Overall judgment	There is a lack of quality evidence for deprescribing to inform evidence-based recommendations.	

Abbreviations: GLP1 glucagon-like peptide-1, Hb_{A1c} haemoglobin A1C, SGLT2 sodium-glucose cotransporter-2

6. Potassium

6.1 Overview of studies targeted potassium

Article	Drug/Class	Study design	Sample size	Follow-up (months)	Withdrawal schedule
Henschke 1981 [145]	Potassium supplementation	Before and after study	33	3	Not described, likely abrupt discontinuation

6.2 Evidence for deprescribing of potassium

Study	Specific outcome	Odds ratio (95% CI)	Mean difference (95% CI)
1. Mortality			
No available evidence			
2. Adverse drug withdrawal events (ADWEs)			
No available evidence			
3. Health outcomes			
No available evidence			
4. Cognitive function			
No available evidence			
5. Quality of life			
No available evidence			
6. Effect on medication regimen			
No available evidence			

6.3 Evidence for deprescribing of potassium (non-controlled outcomes)

Study	Specific outcome	Result
1. Mortality		
Henschke 1981	Mortality	0%
2. Adverse drug withdrawal events (ADWEs)		
Henschke 1981	Adverse effects or symptoms attributable to hypokalaemia	0%
Henschke 1981	Change in serum potassium levels over three months	- 0.37 mmol/L
3. Health outcomes		
No available evidence		
4. Cognitive function		
No available evidence		
5. Quality of life		
No available evidence		
6. Effect on medication regimen		
Henschke 1981	Successfully withdrawn	50%

6.4 GRADE evidence profile (critical or important but not critical outcomes only)

Question: In older people, what are the effects of deprescribing (i.e. dose reduction or complete discontinuation) long-term potassium on mortality, adverse drug withdrawal events, health-related outcomes, cognitive function, and quality of life?

Certainty assessment							Number of participants		Effect	Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Deprescribing	Continuation			
1. Mortality											
1 [145]	Non-controlled study	Serious [1]	Not serious	Serious [2]	Serious [3]	Not serious	14	N/A	0%	⨁◯◯◯	8
2. Adverse drug withdrawal events (ADWEs)											
1 [145]	Non-controlled study	Serious [1]	Not serious	Serious [2]	Serious [3]	Not serious	14	N/A	Adverse effects or symptoms attributable to hypokalaemia, 0% Change in serum potassium levels over three months, - 0.37 mmol/L	⨁◯◯◯	6
3. Health outcomes											
No available evidence											
4. Cognitive function											
No available evidence											
5. Quality of life (QoL)											
No available evidence											

[1] Potential biases including confounding bias as this study lacks a true comparator group. Although this study has a control group, the control group was only measured once and was comprised of people without disease and not taking medicines known to alter potassium levels.
[2] Study only included men receiving diuretic therapy for cardiac failure. This study is also fairly dated. Authors stated that at that time, potassium supplements are regarded as mandatory in elderly patients receiving diuretics for heart failure. This study is, therefore, potentially less representative of the modern diuretic user who is not mandated to receive potassium.
[3] Small sample size

6.5 Evidence-to-Decision table

Question: In older people, what are the effects of deprescribing (i.e. dose reduction or complete discontinuation) long-term potassium on mortality, adverse drug withdrawal events, health-related outcomes, cognitive function, and quality of life?

Decision domain	Summary of reason for decision	Subdomains influencing decision
Certainty of evidence Is there a high or moderate certainty of evidence? Yes ☐ No ☑	The certainty of evidence for the benefits and harms of deprescribing is very low.	Key reasons for downgrading: Risk of bias, indirectness, imprecision Are all critical outcomes measured? Yes ☐ No ☑ There is a lack of evidence on critical outcomes including health outcomes, cognitive function and quality of life.
Benefits and harms Is there certainty that the benefits of deprescribing outweigh the harms? Yes ☐ No ☑	The effects of deprescribing potassium have been tabulated in Appendix B (GRADE evidence profile table) with an overview provided in the guideline document (a narrative overview and GRADE summary of findings table). Below is a summary according to the study designs. <u>Summary of outcomes</u> Non-controlled trial: • No deaths • No adverse effects or symptoms attributable to hypokalaemia during the period of study • No change in mean erythrocyte potassium levels • Mean plasma K level fell significantly after withdrawal <u>Summary of withdrawal schedules:</u> Non-controlled trial (very low certainty): Not described, likely abrupt discontinuation (study=1, n=33)	Is the baseline risk for benefits and harms of deprescribing similar across subgroups? Yes ☑ No ☐ There is no evidence at this time that the benefits or harms of deprescribing differ based on subgroups. Should there be separate recommendations for subgroups? Yes ☑ No ☐ The guideline development group acknowledges that certain subgroups may have factors (e.g. indication for use, other important comorbidities, concomitant medications, and lifestyle factors) that could impact the balance of benefits and risks from deprescribing. However, the available evidence is insufficient to justify distinct evidence-based recommendations.
Values and preferences Is there confidence in the	Potassium is commonly taken in conjunction with other medicines, or in response to other medical conditions that impact electrolyte balance, particularly medicines or medical conditions that can cause potassium depletion.	Perspective taken: The lack of evidence for serious harm as a result of deprescribing and evident benefits related to reduced medication burden and costs. Individual values and preferences determine the deprescribing approaches.

estimate of the relative importance of outcomes and individual preferences? Yes ☑ No ☐	Patients often have concerns over how deprescribing could impact their overall health status, comorbidities, and other medications they are taking. Patients emphasised a careful and holistic coordination of treatment plans as many who are currently taking potassium have additional health issues, such as issues with the cardiovascular system, mobility, or kidney functions. If a trial approach to deprescribing is considered appropriate, patients emphasise potential dose adjustments based on close monitoring of potassium levels, and education on lifestyle interventions such as maintaining adequate potassium intake through diet (e.g., bananas, citrus fruits). The majority of healthcare professionals believe that deprescribing can be beneficial for patients. However, deprescribing is often impeded by barriers such as a lack of time, insufficient knowledge to initiate the plan, and unwillingness to discontinue medications prescribed by another doctor or specialist.	Sources of values and preferences: 1) Consultation with patient and carer representatives 2) Non-systematic review of evidence Source of variability, if any: Difficult to determine the extent of variability; high variability for patient preferences. Method for determining values satisfactory for this recommendation? Yes ☑ No ☐ Yes, but would be improved with direct patient input.
Resources Are the resources worth the expected net benefit? Yes ☑ No ☐	A comprehensive economic evaluation was outside the scope of the current review. However, potential cost and resource implications related to deprescribing interventions and continuation of medications are discussed below. Cost implications: Potassium and other electrolytes are among the high-risk medicines known to be associated with a high potential for medication-related harm. Potassium is routinely used as a prophylaxis against diuretic-induced hypokalaemia. However, unnecessary use of potassium supplementation can lead to increased costs due to medication errors and medication-related harms. Physician implications: There is a lack of robust data informing the cost of the intervention and subsequently, cost-effectiveness. Most clinicians believe that	Feasibility: Is this intervention generally available? Yes ☑ No ☐ Opportunity cost: Is this intervention and its effects worth withdrawing or not allocating resources from other interventions? Yes ☑ No ☐ Economic and preventive benefits for harms: Is there a lot of variability in resource requirements across settings? Yes ☐ No ☑

	deprescribing is a complex process, with barriers to resources commonly reported (e.g. suboptimal deprescribing organisational environment that included competing workloads, staffing issues, and limited financial support). As a result, some patients might continue on medications like potassium supplementation, especially when prescribed alongside diuretics, without regular reassessment of the need for such medications.	
Equity What would be the impact of deprescribing on health inequities? ☑ Uncertain	The social determinants of health equity are complex and multifaceted. The impact of deprescribing on health equity is inadequately explored in the literature. Effective deprescribing of potassium requires regular monitoring of potassium levels. Patients with limited access to healthcare services might face challenges in adhering to monitoring requirements, which could lead to inequities if they are unable to follow the deprescribing plan effectively. Ensuring equitable implementation and addressing potential challenges faced by people with varying health literacy and access disparities is crucial to maximising these benefits. Culturally and linguistically diverse populations, Aboriginal and Torres Strait Islander populations, people with low socioeconomic status, and those living in rural or remote areas may require additional support or considerations when implementing deprescribing intervention, including the ongoing monitoring process.	
Acceptability Is the option of deprescribing acceptable to key stakeholders? ☑ Probably yes	Healthcare practitioners: Deprescribing is likely acceptable to most healthcare practitioners, especially when supported by clinical practice guidelines and a shared decision-making process with patients. The term deprescribing may be new to healthcare practitioners but the concept is not. Healthcare practitioners are very familiar with discontinuing ineffective medications or those causing adverse effects worse than the condition being treated. Patients, their caregivers and family members: Many are open to deprescribing if they understand the potential benefits and risks, especially when given the option to restart medications when necessary. Policymakers and health systems: From a broader perspective, deprescribing can be seen as a way to reduce healthcare costs and improve patient outcomes. However, the short-term impacts on patient care and the resources required to implement effective deprescribing strategies may be a concern.	
Overall judgment	There is a lack of quality evidence for deprescribing to inform evidence-based recommendations.	

7. Antithrombotic agents

7.1 Overview of studies targeted antithrombotic agents

Article	Drug/Class	Study design	Sample size	Follow-up (months)	Withdrawal schedule
Patel 2013 [146]	Rivaroxaban	RCT	9239	0.1 to 1	Not described
Sambu 2011 [147]	Clopidogrel	Before and after study	38	1	Not described
Derogar 2013 [148]	Aspirin	Retrospective cohort study	118	Median 24.4 months (range 0.2 to 54.8 months)	Not described
Ramos 2024 [149]	Aspirin	Before and after study	131	Not stated	Not described
Varghese 2024 [150]	Aspirin	Before and after study	122	4 months	Not described
Zhou 2024 [151]	Aspirin	Cohort study	6103	48 months	Not described

7.2 Evidence for deprescribing of antithrombotic agents

Study	Specific outcome	Odds ratio (95% CI)	Mean difference (95% CI)
1. Mortality			
Zhou 2024	Mortality at 48 months	0.69 (0.53, 0.90)	
2. Adverse drug withdrawal events (ADWEs)			
Adverse events/ serious adverse events/ cardiovascular events			
Patel 2013	Acute cardiovascular events	3.73 (1.51, 9.21)	
Derogar 2013	Death or cardiovascular events in patients with cardiovascular comorbidities at 6 months	10.67 (2.07, 55.07)	
Derogar 2013	Death or cardiovascular events in patients with cardiovascular comorbidities after the initial follow-up (median 24 months)	0.97 (0.32, 2.95)	
Derogar 2013	Death or cardiovascular events in patients without cardiovascular comorbidities after the initial follow-up (median 24 months)	1.87 (0.39, 9.12)	
Zhou 2024	Cardiovascular disease	0.75 (0.54, 1.03)	
Zhou 2024	Major adverse cardiovascular events	0.88 (0.60, 1.30)	
3. Health outcomes			
Health service use			
Derogar 2013	Re-hospitalised due to peptic ulcer bleeding	2.11 (0.45, 9.88)	
Adverse drug events			
Patel 2013	Major bleeding	3.64 (1.57, 8.42)	
Zhou 2024	Major bleeding	0.64 (0.42, 0.99)	
4. Cognitive function			
No available evidence			
5. Quality of life			
No available evidence			
6. Effect on medication regimen			
Varghese 2024	Deprescribing successful	0.18 (0.08, 0.42)	

7.3 Evidence for deprescribing of antithrombotic agents (non-controlled outcomes)

Study	Specific outcome	Result
1. Mortality		
Sambu 2011	Mortality at 1 month	0%
2. Adverse drug withdrawal events (ADWEs)		
Adverse events/ serious adverse events/ cardiovascular events		
Sambu 2011	Occluded stent	3%
3. Health outcomes		
No available evidence		
4. Cognitive function		
No available evidence		
5. Quality of life		
No available evidence		
6. Effect on medication regimen		
Ramos 2024	Deprescribing successful	60% (78/131)

7.4 GRADE evidence profile (critical or important but not critical outcomes only)

Question: In older people, what are the effects of deprescribing (i.e. dose reduction or complete discontinuation) long-term antithrombotic agents on mortality, adverse drug withdrawal events, health-related outcomes, cognitive function, and quality of life?

Certainty assessment							Number of participants		Effect	Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Deprescribing	Continuation			
1. Mortality											
1 [151]	Non-randomised study	Serious [1]	Not serious	Not serious	Not serious	Not serious	5427	676	In patients without cardiovascular comorbidities: Mortality at 48-month OR 0.69 (95% CI 0.53, 0.90)		8
1 [147]	Non-controlled study	Serious [2]	Not serious	Not serious	Serious [3]	Not serious	33	N/A	0%		8
2. Adverse drug withdrawal events (ADWEs)											
Adverse events/ serious adverse events/ cardiovascular events											
1 [146]	RCT	Serious [4,5,6]	Not serious	Serious [7]	Serious [8]	Serious [9]	4587	4652	This study compared the incidence of stroke or non-central nervous system embolism during the transition to vitamin K antagonists in participants previously treated with rivaroxaban versus warfarin of which both groups had a temporary interruption of therapy. The rivaroxaban group had poor anticoagulant coverage through the transition, whereas the warfarin group had no uncovered period, as evidenced by the time to a therapeutic international normalised ratio (INR). The study reported an increased risk of stroke and systemic embolism for patients who transitioned from rivaroxaban compared with those who transitioned from warfarin (OR 3.73, 95% CI 1.51, 9.21).		7
1 [148]	Non-randomised study	Serious [1]	Not serious	Serious [10]	Serious [3,8]	Not serious	26	50	In patients with cardiovascular comorbidities Death or cardiovascular events in patients with cardiovascular comorbidities at 6 months 10.67 (2.07, 55.07) Death or cardiovascular events in patients with cardiovascular comorbidities after the initial follow-up (median 24 months)		7

									0.97 (0.32, 2.95) In patients without cardiovascular comorbidities Death or cardiovascular events after the initial follow-up (median 24 months) 1.87 (0.39, 9.12)		
1 [151]	Non-randomised study	Serious [1]	Not serious	Not serious	Not serious	Not serious	5427	676	Cardiovascular disease OR 0.75 (0.54, 1.03) Major adverse cardiovascular events OR 0.88 (0.60, 1.30)		7
1 [147]	Non-controlled study	Serious [2]	Not serious	Not serious	Serious [3]	Not serious	33	N/A	Stent thrombosis 3%		7
3. Health outcomes											
Adverse drug events											
1 [146]	RCT	Serious [4,5,6]	Not serious	Serious [7]	Serious [8]	Serious [9]	4587	4652	This study compared the incidence of stroke or non-central nervous system embolism during the transition to vitamin K antagonists in participants previously treated with rivaroxaban versus warfarin of which both groups had a temporary interruption of therapy. The rivaroxaban group had poor anticoagulant coverage through the transition, whereas the warfarin group had no uncovered period, as evidenced by the time to a therapeutic INR. The study reported an increased risk of major bleeding for patients who transitioned from rivaroxaban compared with those who transitioned from warfarin (OR 3.64, 95% CI 1.57, 8.42).		5
Health service use											
1 [148]	Non-randomised study	Serious [1]	Not serious	Serious [10]	Serious [3,8]	Not serious	47	71	Re-hospitalised due to peptic ulcer bleeding OR 2.11 (0.45, 9.88)		5
4. Cognitive function											
No available evidence											
5. Quality of life (QoL)											
No available evidence											

[1] Non-randomised study/studies. Zhou 2024 was a cohort study based on a post-hoc analysis of a randomised controlled trial (ASPREE). There is a potential for misclassification bias in the cohort study as the group allocation was based on the assumption that participants would have discontinued study treatment immediately upon receiving the study letter at the conclusion of the ASPREE trial. Derogar 2013 was a retrospective cohort study.

[2] Single-arm study without a concurrent control group
[3] Small sample size
[4] Potential for confounding bias. No mention of the use of other drugs which may impact the outcomes e.g. selective serotonin reuptake inhibitors (SSRIs).
[5] This is a post-hoc analysis of data from a double-blind randomised controlled trial. However, the deprescribing phase was not blinded, and the outcome assessors and personnel were aware of allocation during the deprescribing phase of the study. The results may reflect differences in the effective half-life of the two drugs. It is unclear if the greater number of incidences for rivaroxaban is related to this, but there would appear to be reasonable doubt. In addition, other medical therapy is not considered in the analysis which may be significant. The therapeutic INR is relevant before withdrawal for the warfarin group, and after transitioning to warfarin for both groups.
[6] Very brief follow-up duration (from 3 to 30 days)
[7] Study only included patients with nonvalvular atrial fibrillation after discontinuation which limits the generalisability
[8] Wide confidence intervals in the estimates of effect
[9] The study was supported by grants from pharmaceutical companies
[10] Derogar 2013 only included patients with prior peptic ulcer bleeding which limits the generalisability of findings. The two groups were also unequal with a greater percentage of the continuation group having cancer, and at admission having signs of circulatory shock.

7.5 Evidence-to-Decision table

Question: In older people, what are the effects of deprescribing (i.e. dose reduction or complete discontinuation) long-term antithrombotic agents on mortality, adverse drug withdrawal events, health-related outcomes, cognitive function, and quality of life?

Decision domain	Summary of reason for decision	Subdomains influencing decision
Certainty of evidence Is there a high or moderate certainty of evidence? Yes ☐ No ☑	The certainty of evidence for the benefits of deprescribing is very low. The certainty of evidence for the harms of deprescribing is very low.	Key reasons for downgrading: Risk of bias, imprecision Are all critical outcomes measured? Yes ☐ No ☑ There is a lack of evidence on critical outcomes including cognitive function and quality of life.
Benefits and harms Is there certainty that the benefits of deprescribing outweigh the harms? Yes ☐ No ☑	The effects of deprescribing antithrombotic agents have been tabulated in Appendix B (GRADE evidence profile table) with an overview provided in the guideline document (a narrative overview and GRADE summary of findings table). Below is a summary according to the study designs. <u>Summary of outcomes</u> Randomised and non-randomised controlled trials: • Significant reduction in mortality and major bleeding in primary prevention • No significant difference in mortality for atrial fibrillation patients who had poor anticoagulant coverage • No significant difference in hospitalisation caused by gastrointestinal bleeding • Increased risk of death or cardiovascular events among patients with cardiovascular comorbidities • No significant difference in cardiovascular disease or major adverse cardiovascular events in primary prevention • Significantly more major bleeding events for rivaroxaban-treated atrial fibrillation patients	Is the baseline risk for benefits and harms of deprescribing similar across subgroups? Yes ☑ No ☐ The evidence from our systematic review and meta-analysis at this time suggests some individuals with the presence of cardiovascular comorbidities (chronic ischemic heart disease or angina, chronic heart failure, previous myocardial infarction, atrial fibrillation, previous stroke or transient cerebral ischemia) could be at risk of developing adverse events from the withdrawal of antithrombotic agents, although the certainty was very low. Should there be separate recommendations for subgroups? Yes ☑ No ☐ The guideline development group acknowledges that certain subgroups may have factors (e.g. primary or secondary prevention, types of antithrombotic agents, and other important comorbidities) that could impact the balance of benefits and risks from deprescribing. However, the available evidence is insufficient to justify distinct evidence-based recommendations.

	who had poor anticoagulant coverage compared with warfarin-treated individuals Non-controlled trial: • Mortality (0%) • Stent thrombosis (3%) <u>Summary of withdrawal schedules:</u> Withdrawal schedules were not described in all six identified studies.	
Values and preferences Is there confidence in the estimate of the relative importance of outcomes and individual preferences? Yes ☐ No ☑	Patients' values and preferences regarding deprescribing antithrombotic agents vary significantly. While some patients are unwilling to accept a small increase in the risk of mortality as a result of deprescribing, others may be more inclined to deprescribe if adequate information is provided about the cumulative benefits of risk reduction and the risk of bleeding. Patients tend to be more averse to stroke than clinicians, though both groups share a similar concern about bleeding. In all cases, individual preferences should guide decisions, with adequate education at the initiation of therapy to help patients understand side effects and select treatments with minimal risk in making an informed consent. As with other drug classes, a one-size-fits-all approach is not appropriate. Although bleeding risks are a significant factor in deprescribing decisions, trialling different types of antithrombotic agents with fewer concerns about side effects may offer a viable alternative in many cases.	Perspective taken: We have taken the perspective that more patients may value the risk reduction of thrombotic events than the potential harms of the treatment. However, individual patient's preferences determine the deprescribing approaches. Sources of values and preferences: 1) Consultation with patient and carer representatives 2) Non-systematic review of evidence Source of variability, if any: Difficult to determine the extent of variability; high variability for patient preferences, formulation (oral or subcutaneous) and previous experience with antithrombotic treatment. Method for determining values satisfactory for this recommendation? Yes ☑ No ☐ Yes, but would be improved with direct patient input
Resources Are the resources worth the expected net benefit? Yes ☑ No ☐	A comprehensive economic evaluation was outside the scope of the current review. However, potential cost and resource implications related to deprescribing interventions and continuation of medications are discussed below.	Feasibility: Is this intervention generally available? Yes ☑ No ☐ Opportunity cost: Is this intervention and its effects worth withdrawing or not allocating resources from other

	Cost implications: There have been many cost-effectiveness studies comparing the alternative options for antithrombotic agents. However, there is little evidence on the cost implications and cost-effective analysis of discontinuing antithrombotic agents. The cost-effectiveness analysis of continuation and discontinuation may be difficult to estimate as it is sensitive to the type of deprescribing intervention and the rate of successful implementation. The cost outcomes are also likely to be strongly dependent on the type of antithrombotic agents being deprescribed. Deprescribing is likely to result in cost savings from reduced medication expenses and mitigate the risk of adverse events associated with antithrombotic therapy (e.g. bleeding events). However, these potential cost savings should take into account the increased risk of serious incidental cardiovascular complications (e.g. thromboembolic events) and their associated medical costs. Physician implications: Healthcare providers will need to closely monitor patients to assess the impact of deprescribing on ongoing risk-benefit profiles. This may involve additional clinic visits, laboratory tests and extended consultation time. There is a lack of robust data informing the cost of the intervention and subsequently, cost-effectiveness. Most clinicians believe that deprescribing is a complex process, with barriers to resources commonly reported (e.g. suboptimal deprescribing organisational environment that included competing workloads, staffing issues, and limited financial support).	interventions? Yes ☑ No ☐ Economic and preventive benefits for harms: Is there a lot of variability in resource requirements across settings? Yes ☐ No ☑

Equity What would be the impact of deprescribing on health inequities? ☑ Uncertain	The social determinants of health equity are complex and multifaceted. The impact of deprescribing on health equity is inadequately explored in the literature. Older people affected by the inappropriate use of medications are likely to derive substantial benefits in terms of health equity from deprescribing. By reducing medication burdens, lowering costs, and simplifying medicine regimens, deprescribing may enhance access to care and improve health outcomes for this vulnerable population. However, ensuring equitable implementation and addressing potential challenges faced by people with varying health literacy and access disparities is crucial to maximising these benefits. Culturally and linguistically diverse populations, Aboriginal and Torres Strait Islander populations, people with low socioeconomic status, and those living in rural or remote areas may require additional support or considerations when implementing deprescribing intervention. Patients with limited access to healthcare resources may face barriers in accessing necessary care, including follow-up appointments and laboratory testing, hence finding it challenging to adhere to the deprescribing plan.
Acceptability Is the option of deprescribing acceptable to key stakeholders? ☑ Probably yes	Healthcare practitioners: Deprescribing is likely acceptable to most healthcare practitioners, especially when supported by clinical practice guidelines and a shared decision-making process with patients. The term deprescribing may be new to healthcare practitioners but the concept is not. Healthcare practitioners are very familiar with discontinuing ineffective medications or those causing adverse effects worse than the condition being treated. Patients, their caregivers and family members: Many are open to deprescribing if they understand the potential benefits and risks, especially when given the option to restart medications when necessary. There needs to be clear communication on the rationale for deprescribing and how it might affect their ongoing benefit-risk profile especially as many older people express being stroke-averse. This approach supports informed choices that align with their health priorities and risk tolerance. Policymakers and health systems: From a broader perspective, deprescribing can be seen as a way to reduce healthcare costs and improve patient outcomes. However, the short-term impacts on patient care and the resources required to implement effective deprescribing strategies may be a concern.
Overall judgment	There is a lack of quality evidence for deprescribing to inform evidence-based recommendations.

8. Iron/ Vitamin B12 (anti-anaemic preparations)

We were unable to identify a study that assessed deprescribing iron/vitamin B12 from the systematic search.

9. Digoxin/ Sotalol

9.1 Overview of studies targeted digoxin

Article	Drug/Class	Study design	Sample size	Follow-up (months)	Withdrawal schedule
Daly & Edwards 1983 [152]	Digoxin	Before and after study	15	1	Not described
Fair 1990 [153]	Digoxin	Before and after study	32	11	Not described
Fonrose 1974 [154]	Digoxin	Before and after study	31	Unstated	Not described
Macarthur 1990 [155]	Digoxin	Before and after study	14	16	Not described
Sommers 1981, Reitz 1981 [156]	Digoxin	Before and after study	20	15	Abrupt discontinuation
Wilkins & Khurana 1985 [157]	Digoxin	Before and after study	19	Unstated	Not described

9.2 Evidence for deprescribing of DIGOXIN

Study	Specific outcome	Odds ratio (95% CI)	Mean difference (95% CI)
1. Mortality			
No available evidence			
2. Adverse drug withdrawal events (ADWEs)			
No available evidence			
3. Health outcomes			
No available evidence			
4. Cognitive function			
No available evidence			
5. Quality of life			
No available evidence			
6. Effect on medication regimen			
No available evidence			

9.3 Evidence for deprescribing of digoxin (non-controlled outcomes)

Study	Specific outcome	Result
1. Mortality		
Fonrose 1974	Mortality	0%
2. Adverse drug withdrawal events (ADWEs)		
Daly & Edwards 1983	Recurrence of the underlying condition	10-56%
Fonrose 1974	Recurrence of the underlying condition	
Macarthur 1990	Recurrence of the underlying condition	
Sommers 1981	Recurrence of the underlying condition	
Wilkins & Khurana 1985	Recurrence of the underlying condition	
3. Health outcomes		
Physical function		
Macarthur 1990	Exercise tolerance unchanged	100%
Wilkins 1985	Weight gain	53%
Wilkins 1985	Weight loss	26%
Wilkins 1985	Increased pulse	47%
Wilkins 1985	Decreased pulse	5%
Wilkins 1985	Unchanged pulse	47%
4. Cognitive function		
No available evidence		
5. Quality of life		
No available evidence		
6. Effect on medication regimen		
Daly & Edwards 1983	New or increased diuretic dose	0-5%
Wilkins 1985	New or increased diuretic dose	
Daly & Edwards 1983	Successful deprescribing after one month	48-95%
Fonrose 1974	Successful deprescribing after one month	
Macarthur 1990	Successful deprescribing after one month	
Wilkins 1985	Successful deprescribing after one month	
Fair 1990	Successfully withdrawn	44%

9.4 GRADE evidence profile (critical or important but not critical outcomes only)

Question: In older people, what are the effects of deprescribing (i.e. dose reduction or complete discontinuation) long-term digoxin on mortality, adverse drug withdrawal events, health-related outcomes, cognitive function, and quality of life?

Certainty assessment							Number of participants		Effect	Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Deprescribing	Continuation			
1. Mortality											
1 [154]	Non-controlled study	Serious [1]	Not serious	Serious [2,3]	Serious [4]	Not serious	31	N/A	0%		8
2. Adverse drug withdrawal events (ADWEs)											
5 [152, 154-157]	Non-controlled studies	Serious [5]	Not serious	Serious [2]	Serious [4]	Not serious	109	N/A	10-56%		6
3. Health outcomes											
Physical function											
2 [155, 157]	Non-controlled studies	Serious [5]	Not serious	Serious [2]	Serious [4]	Not serious	33	N/A	Exercise tolerance unchanged, 100% [155] Weight gain, 52% [157] Weight loss, 26% [157] Increased pulse, 47% [157] Decreased pulse, 5% [157] Unchanged pulse, 47% [157]		6
4. Cognitive function											
No available evidence											
5. Quality of life (QoL)											
No available evidence											

[1] Potential biases including confounding bias as the study lacks a comparator group. There is potential for selection bias as patient selection criteria are not clearly defined.
[2] Potential indirectness – All of these studies are fairly dated and predate the introduction of many modern angiotensin blockades, beta-blockers or loop

diuretics. This does not introduce bias but does reduce the relevance of the findings to the current medical practice.
[3] One study (Fonrose 1974) only included patients without evidence of heart disease, limiting the generalisability of the findings.
[4] Small sample size
[5] The pooled studies consisted of observational designs with small sample sizes, potential biases, and inadequate control for confounding factors. The studies directly addressed the research question in relevant populations. The small sample sizes and lack of detailed data in some studies led to imprecision. The studies attempted to control for some confounding factors, but the lack of control groups and other limitations hindered the ability to fully account for confounding variables.

9.5 Evidence-to-Decision table

Question: In older people, what are the effects of deprescribing (i.e. dose reduction or complete discontinuation) long-term digoxin on mortality, adverse drug withdrawal events, health-related outcomes, cognitive function, and quality of life?		
Decision domain	Summary of reason for decision	Subdomains influencing decision
Certainty of evidence Is there a high or moderate certainty of evidence? Yes ☐ No ☑	The certainty of evidence for the benefits of deprescribing is very low. The certainty of evidence for the harms of deprescribing is very low.	Key reasons for downgrading: Risk of bias, indirectness, imprecision Are all critical outcomes measured? Yes ☐ No ☑ There is a lack of evidence on critical outcomes including cognitive function and quality of life.
Benefits and harms Is there certainty that the benefits of deprescribing outweigh the harms? Yes ☐ No ☑	The effects of deprescribing antiarrhythmics have been tabulated in Appendix B (GRADE evidence profile table) with an overview provided in the guideline document (a narrative overview and GRADE summary of findings table). Below is a summary according to the study designs. <u>Summary of outcomes</u> Non-controlled trials: • Mortality (0%) • No change in exercise tolerance • 47% had no change in pulse • ADWEs (10-56%) • Changes in pulse (52%) • Changes in weight (78%) <u>Summary of withdrawal schedules:</u> Non-controlled trials (very low certainty): Abrupt discontinuation (study=1, n=20), Not described (studies=5, n=111)	Is the baseline risk for benefits and harms of deprescribing similar across subgroups? Yes ☐ No ☑ There is no evidence at this time that the harms of deprescribing differ based on subgroups. However, evidence at this time suggests successful deprescribing was more likely in participants who had been in sinus rhythm. Should there be separate recommendations for subgroups? Yes ☑ No ☐ The guideline development group acknowledges that certain subgroups may have factors (e.g. clinical state and other important comorbidities) that could impact the balance of benefits and risks from deprescribing. However, the available evidence is insufficient to justify distinct evidence-based recommendations.
Values and preferences Is there confidence	There are limited reports on the perspective of patients and clinicians on deprescribing antiarrhythmics.	Perspective taken: The lack of evidence for serious harm as a result of deprescribing and evident benefits related to reduced medication burden and costs.

in the estimate of the relative importance of outcomes and individual preferences? Yes ☐ No ☑	Patients appreciate a thorough explanation of the underlying mechanisms of their condition in addition to the rationale behind treatment options. Deprescribing antiarrhythmic medicines requires a patient-centred approach, informed consent, and careful monitoring. When faced with unfavourable side effects, patients are generally open to deprescribing, but they may prefer to explore alternative treatments first. Many patients are willing to deprescribe and maintain the lowest effective dose for atrial fibrillation, provided it does not interfere with their daily function. Additionally, many are open to trialling different antiarrhythmic medicines to find the one with the least side effects. Patient education is frequently emphasised, as all patients value more clarity about the monitoring process, as it is challenging for them to relate side effects with their condition or medications. Patients, particularly those with multimorbidity or complex drug regimens, are often concerned about potential drug interactions, including those influenced by food intake, climate, or genetics. As such, they prefer close supervision, especially when there is a change in their medicine regimen. Physicians: Guidelines generally recommend digoxin as a second or third line of therapy for atrial fibrillation and heart failure. The use of digoxin depends on the individual context. Clinicians may be hesitant to deprescribe digoxin, especially in select patients unable to tolerate or refractory to standard therapies.	Individual values and preferences determine the deprescribing approaches. Sources of values and preferences: Consultation with patient and carer representatives Source of variability, if any: Difficult to determine the extent of variability; high variability for patient preferences. Method for determining values satisfactory for this recommendation? Yes ☑ No ☐ Yes, but would be improved with direct patient input
Resources Are the resources worth the expected net benefit? Yes ☑ No ☐	A comprehensive economic evaluation was outside the scope of the current review. However, potential cost and resource implications related to deprescribing interventions and continuation of medications are discussed below. Cost implications: Despite digoxin not being the first line of treatment for atrial fibrillation and more effective alternatives are available, digoxin is still being over-prescribed. However,	Feasibility: Is this intervention generally available? Yes ☑ No ☐ Opportunity cost: Is this intervention and its effects worth withdrawing or not allocating resources from other interventions? Yes ☑ No ☐

	it has a narrow therapeutic window and is associated with a high incidence of serious toxicity. The incidence of digoxin toxicity increases with age. Inappropriate use of digoxin can lead to increased costs due to medication errors and medication-related harms. Physician implications: There is a lack of robust data informing the cost of the intervention and subsequently, cost-effectiveness. Most clinicians believe that deprescribing is a complex process, with barriers to resources commonly reported (e.g. suboptimal deprescribing organisational environment that included competing workloads, staffing issues, and limited financial support).	Economic and preventive benefits for harms: Is there a lot of variability in resource requirements across settings? Yes ☐ No ☑
Equity What would be the impact of deprescribing on health inequities? ☑ Uncertain	The social determinants of health equity are complex and multifaceted. The impact of deprescribing on health equity is inadequately explored in the literature. Older people affected by the inappropriate use of medications are likely to derive substantial benefits in terms of health equity from deprescribing. By reducing medication burdens, lowering costs, and simplifying medicine regimens, deprescribing may enhance access to care and improve health outcomes for this vulnerable population. However, ensuring equitable implementation and addressing potential challenges faced by people with varying health literacy and access disparities is crucial to maximising these benefits. Culturally and linguistically diverse populations, Aboriginal and Torres Strait Islander populations, people with low socioeconomic status, and those living in rural or remote areas may require additional support or considerations when implementing deprescribing intervention. Patients with limited access to healthcare resources may face barriers in accessing necessary care, including follow-up appointments and laboratory testing, hence finding it challenging to adhere to the deprescribing plan.	
Acceptability Is the option of deprescribing acceptable to key stakeholders? ☑ Probably yes	Healthcare practitioners: Deprescribing is likely acceptable to most healthcare practitioners, especially when supported by clinical practice guidelines and a shared decision-making process with patients. The term deprescribing may be new to healthcare practitioners but the concept is not. Healthcare practitioners are very familiar with discontinuing ineffective medications or those causing adverse effects worse than the condition being treated. Patients, their caregivers and family members: Many are open to deprescribing if they understand the potential benefits and risks, especially when given the option to restart medications when necessary. Policymakers and health systems: From a broader perspective, deprescribing can be seen as a way to reduce healthcare costs and improve patient outcomes. However, the short-term impacts on patient care and the resources required to implement effective deprescribing strategies may be a concern.	

Overall judgment	There is a lack of quality evidence for deprescribing to inform evidence-based recommendations.

10. Organic nitrates

10.1 Overview of studies targeted organic nitrates

Article	Drug/Class	Study design	Sample size	Follow-up (months)	Withdrawal schedule
George 2003 [158]	Nitrates	RCT	120	3	Abrupt discontinuation
Jackson 2005 [159]	Nitrates	Before and after study	55	3	Dose halved for two days then discontinued if no increase in symptoms occurred

10.2 Evidence for deprescribing of organic nitrates

Study	Specific outcome	Odds ratio (95% CI)	Mean difference (95% CI)
1. Mortality			
No available evidence			
2. Adverse drug withdrawal events (ADWEs)			
George 2003	Number of participants who experienced at least one exacerbation	4.33 (0.52, 35.92)	
3. Health outcomes			
No available evidence			
4. Cognitive function			
No available evidence			
5. Quality of life			
No available evidence			
6. Effect on medication regimen			
No available evidence			

10.3 Evidence for deprescribing of organic nitrates (non-controlled outcomes)

Study	Specific outcome	Result
1. Mortality		
No available evidence		
2. Adverse drug withdrawal events (ADWEs)		
ADWEs		
Jackson 2005	Recurrence of the underlying condition (breathlessness)	5%
Adverse events		
Jackson 2005	Cardiac events	0%
3. Health outcomes		
Jackson 2005	Deterioration in exercise tolerance	0%
Jackson 2005	Change in five-item Sexual Health Inventory for Men scores	7.9 ± 5.15 to 21.8 ± 4.3
4. Cognitive function		
No available evidence		
5. Quality of life		
No available evidence		
6. Effect on medication regimen		
No available evidence		

10.4 GRADE evidence profile (critical or important but not critical outcomes only)

Question: In older people, what are the effects of deprescribing (i.e. dose reduction or complete discontinuation) long-term organic nitrates on mortality, adverse drug withdrawal events, health-related outcomes, cognitive function, and quality of life?

Certainty assessment							Number of participants		Effect	Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Deprescribing	Continuation			
1. Mortality											
No available evidence											
2. Adverse drug withdrawal events (ADWEs)											
ADWEs											
1 [159]	Non-controlled study	Serious [1]	Not serious	Serious [2]	Serious [3]	Not serious	55	N/A	Recurrence of the underlying condition (breathlessness) 5%	⨁◯◯◯	6
Exacerbation /return of underlying condition											
1 [158]	RCT	Serious [4]	Not serious	Not serious	Serious [5]	Not serious	80	40	The first month, eight study patients (10%) had a recurrence of anginal symptoms, compared with one control subject (2.5%), OR 4.33 (0.52, 35.92)	⨁◯◯◯	6
Adverse events											
1 [159]	Non-controlled study	Serious [1]	Not serious	Serious [2]	Serious [3]	Not serious	55	N/A	Adverse cardiac events, 0%	⨁◯◯◯	7
3. Health outcomes											
Physical function											
1 [159]	Non-controlled study	Serious [1]	Not serious	Serious [2]	Serious [3]	Not serious	55	N/A	Deterioration in subjective exercise ability, 0% Change in five-item Sexual Health Inventory for Men scores (to assess erectile dysfunction in men) from 7.9 ± 5.15 to 21.8 ± 4.3, indicating an improvement.	⨁◯◯◯	6
4. Cognitive function											
No available evidence											
5. Quality of life (QoL)											
No available evidence											

[1] Potential confounding bias as this study lacks a comparator group. Potential detection bias due to the outcome assessment was partly subjective (patient self-report).

[2] Potential indirectness – Jackson 2005 paper only included men who have erectile dysfunction to facilitate subsequent use of PDE5 therapy which may limit the generalisability of the findings.
[3] Small sample size
[4] Potential selection bias, performance bias, and detection bias. Limited detail about the randomisation method but appears to not be a truly random process as patients were randomised consecutively with a 2:1 distribution between groups. The recruitment method is unclear, and limited detail is available regarding the setting. It is unclear if this would have affected the risk of bias. No conflicts or funding information was given. It is an open-label study. As the target symptoms in this study are well-known to be affected by psychological stress, it is more important than usual to minimise psychological confounding factors e.g. a placebo arm is necessary.
[5] Small sample size and wide confidence intervals in the estimates of effect.

10.5 Evidence-to-Decision table

Question: In older people, what are the effects of deprescribing (i.e. dose reduction or complete discontinuation) long-term organic nitrates on mortality, adverse drug withdrawal events, health-related outcomes, cognitive function, and quality of life?

Decision domain	Summary of reason for decision	Subdomains influencing decision
Certainty of evidence Is there a high or moderate certainty of evidence? Yes ☐ No ☑	The certainty of evidence for the benefits of deprescribing is low to very low. The certainty of evidence for the harms of deprescribing is low to very low.	Key reasons for downgrading: Risk of bias, indirectness, imprecision Are all critical outcomes measured? Yes ☐ No ☑ There is a lack of evidence on critical outcomes including mortality, cognitive function, and quality of life.
Benefits and harms Is there certainty that the benefits of deprescribing outweigh the harms? Yes ☐ No ☑	The effects of deprescribing organic nitrates have been tabulated in Appendix B (GRADE evidence profile table) with an overview provided in the guideline document (a narrative overview and GRADE summary of findings table). Below is a summary according to the study designs. <u>Summary of outcomes</u> Randomised controlled trial • No significant difference in the exacerbation or return of the underlying condition Non-controlled trial: • Adverse events (0%) • Breathlessness (5%) • No deterioration in subjective exercise ability • Facilitate subsequent use of PDE5 therapy in men for erectile dysfunction <u>Summary of withdrawal schedules:</u> Randomised controlled trial (low certainty): Abrupt discontinuation (study=1, n=120)	Is the baseline risk for benefits and harms of deprescribing similar across subgroups? Yes ☐ No ☑ There is no evidence at this time that the harms of deprescribing differ based on subgroups. However, evidence at this time suggests successful deprescribing may be more likely in patients treated with either beta-blockers or calcium antagonists for stable coronary heart diseases Should there be separate recommendations for subgroups? Yes ☑ No ☐ The guideline development group acknowledges that certain subgroups may have factors (e.g. clinical state and other important comorbidities) that could impact the balance of benefits and risks from deprescribing. However, the available evidence is insufficient to justify distinct evidence-based recommendations.

	Non-controlled trial (very low certainty): Dose halved for two days then discontinued if no increase in symptoms occurred (study=1, n=55)	
Values and preferences Is there confidence in the estimate of the relative importance of outcomes and individual preferences? Yes ☐ No ☑	Long-acting nitrates are commonly associated with side effects such as headache and dizziness. Both patients and clinicians generally express reluctance toward long-term use of nitrates, with nitrate tolerance being a significant deterrent, alongside conflicting evidence suggesting that prolonged nitrate use may lead to endothelial dysfunction. Many patients are open to deprescribing long-term nitrates, provided that short-acting nitrates are available for symptom relief if needed. Monitoring is frequently emphasised, along with the option to consider restarting long-term nitrates when clinically indicated, with informed consent from the patient.	Perspective taken: The lack of evidence for serious harm as a result of deprescribing and evident benefits related to reduced medication burden and costs. Individual values and preferences determine the deprescribing approaches. Sources of values and preferences: 1) Consultation with patient and carer representatives 2) Non-systematic review of evidence Source of variability, if any: Difficult to determine the extent of variability; high variability for patient preferences. Method for determining values satisfactory for this recommendation? Yes ☑ No ☐ Yes, but would be improved with direct patient input
Resources Are the resources worth the expected net benefit? Yes ☑ No ☐	A comprehensive economic evaluation was outside the scope of the current review. However, potential cost and resource implications related to deprescribing interventions and continuation of medications are discussed below. Cost implications: There may be costs associated with managing the common side effects oflong-acting nitrates (e.g. headache, dizziness, and orthostatic hypotension). With increasing age, older people may be at a higher risk of falls or prescribing cascades due to nitrate-induced side effects. Inappropriate use of long-acting nitrates can lead to increased costs due to medication-related harms. Physician implications: There is a lack of robust data	Feasibility: Is this intervention generally available? Yes ☑ No ☐ Opportunity cost: Is this intervention and its effects worth withdrawing or not allocating resources from other interventions? Yes ☑ No ☐ Economic and preventive benefits for harms: Is there a lot of variability in resource requirements across settings? Yes ☐ No ☑

	informing the cost of the intervention and subsequently, cost-effectiveness. Most clinicians believe that deprescribing is a complex process, with barriers to resources commonly reported (e.g. suboptimal deprescribing organisational environment that included competing workloads, staffing issues, and limited financial support).	
Equity What would be the impact of deprescribing on health inequities? ☑ Uncertain	The social determinants of health equity are complex and multifaceted. The impact of deprescribing on health equity is inadequately explored in the literature. Older people affected by the inappropriate use of medications are likely to derive substantial benefits in terms of health equity from deprescribing. By reducing medication burdens, lowering costs, and simplifying medicine regimens, deprescribing may enhance access to care and improve health outcomes for this vulnerable population. However, ensuring equitable implementation and addressing potential challenges faced by people with varying health literacy and access disparities is crucial to maximising these benefits. Culturally and linguistically diverse populations, Aboriginal and Torres Strait Islander populations, people with low socioeconomic status, and those living in rural or remote areas may require additional support or considerations when implementing deprescribing intervention. Patients with limited access to healthcare resources may face barriers in accessing necessary care, including follow-up appointments and laboratory testing, hence finding it challenging to adhere to the deprescribing plan.	
Acceptability Is the option of deprescribing acceptable to key stakeholders? ☑ Probably yes	Healthcare practitioners: Deprescribing is likely acceptable to most healthcare practitioners, especially when supported by clinical practice guidelines and a shared decision-making process with patients. The term deprescribing may be new to healthcare practitioners but the concept is not. Healthcare practitioners are very familiar with discontinuing ineffective medications or those causing adverse effects worse than the condition being treated. Patients, their caregivers and family members: Many are open to deprescribing if they understand the potential benefits and risks, especially when given the option to restart medications when necessary. Policymakers and health systems: From a broader perspective, deprescribing can be seen as a way to reduce healthcare costs and improve patient outcomes. However, the short-term impacts on patient care and the resources required to implement effective deprescribing strategies may be a concern.	
Overall judgment	There is a lack of quality evidence for deprescribing to inform evidence-based recommendations.	

11. Antihypertensives

11.1 Overview of studies targeted antihypertensives

Article	Drug/Class	Study design	Sample size	Follow-up (months)	Withdrawal schedule
Espeland 1999 [160]	Antihypertensive	RCT (post hoc analysis)	975	26.7	Not described
Moonen 2015 [161]	Antihypertensive	RCT	356	4	Abruptly discontinued or tapered within four weeks until a maximum increase of 20mm Hg in systolic blood pressure
Sheppard 2020, 2024 [162, 163]	Antihypertensive	RCT	569	3	Abrupt discontinuation
Nelson 2002, 2003 [164, 165]	Antihypertensive	Case-control study AND before and after study (2 papers)	6833	12	Stepwise withdrawal (i.e., one drug at a time, half doses at weekly intervals to the lowest usual therapeutic dose then cease, and withdrawal)
Lernfelt 1990 [166]	Antihypertensive	Before and after study	25	48	Not described
Hajjar 2013 [167]	Antihypertensive	Before and after study	53	0.75	Slowly taper over 3 weeks
Alsop 2001 [168]	Antihypertensive	Before and after study	65	30	Not described
Ekbom 1994 [169]	Antihypertensive	Before and after study	333	60	For beta-blockers, stepwise discontinuation over a few days.
Fotherby 1994 [170]	Antihypertensive	Before and after study	78	12	Not described
Gulla 2018 [171]	Antihypertensive	Cluster RCT	295	9	Not described
Nadal 1994 [172]	Antihypertensive	Before and after study	86	36	Not described

Hansen 1983 [173]	Antihypertensive	Before and after study	169	12	Not described
Hassan 2022 [174]	Antihypertensive	Before and after study	14	12	Not described
Juraschek 2022 [175]	Antihypertensive	Before and after study	975	36	Individualised – drug-specific tapering regimens
Song 2018 [176]	Antihypertensive	Retrospective cohort study	2212	1	Not described
Silva 2024 [177]	Antihypertensive	RCT	72	1.5	Not described
Bogaerts 2024 [178]	Antihypertensive	RCT	205	6	Not described
Hearing 1999 [179]	Antihypertensive (Atenolol)	RCT	37	0.5	Over one week
Jondeau 2009 [180]	Antihypertensive (Beta-blocker)	RCT	169	3	Abrupt discontinuation
Jimenez-Candil 2005 [181]	Antihypertensive (Angiotensin converting enzyme inhibitors)	Before and after study	22	3	Daily dose reduction or increase equivalent to 1.25 mg of enalapril

11.2 Evidence for deprescribing antihypertensives

Study	Specific outcome	Odds ratio (95% CI)	Mean difference (95% CI)
1. Mortality			
Gulla 2018	Mortality at 9 months	0.99 (0.57, 1.72)	
Moonen 2015	Mortality at 4 months	0.93 (0.06, 15.05)	
Bogaerts 2024	Mortality at 6 months	1.71 (0.92, 3.18)	
Jondeau 2009	Mortality at 3 months (beta-blocker)	0.88 (0.27, 2.85)	
2. Adverse drug withdrawal events (ADWEs)			
ADWEs, blood pressure			
Hearing 1999	Sustained normotensive after discontinuation (beta-blocker)	15.90 (0.84, 301.03)	
Sheppard 2020	Blood pressure, systolic		3.40 (1.0, 5.8)
Bogaerts 2024	Blood pressure, systolic		4.9 (-0.8, 10.6)
Bogaerts 2024	Blood pressure, diastolic		3.3 (-0.5, 7.2)
Silva 2025	Blood pressure, systolic (in-office)		8.06 (4.97, 11.15)
Silva 2025	Blood pressure, diastolic (in-office)		4.49 (2.51, 6.47)
Silva 2025	Blood pressure, systolic (at-home)		7.37 (4.42, 10.32)
Silva 2025	Blood pressure, diastolic (at-home)		4.31 (2.53, 6.09)
Adverse events/ serious adverse events/ cardiovascular events			
Sheppard 2020	Adverse events	1.50 (1.07, 2.09)	
Moonen 2015	Serious adverse event	1.41 (0.23, 8.52)	
Sheppard 2020	Serious adverse event	1.78 (0.69, 4.58)	
Bogaerts 2024	Serious adverse event	1.75 (0.95, 3.21)	
Sheppard 2020	All-cause hospitalisation or mortality	0.78 (0.54, 1.15)	
3. Health outcomes			
Adverse drug events			
Moonen 2015	Orthostatic hypotension	0.62 (0.33, 1.15)	
Silva 2025	Hypotension	0.14 (0.05, 0.39)	
Health service use			
Gulla 2018	Unplanned hospital admission	0.38 (0.19, 0.76)	

Moonen 2015	Unplanned hospital admission	0.83 (0.33, 2.10)	
Frailty			
Sheppard 2020	Frailty index		-0.01 (-0.02, 0.00)
Neuropsychiatric symptoms			
Bogaerts 2024	Change in neuropsychiatric inventory nursing home score		6.2 (1.9, 10.6)
4. Cognitive function			
Moonen 2015	Change in cognition, measured using the overall cognition compound score		-0.02 (-0.23, 0.19)
5. Quality of life			
Moonen 2015	Quality of life, measured using Cantril's Ladder quality of life score		-0.10 (-0.35, 0.15)
Bogaerts 2024	Quality of life, measured using QUALIDEM		-3.5 (-8.1, 1.1)
6. Effect on medication regimen			
Gulla 2018	Deprescribing successful	0.24 (0.11, 0.48)	
Jondeau 2009	Deprescribing successful (beta-blocker)	0.38 (0.16, 0.93)	
Sheppard 2020	Deprescribing successful	0.02 (0.01, 0.04)	
Silva 2025	Number of antihypertensives	0.71 (0.33, 1.09)	

11.3 Evidence for deprescribing antihypertensives (non-controlled outcomes)

Study	Specific outcome	Result
1. Mortality		
Ekbom 1994	Mortality at 5 years	74/333 (22%)
Fotherby 1994	Mortality at 24 months	1/78 (1%)
Lernfelt 1990	Mortality at 6 months	1/25 (4%)
2. Adverse drug withdrawal events (ADWEs)		
ADWE, Blood pressure		
Hajjar 2013	ADWEs	0/53 (0%)
Nadal 1994	ADWEs	34/86 (40%)
Nelson 2002	ADWEs	273/503 (40%)
Hajjar 2013	Systolic blood pressure three weeks after deprescribing	151 ± 13.4 mmHg
Hajjar 2013	Change in systolic blood pressure at three weeks	12 ± 31 mmHg
Lernfelt 1990	Change in systolic blood pressure at 24 months	23.8 ± 26.2 mmHg
Juraschek 2022	Change in systolic blood pressure	4.59 ± 11.1 mmHg
Ekbom 1994	Systolic blood pressure three months after 12 months	169 ± 15 mmHg
Jimenez-Candil 2005	Systolic blood pressure three months after deprescribing (angiotensin-converting enzyme [ACE] inhibitor)	159 ± 12 mmHg
Hassan 2022	Change in systolic blood pressure after 12 months	16 ± 49.2 mmHg
Hajjar 2013	Diastolic blood pressure three weeks after deprescribing	83 ± 8.9 mmHg
Ekbom 1994	Diastolic blood pressure three months after 12 months	88 ± 8 mmHg
Jimenez-Candil 2005	Diastolic blood pressure three months after deprescribing (ACE inhibitor)	80 ± 10 mmHg
Hajjar 2013	Change in diastolic blood pressure at three weeks	6 ± 18 mmHg
Lernfelt 1990	Change in diastolic blood pressure at 24 months	9.6 ± 21.4 mmHg
Hassan 2022	Change in diastolic blood pressure after 12 months	8 ± 27.7 mmHg
Hansen 1983	Remained normotensive and without treatment at 11 months follow-up	43/105 (41%)
Adverse events/ serious adverse events/ cardiovascular events		
Ekbom 1994	Cardiovascular events	54/333 (16%)
Espeland 1999	Cardiovascular events	57/886 (6%)

Lernfelt 1990	Cardiovascular events	2/25 (8%)
Nadal 1994	Cardiovascular events	34/86 (40%)
3. Health outcomes		
Adverse drug events		
Hassan 2022	Adverse drug events	5/14 (36%)
Juraschek 2022	Adverse drug events	95/975 (10%)
Alsop 2001	Improved symptoms of syncope or pre-syncope	78%
Exercise tolerance		
Jimenez-Candil 2005	Change in exercise duration tolerated (ACE inhibitor)	7.0 (2.3) minutes vs. 7.0 (4.1) minutes, p = 0.4
4. Cognitive function		
No available evidence		
5. Quality of life		
No available evidence		
6. Effect on medication regimen		
Fotherby 1994	Successfully deprescribed at 12 months	27%
Fotherby 1994	Successfully deprescribed at 24 months	20%
Alsop 2001	Successfully deprescribed at 30 months	70%
Nadal 1994	Successfully deprescribed at 36 months	27%
Ekbom 1994	Successfully deprescribed at 60 months	18%
Hassan 2022	Successfully withdrawn completely or dose reduced after 12 months	79%

11.4 GRADE evidence profile (critical or important but not critical outcomes only)

Question: In older people, what are the effects of deprescribing (i.e. dose reduction or complete discontinuation) long-term antihypertensives on mortality, adverse drug withdrawal events, health-related outcomes, cognitive function, and quality of life?

Certainty assessment							Number of participants		Effect	Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Deprescribing	Continuation			
1. Mortality											
3 [43, 161, 178]	RCTs	Serious [1,2]	Not serious	Serious [21]	Serious [3,4]	Not serious	464	421	OR 1.25 (0.83, 1.88)	⨁⨁◯◯	8
1 [180]	RCT (beta-blocker)	Serious [5]	Not serious	Serious [6]	Serious [3,4]	Not serious	78	69	OR 0.88 (0.27, 2.85)	⨁⨁◯◯	8
1 [176]	Non-randomised study	Serious [2]	Not serious	Not serious	Serious [3]	Not serious	239	1973	OR 2.64 (1.40, 5.00)	⨁⨁◯◯	8
3 [166, 169, 170]	Non-controlled studies	Serious [7]	Serious [8]	Not serious	Not serious	Serious[9]	2648	N/A	2/25 (8%) [166] 74/333 (22%) [169] 1/78 (1%) [170]	⨁⨁◯◯	8
2. Adverse drug withdrawal events (ADWEs)											
ADWEs, blood pressure											
3 [163, 177, 178]	RCTs	Not serious	Not serious	Serious [10,21,23]	Serious [3,4,22]	Not serious	354	369	Deprescribing was associated with a significant change in systolic blood pressure (MD 7.30, 95% CI 4.60, 10.01). Additionally, in one of these studies [177], at-home systolic blood pressure was also reported and deprescribing was associated with a significant change, MD 7.37 (4.42, 10.32).	⨁⨁◯◯	6
2 [177, 178]	RCTs	Not serious	Not serious	Serious [10,21,23]	Serious [4,22]	Not serious	89	100	Deprescribing was associated with a significant change in diastolic blood pressure (MD 4.24, 95% CI 2.48, 5.99). In one study [177], at-home systolic blood pressure was also reported and deprescribing was associated with a significant change, MD 4.31 (2.53, 6.09).	⨁⨁◯◯	6

1 [179]	RCT (beta-blocker)	Serious [11]	Not serious	Serious [10]	Serious [3,4]	Not serious	23	14	This study compared the discontinuation of beta-blocker to continuation at 2 weeks, 8 out of 23 participants (35%) in the intervention group were normotensive following the discontinuation of antihypertensive medication (OR 15.90, 95% CI 0.84, 301.03).		6
9 [165-167, 169, 172-175, 181]	Non-controlled studies	Serious [12]	Serious [8]	Serious [10]	Serious [13]	Serious[1] [5]	2011	N/A	Following the discontinuation of antihypertensive medications, systolic blood pressure appeared to increase by: 23.8 ± 26.2 mmHg [166] 12 ± 31 mmHg [167] 16 ± 49.2 mmHg [174] 4.59 ± 11.1 mmHg [175] Similarly, diastolic blood pressure appeared to increase by: 9.6 ± 21.4 mmHg [166] 6 ± 18 mmHg [167] 8 ± 27.7 mmHg [174] In three studies, systolic blood pressure at the end of the follow-up was: 151 ± 13.4 mmHg [167] 169 ± 15 mmHg [169] 159 ± 12 mmHg [181] Diastolic blood pressure at the end of the follow-up was: 83 ± 8.9 mmHg [167] 88 ± 8 mmHg [169] 80 ± 10 mmHg [181] During the withdrawal of antihypertensives, none of the participants reported two consecutive blood pressure (BP) readings above the threshold and none reported headaches, dizziness, visual changes, or focal weakness during the tapering phase, 0/53 (0%) [167]. A study also reported that 43 out of the 105 participants (41%) with a history of hypertension remained normotensive and without treatment at 11 months follow-up [173]. In contrast, in a study of 86 participants, 34		6

									(40%) had their blood pressure rise to the levels contemplated in the study exclusion criteria (systolic BP ≥ 220 mmHg or diastolic BP ≥ 110 mmHg) [172]. Similarly, another study reported 273/503 participants returned to hypertension following the discontinuation of antihypertensive medication (40%) [165]		
Adverse events/ serious adverse events/ cardiovascular events											
2 [161, 162]	RCTs	Serious [2]	Not serious	Not serious	Serious [3]	Not serious	481	473	Deprescribing was not associated with a significant change in the proportion of participants with a serious adverse event (OR 1.69, 95% CI, 0.73, 3.91, studies = 2, n = 954). However, in one study, the number of participants experiencing at least one adverse event was significantly higher in the intervention group (OR 1.50, 95% CI 1.07, 2.09) [162]. Approximately one-fourth of the adverse events that occurred in the intervention group were considered possibly related to discontinuation of antihypertensive medication. In this study, adverse drug events were reported by the participant or observed by the investigator during trial follow-up [162].		7
4 [160, 166, 169, 172]	Non-controlled studies	Serious [14]	Not serious	Not serious	Serious [3]	Serious[1] [5]	1295	N/A	Cardiovascular events 57/886 (6%) [160] 1/25 (4%) [166] 54/333 (16%) [169] 0/52 (0%) [172]		7
3. Health outcomes											
Adverse drug events											
2 [161, 177]	RCTs	Serious [2,16]	Not serious	Serious [23]	Serious [3]	Not serious	123	111	Deprescribing was associated with significantly fewer participants with hypotension (OR 0.41, 95% CI 0.24, 0.70).		5
3 [168, 174, 175]	Non-controlled studies	Serious [17]	Not serious	Serious [18]	Serious [3]	Not serious	1054	N/A	In one study, 11 out of 14 participants had their antihypertensive medication discontinued or lowered during the 12-month follow-up. Adverse drug events (e.g. syncope, dizziness and falls) were reported in 5 out of 14 participants (36%) [174]. Of the 9 participants who did not experience any adverse drug events, 7 had their antihypertensive medication		5

									discontinued. In another study, 95 out of all 975 participants (10%) had experienced adverse events (light-headedness, dizziness, vertigo, fall, fracture, syncope) [175]. In one study, 78% of all participants who stopped their cardiovascular medicines reported an improvement in their original symptoms of syncope or pre-syncope at follow-up [168].		
Health service use											
2 [161, 171]	RCTs	Serious [1,2]	Serious [8]	Not serious	Serious [3,4]	Not serious	363	317	Deprescribing was not associated with a significant change in the proportion of participants with an unplanned hospital admission (OR 0.53, 95% CI 0.24, 1.14).		5
1 [176]	Non-randomised study	Serious [2]	Not serious	Not serious	Serious [3]	Not serious	239	1973	OR 1.41 (0.99, 2.02)		5
Frailty											
1 [162]	RCT	Serious [2]	Not serious	Not serious	Serious [3]	Not serious	282	287	Deprescribing was not associated with a significant change in the frailty index (MD -0.01, 95% CI -0.02, 0.00).		6
Falls											
1 [176]	Non-randomised study	Serious [2]	Not serious	Not serious	Serious [3]	Not serious	239	1973	OR 0.89 (0.62, 1.26)		5
Exercise tolerance											
1 [181]	Non-controlled study (ACE inhibitors)	Serious [2,7]	Not serious	Serious [10,19]	Serious [3]	Not serious	20	N/A	Following the discontinuation of ACE inhibitors, there was no change in the exercise duration (7.0 (2.3) minutes versus 7.0 (4.1) minutes, p = 0.4).		5
Neuropsychiatric symptoms											
1 [178]	RCT	Serious [2]	Not serious	Serious [21]	Serious [4,22]	Not serious	101	104	Change in neuropsychiatric inventory nursing home score. A higher score indicates more disruptive behaviour MD 6.2 (95% CI 1.9, 10.6), favouring control group		6
4. Cognitive function											
1 [161]	RCT	Serious [2,20]	Not serious	Not serious	Serious [3]	Not serious	180	176	Deprescribing was not associated with a significant change in the overall cognition compound score (MD -0.02, 95% CI -0.23,		7

									0.19). A compound score was computed if 5 out of 6 tests were available: Stroop interference, Trail Making Test delta, 15-word Verbal Learning Test immediate, 15-word Verbal Learning Test delayed, Visual Association Test, and Letter Digit Substitution Test.		
5.	Quality of life (QoL)										
2 [161, 178]	RCTs	Serious [2,20]	Not serious	Serious [21]	Serious [3,22]	Not serious	281	280	Deprescribing was not associated with a significant change in the quality of life measured using Cantril's Ladder quality-of-life score (MD -0.10, 95% CI -0.35, 0.15) and QUALIDEM (MD -3.5, 95% CI -8.1, 1.1).		7

[1] Potential for selection bias in one study (Gulla 2018)
[2] Follow-up duration of 6 months or less may not be sufficient to observe long-term effects
[3] Small sample size or small number of events which limits the precision of effect estimates.
[4] Wide confidence intervals in the estimates of effect
[5] Potential for confounding bias - it is unclear if the concurrent use of angiotensin-converting enzyme inhibitors and diuretics would have affected the outcomes although it was similar across the two groups at baseline.
[6] Potential indirectness – one study (Jondeau 2009) targeted beta-blocker use in patients hospitalised for acute heart failure with pulmonary oedema in which only 64.6% of the participants were hypertensive.
[7] All studies had a serious risk of bias due to lack of control groups and potential confounding
[8] Considerable heterogeneity in the outcome reported across the studies
[9] One or more studies were supported by pharmaceutical companies
[10] Potential indirectness – blood pressure is a surrogate outcome (i.e. a risk factor for cardiovascular events)
[11] Data used from Hearing 1999 were from the 2 weeks washout period of beta-blocker compared to the group that continued to take a beta-blocker. The deprescribing period was too brief to allow true results to be observed. Subjects who were normotensive were then excluded from the later part of the study.
[12] Observational studies with varying levels of risk of bias,
[13] Small sample sizes, and potential for confounding factors.
[14] Non-controlled study. Potential for selection, reporting and performance bias. In one or more studies, the follow-up duration may not be long enough for outcomes to occur. In the Espeland 1999 study, there were additional lifestyle interventions (sodium restriction, weight loss, and sodium restriction combined with weight loss). This means that it is unclear to what extent the deprescribing affected the outcomes compared to the lifestyle modification.
[15] One or more studies were supported by pharmaceutical companies.
[16] Lack of blinding – potential for performance bias and residual confounding.
[17] Two studies (Alsop 2001 and Hassan 2022) have a serious risk of bias due to a lack of a control group and the potential for selection and detection biases. In one study (Hassan 2022), reporting of adverse drug events included all participants regardless of whether they had their antihypertensive medications deprescribed.
[18] Potential indirectness – In one study (Alsop 2001), data were sourced from participants who attended a falls/syncope clinic. Cardiovascular medications that were stopped not only include antihypertensive medications, but also include thiazides, antianginal such as nitrates, and antiarrhythmics such as amiodarone and digoxin.
[19] Potential indirectness – the study included only patients with aortic valve stenosis.
[20] Participants in one or more studies were not blinded. Study outcomes were assessed by research personnel masked to the group allocation. However, it was unclear whether outcome measures such as quality of life were reported through the observations from the research personnel or self-reported by the participants.

[21] Moonen 2015 included only people with mild cognitive deficits. Gulla 2018 included nursing home residents, and the majority had moderate to severe dementia. Bogaerts 2024 only included nursing home residents with moderate to severe dementia. The study populations limit the generalisability of the findings.
[22] The planned sample size for the study by Bogaerts 2024 was 492. However, due to safety concerns and lacking benefits, the study was terminated early. The small sample size may mean the study was underpowered.
[23] Silva 2024 only included participants with hypotension in the study which may limit the generalisability of the finding.

11.5 Evidence-to-Decision table

Question: In older people, what are the effects of deprescribing (i.e. dose reduction or complete discontinuation) long-term antihypertensives on mortality, adverse drug withdrawal events, health-related outcomes, cognitive function, and quality of life?		
Decision domain	Summary of reason for decision	Subdomains influencing decision
Certainty of evidence Is there a high or moderate certainty of evidence? Yes ☐ No ☑	The certainty of evidence for the benefits of deprescribing is low to very low. The certainty of evidence for the harms of deprescribing is low to very low.	Key reasons for downgrading: Risk of bias, imprecision Are all critical outcomes measured? Yes ☑ No ☐
Benefits and harms Is there certainty that the benefits of deprescribing outweigh the harms? Yes ☐ No ☑	The effects of deprescribing antihypertensives have been tabulated in Appendix B (GRADE evidence profile table) with an overview provided in the guideline document (a narrative overview and GRADE summary of findings table). Below is a summary according to the study designs. <u>Summary of outcomes</u> Randomised and non-randomised controlled trials: • No significant difference in serious adverse events, unplanned hospital admission, frailty, falls, exercise tolerance, cognitive function, and quality of life. • Significantly reduced orthostatic hypotension • Significantly increased neuropsychiatric symptoms • Increased number of participants experiencing at least one adverse event Inconsistent findings across studies for blood pressure, adverse events, and mortality (randomised controlled trials reported no change but one non-randomised study found increased mortality with deprescribing in residents in aged care facilities).	Is the baseline risk for benefits and harms of deprescribing similar across subgroups? Yes ☐ No ☑ There is no evidence at this time that the benefits or harms of deprescribing differ based on subgroups. However, there will be some groups at a higher risk. Should there be separate recommendations for subgroups? Yes ☑ No ☐ The guideline development group acknowledges that certain subgroups may have factors (e.g. stage of hypertension, indication for use of antihypertensives, life expectancy, and other important comorbidities such as cardiovascular diseases, and dementia) that could impact the balance of benefits and risks from deprescribing. However, the available evidence is insufficient to justify distinct evidence-based recommendations.

	Non-controlled trials: • Reduced number of adverse drug events associated with antihypertensive use • Mortality (1-22%) • Increased in blood pressure (40-59%) • Cardiovascular events (0-16%) <u>Summary of withdrawal schedules:</u> Randomised controlled trials: Tapered until a maximum increase of 20 mmHg in systolic blood pressure was reached (study=1, n=356, Low certainty), One week (study=1, n=37, Very low certainty), Abrupt discontinuation (studies=2, n=738, Very low certainty), Not described (studies=4, n=1547, Very low certainty) Non-controlled trials: (Very low certainty) Not described (studies=7, n=2649), Individualised (study=1, n=975), Reduced step-wise over a few days (study=1, n=333), Step-wise withdrawal (i.e., one drug at a time, half doses at weekly intervals to the lowest usual therapeutic dose then cease, and withdrawal) (study=1, n=6833), Tapered over three weeks (study=1, n=53), Withdrawal and re-introduction were progressive, with a daily dose reduction or increase equivalent to 1.25 mg of enalapril (study=1, n=22)	
Values and preferences Is there confidence in the estimate of the relative importance of outcomes and individual	Patients currently taking antihypertensives often worry about their ability to stop the medication. The possibility of increased blood pressure following deprescribing raises safety concerns, where careful management of risks is essential. Some patients commonly experience side effects from the use of antihypertensives such as dizziness, and subsequently missed taking a dose. However, many	Perspective taken: The lack of consistent evidence for serious harms following antihypertensive withdrawal and the evident benefits related to reduced adverse drug events related to antihypertensive, lower medication burden and costs. Individual values and preferences determine the deprescribing approaches. Sources of values and preferences:

preferences? Yes ☑ No ☐	are worried that the risk of stroke could increase if antihypertensives are discontinued completely. Patient education plays a critical role in addressing these concerns and helping people understand their risks. Patients expressed that the fear of worse outcomes following deprescribing is often instilled by prior experiences. Clear communication and ongoing support are vital to ease these concerns and empower patients and carers in making informed decisions about their treatment. Reducing the pill burden and side effects associated with antihypertensives may be a more important factor for both older people living with dementia and their carers when considering deprescribing antihypertensives. Healthcare professionals, on the other hand, place a high value on the considerations of cardiovascular events, risk of falls and cognitive decline. For healthcare professionals, controlling blood pressure is essential to ensure that any adjustments in therapy do not unintentionally elevate the patient's overall health risks.	1) Consultation with patient and carer representatives 2) Non-systematic review of evidence Source of variability, if any: Difficult to determine the extent of variability; high variability for patient preferences. Method for determining values satisfactory for this recommendation? Yes ☑ No ☐ Yes, but would be improved with direct patient input
Resources Are the resources worth the expected net benefit? Yes ☑ No ☐	A comprehensive economic evaluation was outside the scope of the current review. However, potential cost and resource implications related to deprescribing interventions and continuation of medications are discussed below. Cost implications: All antihypertensives including diuretics are in general more cost-effective than no treatment. A cost-effective study showed deprescribing resulted in reduced medication costs but also lower quality-adjusted life years.	Feasibility: Is this intervention generally available? Yes ☑ No ☐ Opportunity cost: Is this intervention and its effects worth withdrawing or not allocating resources from other interventions? Yes ☑ No ☐ Economic and preventive benefits for harms: Is there a lot of variability in resource requirements across settings? Yes ☐ No ☑

	Deprescribing antihypertensive may not be cost-effective for older people with controlled systolic blood pressure. While deprescribing led to fewer adverse drug events, the increase in cardiovascular events (e.g. heart failure and stroke or transient ischemic attack) may offset the cost-benefit. However, those who are at a higher risk of adverse drug effects from antihypertensives may consider a targeted deprescribing approach. Physician implications: Healthcare providers will need to closely monitor patients to assess the impact of deprescribing on ongoing risk-benefit profiles. This may involve additional clinic visits and extended consultation time. The OPTIMISE trial reported that intervention group participants attended significantly more follow-up appointments than the usual care group. There is a lack of robust data informing the cost of the intervention and subsequently, cost-effectiveness. Most clinicians believe that deprescribing is a complex process, with barriers to resources commonly reported (e.g. suboptimal deprescribing organisational environment that included competing workloads, staffing issues, and limited financial support).	
Equity What would be the impact of deprescribing on health inequities? ☑ Uncertain	The social determinants of health equity are complex and multifaceted. The impact of deprescribing on health equity is inadequately explored in the literature. Effective deprescribing of antihypertensive requires regular monitoring of blood pressure and ongoing cardiovascular risks which are dynamic. Patients with limited access to healthcare services might face challenges in adhering to monitoring requirements, which could lead to inequities if they are unable to follow the deprescribing plan effectively. Ensuring equitable implementation and addressing potential challenges faced by people with varying health literacy and access disparities is crucial to maximising these benefits. Culturally and linguistically diverse populations, Aboriginal and Torres Strait Islander populations, people with low socioeconomic status, and those living in rural or remote areas may require additional support or considerations when implementing deprescribing intervention.	
Acceptability	Healthcare practitioners: Deprescribing is likely acceptable to most healthcare practitioners, especially when supported	

Is the option of deprescribing acceptable to key stakeholders? ☑ Probably yes	by clinical practice guidelines and a shared decision-making process with patients. The term deprescribing may be new to healthcare practitioners but the concept is not. Healthcare practitioners are very familiar with discontinuing ineffective medications or those causing adverse effects worse than the condition being treated. Patients, their caregivers and family members: Many are open to deprescribing if they understand the potential benefits and risks, especially when given the option to restart medications when necessary. Policymakers and health systems: From a broader perspective, deprescribing can be seen as a way to reduce healthcare costs and improve patient outcomes. However, the short-term impacts on patient care and the resources required to implement effective deprescribing strategies may be a concern.
Overall judgment	There is a lack of quality evidence for deprescribing to inform evidence-based recommendations.

12. Diuretics

12.1 Overview of studies targeted diuretics

Article	Drug/Class	Study design	Sample size	Follow-up (months)	Withdrawal schedule
van Kraaij 2000 [182, 183]	Diuretics	RCT	32	Unstated	Dose halved for one week, and then placebo
Walma 1997 [184]	Diuretics	RCT	202	6	Depending on baseline frusemide dose – if 40 mg daily: halve the dose for one week; if 80 mg daily: halve the dose for two weeks.
De Jonge 1994 [185]	Diuretics	RCT	63	1.5	Not described
Myers 1982 [186]	Diuretics	RCT	77	12	Not described
Burr 1977 [187]	Diuretics	RCT	106	3	Not described
Straand 1993 [188]	Diuretics	Before and after study	33	6	Not described
Walma 1993 [189]	Diuretics	Before and after study	15	6	Thiazides and furosemide in daily dosages of <40 mg were stopped abruptly. Frusemide daily dosages of 40 mg were halved for one week before complete withdrawal.

12.2 Evidence for deprescribing diuretics

Study	Specific outcome	Odds ratio (95% CI)	Mean difference (95% CI)
1. Mortality			
Burr 1977	Mortality at 3 months	3.00 (0.30, 29.81)	
Myers 1982	Mortality at 12 months	3.20 (0.78, 13.14)	
2. Adverse drug withdrawal events (ADWEs)			
De Jonge 1994	Exacerbation of underlying condition	8.70 (0.45, 168.87)	
Burr 1977	Oedema, increased	2.55 (1.06, 6.11)	
Burr 1977	Oedema, decreased	0.38 (0.13, 1.09)	
Myers 1982	Ankle oedema - scaled (0 = no oedema; 1 = trace; 2 = ankle; 3 = mid-calf; 4 = above mid-calf)		0.30 (-1.01, 1.61)
3. Health outcomes			
Blood pressure			
Burr 1977	Blood pressure, systolic		4.50 (-0.66, 9.66)
Myers 1982	Blood pressure, systolic		9.70 (7.87, 11.53)
Walma 1997	Blood pressure, systolic		13.50 (9.20, 17.80)
Burr 1977	Blood pressure, diastolic		1.40 (-2.34, 5.14)
Myers 1982	Blood pressure, diastolic		4.10 (3.05, 5.15)
Walma 1997	Blood pressure, diastolic		4.60 (1.90, 7.30)
Heart rate			
Burr 1977	Heart rate		-2.20 (-5.90, 1.50)
4. Cognitive function			
No available evidence			
5. Quality of life			
No available evidence			
6. Effect on medication regimen			
De Jonge 1994	Successful deprescribing	0.32 (0.01, 17.43)	
Myers 1982	Successful deprescribing	1.64 (0.42, 6.35)	
van kraaij 2000	Successful deprescribing	7.67 (0.39, 152.66)	
Walma 1997	Successful deprescribing	6.43 (3.19, 12.96)	

12.3 Evidence for deprescribing diuretics (non-controlled outcomes)

Study	Specific outcome	Result
1. Mortality		
No available evidence		
2. Adverse drug withdrawal events (ADWEs)		
Straand 1993	Recurrence of the underlying condition	8/33 (24%)
Walma 1993	Recurrence of the underlying condition	8/15 (53%)
Straand 1993	Peripheral oedema	3/33 (9%)
Walma 1993	Peripheral oedema	2/15 (13%)
Straand 1993	Hypertensive	3/33 (9%)
Walma 1993	Hypertensive	3/15 (20%)
Straand 1993	Symptoms of congestive heart failure	2/33 (6%)
Walma 1993	Symptoms of congestive heart failure	1/15 (7%)
Walma 1993	Subjective withdrawal symptoms	2/15 (13%)
3. Health outcomes		
Weight		
Walma 1993	Change in body weight	+ 1.2 kg
Adverse events/ serious adverse events/ cardiovascular events		
Straand 1993	Cardiovascular events	4/33 (12%)
4. Cognitive function		
No available evidence		
5. Quality of life		
No available evidence		
6. Effect on medication regimen		
Straand 1993	Successful deprescribing at six months	18/33 (55%)
Walma 1993	Successful deprescribing at six months	6/15 (40%)

12.4 GRADE evidence profile (critical or important but not critical outcomes only)

Question: In older people, what are the effects of deprescribing (i.e. dose reduction or complete discontinuation) long-term diuretics on mortality, adverse drug withdrawal events, health-related outcomes, cognitive function, and quality of life?

Certainty assessment							Number of participants		Effect	Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Deprescribing	Continuation			
1. Mortality											
2 [186, 187]	RCTs	Not serious	Not serious	Serious [1]	Serious [2,3]	Not serious	92	91	OR 3.14 (0.94, 10.47)	⨁◯◯◯	8
2. Adverse drug withdrawal events (ADWEs)											
Exacerbation/return of underlying condition											
3 [185-187]	RCTs	Serious [4,5]	Not serious	Serious [1]	Serious [2,3]	Not serious	114	115	In one study, 4 out of 34 participants in the intervention group experienced exacerbations that would have led to serious adverse events without resuming diuretics (OR 8.70, 95% CI 0.45, 168.87) [185]. In another study, ankle oedema was assessed on a scale of 0-4 (0 = no oedema; 1 = trace; 2 = ankle; 3 = mid-calf; 4 = above mid-calf). Significant ankle oedema was noted in both placebo and diuretic groups, although the placebo group had a greater extent of oedema at the end of follow-up (MD 0.30, 95% CI -1.01, 1.61) [186]. Similarly, ankle oedema increased significantly in the intervention group at 12 weeks (OR 2.55, 95% CI 1.06, 6.11) and there was no significant change in the proportion of participants who had an improvement in oedema (OR 0.38, 95% CI 0.13, 1.09) [187].	⨁◯◯◯	6
2 [188, 189]	Non-controlled studies	Serious [8]	Not serious	Serious [9]	Serious [3]	Not serious	48	N/A	Recurrence of the underlying condition was reported in 8/33 (24%) participants in one study [188] and 8/15 (53%) participants in the other study [189]. In the latter study, 2/15 (13%) had subjective complaints that led to the resumption of diuretics. Peripheral oedema was reported in 3/33 (9%)	⨁◯◯◯	6

									participants in one study [188] and 2/15 (13%) participants in the other study [189]. Hypertension was reported in 3/33 (9%) participants in one study [188] and 3/15 (20%) participants in the other study [189]. Symptoms of congestive heart failure were reported in 2/33 (6%) participants in one study [188] and 1/15 (7%) participants in the other study [189].		
3. Health outcomes											
Blood pressure, systolic											
3 [184, 186, 187]	RCTs	Not serious	Serious [7]	Serious [1,10]	Serious [2,3,6]	Not serious	181	187	MD 9.49 (5.55, 13.43)		4
Blood pressure, diastolic											
3 [184, 186, 187]	RCTs	Not serious	Not serious	Serious [1,10]	Serious [2,3]	Not serious	181	186	MD 3.99 (3.04, 4.94)		4
Adverse events/ serious adverse events/ cardiovascular events											
1 [188]	Non-controlled study	Serious [8]	Not serious	Serious [9]	Serious [3]	Not serious	33	N/A	Sudden cardiovascular events occurred in 4 out of 33 participants (12%).		7
4. Cognitive function											
No available evidence											
5. Quality of life (QoL)											
No available evidence											

[1] Potential indirectness – One or more of these studies are quite old and predate the introduction of many first-line drugs e.g. ACE inhibitors. This does not introduce bias but does reduce the relevance of the findings to the current medical practice.
[2] Wide confidence intervals in the estimates of effect.
[3] Small sample size
[4] Potential reporting bias – In one study, those who did not successfully deprescribe were reported as dropouts and these were mostly due to symptoms directly related to the intervention.
[5] Outcome assessment may be limited to subjective measurement bias
[6] Follow-up duration ranged from 3-12 months
[7] Considerable heterogeneity in the outcome reported across the studies
[8] Single-arm study without a concurrent control group (Straand 1993)
[9] In one study (Straand 1993), approximately one-third (n=12) of the participants were taking diuretics for hypertension and another one-third (n=10) were taking them for no identifiable reasons.

[10] Potential indirectness – Surrogate outcome that is not of direct practical importance but is believed to reflect an outcome that is important (i.e. blood pressure is a risk factor for cardiovascular events).

12.5 Evidence-to-Decision table

Question: In older people, what are the effects of deprescribing (i.e. dose reduction or complete discontinuation) long-term diuretics on mortality, adverse drug withdrawal events, health-related outcomes, cognitive function, and quality of life?

Decision domain	Summary of reason for decision	Subdomains influencing decision
Certainty of evidence Is there a high or moderate certainty of evidence? Yes ☐ No ☑	The certainty of evidence for the benefits and harms of deprescribing is low to very low.	Key reasons for downgrading: Risk of bias, indirectness, imprecision Are all critical outcomes measured? Yes ☐ No ☑ There is a lack of evidence on critical outcomes including cognitive function and quality of life.
Benefits and harms Is there certainty that the benefits of deprescribing outweigh the harms? Yes ☐ No ☑	The effects of deprescribing diuretics have been tabulated in Appendix B (GRADE evidence profile table) with an overview provided in the guideline document (a narrative overview and GRADE summary of findings table). Below is a summary according to the study designs. <u>Summary of outcomes</u> Randomised controlled trials: • No significant difference in mortality based on a meta-analysis of two RCTs (see Appendix B for the odds ratio for each study) • Worsened ankle oedema • Increased systolic and diastolic blood pressure Non-controlled trials: • Not reported • Sudden cardiovascular events (12%) • Recurrence of the underlying condition (24-	Is the baseline risk for benefits and harms of deprescribing similar across subgroups? Yes ☐ No ☑ Evidence at this time suggests that deprescribing may be more likely to be successful in patients with stable clinical conditions or without current clinical indications (heart failure, hypertension). Should there be separate recommendations for subgroups? Yes ☑ No ☐ The guideline development group acknowledges that certain subgroups may have factors (e.g. indication for use of diuretics, life expectancy, and other important comorbidities) that could impact the balance of benefits and risks from deprescribing. However, the available evidence is insufficient to justify distinct evidence-based recommendations.

	53%) • Peripheral oedema (9-13%) • Hypertension (9-20%) • Symptoms of congestive heart failure (6-7%) <u>Summary of withdrawal schedules:</u> Randomised controlled trials: Individualised based on the baseline dose (study=1, n=202, low certainty), Dose halved for one week, and then placebo (study=1, n=32), Not described (studies=3, n=246) Non-controlled trials: (very low certainty) Not described (study=1, n=33), Abrupt discontinuation for daily dose less than 40mg or else dose halved for one week before complete withdrawal (study=1, n=15)	
Values and preferences Is there confidence in the estimate of the relative importance of outcomes and individual preferences? Yes ☑ No ☐	Providing clarity, especially when diuretics are used as part of a combination drug regimen, is crucial in ensuring that patients feel informed and supported in making decisions about their treatment. Many patients are particularly averse to the side effects of diuretics, such as increased urinary frequency, urgency, or incontinence. These issues are especially concerning and can lead to significant discomfort and a reduced quality of life, especially for older people with limited mobility, who have difficulty accessing toilets, or with a high risk of falls. If diuretics are considered suitable to be deprescribed, patients emphasise the importance of ongoing, close monitoring to manage potential exacerbations of heart failure or ankle oedema. Additionally, the option to restart and adjust dosage as needed is vital for maintaining patients' quality of life. Patient education plays a key role in managing side effects	Perspective taken: The lack of evidence for serious harm following diuretic withdrawal, and the evident benefits related to reduced medication burden and costs. Individual values and preferences determine the deprescribing approaches. Sources of values and preferences: 1) Consultation with patient and carer representatives 2) Non-systematic review of evidence Source of variability, if any: Difficult to determine the extent of variability; high variability for patient preferences. Method for determining values satisfactory for this recommendation? Yes ☑ No ☐ Yes, but would be improved with direct patient input

	and helping patients understand their condition and lifestyle considerations. Healthcare professionals are more confident in making decisions to deprescribe in the event of a trigger (e.g. fall or adverse drug event) than in response to general concerns about polypharmacy.	
Resources Are the resources worth the expected net benefit? Yes ☑ No ☐	A comprehensive economic evaluation was outside the scope of the current review. However, potential cost and resource implications related to deprescribing interventions and continuation of medications are discussed below. Cost implications: A previous cost-effective study showed that deprescribing resulted in a 39% reduction in diuretic costs which outweighed the operation cost for deprescribing. However, other studies demonstrated that all antihypertensives including diuretics were in general more cost-effective than no treatment. The cost-effectiveness analysis of continuation and discontinuation may be difficult to estimate as it is sensitive to the type of deprescribing intervention and the rate of successful implementation. Physician implications: Healthcare providers will need to closely monitor patients to assess the impact of deprescribing on ongoing risk-benefit profiles. This may involve additional clinic visits, laboratory tests and extended consultation time. There is a lack of robust data informing the cost of the intervention and subsequently, cost-effectiveness. Most clinicians believe that deprescribing is a complex process, with barriers to resources commonly reported (e.g. suboptimal deprescribing organisational environment	Feasibility: Is this intervention generally available? Yes ☑ No ☐ Opportunity cost: Is this intervention and its effects worth withdrawing or not allocating resources from other interventions? Yes ☑ No ☐ Economic and preventive benefits for harms: Is there a lot of variability in resource requirements across settings? Yes ☐ No ☑

	that included competing workloads, staffing issues, and limited financial support).	
Equity What would be the impact of deprescribing on health inequities? ☑ Uncertain	The social determinants of health equity are complex and multifaceted. The impact of deprescribing on health equity is inadequately explored in the literature. Effective deprescribing of diuretics requires regular monitoring. Patients with limited access to healthcare services might face challenges in adhering to monitoring requirements, which could lead to inequities if they are unable to follow the deprescribing plan effectively. Ensuring equitable implementation and addressing potential challenges faced by people with varying health literacy and access disparities is crucial to maximising these benefits. Culturally and linguistically diverse populations, Aboriginal and Torres Strait Islander populations, people with low socioeconomic status, and those living in rural or remote areas may require additional support or considerations when implementing deprescribing intervention.	
Acceptability Is the option of deprescribing acceptable to key stakeholders? ☑ Probably yes	Healthcare practitioners: Deprescribing is likely acceptable to most healthcare practitioners, especially when supported by clinical practice guidelines and a shared decision-making process with patients. The term deprescribing may be new to healthcare practitioners but the concept is not. Healthcare practitioners are very familiar with discontinuing ineffective medications or those causing adverse effects worse than the condition being treated. Patients, their caregivers and family members: Many are open to deprescribing if they understand the potential benefits and risks, especially when given the option to restart medications when necessary. Policymakers and health systems: From a broader perspective, deprescribing can be seen as a way to reduce healthcare costs and improve patient outcomes. However, the short-term impacts on patient care and the resources required to implement effective deprescribing strategies may be a concern.	
Overall judgment	There is a lack of quality evidence for deprescribing to inform evidence-based recommendations.	

13. Lipid-modifying agents

13.1 Overview of studies targeted lipid-modifying agents

Article	Drug/Class	Study design	Sample size	Follow-up (months)	Withdrawal schedule
Kutner 2015 [190]	HMG CoA reductase inhibitors	RCT	381	12	Not described
Chung 2018 [191]	HMG CoA reductase inhibitors	Retrospective cohort study	2468	36	Not described
Korsholm 2024 [192]	HMG CoA reductase inhibitors	Before and after study	98	2	Abrupt discontinuation
Visser 2021 [138]	HMG CoA reductase inhibitors and proton-pump inhibitors	Before and after study	67	6	Not described

13.2 Evidence for deprescribing lipid-modifying agents

Study	Specific outcome	Odds ratio (95% CI)	Mean difference (95% CI)
1. Mortality			
Kutner 2015	Mortality at 2 months	1.23 (0.75, 1.99)	
Chung 2018	Mortality at 3 years	2.29 (1.74, 3.03)	
2. Adverse drug withdrawal events (ADWEs)			
Adverse events/ serious adverse events/ cardiovascular events			
Kutner 2015	Acute cardiovascular events	1.22 (0.53, 2.79)	
Chung 2018	Intracerebral haemorrhage	1.23 (0.82, 1.84)	
Chung 2018	Acute ischemic stroke	0.75 (0.50, 1.12)	
Chung 2018	Any stroke	0.96 (0.71, 1.31)	
3. Health outcomes			
Adverse drug events			
Kutner 2015	Side effects, measured using the 13-item Edmonton Symptom Assessment System scale		−0.2 (−1.4, 0.9)
Kutner 2015	Overall symptoms		−2.5 (−6.0, 1.1)
4. Cognitive function			
No available evidence			
5. Quality of life			
Kutner 2015	Quality of life, measured with the McGill Quality of Life Questionnaire		0.18 (-0.28, 0.64)
6. Effect on medication regimen			
Kutner 2015	Total number of medicines prescribed per participant	-0.67 (-1.29, -0.05)	

13.3 Evidence for deprescribing of lipid-modifying agents (non-controlled outcomes)

Study	Specific outcome	Result
1. Mortality		
No available evidence		
2. Adverse drug withdrawal events (ADWEs)		
No available evidence		
3. Health outcomes		
Cholesterol level, baseline to end-point, mean ± SD		
Korsholm 2024	Total cholesterol level	4.8 ± 0.7 to 6.5 ± 0.9
Korsholm 2024	Low-density lipoprotein cholesterol (LDL-C) level	2.2 ± 0.5 to 3.9 ± 0.8
Muscular symptoms, baseline to end-point, mean ± SD		
Korsholm 2024	Muscle discomfort during rest	0.9 ± 1.7 to 0.6 ± 1.4
Korsholm 2024	Muscle discomfort during activity	2.5 ± 2.6 to 1.9 ± 2.3, p<0.05
Korsholm 2024	Quadriceps muscle test	120 ± 28 kg to 132 ± 35 kg, p<0.05
Korsholm 2024	Lean muscle, total	44.4 ± 8.2 kg to 44.1 ± 8.1 kg
Korsholm 2024	Lean muscle, legs	15.2 ± 3.2 kg to 15.0 ± 3.2 kg
Korsholm 2024	Lean muscle, arms	4.8 ± 1.4 kg to 4.8 ± 1.3 kg
Physical function, baseline to end-point, mean ± SD		
Korsholm 2024	Physical function, chair stand test (number of reps per 30 seconds)	15.7 ± 4.3 to 16.3 ± 4.9, p<0.05
Korsholm 2024	Physical function, power (W)	268 ± 100 to 276 ± 102, p<0.05
Korsholm 2024	Physical function, relative power (W/kg)	3.6 ± 1.1 to 3.7 ± 1.2
Korsholm 2024	Physical function, 6-min walking test	544 ± 78 m to 556 ± 80 m, p<0.05
4. Cognitive function		
No available evidence		
5. Quality of life		
No available evidence		
6. Effect on medication regimen		
Visser 2021	Successfully withdrawn completely or dose reduced (HMG CoA reductase inhibitors and proton-pump inhibitors)	34/66 (52%)

13.4 GRADE evidence profile (critical or important but not critical outcomes only)

Question: In older people, what are the effects of deprescribing (i.e. dose reduction or complete discontinuation) long-term lipid-modifying agents on mortality, adverse drug withdrawal events, health-related outcomes, cognitive function, and quality of life?

Certainty assessment							Number of participants		Effect	Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Deprescribing	Continuation			
1. Mortality											
1 [190]	RCT	Serious [1]	Not serious	Serious [2]	Serious [3]	Not serious	189	192	OR 1.23 (0.75, 1.99)		8
1 [191]	Non-randomised study	Serious [4]	Not serious	Serious [7]	Not serious	Not serious	708	708	OR 2.29 (1.74, 3.03)		8
2. Adverse drug withdrawal events (ADWEs)											
Adverse events/ serious adverse events/ cardiovascular events											
1 [190]	RCT	Serious [1]	Not serious	Serious [2]	Serious [3]	Not serious	189	192	OR 1.22 (0.53, 2.79)		7
1 [191]	Non-randomised study	Serious [4]	Not serious	Serious [7]	Not serious	Not serious	708	708	Intracerebral haemorrhage OR 1.23 (0.82, 1.84) Acute ischemic stroke OR 0.75 (0.50, 1.12) Any stroke OR 0.96 (0.71, 1.31)		7
3. Health outcomes											
Adverse drug events											
1 [190]	RCT	Serious [1]	Not serious	Serious [2]	Serious [3]	Not serious	189	192	There was no significant change in the side effects specific to statin use (muscle-related pain, weakness, headache, and fever) (MD −0.2, 95% CI −1.4, 0.9) measured using the 13-item Edmonton Symptom Assessment System scale. When combined with the 9 standard items on the same scale (pain, fatigue, nausea, depression, anxiousness, drowsiness, appetite, well-being, and breathing), the overall symptoms also did not change significantly (MD –2.5, 95% −6.0, 1.1).		5
Cholesterol level											

1 [192]	Non-controlled study	Serious [6]	Not serious	Not serious	Not serious	Not serious	98	N/A	Total cholesterol level increased from 4.8 ± 0.7 to 6.5 ± 0.9. Low-density lipoprotein cholesterol (LDL-C) level increased from 2.2 ± 0.5 to 3.9 ± 0.8.		4
Physical function											
1 [192]	Non-controlled study	Serious [6]	Not serious	Not serious	Not serious	Not serious	98	N/A	Physical function improved as follows: Chair stand test, number of reps per 30 seconds increased from 15.7 ± 4.3 to 16.3 ± 4.9, p<0.05. Power (W) increased from 268 ± 100 to 276 ± 102, p<0.05. Relative power (W/kg) increased from 3.6 ± 1.1 to 3.7 ± 1.2. 6-min walking test increased from 544 ± 78 m to 556 ± 80 m, p<0.05.		4
4. Cognitive function											
No available evidence											
5. Quality of life (QoL)											
1 [190]	RCT	Serious [1]	Not serious	Serious [2]	Serious [3]	Not serious	189	192	There was no significant change in the overall quality of life following deprescribing of statin therapy (MD 0.18, 95% CI -0.28, 0.64) measured using the McGill Quality of Life Questionnaire.		7

[1] Open-label study design and outcomes were measured through self-report (potential performance and detection bias). Potential volunteer bias - study enrolled patients who were willing to stop taking statins.
[2] This study targeted participants with a documented diagnosis of advanced, life-limiting illness and a life expectancy of more than one month
[3] The study did not achieve its primary endpoint of noninferiority margin for 60-day mortality (primary outcome).
[4] Potential selection bias due to non-random sampling attributed to the study design.
[5] Potential indirectness - Study targeted participants with intracerebral haemorrhage as their admission diagnosis which limits the generalisability.
[6] Potential confounding bias as medication doses were not considered. Higher doses may increase the likelihood of muscular side effects. Additionally, there was no mention of other concurrent medications likely to introduce muscular side effects such as a calcium channel blocker and the changes in physical activity or other factors during the study period could not be ruled out. Potential performance bias due to the lack of blinding. Relatively brief study duration (2 months).

13.5 Evidence-to-Decision table

Question: In older people, what are the effects of deprescribing (i.e. dose reduction or complete discontinuation) long-term lipid-modifying agents on mortality, adverse drug withdrawal events, health-related outcomes, cognitive function, and quality of life?		
Decision domain	Summary of reason for decision	Subdomains influencing decision
Certainty of evidence Is there a high or moderate certainty of evidence? Yes ☐ No ☑	The certainty of evidence for the benefits of deprescribing is very low. The certainty of evidence for the harms of deprescribing is very low.	Key reasons for downgrading: Risk of bias, indirectness, imprecision Are all critical outcomes measured? Yes ☐ No ☑ There is a lack of evidence on cognitive function.
Benefits and harms Is there certainty that the benefits of deprescribing outweigh the harms? Yes ☐ No ☑	The effects of deprescribing statins have been tabulated in Appendix B (GRADE evidence profile table) with an overview provided in the guideline document (a narrative overview and GRADE summary of findings table). Below is a summary according to the study designs. <u>Summary of outcomes</u> Randomised and non-randomised controlled trials: • No significant difference in mortality in patients with advanced, life-limiting illnesses • No significant difference in the occurrence of adverse events and quality of life, reported statin-related side effects • Significant increase in mortality for patients who discontinued statin therapy following an intracerebral haemorrhage event Non-controlled trials: • Improved physical function • Increased total cholesterol level and low-density lipoprotein cholesterol level	Is the baseline risk for benefits and harms of deprescribing similar across subgroups? Yes ☐ No ☑ The evidence from our systematic review and meta-analysis at this time suggests some individuals with severe comorbidities with significant cardiovascular risk factors may be at risk of developing adverse events from the withdrawal of statins. Should there be separate recommendations for subgroups? Yes ☑ No ☐ The guideline development group acknowledges that certain subgroups may have factors (e.g. primary or secondary prevention use, life expectancy, other important comorbidities, presence of significant cardiovascular risk factors, and adverse drug events) that could impact the balance of benefits and risks from deprescribing. However, the available evidence is insufficient to justify distinct evidence-based recommendations.

	<u>Summary of withdrawal schedules:</u> Randomised controlled trial: Not described (study=1, n=381) Non-randomised controlled trial: Not described (study=1, n=2468) Non-controlled trials: (very low certainty) Abrupt discontinuation (study=1, n=98), Not described (study=1, n=67)	
Values and preferences Is there confidence in the estimate of the relative importance of outcomes and individual preferences? Yes ☑ No ☐	Patients are generally open to discussing the option of deprescribing when it is raised by their doctors. Common concerns related to statin use include pill burden, fear of side effects, and uncertainty about the future benefits of continuing the medication. For patients with limited life expectancy, many are less concerned about discontinuing statins and place greater value on the potential improvement in quality of life that deprescribing may offer. Lifestyle factors, including food and drink interactions with medicines, also play a role in these discussions. Additionally, patients often report that lipid-based statins tend to have more side effects, such as cognitive issues, depression, and joint pain, compared to hydrophilic statins. Some patients are willing to try different medicines, adjusting based on tolerance, to find the most suitable option.	Perspective taken: The lack of evidence for serious harm following statin withdrawal in patients with advanced, life-limiting illnesses, evidence for serious harm when statins were deprescribed in patients with intracerebral haemorrhage, and the evident benefits related to reduced medication burden and costs. Individual values and preferences determine the deprescribing approaches. Sources of values and preferences: 1) Consultation with patient and carer representatives 2) Non-systematic review of evidence Source of variability, if any: Difficult to determine the extent of variability; high variability for patient preferences. Method for determining values satisfactory for this recommendation? Yes ☑ No ☐ Yes, but would be improved with direct patient input
Resources Are the resources worth the expected net benefit?	A comprehensive economic evaluation was outside the scope of the current review. However, potential cost and resource implications related to deprescribing interventions and continuation of medications are discussed below.	Feasibility: Is this intervention generally available? Yes ☑ No ☐ Opportunity cost: Is this intervention and its effects worth withdrawing or not allocating resources from other interventions?

Yes ☑ No ☐	Cost implication: In Australia, statins are the most commonly prescribed lipid-lowering medication. The prescribing of non-statin lipid-lowering medications remains low but increasing. Cost-effective analysis showed statin therapy is highly cost-effective across men and women 40–70 years old, including those with a 10-year cardiovascular disease risk of <5%. Compared to lifetime statin therapy, discontinuing statins at 80 years of age substantially reduced benefits and was not cost-effective in any patient category. The use of statins in people aged 75 and over for primary prevention is however debatable. More research on the potential benefits and harms of statins is needed to inform decision-making. Physician implications: Healthcare providers will need to closely monitor patients to assess the impact of deprescribing on ongoing risk-benefit profiles. This may involve additional clinic visits, laboratory tests and extended consultation time. There is a lack of robust data informing the cost of the intervention and subsequently, cost-effectiveness. Most clinicians believe that deprescribing is a complex process, with barriers to resources commonly reported (e.g. suboptimal deprescribing organisational environment that included competing workloads, staffing issues, and limited financial support).	Yes ☑ No ☐ Economic and preventive benefits for harms: Is there a lot of variability in resource requirements across settings? Yes ☐ No ☑
Equity What would be the impact of deprescribing on health inequities? ☑ Uncertain	The social determinants of health equity are complex and multifaceted. The impact of deprescribing on health equity is inadequately explored in the literature. Effective deprescribing of statins requires regular monitoring and follow-up appointments. Patients with limited access to healthcare services might face challenges in adhering to monitoring requirements, which could lead to inequities if they are unable to follow the deprescribing plan effectively. Ensuring equitable implementation and addressing potential challenges faced by people with varying health literacy and access disparities is crucial to maximising these benefits. Culturally and linguistically diverse populations, Aboriginal and Torres Strait Islander populations, people with low socioeconomic status, and those living in rural or remote areas may require	

	additional support or considerations when implementing deprescribing intervention.
Acceptability Is the option of deprescribing acceptable to key stakeholders? ☑ Probably yes	Healthcare practitioners: Deprescribing is likely acceptable to most healthcare practitioners, especially when supported by clinical practice guidelines and a shared decision-making process with patients. The term deprescribing may be new to healthcare practitioners but the concept is not. Healthcare practitioners are very familiar with discontinuing ineffective medications or those causing adverse effects worse than the condition being treated. Patients, their caregivers and family members: Many are open to deprescribing if they understand the potential benefits and risks, especially when given the option to restart medications when necessary. Policymakers and health systems: From a broader perspective, deprescribing can be seen as a way to reduce healthcare costs and improve patient outcomes. However, the short-term impacts on patient care and the resources required to implement effective deprescribing strategies may be a concern.
Overall judgment	There is a lack of quality evidence for deprescribing to inform evidence-based recommendations.

14. Corticosteroids (skin)

We were unable to identify a study that assessed deprescribing topical corticosteroids from the systematic search.

15. Estrogens

15.1 Overview of studies targeted estrogens

Article	Drug/Class	Study design	Sample size	Follow-up (months)	Withdrawal schedule
Gallagher 2002 [193]	Hormone/estrogen replacement therapy	RCT	489	24	Not described

15.2 Evidence for deprescribing estrogens

Study	Specific outcome	Odds ratio (95% CI)	Mean difference (95% CI), comparing hormone replacement therapy withdrawal versus placebo withdrawal, MD > 0 indicates that the outcome is in favour of the untreated placebo group
1. Mortality			
No available evidence			
2. Adverse drug withdrawal events (ADWEs)			
ADWEs, bone mineral density			
Gallagher 2002	Percentage change in bone mineral density, total body		2.89 (2.71, 3.07)
Gallagher 2002	Percentage change in bone mineral density, spine		2.39 (2.02, 2.76)
Gallagher 2002	Percentage change in bone mineral density, femoral neck		1.33 (0.94, 1.72)
Gallagher 2002	Percentage change in bone mineral density, trochanter		-0.11 (-0.55, 0.33)
Gallagher 2002	Percentage change in bone mineral density, total hip		1.19 (0.84, 1.54)
3. Health outcomes			
No available evidence			
4.			
No available evidence			
5. Quality of life			
No available evidence			
6. Effect on medication regimen			
No available evidence			

15.3 Evidence for deprescribing estrogens (non-controlled outcomes)

Study	Specific outcome	Result
1. Mortality		
No available evidence		
2. Adverse drug withdrawal events (ADWEs)		
No available evidence		
3. Health outcomes		
No available evidence		
4. Cognitive function		
No available evidence		
5. Quality of life		
No available evidence		
6. Effect on medication regimen		
No available evidence		

15.4 GRADE evidence profile (critical or important but not critical outcomes only)

Question: In older people, what are the effects of deprescribing (i.e. dose reduction or complete discontinuation) long-term estrogens on mortality, adverse drug withdrawal events, health-related outcomes, cognitive function, and quality of life?

Certainty assessment							Number of participants		Effect	Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Deprescribing	Continuation			
1. Mortality											
No available evidence											
2. Adverse drug withdrawal events (ADWEs)											
ADWEs, bone mineral density											
1 [193]	RCT	Serious [1]	Not serious	Serious [2,3]	Serious [4]	Not serious	56	44	There was no significant difference between the discontinuation and continuation group in bone mineral density of the trochanter (MD -0.11, 95% CI -0.55, 0.33). Those participants who received estrogen replacement therapy for the preceding three years before two years of discontinuation had a lower percentage change in bone mineral density from baseline to five years in total body (MD 2.89, 95% CI 2.71 to 3.07), spinal (MD 2.39, 95% CI 2.02 to 2.76), femoral neck (MD 1.33, 95% CI 0.94 to 1.72), and total hip (MD 1.19, 95% CI 0.84 to 1.54) compared to the group who were untreated (placebo group).		6
3. Health outcomes											
No available evidence											
4. Cognitive function											
No available evidence											
5. Quality of life (QoL)											
No available evidence											

[1] The three-year study was double-blind, but the two-year extension study of therapy discontinuation was probably open-label. Potential attrition and reporting bias.
[2] Potential indirectness - This study compared the discontinuation of placebo to the discontinuation of estrogen replacement therapy. None of the two groups would have received the drug in the two years of discontinuation for comparison, although the group who received estrogen replacement therapy for the preceding three years before discontinuation may have some small residual effect from the therapy. It is unclear if the outcome can be generalised in the absence of a true comparison group.
[3] Bone mineral density is a surrogate outcome that is not of direct practical importance but is believed to reflect an important outcome (i.e. fractures).
[4] Small sample size

15.5 Evidence-to-Decision table

Question: In older people, what are the effects of deprescribing (i.e. dose reduction or complete discontinuation) long-term estrogens on mortality, adverse drug withdrawal events, health-related outcomes, cognitive function, and quality of life?

Decision domain	Summary of reason for decision	Subdomains influencing decision
Certainty of evidence Is there a high or moderate certainty of evidence? Yes ☐ No ☑	The certainty of evidence is very low.	Key reasons for downgrading: Risk of bias, indirectness Are all critical outcomes measured? Yes ☐ No ☑ There is a lack of evidence on critical outcomes including mortality, health outcomes, cognitive function, and quality of life.
Benefits and harms Is there certainty that the benefits of deprescribing outweigh the harms? Yes ☐ No ☑	The effects of deprescribing estrogens have been tabulated in Appendix B (GRADE evidence profile table) with an overview provided in the guideline document (a narrative overview and GRADE summary of findings table). Below is a summary. <u>Summary of outcomes</u> Randomised controlled trial: We did not identify any direct benefits or harms related to the continuation or discontinuation of estrogen. The only evidence we identified was a comparison of deprescribing of estrogen replacement therapy with placebo users which the study did not report a significant impact on the bone mineral density of the trochanter. This study further reported those who received estrogen for the three years before discontinuation had a significantly lower total percentage change in bone mineral density in all other body sites compared to the group who were untreated for five years (placebo group) which was likely due to the residual effect of estrogen before discontinuation.	Is the baseline risk for benefits and harms of deprescribing similar across subgroups? Yes ☐ No ☑ There is no evidence at this time that the benefits or harms of deprescribing differ based on subgroups. However, there will be some groups at a higher risk. Should there be separate recommendations for subgroups? Yes ☑ No ☐ The guideline development group acknowledges that certain subgroups may have factors (e.g. severity of menopausal symptoms, indication for hormone replacement therapy, other important comorbidities, and the presence of adverse drug events) that could impact the balance of benefits and risks from deprescribing. However, the available evidence is insufficient to justify distinct evidence-based recommendations.

	<u>Summary of withdrawal schedules:</u> Randomised controlled trial: Not described (study=1, n=489)	
Values and preferences Is there confidence in the estimate of the relative importance of outcomes and individual preferences? Yes ☑ No ☐	Many women express a lack of sufficient information about current therapies for the physiological changes and symptoms associated with menopause, which leaves them uncertain about making decisions regarding hormone replacement therapy. Women often weigh the effectiveness of medications against concerns about adverse events, such as increased breast cancer risk. For many, the decision to deprescribe should be guided by their individual concerns and the level of symptom acceptability. Women prefer an individualised approach to decision-making, where the severity of symptoms and their impact on quality of life are carefully considered. The timing of treatment cessation – whether at age 70, 80, or later – is often a point of discussion, especially for those still experiencing menopausal symptoms. Women tend to favour a balanced approach, weighing the benefits and risks of treatment, particularly when other health conditions may pose greater risks than menopausal symptoms. Additionally, women value awareness of breast cancer screening programs, monitoring, and surveillance if continuing treatment and they may seek other alternative lifestyle advice for managing menopause.	Perspective taken: Individual values and preferences determine the deprescribing approaches. Sources of values and preferences: 1) Consultation with patient and carer representatives 2) Non-systematic review of evidence Source of variability, if any: Difficult to determine the extent of variability; high variability for patient preferences. Method for determining values satisfactory for this recommendation? Yes ☑ No ☐ Yes, but would be improved with direct patient input
Resources Are the resources worth the expected net benefit? Yes ☑ No ☐	A comprehensive economic evaluation was outside the scope of the current review. However, potential cost and resource implications related to deprescribing interventions and continuation of medications are discussed below.	Feasibility: Is this intervention generally available? Yes ☑ No ☐ Opportunity cost: Is this intervention and its effects worth withdrawing or not allocating resources from other interventions?

	Cost implications: The cost-effectiveness analysis on hormone replacement therapy use is less favourable for women aged 65 years or more due to the greater absolute risks of cardiovascular events and cognitive decline. Starting hormone replacement therapy in older women did not improve quality of life and resulted in a loss of quality-adjusted life years for several years before a small gain can be realised. For those who have been using hormone replacement therapy for several years, there is a small net benefit related to reduced fracture, reduced cardiovascular risk with long-term use and the increase in breast cancer deaths being offset by a reduction in colon cancer deaths. Physician implications: Healthcare providers will need to closely monitor patients to assess the impact of deprescribing on ongoing menopausal symptoms. This may involve additional clinic visits and extended consultation time. However, the time and resources may be offset by the periodic re-evaluation of the benefits and risks of continuing hormone replacement therapy. There is a lack of robust data informing the cost of the intervention and subsequently, cost-effectiveness. Most clinicians believe that deprescribing is a complex process, with barriers to resources commonly reported (e.g. suboptimal deprescribing organisational environment that included competing workloads, staffing issues, and limited financial support).	Yes ☑ No ☐ Economic and preventive benefits for harms: Is there a lot of variability in resource requirements across settings? Yes ☐ No ☑
Equity What would be the impact of deprescribing on health inequities?	The social determinants of health equity are complex and multifaceted. The impact of deprescribing on health equity is inadequately explored in the literature. Effective deprescribing of estrogen requires appropriate monitoring and follow-up to manage symptoms. Women with limited access to healthcare services might face challenges in adhering to monitoring requirements, which could lead to inequities if they are unable to follow the deprescribing plan effectively. Ensuring equitable implementation and addressing potential challenges faced by people with varying health literacy	

☑ Uncertain	and access disparities is crucial to maximising these benefits. Culturally and linguistically diverse populations, Aboriginal and Torres Strait Islander populations, people with low socioeconomic status, and those living in rural or remote areas may require additional support or considerations when implementing deprescribing intervention.
Acceptability Is the option of deprescribing acceptable to key stakeholders? ☑ Probably yes	Healthcare practitioners: Deprescribing is likely acceptable to most healthcare practitioners, especially when supported by clinical practice guidelines and a shared decision-making process with patients. The term deprescribing may be new to healthcare practitioners but the concept is not. Healthcare practitioners are very familiar with discontinuing ineffective medications or those causing adverse effects worse than the condition being treated. Patients, their caregivers and family members: Many are open to deprescribing if they understand the potential benefits and risks, especially when given the option to restart medications when necessary. Policymakers and health systems: From a broader perspective, deprescribing can be seen as a way to reduce healthcare costs and improve patient outcomes. However, the short-term impacts on patient care and the resources required to implement effective deprescribing strategies may be a concern.
Overall judgment	There is a lack of quality evidence for deprescribing to inform evidence-based recommendations.

16. Anticholinergics (genitourinary)

16.1 Overview of studies targeted drugs for urinary frequency and incontinence

Article	Drug/Class	Study design	Sample size	Follow-up (months)	Withdrawal schedule
Ha 2022 [194]	Urinary antimuscarinic	Before and after study	187	9	Individualised

16.2 Evidence for deprescribing of drugs for urinary frequency and incontinence

Study	Specific outcome	Odds ratio (95% CI)	Mean difference (95% CI)
1. Mortality			
No available outcome			
2. Adverse drug withdrawal events (ADWEs)			
No available outcome			
3. Health outcomes			
No available outcome			
4. Cognitive function			
No available outcome			
5. Quality of life			
No available outcome			
6. Effect on medication regimen			
No available outcome			

16.3 Evidence for deprescribing of drugs for urinary frequency and incontinence (non-controlled outcomes)

Study	Specific outcome	Result
1. Mortality		
No available outcome		
2. Adverse drug withdrawal events (ADWEs)		
No available outcome		
3. Health outcomes		
No available outcome		
4. Cognitive function		
No available outcome		
5. Quality of life		
No available outcome		
6. Effect on medication regimen		
Ha 2022	Unsuccessful deprescribing (i.e. urinary antimuscarinics returned to the baseline or higher exposure)	5%
Ha 2022	Anticholinergic exposure, as measured by standardised daily doses	2.6 ± 2.8 to 0.9 ± 2.1

16.4 GRADE evidence profile for deprescribing of drugs for urinary frequency and incontinence

We were unable to identify any critical/important outcome from the systematic search.

16.5 Evidence-to-Decision table

We were unable to identify any critical/important outcome from the systematic search.

17. Drugs used in benign prostatic hypertrophy (BPH)

17.1 Overview of studies targeted drugs used in benign prostatic hypertrophy (BPH)

Article	Drug/Class	Study design	Sample size	Follow-up (months)	Withdrawal schedule
Lin 2014 [195]	Doxazosin/ dutasteride	RCT	240	12	Not described

17.2 Evidence for deprescribing drugs used in benign prostatic hypertrophy (BPH)

Study	Specific outcome	Odds ratio (95% CI), comparing 5-alpha-reductase inhibitor withdrawal versus alpha-blocker withdrawal, OR > 1 indicates a greater likelihood of the event occurring in the group with 5-alpha-reductase inhibitor discontinued	Mean difference (95% CI)
1. Mortality			
No available outcome			
2. Adverse drug withdrawal events (ADWEs)			
Lin 2014	Exacerbation of underlying condition, overall BPH/ lower urinary tract symptom progression	0.67 (0.31, 1.43)	
Lin 2014	Exacerbation of underlying condition, International Prostate Symptom Score ≥ 4	1.00 (0.55, 1.81)	
Lin 2014	Exacerbation of underlying condition, progression to transurethral resection of the prostate (TURP)	2.23 (0.92, 5.40)	
Lin 2014	Exacerbation of underlying condition, maximum flow rate reduced ≥ 2mL/s	1.41 (0.80, 2.48)	
Lin 2014	Exacerbation of underlying condition, post-void residual urine volume increased ≥ 50%	0.66 (0.36, 1.20)	
3. Health outcomes			
No available outcome			
4. Cognitive function			
No available outcome			
5. Quality of life			
No available outcome			
6. Effect on medication regimen			
No available outcome			

17.3 Evidence for deprescribing drugs used in benign prostatic hypertrophy (BPH) (non-controlled outcomes)

Study	Specific outcome	Result
1. Mortality		
No available evidence		
2. Adverse drug withdrawal events (ADWEs)		
No available evidence		
3. Health outcomes		
No available evidence		
4. Cognitive function		
No available evidence		
5. Quality of life		
No available evidence		
6. Effect on medication regimen		
No available evidence		

17.4 GRADE evidence profile (critical or important but not critical outcomes only)

Question: In older people, what are the effects of deprescribing (i.e. dose reduction or complete discontinuation) long-term drugs used in BPH on mortality, adverse drug withdrawal events, health-related outcomes, cognitive function, and quality of life?

Certainty assessment							Number of participants		Effect	Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	5-alpha-reductase inhibitor discontinued	Alpha-blocker discontinued			
1. Mortality											
No available evidence											
2. Adverse drug withdrawal events (ADWEs)											
Exacerbation/return of underlying condition											
1 [195]	RCT	Serious [1]	Not serious	Serious [2]	Serious [3]	Not serious	117	113	One RCT compared the discontinuation of either one drug from the combination therapy consisting of alpha-blocker and 5-alpha-reductase inhibitor. At 12 months, deprescribing of either drug was not associated with a significant difference in the following: • International Prostate Symptom Score ≥ 4, OR 1.00 (0.55, 1.81) • Maximum flow rate reduced ≥ 2mL/s, OR 1.41 (0.80, 2.48) • Post-void residual urine volume increased ≥ 50%, OR 0.66 (0.36, 1.20) • Transurethral resection of the prostate, OR 2.23 (0.92, 5.40) • Overall BPH/ lower urinary tract symptom progression, OR 0.67 (0.31, 1.43) However, there was a significantly greater proportion of participants who had a total prostate volume increased ≥ 20% in the group with 5-alpha-reductase inhibitor discontinued than in the group with alpha-blocker discontinued (OR 4.73, 95% CI 2.15, 10.42). Additionally, a significantly greater proportion of participants who had their 5-alpha-		6

										reductase inhibitor discontinued resumed the medicine compared to the group with alpha-blocker discontinued (OR 2.35, 95% CI 1.37, 4.02). OR > 1 indicates a greater likelihood of the event occurring in the group with 5-alpha-reductase inhibitor discontinued.	
3. Health outcomes											
No available evidence											
4. Cognitive function											
No available evidence											
5. Quality of life (QoL)											
No available evidence											

[1] This was an open-label study and the method of randomisation was unclear. Potential performance and detection biases. Lack of information on blinding of outcome assessors.
[2] Potential indirectness - Study compared the discontinuation of either one drug from the combination therapy consisting of alpha-blocker and 5-alpha-reductase inhibitor. It is unclear if the outcome can be generalised in the absence of a true placebo control group.
[3] Very small sample size

17.5 Evidence-to-Decision table

Question: In older people, what are the effects of deprescribing (i.e. dose reduction or complete discontinuation) long-term drugs used in BPH on mortality, adverse drug withdrawal events, health-related outcomes, cognitive function, and quality of life?

Decision domain	Summary of reason for decision	Subdomains influencing decision
Certainty of evidence Is there a high or moderate certainty of evidence? Yes ☐ No ☑	The certainty of evidence for the benefits of deprescribing is very low. The certainty of evidence for the harms of deprescribing is very low.	Key reasons for downgrading: Risk of bias, indirectness, imprecision Are all critical outcomes measured? Yes ☐ No ☑ There is a lack of evidence on critical outcomes including mortality, health outcomes and cognitive function.
Benefits and harms Is there certainty that the benefits of deprescribing outweigh the harms? Yes ☐ No ☑	The effects of deprescribing drugs used in BPH have been tabulated in Appendix B (GRADE evidence profile table) with an overview provided in the guideline document (a narrative overview and GRADE summary of findings table). Below is a summary according to the study designs. <u>Summary of outcomes</u> Randomised controlled trial: The only study we identified was a comparison of discontinuing either one drug from the combination therapy consisting of an alpha-blocker and a 5-alpha-reductase inhibitor. Deprescribing 5-alpha-reductase inhibitor led to a significantly greater proportion of participants who had a total prostate volume increased ≥ 20% compared to the group with alpha-blocker discontinued. Additionally, a significant greater proportion of participants who had their 5-alpha-reductase inhibitor discontinued resumed the medicine compared to the group with alpha-blocker discontinued. There was no significant difference in discontinuing either drug for other measures of progression of benign prostatic hyperplasia	Is the baseline risk for benefits and harms of deprescribing similar across subgroups? Yes ☐ No ☑ Evidence indicates a greater risk of a 20% increase in total prostate volume in patients on combination therapy who discontinue the 5-alpha-reductase inhibitor compared to those who discontinue the alpha-blocker. Should there be separate recommendations for subgroups? Yes ☑ No ☐ The guideline development group acknowledges that certain subgroups may have varying balance of benefits and risks from deprescribing. While evidence at this stage shows that patients on combination therapy discontinuing the 5-alpha-reductase inhibitor may face a higher risk of disease progression compared to those discontinuing the alpha-blocker, the certainty of evidence is very low. Distinct evidence-based recommendations could not be justified.

	(maximum urine flow rate, post-void residual urine volume, International Prostate Symptom Score, progression to transurethral resection of the prostate, or overall benign prostatic hyperplasia lower urinary tract symptom progression). <u>Summary of withdrawal schedules:</u> Randomised controlled trial: Not described (study=1, n=240)	
Values and preferences Is there confidence in the estimate of the relative importance of outcomes and individual preferences? Yes ☑ No ☐	Many men are open to discontinuing the medicines for BPH if recommended by their doctor. When deciding to start a new drug for BPH, men tend to prioritise reducing the risk of needing surgery in the future over seeking immediate symptomatic relief. Approximately 30% of patients discontinue treatment after one year, often due to reasons related to costs and adverse effects. Medicines for BPH often come with significant side effects, for instance may cause a variety of sexual side effects. Men prefer an individualised approach to decision-making, where the severity of symptoms and their impact on quality of life are carefully considered. When deciding whether to initiate drug therapy, most urologists consider the benign prostatic hyperplasia progression and prostate volume to be very important factors. Most urologists consider watchful waiting an appropriate strategy for asymptomatic patients or those without bothersome symptoms. For men with larger prostate volumes, most urologists consider combination therapy with an alpha blocker and 5-alpha-reductase inhibitor more effective than monotherapy.	Perspective taken: Individual values and preferences determine the deprescribing approaches. Sources of values and preferences: 1) Consultation with patient and carer representatives 2) Non-systematic review of evidence Source of variability, if any: Difficult to determine the extent of variability; high variability for patient preferences. Method for determining values satisfactory for this recommendation? Yes ☑ No ☐ Yes, but would be improved with direct patient input
Resources	A comprehensive economic evaluation was outside	Feasibility: Is this intervention generally available?

Are the resources worth the expected net benefit? Yes ☑ No ☐	the scope of the current review. However, potential cost and resource implications related to deprescribing interventions and continuation of medications are discussed below. Cost implications: The prevalence of benign prostatic hyperplasia in Australia increased by 77% between the years 2000 and 2019. There is little evidence about the cost implications and cost-effectiveness analysis of discontinuing drugs used in benign prostatic hyperplasia. The cost-effectiveness analysis of continuation and discontinuation may be difficult to estimate as it is sensitive to the type of deprescribing intervention and the rate of successful implementation. Most cost-analysis studies tend to compare surgical intervention to pharmacotherapy (alpha-blockers). Cost consideration for continuation or discontinuation must take into account the substantial costs related to quality of life, work productivity, doctor visits, and medication costs including those used to treat adverse events associated with the treatment for benign prostatic hyperplasia. Physician implications: Healthcare providers will need to closely monitor patients to assess the impact of deprescribing on ongoing symptom severity. This may involve additional clinic visits, laboratory tests and extended consultation time. However, it is uncertain if watchful waiting involves less time and resources than periodic re-evaluation for pharmacotherapy.	Yes ☑ No ☐ Opportunity cost: Is this intervention and its effects worth withdrawing or not allocating resources from other interventions? Yes ☑ No ☐ Economic and preventive benefits for harms: Is there a lot of variability in resource requirements across settings? Yes ☐ No ☑
Equity What would be the impact of	The social determinants of health equity are complex and multifaceted. The impact of deprescribing on health equity is inadequately explored in the literature. Effective deprescribing of drugs used for BPH requires appropriate monitoring and follow-up to manage symptoms. Men with limited access to healthcare services might face challenges in adhering to	

deprescribing on health inequities? ☑ Uncertain	monitoring requirements, which could lead to inequities if they are unable to follow the deprescribing plan effectively. Ensuring equitable implementation and addressing potential challenges faced by people with varying health literacy and access disparities is crucial to maximising these benefits. Culturally and linguistically diverse populations, Aboriginal and Torres Strait Islander populations, people with low socioeconomic status, and those living in rural or remote areas may require additional support or considerations when implementing deprescribing intervention.
Acceptability Is the option of deprescribing acceptable to key stakeholders? ☑ Probably yes	Healthcare practitioners: Deprescribing is likely acceptable to most healthcare practitioners, especially when supported by clinical practice guidelines and a shared decision-making process with patients. The term deprescribing may be new to healthcare practitioners but the concept is not. Healthcare practitioners are very familiar with discontinuing ineffective medications or those causing adverse effects worse than the condition being treated. Patients, their caregivers and family members: Many are open to deprescribing if they understand the potential benefits and risks, especially when given the option to restart medications when necessary. Policymakers and health systems: From a broader perspective, deprescribing can be seen as a way to reduce healthcare costs and improve patient outcomes. However, the short-term impacts on patient care and the resources required to implement effective deprescribing strategies may be a concern.
Overall judgment	There is a lack of quality evidence for deprescribing to inform evidence-based recommendations

18. Prednisone/ prednisolone

18.1 Overview of studies targeted prednisone/prednisolone

Article	Drug/Class	Study design	Sample size	Follow-up (months)	Withdrawal schedule
Esselinckx 1977 [196]	Prednisolone for polymyalgia rheumatica	Before and after study	18	Not stated	Abrupt in the first stage, gradual in the second stage with a mean withdrawal rate of 1mg per month over a 4 to 5 months period
Hirano 2016** [197]	Prednisolone for autoimmune pancreatitis	Before and after study	21	36	Daily maintenance prednisolone dose was reduced by 1mg every 8-10 weeks
Rice 2000 [198]	Prednisolone for chronic obstructive pulmonary disease (COPD)	RCT	38	6	Daily maintenance prednisone dose was reduced by 5 mg/week
Hirata 2021 [199]	Prednisolone for rheumatoid arthritis	Before and after study	36	24	Prednisolone was gradually reduced up to 1 mg per month while at the same time, the methotrexate dose was gradually increased up to 16 mg per week and up to 4 mg per month for folate
Almayali 2023 [200]	Prednisolone for rheumatoid arthritis	Before-and-after study	96	3	Dose tapering over 12 weeks
Goto 2023 [201]	Glucocorticoids for rheumatoid arthritis	Retrospective cohort study	248	36	Not described

** The study terminated early due to a high rate of clinical relapse (38% of participants)

18.2 Evidence for deprescribing prednisone/prednisolone

Study	Specific outcome	Odds ratio (95% CI)	Mean difference (95% CI)
1. Mortality			
No available evidence			
2. Adverse drug withdrawal events (ADWEs)			
Rice 2000	At least one exacerbation, chronic obstructive pulmonary disease (COPD)	1.50 (0.35, 6.50)	
Rice 2000	Number of COPD exacerbations		0.20 (-1.46, 1.86)
Rice 2000	Days until first COPD exacerbation		-7.00 (-35.94, 21.94)
3. Health outcomes			
Health service use			
Goto 2023	Unplanned hospitalisation (glucocorticoids for rheumatoid arthritis)	0.35 (0.18, 0.67)	
4. Cognitive function			
No available evidence			
5. Quality of life			
No available evidence			
6. Effect on medication regimen			
Rice 2000	Difference in the daily corticosteroid dose (mg), COPD		-7.4 (-12.38, -2.42)

18.3 Evidence for deprescribing prednisone/prednisolone (non-controlled outcomes)

Study	Specific outcome	Result (proportion of participants reported experiencing outcome, end-point mean value ± SD, baseline to end-point mean ± SD, or mean difference and p-value)
1. Mortality		
Esselinckx 1977	Mortality (prednisolone for polymyalgia rheumatica)	2/18 (11%)
2. Adverse drug withdrawal events (ADWEs)		
Exacerbation/return of underlying condition		
Esselinckx 1977	Recurrence of the underlying condition (polymyalgia rheumatica) after abrupt or gradual discontinuation of prednisolone	18/18 (100%)
Hirano 2016	Clinical relapse, autoimmune pancreatitis	10/21 (48%) – after group
Hirano 2016	Only serological relapse, autoimmune pancreatitis	5/21 (24%)
Hirano 2016	Clinical or serological relapse, autoimmune pancreatitis	15/21 (71%)
Hirata 2021	Clinical Disease Activity Index remission rate, rheumatoid arthritis	25.0% (before) to 38.9% (after)
Almayali 2023	Disease Activity Score 28 joints, rheumatoid arthritis	2.88 ± 1.14 (before) to 3.12 ± 1.15 (after), p=0.04
Almayali 2023	Disease flares, rheumatoid arthritis	43/96 (45%) - after group
3. Health outcomes		
Blood glucose level		
Hirano 2016	Transition of HbA_{1c} (prednisolone for autoimmune pancreatitis)	6.16 ± 0.57% to 6.68 ± 0.69%
Adverse events/ serious adverse events/ cardiovascular events		
Hirano 2016	Frequency of malignancies (prednisolone for autoimmune pancreatitis)	2/21 (10%)
Hirata 2021	Serious adverse events (prednisolone for rheumatoid arthritis)	2/36 (6%)
Adverse drug event		
Almayali 2023	Signs and symptoms of adrenal insufficiency (prednisolone for rheumatoid arthritis)	1.1 ± 1.2 to 0.8 ± 1.3
Adrenocorticotropic hormone level		
Almayali 2023	Adrenocorticotropic hormone level (prednisolone for rheumatoid arthritis)	5.8 ± 4.1 pmol/L

Cortisol hormone level		
Almayali 2023	Cortisol hormone level (prednisolone for rheumatoid arthritis)	310 ± 166 nmol/L
Adrenocorticotropic /cortisol hormone level		
Almayali 2023	Adrenocorticotropic /cortisol hormone level (prednisolone for rheumatoid arthritis)	67 ± 40 nmol/L
4. Cognitive function		
No available evidence		
5. Quality of life		
No available evidence		
6. Effect on medication regimen		
Hirata 2021	Prednisolone use for rheumatoid arthritis	-86.1%, p<0.0001

18.4 GRADE evidence profile (critical or important but not critical outcomes only)

Question: In older people, what are the effects of deprescribing (i.e. dose reduction or complete discontinuation) long-term prednisone/prednisolone on mortality, adverse drug withdrawal events, health-related outcomes, cognitive function, and quality of life?

Certainty assessment							Number of participants		Effect	Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Deprescribing	Continuation			
1. Mortality											
1 [196]	Non-controlled study	Serious [1,2]	Not serious	Serious [3]	Serious [4]	Not serious	18	N/A	2/18 (11%)	⨁◯◯◯	8
2. Adverse drug withdrawal events (ADWEs)											
Exacerbation/return of underlying condition											
1 [198]	RCT	Not serious	Not serious	Serious [5]	Serious [4]	Not serious	18	20	Deprescribing was not associated with a significant change in the proportion of participants having at least one COPD exacerbation (OR 1.50, 95% CI 0.35, 6.50), the number of exacerbations (MD 0.20, 95% CI -1.46, 1.86) or the number of days until first exacerbation (MD -7.00, 95% CI -35.94, 21.94).	⨁◯◯◯	6
4 [196, 197, 199, 200]	Non-controlled studies	Serious [1,2,6]	Not serious	Serious [3,7,8,9]	Serious [4]	Not serious	75	N/A	In one study, recurrence of the polymyalgia rheumatica occurred in all 18 participants after discontinuation of prednisolone [196]. In another study, clinical relapse of autoimmune pancreatitis occurred in 10 out of 21 (48%) participants whereas serological relapse occurred in 5 out of 21 (24%) participants [197]. Hence, 15 out of 21 (71%) participants had either clinical or serological relapse [197]. One other study reported rheumatoid arthritis Clinical Disease Activity Index remission rate increased from 25.0% to 38.9% at follow-up [199]. Additionally in another study, Disease Activity Score 28 joints increased from 2.88 ± 1.14 to 3.12 ± 1.15, p=0.04 and rheumatoid arthritis flares occurred in 45% of all participants [200].	⨁◯◯◯	6
3. Health outcomes											
Adverse events/ serious adverse events/ cardiovascular events											
2 [197, 199]	Non-controlled studies	Serious [1,6]	Not serious	Serious [7,8,9]	Serious [4]	Not serious	57	N/A	Serious adverse events occurred in 2 out of 36 (6%) participants [199].	⨁◯◯◯	7

									Malignancies were detected in 2 out of 21 (10%) participants [197].		
Adverse drug event											
1 [200]	Non-controlled study	Serious [1]	Not serious	Serious [8]	Serious [4]	Not serious	52	N/A	Signs and symptoms of adrenal insufficiency 1.1 ± 1.2 to 0.8 ± 1.3		5
Health service use											
1 [201]	Non-randomised study	Serious [10]	Not serious	Serious [8]	Serious [4]	Not serious	122	126	Unplanned hospitalisation OR 0.35 (0.18, 0.67)		5
Adrenocorticotropic /cortisol hormone level											
1 [200]	Non-controlled study	Serious [1]	Not serious	Serious [8]	Serious [4]	Not serious	23	N/A	Adrenocorticotropic hormone level, 5.8 ± 4.1 pmol/L Cortisol hormone level, 310 ± 166 nmol/L Adrenocorticotropic /cortisol hormone level, 67 ± 40 nmol/L		4
4. Cognitive function											
No available evidence											
5. Quality of life (QoL)											
No available evidence											

[1] Single-arm study without a concurrent control group which introduces potential biases (selection, performance, detection, confounding). Lack of blinding procedures - potential confounding factors not adequately addressed.
[2] Limited methodology was described in one study and a non-standard format due to the age of the paper
[3] Potential indirectness - One study (Esselinckx 1977) targeted patients with polymyalgia rheumatica which limits the generalisability
[4] Very small sample size
[5] Potential indirectness - All participants were male with COPD which limits the generalisability to the wider population
[6] One study (Hirano 2016) was terminated due to high rates of relapse. The study had significant missing data in results due to steroid reintroduction. It is unclear if this would have affected any of the outcome measures.
[7] Potential indirectness – One study (Hirano 2016) targeted patients with autoimmune pancreatitis
[8] Potential indirectness - Hirata 2021, Almayali 2023, and Goto 2023 targeted patients with patients with rheumatoid arthritis
[9] In one study (Hirata 2021), methotrexate dosage was increased at the same time the dosage for prednisolone was reduced. Concomitant biological or targeted synthetic disease-modifying antirheumatic drugs were also used as required. All these concomitant medications would have affected the outcome measures (e.g. disease state) and hence it is unclear if the outcome is generalisable to the wider population taking only glucocorticoids.
[10] Potential for selection, performance, and detection biases due to the non-randomised retrospective cohort design. High risk of confounding bias as patients who were unable to discontinue glucocorticoids may have had more severe disease or comorbidities.

18.5 Evidence-to-Decision table

Question: In older people, what are the effects of deprescribing (i.e. dose reduction or complete discontinuation) long-term prednisone/prednisolone on mortality, adverse drug withdrawal events, health-related outcomes, cognitive function, and quality of life?

Decision domain	Summary of reason for decision	Subdomains influencing decision
Certainty of evidence Is there a high or moderate certainty of evidence? Yes ☐ No ☑	The certainty of evidence for the benefits of deprescribing is low to very low. The certainty of evidence for the harms of deprescribing is very low.	Key reasons for downgrading: Risk of bias, indirectness, imprecision Are all critical outcomes measured? Yes ☐ No ☑ There is a lack of evidence on critical outcomes including cognitive function and quality of life.
Benefits and harms Is there certainty that the benefits of deprescribing outweigh the harms? Yes ☐ No ☑	The effects of deprescribing glucocorticoids have been tabulated in Appendix B (GRADE evidence profile table) with an overview provided in the guideline document (a narrative overview and GRADE summary of findings table). Below is a summary according to the study designs. <u>Summary of outcomes</u> Randomised and non-randomised controlled trials: • No difference in exacerbation • Reduced hospitalisation Non-controlled trials: • Reduced signs and symptoms of adrenal insufficiency • Mortality (11%) • Serious adverse events (6-10%) • Recurrence of disease (45-100%) <u>Summary of withdrawal schedules:</u> Randomised controlled trial: (Low certainty) Reduced by 5mg per week (study=1, n=38)	Is the baseline risk for benefits and harms of deprescribing similar across subgroups? Yes ☐ No ☑ There is evidence at this time that the benefits or harms of deprescribing differ based on subgroups. The exacerbation or return of the underlying condition likely depended on the disease and the severity of the disease. All participants with polymyalgia rheumatica and most participants with autoimmune pancreatitis had a relapse. It remains unclear for participants with rheumatoid arthritis who discontinued glucocorticoids. Should there be separate recommendations for subgroups? Yes ☑ No ☐ The guideline development group acknowledges that certain subgroups may have factors (e.g. severity of the underlying condition, indication for corticosteroid use, presence of adverse drug events, and prior history of infection) that could impact the balance of benefits and risks from deprescribing. However, the available evidence is insufficient to justify distinct evidence-based recommendations.

	Non-randomised controlled trial: (Very low certainty) Not described (study=1, n=248) Non-controlled trials: (Very low certainty) Withdrawn abruptly and gradually titrated at a mean rate of 1mg per month over 4-5 months (study=1, n=18), Tapered by 1mg every 8-10 weeks until complete cessation (study=1, n=21), Individualised (study=1, n=36), Dose tapered over 12 weeks (study=1, n=76)	
Values and preferences Is there confidence in the estimate of the relative importance of outcomes and individual preferences? Yes ☑ No ☐	Patients taking long-term glucocorticoids generally place a high value on adequate disease control, minimising disease progression and complications as well as minimal adverse effects (e.g. bone loss, weight gain, skin thinning, insomnia, mood disturbance and changes in facial shape). Most patients believe that glucocorticoids help with their condition and that the benefits outweigh the adverse effects. Patients value continuous assessment to detect side effects, address drug interactions, and reconsider dosages. Clear education about side effects and contraindications is crucial, as patients often struggle to associate these issues with their medicines. While many aim to stop glucocorticoids, this goal must be balanced with lifestyle factors, underlying disease control, and the risk of flare-ups. Monitoring throughout this process ensures that adjustments align with patient needs and safety. The decision to deprescribe must take into consideration the severity of possible flare-ups related to the underlying symptoms and how these would have an impact on the patient's quality of life. A study reported that healthcare professionals were familiar with the routine monitoring for diabetes,	Perspective taken: Individual values and preferences determine the deprescribing approaches. Sources of values and preferences: 1) Consultation with patient and carer representatives 2) Non-systematic review of evidence Source of variability, if any: Difficult to determine the extent of variability; high variability for patient preferences. Method for determining values satisfactory for this recommendation? Yes ☑ No ☐ Yes, but would be improved with direct patient input

	infection and osteoporosis from long-term glucocorticoid use. However, few clinicians focused on the adverse effects that were important to patients which were harder to measure (e.g. psychological effects).	
Resources Are the resources worth the expected net benefit? Yes ☑ No ☐	A comprehensive economic evaluation was outside the scope of the current review. However, potential cost and resource implications related to deprescribing interventions and continuation of medications are discussed below. Cost implications: There is little evidence on the overall cost implications of long-term corticosteroid exposure. The cost-effectiveness analysis of continuation and discontinuation may be difficult to estimate due to the complexity of health outcomes, the types of deprescribing intervention and the rate of successful implementation. The analysis will need to take into account disease severity and indirect costs such as loss of productivity. Glucocorticoids are believed to be inexpensive, however, the associated costs to treat corticosteroid-related adverse effects can be high. Existing studies generally suggested the economic burden associated with the adverse effects of long-term corticosteroid use was fairly large. Besides, the higher the level of corticosteroid exposure, the higher the health care resource utilisation and cost. Physician implications: Healthcare providers will need to closely monitor patients to assess the impact of deprescribing on ongoing disease severity. Dose tapering may involve additional clinic visits, laboratory tests and extended consultation time. However, it is likely to be feasible compared to the	Feasibility: Is this intervention generally available? Yes ☑ No ☐ Opportunity cost: Is this intervention and its effects worth withdrawing or not allocating resources from other interventions? Yes ☑ No ☐ Economic and preventive benefits for harms: Is there a lot of variability in resource requirements across settings? Yes ☐ No ☑

	workload required for managing potential serious adverse drug reactions and periodic monitoring of fracture risk, adrenal suppression, weight, blood pressure, triglycerides, glucose, urea and electrolytes.	
Equity What would be the impact of deprescribing on health inequities? ☑ Uncertain	The social determinants of health equity are complex and multifaceted. The impact of deprescribing on health equity is inadequately explored in the literature. Older people affected by the inappropriate use of medications are likely to derive substantial benefits in terms of health equity from deprescribing. By reducing medication burdens, lowering costs, and simplifying medicine regimens, deprescribing may enhance access to care and improve health outcomes for this vulnerable population. However, ensuring equitable implementation and addressing potential challenges faced by people with varying health literacy and access disparities is crucial to maximising these benefits. For patients with comorbidities that are managed with glucocorticoids, deprescribing needs to be carefully coordinated to avoid worsening other health issues. This requires a comprehensive approach that may involve a multidisciplinary team which can be difficult to achieve in settings with limited healthcare resources. Culturally and linguistically diverse populations, Aboriginal and Torres Strait Islander populations, people with low socioeconomic status, and those living in rural or remote areas may also require additional support or considerations when implementing deprescribing intervention.	
Acceptability Is the option of deprescribing acceptable to key stakeholders? ☑ Probably yes	Healthcare practitioners: Deprescribing is likely acceptable to most healthcare practitioners, especially when supported by clinical practice guidelines and a shared decision-making process with patients. The term deprescribing may be new to healthcare practitioners but the concept is not. Healthcare practitioners are very familiar with discontinuing ineffective medications or those causing adverse effects worse than the condition being treated. Patients, their caregivers and family members: Many are open to deprescribing if they understand the potential benefits and risks, especially when given the option to restart medications when necessary. They also place a great value on the reassurance of ongoing monitoring from the prescibers. Policymakers and health systems: From a broader perspective, deprescribing can be seen as a way to reduce healthcare costs and improve patient outcomes. However, the short-term impacts on patient care and the resources required to implement effective deprescribing strategies may be a concern.	
Overall judgment	There is a lack of quality evidence for deprescribing to inform evidence-based recommendations.	

19. Levothyroxine

19.1 Overview of studies targeted levothyroxine

Article	Drug/Class	Study design	Sample size	Follow-up (months)	Withdrawal schedule
Coll & Abourizk 2000 [202]	Levothyroxine	Before and after study	22	3	Dose reduced by as close to one-half as was practically possible (125 mcg daily reduced to 75 mcg daily; or 75 mcg daily reduced to 50 mcg daily)

19.2 Evidence for deprescribing levothyroxine

Study	Specific outcome	Odds ratio (95% CI)	Mean difference (95% CI)
1. Mortality			
No available evidence			
2. Adverse drug withdrawal events (ADWEs)			
No available evidence			
3. Health outcomes			
No available evidence			
4. Cognitive function			
No available evidence			
5. Quality of life			
No available evidence			
6. Effect on medication regimen			
No available evidence			

19.3 Evidence for deprescribing levothyroxine (non-controlled outcomes)

Study	Specific outcome	Result
1. Mortality		
No available evidence		
2. Adverse drug withdrawal events (ADWEs)		
Coll & Abourizk 2000	Increased agitation and restlessness	1/22 (5%)
3. Health outcomes		
No available evidence		
4. Cognitive function		
No available evidence		
5. Quality of life		
No available evidence		
6. Effect on medication regimen		
Coll & Abourizk 2000	Successful deprescribing	11/22 (50%)

19.4 GRADE evidence profile (critical or important but not critical outcomes only)

Question: In older people, what are the effects of deprescribing (i.e. dose reduction or complete discontinuation) long-term levothyroxine on mortality, adverse drug withdrawal events, health-related outcomes, cognitive function, and quality of life?

Certainty assessment							Number of participants		Effect	Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Deprescribing	Continuation			
1. Mortality											
No available evidence											
2. Adverse drug withdrawal events (ADWEs)											
ADWEs											
1 [202]	Non-controlled study	Serious [1]	Not serious	Serious [2]	Serious [3]	Not serious	22	N/A	1 out of 22 participants (5%) had an increase in psychiatric symptoms (agitation and restlessness) during the withdrawal phase.	⨁◯◯◯	6
3. Health outcomes											
No available evidence											
4. Cognitive function											
No available evidence											
5. Quality of life (QoL)											
No available evidence											

[1] Single-arm study without a concurrent control group. Lack of blinding with potential selection bias (choice of nursing homes was not described).
[2] Study only included nursing home residents who have borderline thyroid-stimulating hormone levels which is probably representative of the average residential aged care resident on thyroid replacement hormone. However, it is unclear if the outcome is generalisable to the wider older population.
[3] Very small sample size with only half completing the intervention

19.5 Evidence-to-Decision table

Question: In older people, what are the effects of deprescribing (i.e. dose reduction or complete discontinuation) long-term levothyroxine on mortality, adverse drug withdrawal events, health-related outcomes, cognitive function, and quality of life?

Decision domain	Summary of reason for decision	Subdomains influencing decision
Certainty of evidence Is there a high or moderate certainty of evidence? Yes ☐ No ☑	The certainty of evidence is very low.	Key reasons for downgrading: Risk of bias, indirectness, imprecision Are all critical outcomes measured? Yes ☐ No ☑ There is a lack of evidence on critical outcomes including mortality, health outcomes, cognitive function, and quality of life.
Benefits and harms Is there certainty that the benefits of deprescribing outweigh the harms? Yes ☐ No ☑	The effects of deprescribing thyroid hormones have been tabulated in Appendix B (GRADE evidence profile table) with an overview provided in the guideline document (a narrative overview and GRADE summary of findings table). Below is a summary according to the study designs. <u>Summary of outcomes</u> Non-controlled trial: 5% of participants (1/22) had an increase in psychiatric symptoms (agitation and restlessness) during the withdrawal phase. No other adverse effects were observed. Eleven participants (50 %) had their thyroid hormone therapy withdrawn successfully. <u>Summary of withdrawal schedules:</u> Non-controlled trial: (Very low certainty) Dose reduced by as close to one-half as was practically possible (study=1, n=22)	Is the baseline risk for benefits and harms of deprescribing similar across subgroups? Yes ☑ No ☐ Should there be separate recommendations for subgroups? Yes ☑ No ☐ The guideline development group acknowledges that certain subgroups may have factors (e.g. type of hypothyroidism [aetiology], thyroid status [euthyroid, subclinical, overt], and presence of adverse drug events) that could impact the balance of benefits and risks from deprescribing. However, the available evidence is insufficient to justify distinct evidence-based recommendations.

Values and preferences Is there confidence in the estimate of the relative importance of outcomes and individual preferences? Yes ☑ No ☐	Patients generally view optimal thyroid hormone replacement as essential for their well-being and performance, but many have limited understanding of their condition, susceptibility to complications, or the risks of over-replacement. Increased awareness is needed regarding the importance of monitoring thyroid levels (e.g., thyroid-stimulating hormone (TSH), T4) and related factors. Many patients assume thyroid treatment is lifelong without fully understanding the rationale behind it. Additionally, patients taking thyroxine often struggle with complex administration instructions, such as taking the medicine on an empty stomach, and are concerned about potential interactions with food, medicines, or other minerals, particularly for those on multiple medicines. Clear education on the symptoms of thyroxine imbalance, the purpose of the medicine, and the risks of self-adjusting doses based on symptoms is crucial for making informed deprescribing decisions. When asked about potential inappropriate prescribing for older people with frailty, physicians would generally prefer continuing thyroid therapy. Physicians tend to follow local guidelines and rely on blood tests over clinical symptoms to determine the levothyroxine dose.	Perspective taken: Individual values and preferences determine the deprescribing approaches. Sources of values and preferences: 1) Consultation with patient and carer representatives 2) Non-systematic review of evidence Source of variability, if any: Difficult to determine the extent of variability; high variability for patient preferences. Method for determining values satisfactory for this recommendation? Yes ☑ No ☐ Yes, but would be improved with direct patient input
Resources Are the resources worth the expected net benefit? Yes ☑ No ☐	A comprehensive economic evaluation was outside the scope of the current review. However, potential cost and resource implications related to deprescribing interventions and continuation of medications are discussed below. Cost implications: The cost-effectiveness analysis of continuation and discontinuation may be difficult to	Feasibility: Is this intervention generally available? Yes ☑ No ☐ Opportunity cost: Is this intervention and its effects worth withdrawing or not allocating resources from other interventions? Yes ☑ No ☐

	estimate due to the complexity of health outcomes, the types of deprescribing intervention and the rate of successful implementation. In older people, over- and under-treatment can lead to severe cardiovascular complications that increase morbidity and mortality. Overtreatment and undertreatment of hypothyroidism with exogenous thyroid hormone were accompanied by a greater risk of adverse events which causes high healthcare expenditure. Reducing unnecessary use of thyroid hormone replacement can improve health status and reduce healthcare costs. Physician implications: Healthcare providers will need to closely monitor patients to assess the impact of deprescribing on ongoing symptoms. Additional clinic visits, laboratory tests and extended consultation time are likely required. However, all treatments for hypothyroidism, even borderline cases are closely monitored by clinicians which typically involves measuring TSH levels 4-8 weeks after treatment initiation or changing a dose, and every 6 weeks until the dose is stabilised, then every 12 months.	Economic and preventive benefits for harms: Is there a lot of variability in resource requirements across settings? Yes ☐ No ☑
Equity What would be the impact of deprescribing on health inequities? ☑ Uncertain	The social determinants of health equity are complex and multifaceted. The impact of deprescribing on health equity is inadequately explored in the literature. Effective deprescribing of thyroid hormones requires regular monitoring of thyroid functions to avoid complications. Patients with limited access to healthcare services might face challenges in adhering to monitoring requirements, which could lead to inequities if they are unable to follow the deprescribing plan effectively. Ensuring equitable implementation and addressing potential challenges faced by people with varying health literacy and access disparities is crucial to maximising these benefits. Culturally and linguistically diverse populations, Aboriginal and Torres Strait Islander populations, people with low socioeconomic status, and those living in rural or remote areas may require additional support or considerations when implementing deprescribing intervention.	
Acceptability Is the option of	Healthcare practitioners: Deprescribing is likely acceptable to most healthcare practitioners, especially when supported by clinical practice guidelines and a shared decision-making process with patients. The term deprescribing	

deprescribing acceptable to key stakeholders? ☑ Probably yes	may be new to healthcare practitioners but the concept is not. Healthcare practitioners are very familiar with discontinuing ineffective medications or those causing adverse effects worse than the condition being treated. Patients, their caregivers and family members: Many are open to deprescribing if they understand the potential benefits and risks, especially when given the option to restart medications when necessary. Policymakers and health systems: From a broader perspective, deprescribing can be seen as a way to reduce healthcare costs and improve patient outcomes. However, the short-term impacts on patient care and the resources required to implement effective deprescribing strategies may be a concern.
Overall judgment	There is a lack of quality evidence for deprescribing to inform evidence-based recommendations

Abbreviation: TSH thyroid-stimulating hormone

20. Teriparatide

20.1 Overview of studies targeted teriparatide

Article	Drug/Class	Study design	Sample size	Follow-up (months)	Withdrawal schedule
Leder 2009 [203]	Teriparatide	Cohort study	31	42	Not described, likely abrupt discontinuation

20.2 Evidence for deprescribing of teriparatide

Study	Specific outcome	Odds ratio (95% CI)	Mean difference (95% CI)
1. Mortality			
No available outcome			
2. Adverse drug withdrawal events (ADWEs)			
No available outcome			
3. Health outcomes			
No available outcome			
4. Cognitive function			
No available outcome			
5. Quality of life			
No available outcome			
6. Effect on medication regimen			
No available outcome			

20.3 Evidence for deprescribing of teriparatide (non-controlled outcomes)

Study	Specific outcome	Result (End-point mean ± SD)
1. Mortality		
No available outcome		
2. Adverse drug withdrawal events (ADWEs)		
No available outcome		
3. Health outcomes		
Bone mass density		
Leder 2009	Spinal Bone Mass Density 12 months after deprescribing	Reduced by 0.07 ± 0.04 g/cm2 (7.1 ± 3.8%) in women 0.04 ± 0.04 g/cm2 (4.1 ± 3.5%) in men
Leder 2009	Trabecular Bone Mass Density 12 months after deprescribing	Reduced by 21.6 ± 14.3 mg/cm3 (17.0 ± 8.9%) in women 15.4 ± 13.0 mg/cm3 (11.1 ± 12.2%) in men
Leder 2009	Total hip Bone Mass Density 12 months after deprescribing	Reduced by 3.8 ± 3.9% in women Remained stable in men
Leder 2009	Bone Mass Density in the trabecular 12 months after deprescribing	Reduced by 3.1 ± 4.3% in women Remained stable in men
4. Cognitive function		
No available outcome		
5. Quality of life		
No available outcome		
6. Effect on medication regimen		
No available outcome		

20.4 GRADE evidence profile (critical or important but not critical outcomes only)

Question: In older people, what are the effects of deprescribing (i.e. dose reduction or complete discontinuation) long-term teriparatide on mortality, adverse drug withdrawal events, health-related outcomes, cognitive function, and quality of life?

Certainty assessment							Number of participants		Effect	Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Deprescribing	Continuation			
1. Mortality											
No available evidence											
2. Adverse drug withdrawal events (ADWEs)											
No available evidence											
3. Health outcomes											
Bone mass density (BMD)											
1 [203]	Non-controlled study	Serious [1]	Not serious	Not serious	Serious [2]	Not serious	31	N/A	12 months after deprescribing: • Spinal BMD: Reduced by 0.07 ± 0.04 g/cm^2 (7.1 ± 3.8%) in women 0.04 ± 0.04 g/cm^2 (4.1 ± 3.5%) in men • Trabecular BMD: Reduced by 21.6 ± 14.3 mg/cm^3 (17.0 ± 8.9%) in women 15.4 ± 13.0 mg/cm^3 (11.1 ± 12.2%) in men • Total hip BMD: Reduced by 3.8 ± 3.9% in women Remained stable in men • Femoral neck BMD: Reduced by 3.1 ± 4.3% in women Remained stable in men		6
4. Cognitive function											
No available evidence											
5. Quality of life (QoL)											
No available evidence											

[1] Potential confounding bias as this study lacks a true comparator group. Although there were two arms to the study. It was a two single-arm study rather than a concurrent control group. Potential selection bias – participants were recruited through various means, including mailings and clinic referrals. Attrition bias - some participants did not complete the full study period.
[2] Small sample size

20.5 Evidence-to-Decision table

Question: In older people, what are the effects of deprescribing (i.e. dose reduction or complete discontinuation) long-term teriparatide on mortality, adverse drug withdrawal events, health-related outcomes, cognitive function, and quality of life?

Decision domain	Summary of reason for decision	Subdomains influencing decision
Certainty of evidence Is there a high or moderate certainty of evidence? Yes ☐ No ☑	The certainty of evidence for the harms of deprescribing is very low.	Key reasons for downgrading: Risk of bias, imprecision Are all critical outcomes measured? Yes ☐ No ☑ There is a lack of evidence on critical outcomes including mortality, adverse drug withdrawal events, cognitive function, and quality of life.
Benefits and harms Is there certainty that the benefits of deprescribing outweigh the harms? Yes ☐ No ☑	The effects of deprescribing teriparatide have been tabulated in Appendix B (GRADE evidence profile table) with an overview provided in the guideline document (a narrative overview and GRADE summary of findings table). Below is a summary according to the study designs. <u>Summary of outcomes</u> Non-controlled trial: Rapid reduction in bone mass density <u>Summary of withdrawal schedules:</u> Non-controlled trial: (Very low certainty) Not described, likely abrupt discontinuation (study=1, n=31)	Is the baseline risk for benefits and harms of deprescribing similar across subgroups? Yes ☐ No ☑ Results from the single-arm study indicated the decline in bone mass density following discontinuation of teriparatide was greater in women than men. Should there be separate recommendations for subgroups? Yes ☑ No ☐ The guideline development group acknowledges that certain subgroups may have factors that could impact the balance of benefits and risks from deprescribing (e.g. risk of osteoporosis, indication for use, and presence of adverse drug events). However, the available evidence is insufficient to justify distinct evidence-based recommendations.
Values and preferences Is there confidence in the estimate of	Patients highly value effective risk communication strategies and seek adequate information to weigh the benefits versus the risks, enabling them to make informed decisions about their treatment. They prefer to be informed	Perspective taken: The lack of evidence for serious harm as a result of deprescribing and evident benefits related to reduced medication burden and costs. Individual values and preferences determine the deprescribing approaches.

the relative importance of outcomes and individual preferences? Yes ☑ No ☐	about the expected duration of treatment and value continuous monitoring throughout therapy. Side effects, such as nausea and leg cramps, are common with teriparatide. Phase 3 clinical trial data show that 7.1% of patients discontinued treatment due to these adverse effects. Those who experienced them are likely more inclined to discontinue treatment than those who tolerated the medication well. For individuals with borderline osteoporosis, deprescribing may be preferred if the adverse effects and risks outweigh the benefits. However, for those with ongoing risk factors for osteoporosis, many are open to deprescribing teriparatide if followed by appropriate alternative treatments. The majority of healthcare professionals believe that deprescribing can be beneficial for patients. Clinicians take into consideration the possible risk of osteosarcoma for long-term teriparatide therapy (> 18 months).	Sources of values and preferences: 1) Consultation with patient and carer representatives 2) Non-systematic review of evidence Source of variability, if any: Difficult to determine the extent of variability; high variability for patient preferences. Method for determining values satisfactory for this recommendation? Yes ☑ No ☐ Yes, but would be improved with direct patient input
Resources Are the resources worth the expected net benefit? Yes ☑ No ☐	A comprehensive economic evaluation was outside the scope of the current review. However, potential cost and resource implications related to deprescribing interventions and continuation of medications are discussed below. Cost implications: Among older osteoporotic women with prior vertebral fractures, teriparatide followed by bisphosphonate was not cost-effective when compared with a placebo followed by bisphosphonate. Teriparatide has a substantial drug cost, hence affecting the incremental cost-effectiveness ratios when compared with no treatment, a placebo, and a bisphosphonate alone. Physician implications: Discontinuation of teriparatide therapy after the recommended duration of use is commonly practised in Australia.	Feasibility: Is this intervention generally available? Yes ☑ No ☐ Opportunity cost: Is this intervention and its effects worth withdrawing or not allocating resources from other interventions? Yes ☑ No ☐ Economic and preventive benefits for harms: Is there a lot of variability in resource requirements across settings? Yes ☐ No ☑

Equity What would be the impact of deprescribing on health inequities? ☑ Uncertain	The social determinants of health equity are complex and multifaceted. The impact of deprescribing on health equity is inadequately explored in the literature. Deprescribing may enhance access to care and improve health outcomes. However, ensuring equitable implementation and addressing potential challenges faced by people with varying health literacy and access disparities is crucial to maximising these benefits. Culturally and linguistically diverse populations, Aboriginal and Torres Strait Islander populations, people with low socioeconomic status, and those living in rural or remote areas may require additional support or considerations when implementing deprescribing intervention, including the ongoing monitoring process.
Acceptability Is the option of deprescribing acceptable to key stakeholders? ☑ Yes	Healthcare practitioners: Deprescribing of teriparatide is likely acceptable to most healthcare practitioners. At the time of preparing this guideline, teriparatide therapy is limited to a maximum of 18 months of therapy in Australia. Patients, their caregivers and family members: Many are open to deprescribing if they understand the potential benefits and risks. Policymakers and health systems: Likely acceptable.
Overall judgment	There is a lack of quality evidence for deprescribing to inform evidence-based recommendations.

21. Non-steroidal anti-inflammatory drugs (NSAIDs)

21.1 Overview of studies targeted non-steroidal anti-inflammatory drugs (NSAIDs)

Article	Drug/Class	Study design	Sample size	Follow-up (months)	Withdrawal schedule
O'Mahony 2021 [204]	Non-steroidal anti-inflammatory drugs	Before and after study	51	3	Not described
Rashid 2020 [205]	Non-steroidal anti-inflammatory drugs	Retrospective cohort study	2155	6	Individualised

21.2 Evidence for deprescribing non-steroidal anti-inflammatory drugs (NSAIDs)

Study	Specific outcome	Odds ratio (95% CI)	Mean difference (95% CI)
1. Mortality			
No available evidence			
2. Adverse drug withdrawal events (ADWEs)			
Rashid 2020	At least one exacerbation	0.58 (0.39, 0.86)	
3. Health outcomes			
Adverse drug events			
Rashid 2020	Risk of gastrointestinal bleed events	0.59 (0.35, 0.99)	
Rashid 2020	Risk of acute kidney injury	0.58 (0.30, 1.13)	
Health service use			
Rashid 2020	Unplanned hospitalisation	0.53 (0.33, 0.84)	
Rashid 2020	At least one emergency department visit	0.69 (0.42, 1.14)	
4. Cognitive function			
No available evidence			
5. Quality of life			
No available evidence			
6. Effect on medication regimen			
No available evidence			

21.3 Evidence for deprescribing non-steroidal anti-inflammatory drugs (NSAIDs) (non-controlled outcomes)

Study	Specific outcome	Result
1. Mortality		
No available evidence		
2. Adverse drug withdrawal events (ADWEs)		
No available evidence		
3. Health outcomes		
No available evidence		
4. Cognitive function		
No available evidence		
5. Quality of life		
No available evidence		
6. Effect on medication regimen		
O'Mahony 2021	Successfully withdrawn	37%

21.4 GRADE evidence profile (critical or important but not critical outcomes only)

Question: In older people, what are the effects of deprescribing (i.e. dose reduction or complete discontinuation) long-term NSAIDs on mortality, adverse drug withdrawal events, health-related outcomes, cognitive function, and quality of life?

Certainty assessment							Number of participants		Effect	Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Deprescribing	Continuation			
1. Mortality											
No available evidence											
2. Adverse drug withdrawal events (ADWEs)											
Exacerbation /return of underlying condition											
1 [205]	Non-randomised study	Serious [1,2]	Not serious	Not serious	Serious [3,4]	Not serious	342	1463	Deprescribing of NSAIDs was associated with a significantly reduced risk of at least one pain exacerbation (OR 0.58, 95% CI 0.39, 0.86).		6
3. Health outcomes											
Adverse drug events											
1 [205]	Non-randomised study	Serious [1,2]	Not serious	Not serious	Serious [3,4]	Not serious	431	1724	Deprescribing of NSAIDs was associated with a significantly reduced risk of gastrointestinal bleeding events (OR 0.59, 95% CI 0.35, 0.99). However, there was no significant change in the risk of acute kidney injury (OR 0.58, 95% CI 0.30, 1.13) following the deprescribing of NSAIDs.		5
Health service use											
1 [205]	Non-randomised study	Serious [1,2]	Not serious	Not serious	Serious [3,4]	Not serious	431	1724	Deprescribing of NSAIDs was associated with a significantly reduced risk of unplanned hospitalisation (OR 0.53, 95% CI 0.33, 0.84). However, there was no significant change in the proportion of participants with at least one emergency department visit (OR 0.69, 95% CI 0.42, 1.14) following the deprescribing of NSAIDs.		5
4. Cognitive function											
No available evidence											
5. Quality of life (QoL)											
No available evidence											

[1] Non-randomised study with the control group matched to the deprescribed group using propensity score matching at a 4:1 ratio. Potential for selection bias, short follow-up period, reliance on International Classification of Diseases (ICD) codes for outcome ascertainment.
[2] Study was limited by unobservable confounding variables such as lifestyle habits, diet, and any over-the-counter use of NSAIDs or aspirin as well as the severity of pain and the strength of NSAID use at baseline (despite the study used propensity score matching to account for potential confounding factors).
[3] Small sample size
[4] Wide confidence intervals in the estimates of effect.

21.5 Evidence-to-Decision table

Question: In older people, what are the effects of deprescribing (i.e. dose reduction or complete discontinuation) long-term NSAIDs on mortality, adverse drug withdrawal events, health-related outcomes, cognitive function, and quality of life?

Decision domain	Summary of reason for decision	Subdomains influencing decision
Certainty of evidence Is there a high or moderate certainty of evidence? Yes ☐ No ☑	The certainty of evidence for the benefits of deprescribing is very low. The certainty of evidence for the harms of deprescribing is very low.	Key reasons for downgrading: Risk of bias, imprecision Are all critical outcomes measured? Yes ☐ No ☑ There is a lack of evidence on critical outcomes including mortality, cognitive function, and quality of life.
Benefits and harms Is there certainty that the benefits of deprescribing outweigh the harms? Yes ☐ No ☑	The effects of deprescribing NSAIDs have been tabulated in Appendix B (GRADE evidence profile table) with an overview provided in the guideline document (a narrative overview and GRADE summary of findings table). Below is a summary according to the study designs. <u>Summary of outcomes</u> Non-randomised controlled trial: • Significant reduction in pain exacerbation, gastrointestinal bleeding, and unplanned hospitalisations • No significant difference in the risk of acute kidney injury and the proportion of participants with at least one emergency department visit. <u>Summary of withdrawal schedules:</u> Non-randomised controlled trial: (very low certainty) Individualised (study=1, n=2155) Non-controlled trial: Not described (study=1, n=51)	Is the baseline risk for benefits and harms of deprescribing similar across subgroups? Yes ☐ No ☑ There is no evidence at this time that the harms of deprescribing differ based on subgroups. However, the benefits of deprescribing may be more pronounced in people experiencing adverse drug events (e.g. gastrointestinal bleeding). Should there be separate recommendations for subgroups? Yes ☑ No ☐ The guideline development group acknowledges that certain subgroups may have factors that could impact the balance of benefits and risks from deprescribing (e.g. nature of the inflammatory condition [aetiology], pain severity, symptom control, other important comorbidities, previous history of gastrointestinal complications, and the presence of adverse drug events). However, the available evidence is insufficient to justify distinct evidence-based recommendations.

Values and preferences Is there confidence in the estimate of the relative importance of outcomes and individual preferences? Yes ☑ No ☐	Patients with osteoarthritis prioritise physical functioning when choosing treatment options. They often weigh the perceived benefits, potential side effects, the presence of other health conditions, the nature of their pain, advice from doctors, and practicality. Some patients place greater value on maintaining their ability to function than on safety concerns. Side effects are common, and many patients struggle with tolerating certain treatments. For some, as-needed (PRN) use or alternative therapies may be preferable. Managing pain, flare-ups, and functionality is complex, especially when surgery is considered but has a long waiting list. Restrictions due to pain can significantly affect the quality of life. Many patients also turn to over-the-counter medications or self-medicate, which can lead to excessive use and toxicity. Ongoing monitoring is essential to manage potential withdrawal effects, such as pain exacerbation, ensuring the treatment remains appropriate and effective. Physicians often consider the uncertainty and safety concerns (particularly with COX-2 inhibitors) when deciding to prescribe (or not prescribe) an NSAID.	Perspective taken: Patients have varying perceptions and beliefs about NSAIDs. Individual values and preferences determine the deprescribing approaches. Sources of values and preferences: 1) Consultation with patient and carer representatives 2) Non-systematic review of evidence Source of variability, if any: Difficult to determine the extent of variability; high variability for patient preferences. Method for determining values satisfactory for this recommendation? Yes ☑ No ☐ Yes, but would be improved with direct patient input
Resources Are the resources worth the expected net benefit? Yes ☑ No ☐	A comprehensive economic evaluation was outside the scope of the current review. However, potential cost and resource implications related to deprescribing interventions and continuation of medications are discussed below. Cost implications: The D-PRESCRIBE trial which adopted an educational pharmacist-led intervention in Canada suggested deprescribing intervention to reduce inappropriate use of NSAIDs was less costly (-$1008.61) than routine care and there was a	Feasibility: Is this intervention generally available? Yes ☑ No ☐ Opportunity cost: Is this intervention and its effects worth withdrawing or not allocating resources from other interventions? Yes ☑ No ☐ Economic and preventive benefits for harms: Is there a lot of variability in resource requirements across settings? Yes ☐ No ☑

	modest gain in the quality-adjusted life years (0.11). The cost-effectiveness of discontinuing NSAIDs is even greater if patients were taking concurrent PPIs with NSAIDs to reduce the risk of gastrointestinal complications. However, the study did not take into account the indirect costs contributed by lost productivity or any additional patient costs. Physician implications: Healthcare providers will need to closely monitor patients to assess the impact of deprescribing on patient outcomes. Additional consultations are likely required by patients to manage ongoing pain or inflammation.	
Equity What would be the impact of deprescribing on health inequities? ☑ Uncertain	The social determinants of health equity are complex and multifaceted. The impact of deprescribing on health equity is inadequately explored in the literature. Effective deprescribing of NSAIDs requires appropriate monitoring and follow-up to manage symptoms. If deprescribing NSAIDs leads to the need for more expensive or less accessible alternatives, it could exacerbate disparities, particularly for those with limited financial resources. If NSAIDs are deprescribed without adequate supporting alternatives, patients might experience unmanaged pain or reduced quality of life, which could disproportionately affect those with limited access to healthcare services. For patients with comorbidities that are managed with NSAIDs, deprescribing needs to be carefully coordinated to avoid worsening other health issues. Ensuring equitable implementation and addressing potential challenges faced by people with varying health literacy and access disparities is crucial to maximising these benefits. Culturally and linguistically diverse populations, Aboriginal and Torres Strait Islander populations, people with low socioeconomic status, and those living in rural or remote areas may require additional support or considerations when implementing deprescribing intervention, including the ongoing monitoring process.	
Acceptability Is the option of deprescribing acceptable to key stakeholders? ☑ Probably yes	Healthcare practitioners: Deprescribing is likely acceptable to most healthcare practitioners, especially when supported by clinical practice guidelines and a shared decision-making process with patients. The term deprescribing may be new to healthcare practitioners but the concept is not. Healthcare practitioners are very familiar with discontinuing ineffective medications or those causing adverse effects worse than the condition being treated. Patients, their caregivers and family members: Many are open to deprescribing if they understand the potential benefits and risks, especially when given the option to restart medications when necessary. Policymakers and health systems: From a broader perspective, deprescribing can be seen as a way to reduce healthcare costs and improve patient outcomes. However, the short-term impacts on patient care and the resources	

	required to implement effective deprescribing strategies may be a concern.
Overall judgment	There is a lack of quality evidence for deprescribing to inform evidence-based recommendations

Abbreviations: ACE inhibitors angiotensin-converting enzyme inhibitors, ARB angiotensin receptor blockers, COX-2 inhibitors cyclooxygenase-2 inhibitors, NSAIDs non-steroidal anti-inflammatory drugs

22. Anti-gout preparations

We were unable to identify a study that assessed deprescribing anti-gout preparations from the systematic search.

23. Calcium and/or Vitamin D

23.1 Overview of studies targeted calcium and/or vitamin D

Article	Drug/Class	Study design	Sample size	Follow-up (months)	Withdrawal schedule
Radford 2014 [206]	Calcium	Prospective cohort study	1408	60	Abrupt discontinuation
Dawson-Hughes 2000 [207]	Calcium and vitamin D	RCT	295	60	Not described
Gallagher 2002 [193]	Calcitriol	RCT	489	24	Not described

23.2 Evidence for deprescribing of calcium and/or vitamin D

Study	Specific outcome	Odds ratio (95% CI)	Mean difference (95% CI)
1. Mortality			
Radford 2014	Mortality at 10 years	0.83 (0.63, 1.08)	
2. Adverse drug withdrawal events (ADWEs)			
ADWEs, bone mineral density			
Dawson-Hughes 2000	Bone mass density, g/cm^2 (female)		-0.14 (-0.29, 0.01)
Dawson-Hughes 2000	Bone mass density, g/cm^2 (male)		1.59 (1.45, 1.73)
Gallagher 2002	Percentage change in bone mass density, total body		1.31 (1.14, 1.48)
Gallagher 2002	Percentage change in bone mass density, spine		0.89 (0.55, 1.23)
Gallagher 2002	Percentage change in bone mass density, femoral neck		-0.34 (-0.65, -0.03)
Gallagher 2002	Percentage change in bone mass density, trochanter		0.27 (-0.12, 0.66)
Gallagher 2002	Percentage change in bone mass density, total hip		1.04 (0.73, 1.35)
ADWEs, fractures			
Radford 2014	Fracture, any	1.12 (0.90, 1.40)	
Radford 2014	Fracture, osteoporotic	1.20 (0.95, 1.52)	
Radford 2014	Fracture, vertebral	1.96 (1.18, 3.24)	
Radford 2014	Fracture, forearm	1.65 (1.13, 2.41)	
Radford 2014	Fracture, hip	0.71 (0.44, 1.13)	
Dawson-Hughes 2000	Fractures, non-vertebral	1.84 (0.60, 5.62)	
3. Health outcomes			
Adverse events/ serious adverse events/ cardiovascular events			
Radford 2014	Stroke	0.96 (0.69, 1.34)	
Radford 2014	Myocardial infarction	0.96 (0.67, 1.36)	
4. Cognitive function			
No available evidence			
5. Quality of life			
No available evidence			

6. Effect on medication regimen	
No available evidence	

23.3 Evidence for deprescribing of calcium and/or vitamin D (non-controlled outcomes)

Study	Specific outcome	Result
1. Mortality		
No available evidence		
2. Adverse drug withdrawal events (ADWEs)		
No available evidence		
3. Health outcomes		
No available evidence		
4. Cognitive function		
No available evidence		
5. Quality of life		
No available evidence		
6. Effect on medication regimen		
No available evidence		

23.4 GRADE evidence profile (critical or important but not critical outcomes only)

Question: In older people, what are the effects of deprescribing (i.e. dose reduction or complete discontinuation) long-term calcium and/or vitamin D on mortality, adverse drug withdrawal events, health-related outcomes, cognitive function, and quality of life?

Certainty assessment							Number of participants		Effect	Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Deprescribing	Continuation			
1. Mortality											
1 [206]	Non-randomised study	Serious [1]	Not serious	Serious [2]	Serious [3]	Not serious	739	732	OR 0.83 (0.63, 1.08)	⨁◯◯◯	8
2. Adverse drug withdrawal events (ADWEs)											
ADWEs, bone mineral density											
2 [193, 207]	RCTs	Serious [1,4,5]	Not serious	Serious [6,7]	Serious [3]	Not serious	204	191	Two years following the discontinuation of calcium and vitamin D supplements, supplement-induced increases in spinal and femoral neck BMD were lost but small benefits in total body BMD remained for men (MD 1.59, 95% CI 1.45, 1.73). In women, there were no lasting benefits in total-body BMD (MD -0.14, 95% CI -0.29, 0.01) or at any bone site [207]. In another study, participants who took calcitriol for the preceding three years before two years of discontinuation had a lower percentage change from baseline to five years in the BMD for total body (MD 1.31, 95% CI 1.14 to 1.48; study = 1, n = 100), spine (MD 0.89, 95% CI 0.55 to 1.23), total hip (MD 1.04, 95% CI 0.73 to 1.35), but higher percentage change in the BMD for femoral neck (MD -0.34, 95% CI -0.65 to -0.03) compared to the group who were untreated (placebo group) [193]. However, there was no significant difference in the percentage change for trochanter BMD (MD 0.27, 95% CI -0.12 to 0.66) between the two groups [193].	⨁◯◯◯	6
ADWEs, fractures											
1 [207]	RCT	Serious [1,4]	Not serious	Not serious	Serious [3]	Not serious	148	147	Non-vertebral fractures OR 1.84 (0.60, 5.62)	⨁◯◯◯	6

1 [206]	Non-randomised study	Serious [1]	Not serious	Serious [2]	Serious [3]	Not serious	739	732	There was no significant difference in the incidence of total fracture (OR 1.12, 95% CI 0.90, 1.40), osteoporotic fracture (OR 1.20, 95% CI 0.95, 1.52), and hip fracture (OR 0.71, 95% CI 0.44, 1.13) between those who took calcium and placebo for the entire follow-up period (10 years). However, there were significant reductions in forearm fracture (OR 1.65, 95% CI 1.13, 2.41) and vertebral fracture (OR 1.96, 95% CI 1.18, 3.24) for those who took calcium.		6
3. Health outcomes											
Adverse events/ serious adverse events/ cardiovascular events											
1 [206]	Non-randomised study	Serious [1]	Not serious	Serious [2]	Serious [3]	Not serious	739	732	Stroke OR 0.96 (0.69, 1.34) Myocardial infarction OR 0.96 (0.67, 1.36)		7
4. Cognitive function											
No available evidence											
5. Quality of life (QoL)											
No available evidence											

[1] The original study was a randomised controlled trial, but this extended follow-up study was non-randomised and open-label. Potential selection, attrition and performance biases. This study relied on follow-up data five years after the completion of the study. It was, therefore, reliant on those that could be contacted.
[2] Study only considered postmenopausal women
[3] Small sample size
[4] There was a potential for four groups in the Dawson-Hughes 2000 study, only one of which is a true deprescribing study (the randomly assigned intervention group who then went on to stop supplements in the follow-up). Participants self-selected whether they would take calcium and vitamin D supplements or not.
[5] Gallagher 2002 original study was double-blind, but the two-year extension study was probably open-label.
[6] Potential indirectness - Gallagher 2002 compared the discontinuation of placebo to the discontinuation of calcitriol. None of the two groups would have received the drug in the two years of discontinuation for comparison, although the group who received calcitriol for the preceding three years before discontinuation may have some small residual effect from the therapy. It is unclear if the outcome can be generalised in the absence of a true comparison group.
[7] Potential indirectness - bone mineral density is a surrogate outcome that is not of direct practical importance but is believed to reflect an outcome that is important (i.e. fractures).

23.5 Evidence-to-Decision table

Question: In older people, what are the effects of deprescribing (i.e. dose reduction or complete discontinuation) long-term calcium and/or vitamin D on mortality, adverse drug withdrawal events, health-related outcomes, cognitive function, and quality of life?		
Decision domain	Summary of reason for decision	Subdomains influencing decision
Certainty of evidence Is there a high or moderate certainty of evidence? Yes ☐ No ☑	The certainty of evidence for the harms of deprescribing is low to very low.	Key reasons for downgrading: Risk of bias, indirectness, imprecision Are all critical outcomes measured? Yes ☐ No ☑ There is a lack of evidence on critical outcomes including cognitive function and quality of life.
Benefits and harms Is there certainty that the benefits of deprescribing outweigh the harms? Yes ☐ No ☑	The effects of deprescribing calcium and/or vitamin D have been tabulated in Appendix B (GRADE evidence profile table) with an overview provided in the guideline document (a narrative overview and GRADE summary of findings table). Below is a summary according to the study designs. <u>Summary of outcomes</u> Randomised and non-randomised controlled trials: • Significantly higher forearm fractures and vertebral fractures compared to those who continued taking calcium • Reduction in bone mineral density • No difference in mortality, non-vertebral fractures, incidence of total fracture, osteoporotic fracture, hip fracture, stroke, and myocardial infarction. <u>Summary of withdrawal schedules:</u> Randomised controlled trial: (low certainty evidence) Not described (studies=2, n=784) Non-randomised controlled trial: (very low certainty	Is the baseline risk for benefits and harms of deprescribing similar across subgroups? Yes ☐ No ☑ Evidence at this time suggests that individuals at a higher risk of fractures (particularly forearm and vertebral fractures) may have a greater risk of harm from deprescribing. Should there be separate recommendations for subgroups? Yes ☑ No ☐ The guideline development group acknowledges that certain subgroups may have factors that could impact the balance of benefits and risks from deprescribing (e.g. risk of osteoporosis, indication for use, and presence of adverse drug events). However, the available evidence is insufficient to justify distinct evidence-based recommendations.

	evidence) Abrupt discontinuation (study=1, n=1408)	
Values and preferences Is there confidence in the estimate of the relative importance of outcomes and individual preferences? Yes ☑ No ☐	Patients generally recognise the health benefits of calcium and vitamin D, particularly for bone health. However, many are unaware of their baseline risk for needing these supplements. Around 50% of patients report taking these supplements regularly, though a minority do so without consulting their physicians. Patients believe that discussing supplements and their interactions with other medicines with healthcare providers is essential for effective medication management. However, many report that most of their doctors do not inquire about lifestyle or supplement use during consultations, highlighting the need for more comprehensive patient education on the duration of supplement intake and the potential for lifestyle or dietary changes. While some individuals may prefer supplements over lifestyle changes to manage their bone health, others may opt for dietary adjustments when suggested by their healthcare providers. Physicians value highly the clinical guidelines for patients with a diagnosis of established osteoporosis. For those with osteopenia or bone deficits, physicians consider the patient's view and their ability or commitment to adhere to lifestyle interventions to be important factors.	Perspective taken: Patients have varying perceptions and beliefs about calcium and vitamin D. Individual values and preferences determine the deprescribing approaches. Sources of values and preferences: 1) Consultation with patient and carer representatives 2) Non-systematic review of evidence Source of variability, if any: Difficult to determine the extent of variability; high variability for patient preferences. Method for determining values satisfactory for this recommendation? Yes ☑ No ☐ Yes, but would be improved with direct patient input
Resources Are the resources worth the expected net benefit? Yes ☑ No ☐	A comprehensive economic evaluation was outside the scope of the current review. However, potential cost and resource implications related to deprescribing interventions and continuation of medications are discussed below.	Feasibility: Is this intervention generally available? Yes ☑ No ☐ Opportunity cost: Is this intervention and its effects worth withdrawing or not allocating resources from other

	Cost implications: For older patients with osteoporosis, calcium and vitamin D supplements were highly cost-effective and could considerably reduce costs related to fractures. Treatment cost with calcium and/or vitamin D was less than the cost of treating osteoporotic fractures of the no-treatment group. In older patients without prior hip fractures, screening for vitamin D insufficiency followed by treatment with vitamin D was the most cost-effective strategy for preventing hip fractures. The low cost of vitamin D was found to be the most important driver of the favourable cost-effectiveness ratio. There is little evidence on the cost-effectiveness analysis for calcium supplementations. It is likely that calcium supplements have no added benefit for people not at risk of osteoporosis owing to the risk of hypercalcemia including constipation, kidney stones and heart calcification. Physician implications: Healthcare providers will need to closely monitor patients to assess the impact of deprescribing on ongoing fracture risk. This may involve additional clinic visits, laboratory tests and extended consultation time. There will need to be discussions on dietary alternatives for ongoing management of risk.	interventions? Yes ☑ No ☐ Economic and preventive benefits for harms: Is there a lot of variability in resource requirements across settings? Yes ☐ No ☑
Equity What would be the impact of deprescribing on health inequities? ☑ Uncertain	The social determinants of health equity are complex and multifaceted. The impact of deprescribing on health equity is inadequately explored in the literature. Older people affected by the inappropriate use of medications are likely to derive substantial benefits in terms of health equity from deprescribing. By reducing medication burdens, lowering costs, and simplifying medicine regimens, deprescribing may enhance access to care and improve health outcomes for this vulnerable population. However, ensuring equitable implementation and addressing potential challenges faced by people with varying health literacy and access disparities is crucial to maximising these benefits. Culturally and linguistically diverse populations, Aboriginal and Torres Strait Islander populations, people with low socioeconomic status, and those living in rural or remote areas may require additional support or considerations when implementing	

	deprescribing intervention, including the ongoing monitoring process.
Acceptability Is the option of deprescribing acceptable to key stakeholders? ☑ Probably yes	Healthcare practitioners: Deprescribing is likely acceptable to most healthcare practitioners, especially when supported by clinical practice guidelines and a shared decision-making process with patients. The term deprescribing may be new to healthcare practitioners but the concept is not. Healthcare practitioners are very familiar with discontinuing ineffective medications or those causing adverse effects worse than the condition being treated. Patients, their caregivers and family members: Many are open to deprescribing if they understand the potential benefits and risks, especially when given the option to restart medications when necessary. Policymakers and health systems: From a broader perspective, deprescribing can be seen as a way to reduce healthcare costs and improve patient outcomes. However, the short-term impacts on patient care and the resources required to implement effective deprescribing strategies may be a concern.
Overall judgment	There is a lack of quality evidence for deprescribing to inform evidence-based recommendations.

24. Denosumab/ Bisphosphonates

24.1 Overview of studies targeted denosumab/bisphosphonates

Article	Drug/Class	Study design	Sample size	Follow-up (months)	Withdrawal schedule
Black 2006 [208]	Bisphosphonates (Alendronate)	RCT	1099	60	Not described
da Silva 2011 [209]	Bisphosphonate (Alendronate)	Prospective cohort study	88	12	Not described
OrrWalker 1997 [210]	Bisphosphonate (Pamidronate)	Before and after study	22	48	Not described
Eastell 2011 [211]	Bisphosphonate (Risedronate)	Prospective cohort study	61	12	Not described
Watts 2008 [212]	Bisphosphonates (Risedronate)	Before and after study	759	12	Not described
Black 2012 [213]	Bisphosphonates (Zoledronic acid)	RCT	1233	36	Not described

24.2 Evidence for deprescribing of denosumab/bisphosphonates

Study	Specific outcome	Odds ratio (95% CI)	Mean difference (95% CI)
1. Mortality			
Black 2006	Mortality	1.54 (0.80, 2.94)	
Black 2012	Mortality	0.68 (0.37, 1.25)	
2. Adverse drug withdrawal events (ADWEs)			
No available evidence			
3. Health outcomes			
Bone mass density			
Black 2006	Percentage change in bone mass density, total body		1.28 (1.25, 1.31)
Black 2006	Percentage change in bone mass density, trochanter		3.17 (3.14, 3.20)
Watts 2008	Percentage change in bone mass density, trochanter		3.08 (2.06, 4.10)
Black 2006	Percentage change in bone mass density, spine		3.74 (3.71, 3.77)
Black 2012	Percentage change in bone mass density, spine		2.03 (0.76, 3.30)
Eastell 2011	Percentage change in bone mass density, lumbar spine		7.82 (6.44, 9.20)
Watts 2008	Percentage change in bone mass density, lumbar spine		2.60 (1.56, 3.64)
Black 2006	Percentage change in bone mass density, femoral neck		1.94 (1.91, 1.97)
Black 2012	Percentage change in bone mass density, femoral neck		1.04 (0.43, 1.65)
Black 2006	Percentage change in bone mass density, total hip		2.36 (2.33, 2.39)
Black 2012	Percentage change in bone mass density, total hip		1.22 (0.75, 1.69)
Eastell 2011	Percentage change in bone mass density, femoral neck		4.33 (2.90, 5.76)
Watts 2008	Percentage change in bone mass density, femoral neck		2.32 (1.40, 3.24)
Da silva 2011	Clinically significant bone mass density loss, spine	10.67 (1.43, 100.39)	
Da silva 2011	Clinically significant bone mass density loss, femoral neck	7.20 (0.84, 61.38)	
Vertebral fractures			
Black 2006	Non-vertebral fractures	1.01 (0.74, 1.37)	
Da silva 2011	Non-vertebral fractures	1.94 (0.08, 49.40)	
Eastell 2011	Non-vertebral fractures	0.33 (0.01, 8.51)	
Watts 2008	Non-vertebral fractures	0.96 (0.49, 1.85)	

Non-vertebral fractures			
Black 2006	Vertebral fractures	2.24 (1.17, 4.30)	
Black 2012	Vertebral fractures	2.14 (1.12, 4.09)	
Watts 2007	Vertebral fractures	0.53 (0.32, 0.89)	
Adverse drug events			
Black 2006	Adverse drug events, number of participants who experienced once	1.11 (0.75, 1.63)	
Black 2012	Adverse drug events, number of participants who experienced once	0.95 (0.66, 1.38)	
Eastell 2011	Adverse drug events, number of participants who experienced once	1.24 (0.45, 3.41)	

4. Cognitive function

No available evidence

5. Quality of life

No available evidence

6. Effect on medication regimen

No available evidence

24.3 Evidence for deprescribing of denosumab/bisphosphonates (non-controlled outcomes)

Study	Specific outcome	Result
1. Mortality		
No available evidence		
2. Adverse drug withdrawal events (ADWEs)		
No available evidence		
3. Health outcomes		
Bone mass density		
OrrWalker 1997	Percentage change in bone mass density, total body (from baseline to 1 year after discontinuation)	-0.3 ± 0.7%, p = 0.7
OrrWalker 1997	Percentage change in bone mass density, lumbar spine (from baseline to 1 year after discontinuation)	7.1 ± 1.1%, p < 0.0001
OrrWalker 1997	Percentage change in bone mass density, femoral neck (from baseline to 1 year after discontinuation)	2.2 ± 1.3%, p not stated
OrrWalker 1997	Percentage change in bone mass density, ward's triangle (from baseline to 1 year after discontinuation)	0.1 ± 2.5%, p not stated
OrrWalker 1997	Percentage change in bone mass density, trochanter (from baseline to 1 year after discontinuation)	4.5 ± 1.8%, p < 0.03
4. Cognitive function		
No available evidence		
5. Quality of life		
No available evidence		
6. Effect on medication regimen		
No available evidence		

24.4 GRADE evidence profile (critical or important but not critical outcomes only)

Question: In older people, what are the effects of deprescribing (i.e. dose reduction or complete discontinuation) long-term denosumab/bisphosphonates on mortality, adverse drug withdrawal events, health-related outcomes, cognitive function, and quality of life?

Certainty assessment							Number of participants		Effect	Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Depresscribing	Continuation			
1. Mortality											
2 [208, 213]	RCTs	Serious [1]	Serious [2]	Not serious	Serious[3]	Serious[4]	1053	1275	OR 1.02 (0.46, 2.26)	⊕◯◯◯	8
2. Adverse drug withdrawal events (ADWEs)											
No available evidence											
3. Health outcomes											
Vertebral fractures											
2 [208, 213]	RCTs	Serious [1]	Not serious	Not serious	Serious[3]	Serious[4]	923	1131	OR 2.19 (1.38, 3.46)	⊕◯◯◯	5
1 [212]	Non-randomised study	Serious [5]	Not serious	Not serious	Serious[3]	Serious[4]	361	398	OR 0.53 (0.32, 0.89)	⊕◯◯◯	5
Non-vertebral fractures											
1 [208]	RCT	Serious [1]	Serious [2]	Not serious	Serious[3]	Serious[4]	437	662	OR 1.01 (0.74, 1.37)	⊕◯◯◯	5
3 [209, 211, 212]	Non-randomised studies	Serious [5,6,7]	Not serious	Not serious	Serious[3]	Serious[4]	468	417	OR 0.94 (0.50, 1.78)	⊕◯◯◯	5
Bone mass density (BMD)											
2 [208, 213]	RCTs	Serious [1]	Serious [2]	Not serious	Serious[3]	Serious[4]	898	1094	Percentage change in bone mass density • Spine (MD 3.01, 95% CI 1.35, 4.67, studies = 2) • Femoral neck (MD 1.54, 95% CI 0.67, 2.42, studies = 2) • Trochanter (MD 3.17, 95% CI 3.14, 3.20, study = 1) • Total hip (MD 1.82, 95% CI 0.70, 2.93, studies = 2)	⊕◯◯◯	6

2 [211, 212]	Non-randomised studies	Serious [5,6]	Not serious	Not serious	Serious[3]	Serious[4]	301	327	Percentage change in bone mass density • Spine (MD 5.19, 95% CI 0.07, 10.30) • Femoral neck (MD 3.25, 95% 1.28, 5.21) • Trochanter (MD 3.08, 95% CI 2.06, 4.10)		6
1 [210]	Non-controlled study	Serious [8]	Not serious	Not serious	Serious[3]	Not serious	22	N/A	Percentage change in bone mass density from baseline to 1 year after discontinuation • Total body, -0.3 ± 0.7%, p =0.7 • Lumbar spine, 7.1 ± 1.1%, p < 0.0001 • Femoral neck, 2.2 ± 1.3%, p not stated • Ward's triangle, 0.1 ± 2.5%, p not stated • Trochanter, 4.5 ± 1.8%, p < 0.03		6
Adverse drug events											
2 [208, 213]	RCTs	Serious [1]	Not serious	Not serious	Serious[3]	Serious[4]	1053	1275	OR 1.03 (0.79, 1.34)		5
1 [211]	Non-randomised study	Serious [6]	Not serious	Not serious	Serious[3]	Serious[4]	30	31	OR 1.24 (0.45, 3.41)		5
4. Cognitive function											
No available evidence											
5. Quality of life (QoL)											
No available evidence											

[1] Method of randomisation was not well described for the current extension studies which may introduce selection bias.
[2] Significant variability in the reported outcome among the studies included in the meta-analysis.
[3] Wide confidence intervals in the estimates of effect or small sample size.
[4] Investigators in these studies (Black 2006, Black 2012, Watts 2008, Eastell 2011, da Silva 2011) were sponsored by pharmaceutical companies.
[5] Non-randomised study (Watts 2008) which may introduce selection bias. Allocation based on group assignment from the parent study.
[6] Non-randomised study (Eastell 2011) which may introduce selection bias. Allocation based on group assignment from the parent study). The study design does not fully account for potential confounding factors such as changes in lifestyle, diet, or other medications over the long study period.
[7] One study (da Silva 2011) is unblinded which may introduce reporting bias. The risk of bias was low for the initial 3 years (double-blind) and moderate for the 1-year extension (open-label). Allocation in the extension study was based on consecutive patients. Reasons for attrition were not given. The number of drop-outs from group 3 was not available. Missing outcome data for groups 2 and 3 for some outcomes, and no numbers provided for other outcomes (p-values given but no numbers to state effect size). Results indicate a sizable proportion of drop-outs, but this was not addressed in the paper.

[8] Single-arm study with potential risk of selection, performance, attrition, confounding, and reporting biases. Few confounders were considered. No account of other medications was taken e.g. vitamin D, calcium, proton-pump inhibitor, hormonal status. Inadequate follow-up of cohorts: 27% lost. Analysis was as-treated.

24.5 Evidence-to-Decision table

Question: In older people, what are the effects of deprescribing (i.e. dose reduction or complete discontinuation) long-term denosumab/bisphosphonates on mortality, adverse drug withdrawal events, health-related outcomes, cognitive function, and quality of life?

Decision domain	Summary of reason for decision	Subdomains influencing decision
Certainty of evidence Is there a high or moderate certainty of evidence? Yes ☐ No ☑	The certainty of evidence for the harms of deprescribing is very low.	Key reasons for downgrading: Risk of bias, inconsistency, imprecision, and other considerations. Are all critical outcomes measured? Yes ☐ No ☑ There is a lack of evidence on critical outcomes including adverse drug withdrawal events, cognitive function, and quality of life.
Benefits and harms Is there certainty that the benefits of deprescribing outweigh the harms? Yes ☐ No ☑	The effects of deprescribing drugs affecting bone structure and mineralization have been tabulated in Appendix B (GRADE evidence profile table) with an overview provided in the guideline document (a narrative overview and GRADE summary of findings table). Below is a summary according to the study designs. <u>Summary of outcomes</u> Randomised and non-randomised controlled trials: • No significant difference in mortality, non-vertebral fractures, adverse drug events • Reduction in bone mass density • Increased vertebral fractures <u>Summary of withdrawal schedules:</u> Randomised controlled trials: (very low certainty evidence) Not described, likely abrupt discontinuation (studies=2,	Is the baseline risk for benefits and harms of deprescribing similar across subgroups? Yes ☑ No ☐ Evidence at this time suggests that individuals at a higher risk of fractures may have a greater risk of harm from deprescribing. Should there be separate recommendations for subgroups? Yes ☑ No ☐ While insufficient evidence to inform whether separate recommendations are needed, there are subgroups for consideration for opioid analgesics from expert opinions. In favour of deprescribing: Adapted from Primary Health Tasmania • Normal bone mineral density • Limited life expectancy due to comorbidities

	n=2332) Non-randomised controlled trials: (very low certainty evidence) Not described, likely abrupt discontinuation (studies=3, n=908) Non-controlled trials: (very low certainty evidence) Not described, likely abrupt discontinuation (study=1, n=22)	• Low fracture risk • Five or more years of continuous treatment Against deprescribing: Adapted from Primary Health Tasmania • High fracture risk • Recurrent fractures during treatment (that is not associated with noncompliance)
Values and preferences Is there confidence in the estimate of the relative importance of outcomes and individual preferences? Yes ☑ No ☐	Many patients taking osteoporosis medications did not receive adequate information about the potential side effects of the medications from their healthcare providers, indicating a lack of informed consent. Specifically, those who are taking denosumab often receive it as a first-line treatment without thorough discussions of alternative management options. Patients emphasise the importance of informed consent in both prescribing and deprescribing processes. To facilitate informed decision-making, it is essential for healthcare providers to offer comprehensive information regarding treatment options and associated risks. The majority of healthcare professionals believe that deprescribing can be beneficial for patients. When treating osteoporosis, clinicians generally consider fracture risk profile, patient preferences, benefits, harms, and costs of medications.	Perspective taken: The lack of evidence for serious harm as a result of deprescribing and evident benefits related to reduced medication burden and costs. Individual values and preferences determine the deprescribing approaches. Source of values and preferences: Consultation with patient and carer representatives Source of variability, if any: Difficult to determine the extent of variability; high variability for patient preferences. Method for determining values satisfactory for this recommendation? Yes ☑ No ☐ Yes, but would be improved with direct patient input
Resources Are the resources worth the expected net benefit? Yes ☑ No ☐	A comprehensive economic evaluation was outside the scope of the current review. However, potential cost and resource implications related to deprescribing interventions and continuation of medications are discussed below. Cost implications: An international example showed that,	Feasibility: Is this intervention generally available? Yes ☑ No ☐ Opportunity cost: Is this intervention and its effects worth withdrawing or not allocating resources from other interventions? Yes ☑ No ☐

	at a cost per Quality Adjusted Life Year (QALY) threshold equivalent to gross domestic product per capita in 2020 in Taiwan (USD $30,038), continued treatment with denosumab in postmenopausal women with osteoporosis is cost-effective compared with treatment discontinuation. For older men with osteoporosis, denosumab had an incremental cost-effectiveness ratio of USD $16,888 compared to generic alendronate and dominated all other treatments. Physician implications: Healthcare providers will need to closely monitor patients to assess the impact of deprescribing on ongoing fracture risk. This may involve additional clinic visits, laboratory tests and extended consultation time.	Economic and preventive benefits for harms: Is there a lot of variability in resource requirements across settings? Yes ☐ No ☑
Equity What would be the impact of deprescribing on health inequities? ☑ Uncertain	The social determinants of health equity are complex and multifaceted. The impact of deprescribing on health equity is inadequately explored in the literature. Deprescribing may enhance access to care and improve health outcomes. However, ensuring equitable implementation and addressing potential challenges faced by people with varying health literacy and access disparities is crucial to maximising these benefits. Culturally and linguistically diverse populations, Aboriginal and Torres Strait Islander populations, people with low socioeconomic status, and those living in rural or remote areas may require additional support or considerations when implementing deprescribing intervention, including the ongoing monitoring process.	
Acceptability Is the option of deprescribing acceptable to key stakeholders? ☑ Probably yes	Healthcare practitioners: Deprescribing is likely acceptable to most healthcare practitioners, especially when supported by clinical practice guidelines and a shared decision-making process with patients. The term deprescribing may be new to healthcare practitioners but the concept is not. Healthcare practitioners are very familiar with discontinuing ineffective medications or those causing adverse effects worse than the condition being treated. Patients, their caregivers and family members: Many are open to deprescribing if they understand the potential benefits and risks, especially when given the option to restart medications when necessary. Policymakers and health systems: From a broader perspective, deprescribing can be seen as a way to reduce healthcare costs and improve patient outcomes. However, the short-term impacts on patient care and the resources required to implement effective deprescribing strategies may be a concern.	
Overall judgment	There is a lack of quality evidence for deprescribing to inform evidence-based recommendations.	

25. Analgesics

25.1 Overview of studies targeted analgesics

Article	Drug/Class	Study design	Sample size	Follow-up (months)	Withdrawal schedule
Kawai 2022 [214]	Tramadol	RCT	159	2	Not described

25.2 Evidence for deprescribing analgesics

Study	Specific outcome	Odds ratio (95% CI)	Mean difference (95% CI)
1. Mortality			
No available evidence			
2. Adverse drug withdrawal events (ADWEs)			
Kawai 2022	Inadequate analgesic effect (tramadol)	2.46 (1.13, 5.33)	
3. Health outcomes			
Adverse drug events			
Kawai 2022	Adverse drug events (tramadol)	0.46 (0.20, 1.03)	
4. Cognitive function			
No available evidence			
5. Quality of life			
No available evidence			
6. Effect on medication regimen			
No available evidence			

25.3 Evidence for deprescribing analgesics (non-controlled outcomes)

Study	Specific outcome	Result
1. Mortality		
No available evidence		
2. Adverse drug withdrawal events (ADWEs)		
No available evidence		
3. Health outcomes		
No available evidence		
4. Cognitive function		
No available evidence		
5. Quality of life		
No available evidence		
6. Effect on medication regimen		
No available evidence		

25.4 GRADE evidence profile (critical or important but not critical outcomes only)

Question: In older people, what are the effects of deprescribing (i.e. dose reduction or complete discontinuation) long-term analgesics on mortality, adverse drug withdrawal events, health-related outcomes, cognitive function, and quality of life?

Certainty assessment							Number of participants		Effect	Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Deprescribing	Continuation			
1. Mortality											
No available evidence											
2. Adverse drug withdrawal events (ADWEs)											
ADWEs											
1 [214]	RCT	Serious [1]	Not serious	Serious [2]	Serious [3,4]	Serious[5]	81	78	Inadequate analgesic effect OR 2.46 (95% CI, 1.13, 5.33)	⨁⨁◯◯	6
3. Health outcomes											
Adverse drug events											
1 [214]	RCT	Serious [1]	Not serious	Serious [2]	Serious [3,4]	Serious[5]	81	78	Adverse drug events related to opioids included nausea, vomiting, constipation, somnolence, and dizziness. OR 0.46 (95% CI 0.20, 1.03)	⨁⨁◯◯	5
4. Cognitive function											
No available evidence											
5. Quality of life (QoL)											
No available evidence											

[1] Limited information on possible confounding factors (e.g. use of NSAID) and whether they were considered in the analysis. Potential attrition bias - significant dropout rate in the placebo group due to inadequate efficacy. Short treatment duration (up to 8 weeks) might not adequately capture the chronic nature of knee osteoarthritis pain.
[2] Potential indirectness - This study targeted exclusively the use of tramadol hydrochloride in chronic pain associated with knee osteoarthritis. It is unclear if the findings can be generalised to deprescribing of other non-opioid analgesics.
[3] Small sample size
[4] Wide confidence intervals in the estimates of effect.
[5] Potential conflicts of interest due to the study being funded by the Nippon Zoki Pharmaceutical Company.

25.5 Evidence-to-Decision table

Question: In older people, what are the effects of deprescribing (i.e. dose reduction or complete discontinuation) long-term analgesics on mortality, adverse drug withdrawal events, health-related outcomes, cognitive function, and quality of life?		
Decision domain	Summary of reason for decision	Subdomains influencing decision
Certainty of evidence Is there a high or moderate certainty of evidence? Yes ☐ No ☑	The certainty of evidence for the benefits of deprescribing is very low. The certainty of evidence for the harms of deprescribing is very low.	Key reasons for downgrading: Risk of bias, indirectness, imprecision, and other considerations due to industry funding Are all critical outcomes measured? Yes ☐ No ☑ There is a lack of evidence on critical outcomes including mortality, cognitive function, and quality of life.
Benefits and harms Is there certainty that the benefits of deprescribing outweigh the harms? Yes ☐ No ☑	The effects of deprescribing analgesics have been tabulated in Appendix B (GRADE evidence profile table) with an overview provided in the guideline document (a narrative overview and GRADE summary of findings table). Below is a summary according to the study designs. <u>Summary of outcomes</u> Randomised controlled trial: There is a paucity of evidence on the potential benefits or harms related to the continuation or discontinuation of opioid and non-opioid analgesics in general. One study that targeted tramadol reported a significant increase in adverse drug withdrawal effects, specifically inadequate analgesic coverage. However, there was no significant difference between the two groups in the occurrence of adverse drug events related to tramadol use (nausea, vomiting, constipation, somnolence, and dizziness). Non-randomised study: A study targeted gabapentinoid found no significant	Is the baseline risk for benefits and harms of deprescribing similar across subgroups? Yes ☐ No ☑ There is no evidence at this time that the benefits or harms of deprescribing differ based on subgroups. However, there will be some groups at a higher risk. Should there be separate recommendations for subgroups? Yes ☑ No ☐ The guideline development group acknowledges that certain subgroups may have factors that could impact the balance of benefits and risks from deprescribing (e.g. type of analgesics [opioid or non-opioid analgesics], nature of pain [aetiology], pain severity, pain duration, symptom control, psychological factors, life expectancy, other important comorbidities, previous history of opioid use disorders, and the presence of adverse drug events). However, the available evidence is insufficient to justify distinct evidence-based recommendations.

	differences between the intervention and control groups in physical health, pain intensity, and cognitive function. <u>Summary of withdrawal schedules:</u> Randomised controlled trial: Not described (studies=2, n=301)	
Values and preferences Is there confidence in the estimate of the relative importance of outcomes and individual preferences? Yes ☑ No ☐	Patients' perspectives on analgesic use are varied, with some valuing pain relief from medications, while others are averse to them. There is limited evidence regarding patient views on non-opioid analgesics, though, for opioid analgesics, many patients take them for chronic non-cancer pain under strict medical supervision, sometimes maintaining the same dose for years. Some of these patients report a good clinical response and lead fulfilling lives. Unmanaged pain can significantly impact mental health, quality of life, and productivity, leading many chronic pain patients to seek psychological support for their physical pain. While pain relief and quality of life are highly valued, patients also aim to avoid adverse events. Patients value the use of a pain scale in assessing pain levels, as patients' pain thresholds vary, and some patients may prefer non-pharmacologic therapies or pain coping strategies over pharmacological treatment due to concerns about the adverse effects of analgesics. In general, patients expressed that stronger regulations or care may be needed for opioids to ensure safe and quality care. Many patients may not fully understand the risks of opioids, and some are concerned about	Perspective taken: Individual values and preferences determine the deprescribing approaches. Sources of values and preferences: 1) Consultation with patient and carer representatives 2) Non-systematic review of evidence Source of variability, if any: Difficult to determine the extent of variability; high variability for patient preferences. Method for determining values satisfactory for this recommendation? Yes ☑ No ☐ Yes, but would be improved with direct patient input

	addiction and overdose. Some opioid users may be open to reducing or stopping opioid therapy, despite concerns about withdrawal symptoms, increased pain, and functional limitations. However, many believe they are stigmatised and unsupported by healthcare professionals when attempting to taper their opioid use. Additionally, prolonged wait times for surgeries, particularly when coupled with increasing pain, necessitate effective management. Pain management should be individualised, with clear information from doctors about the risks of addiction, overdose, and tolerance. Prescribing practices for pain management vary significantly between clinicians. However, most physicians are highly aware of the potential for opioid misuse, addiction, and physiological dependence. Many physicians believe deprescribing opioids is more challenging than other medication classes. Physicians consider peer support, patient motivation and doctor-patient rapport to be the most important factors to assist in deprescribing.	
Resources Are the resources worth the expected net benefit? Yes ☑ No ☐	A comprehensive economic evaluation was outside the scope of the current review. However, potential cost and resource implications related to deprescribing interventions and continuation of medications are discussed below. Cost implications: There is little evidence about the cost implications and cost-effectiveness analysis of deprescribing of non-opioid and opioid analgesics. The cost-effectiveness analysis of continuation and discontinuation may be difficult to estimate as it is	Feasibility: Is this intervention generally available? Yes ☑ No ☐ Opportunity cost: Is this intervention and its effects worth withdrawing or not allocating resources from other interventions? Yes ☑ No ☐ Economic and preventive benefits for harms: Is there a lot of variability in resource requirements across settings? Yes ☐ No ☑

	sensitive to the type of deprescribing intervention and the rate of successful implementation. It is foreseeable that deprescribing of analgesics will involve multidisciplinary and pain rehabilitation programs which may be resource- and time-intensive. In comparison, non-opioid and opioid analgesics are widely accessible and relatively less costly. However, cost-effectiveness analysis will need to factor in the far-reaching societal costs associated with the continuation or discontinuation of analgesics. Inadequate pain relief may lead to loss of productivity, mental health strain, caregiver burden, and increased need for social support. Physician implications: Physicians will need to closely monitor patients to assess the impact of deprescribing on ongoing symptoms. Additional clinic visits and extended consultation time are likely required to explain the ongoing risk and benefit to patients. However, the extra workload could potentially be justified from time saved to manage adverse effects related to opioid and non-opioid analgesics.	
Equity What would be the impact of deprescribing on health inequities? ☑ Uncertain	The social determinants of health equity are complex and multifaceted. The impact of deprescribing on health equity is inadequately explored in the literature. Effective deprescribing of analgesics requires appropriate monitoring and follow-up to manage symptoms. If deprescribing analgesics leads to the need for more expensive or less accessible alternatives, it could exacerbate disparities, particularly for those with limited financial resources. If analgesics are deprescribed without adequate supporting alternatives, patients might experience unmanaged pain or reduced quality of life, which could disproportionately affect those with limited access to healthcare services. For patients with comorbidities that are managed with analgesics, deprescribing needs to be carefully coordinated to avoid worsening other health issues. Ensuring equitable implementation and addressing potential challenges faced by people with varying health literacy and access disparities is crucial to maximising these benefits. Culturally and linguistically diverse populations, Aboriginal and Torres Strait Islander populations, people with low socioeconomic status, and those living in rural or remote areas may require additional support or considerations when implementing deprescribing intervention, including the ongoing monitoring process.	

Acceptability Is the option of deprescribing acceptable to key stakeholders? ☑ Probably yes	Healthcare practitioners: Deprescribing is likely acceptable to most healthcare practitioners, especially when supported by clinical practice guidelines and a shared decision-making process with patients. The term deprescribing may be new to healthcare practitioners but the concept is not. Healthcare practitioners are very familiar with discontinuing ineffective medications or those causing adverse effects worse than the condition being treated. Patients, their caregivers and family members: Many are open to deprescribing if they understand the potential benefits and risks, especially when given the option to restart medications when necessary. Policymakers and health systems: From a broader perspective, deprescribing can be seen as a way to reduce healthcare costs and improve patient outcomes. However, the short-term impacts on patient care and the resources required to implement effective deprescribing strategies may be a concern.
Overall judgment	There is a lack of quality evidence for deprescribing to inform evidence-based recommendations.

26. Antiepileptics

26.1 Overview of studies targeted antiepileptics

Article	Drug/Class	Study design	Sample size	Follow-up (months)	Withdrawal schedule
Tariot 1999 [215]	Carbamazepine for behavioural and psychological symptoms of dementia (BPSD)	RCT	51	0.75	Not described
Gingras 2024 [216]	Gabapentinoids	Before-and-after study	142	2	Not described

26.2 Evidence for deprescribing antiepileptics

Study	Specific outcome	Odds ratio (95% CI)	Mean difference (95% CI)
1. Mortality			
No available evidence			
2. Adverse drug withdrawal events (ADWEs)			
Gingras 2024	Global physical health, measured using Patient-Reported Outcomes Measurement Information System (PROMIS) Questionnaires		-0.80 (-3.0, 1.3)
Gingras 2024	Pain intensity, measured using PROMIS		-2.5 (-5.8, 0.8)
3. Health outcomes			
Physical function			
Tariot 1999	Physical self-maintenance scale		-1.70 (-4.42, 1.02)
Behaviours and psychological symptoms			
Tariot 1999	Total behaviour rating scale of dementia		-5.20 (-17.36, 6.96)
Tariot 1999	Total Brief Psychiatric Rating Scale (BPRS) score		0.60 (-4.94, 6.14)
Tariot 1999	Aggression, measured using the Overt Aggression scale		0.10 (-3.23, 3.43)
4. Cognitive function			
Tariot 1999	Change in cognition, measured using the Mini-Mental State Examination		-0.70 (-2.96, 1.56)
Gingras 2024	Cognitive function, measured using PROMIS		1.8 (-1.1, 4.7)
5. Quality of life			
No available evidence			
6. Effect on medication regimen			
Gingras 2024	Discontinuation or ongoing tapering (gabapentinoid)	0.41 (0.16, 1.07)	
Gingras 2024	Dose reduction with no intention of further tapering (gabapentinoid)	1.00 (0.37, 2.69)	
Gingras 2024	New pain medicine prescribed	1.24 (0.50, 3.09)	
Gingras 2024	Existing pain medicine increased	0.15 (0.02, 1.32)	

26.3 Evidence for deprescribing antiepileptics (non-controlled outcomes)

Study	Specific outcome	Result
1. Mortality		
No available evidence		
2. Adverse drug withdrawal events (ADWEs)		
No available evidence		
3. Health outcomes		
No available evidence		
4. Cognitive function		
No available evidence		
5. Quality of life		
No available evidence		
6. Effect on medication regimen		
No available evidence		

26.4 GRADE evidence profile (critical or important but not critical outcomes only)

Question: In older people, what are the effects of deprescribing (i.e. dose reduction or complete discontinuation) long-term antiepileptics on mortality, adverse drug withdrawal events, health-related outcomes, cognitive function, and quality of life?

Certainty assessment							Number of participants		Effect	Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Depresscribing	Continuation			
1. Mortality											
No available evidence											
2. Adverse drug withdrawal events (ADWEs)											
1 [216]	Non-randomised study	Serious [1,2,3]	Not serious	Not serious	Serious [4]	Not serious	71	71	Physical health, measured using Patient-Reported Outcomes Measurement Information System (PROMIS) MD -0.80 (95% CI -3.0, 1.3) Pain intensity, measured using PROMIS MD -2.5 (95% CI -5.8, 0.8)	⨁◯◯◯	6
3. Health outcomes											
Physical function											
1 [215]	RCT	Serious [5]	Not serious	Serious [6]	Serious [4]	Not serious	22	23	At the end of the washout period, there was no significant difference between the group previously taking placebo and the group previously taking carbamazepine for behavioural and psychological symptoms of dementia in the Physical Self-Maintenance Scale (MD -1.70, 95% CI -4.42, 1.02).	⨁◯◯◯	6
Behavioural and psychological symptoms											
1 [215]	RCT	Serious [5]	Not serious	Serious [6]	Serious [4]	Not serious	22	23	There was no significant difference between the group previously taking placebo and the group previously taking carbamazepine for behavioural and psychological symptoms of dementia in aggression (MD 0.10, 95% CI -3.23 to 3.43), total behaviour rating scale of dementia (MD -5.20, 95% CI -17.36 to 6.96) or Total Brief Psychiatric Rating Scale (BPRS) score (MD 0.60, 95% CI -4.94, 6.14).	⨁◯◯◯	6
4. Cognitive function											

1 [215]	RCT	Serious [5]	Not serious	Serious [6]	Serious [4]	Not serious	22	23	Washout of carbamazepine administered for behavioural and psychological symptoms of dementia (BPSD) versus placebo, MD -0.70 (95% CI -2.96, 1.56).		7
1 [216]	Non-randomised study	Serious [6,7,8]	Not serious	Not serious	Serious [4]	Not serious	71	71	Cognitive functions, measured using PROMIS MD 1.8 (95% CI -1.1, 4.7)		7
5. Quality of life (QoL)											
No available evidence											

[1] Single-arm study without a comparison group
[2] Follow-up duration of 2 months may not be sufficient to observe long-term effects
[3] Study outcomes were self-reported by the participants and there was a lack of blinding which can potentially introduce biases and residual confounding.
[4] Small sample size and wide confidence intervals in the estimates of effect for some outcomes measured
[5] The randomisation method was not described and the deprescribing phase was not blinded. Very brief follow-up period and potential for unmeasured confounding factors. During the washout phase, raters were blinded to the original treatment condition, minimising detection bias. However, during the open-label extension phase, raters were not blinded, potentially introducing detection bias. Moreover, there could be a high risk of reporting bias as the authors stated the study design was changed for administrative reasons after several subjects were enrolled when they received funding to perform a larger, simpler, parallel-group study.
[6] Potential indirectness - Study population has limited generalisability to a wider population as carbamazepine was used for behavioural and psychological symptoms of dementia in this study instead of epilepsy. This study is quite old and thus the findings have low relevance to the current medical practice. Non-pharmacological approaches are now preferred as the first-line treatments for BPSD.

26.5 Evidence-to-Decision table

Question: In older people, what are the effects of deprescribing (i.e. dose reduction or complete discontinuation) long-term antiepileptics on mortality, adverse drug withdrawal events, health-related outcomes, cognitive function, and quality of life?		
Decision domain	Summary of reason for decision	Subdomains influencing decision
Certainty of evidence Is there a high or moderate certainty of evidence? Yes ☐ No ☑	The certainty of evidence is very low.	Key reasons for downgrading: Risk of bias, indirectness, imprecision Are all critical outcomes measured? Yes ☐ No ☑ There is a lack of evidence on critical outcomes including mortality, adverse drug withdrawal events, and quality of life.
Benefits and harms Is there certainty that the benefits of deprescribing outweigh the harms? Yes ☐ No ☑	The effects of deprescribing antiepileptics have been tabulated in Appendix B (GRADE evidence profile table) with an overview provided in the guideline document (a narrative overview and GRADE summary of findings table). Below is a summary according to the study designs. <u>Summary of outcomes</u> Randomised controlled trial: There is a paucity of evidence on the potential benefits or harms related to the continuation or discontinuation of antiepileptics. We only identified one randomised controlled trial published in 1999 that reported deprescribing outcomes on patients taking antiepileptics for behavioural and psychological symptoms of dementia (BPSD). At the end of the washout period, there was no significant difference between the groups previously taken placebo and carbamazepine in terms of the Physical Self-Maintenance Scale, aggression, total behaviour rating scale of dementia, Total Brief Psychiatric Rating Scale score, or cognition.	Is the baseline risk for benefits and harms of deprescribing similar across subgroups? Yes ☐ No ☑ There is no evidence at this time that the benefits or harms of deprescribing differ based on subgroups. However, there will be some groups at a high risk depending on the indications for use. Should there be separate recommendations for subgroups? Yes ☑ No ☐ The guideline development group acknowledges that certain subgroups may have factors that could impact the balance of benefits and risks from deprescribing (e.g. indication for the use of antiepileptics, symptom control, concomitant medications, cognitive status, presence of adverse drug events, social aspects, emotional elements, and personal factors). However, the available evidence is insufficient to justify distinct evidence-based recommendations.

	Summary of withdrawal schedules: Randomised controlled trial: Not described (study=1, n=51)	
Values and preferences Is there confidence in the estimate of the relative importance of outcomes and individual preferences? Yes ☑ No ☐	When used for epilepsy In addition to the uncertainty of seizure recurrence, challenges with medications, and the stigma of being diagnosed with epilepsy, the timing in a patient's life plays a significant role in the decision-making process regarding the discontinuation of antiepileptic medication. Most patients prefer to continue antiepileptics following a seizure-free period of two years. The decision to continue treatment is influenced by concerns about potential seizure recurrence and the devastating physical, psychological, and social consequences, such as unemployment or loss of the ability to drive. Older patients tend to be less concerned about the potential adverse effects of withdrawal. Clinicians may be more hesitant to discontinue preventative medications when there is no surrogate measure to measure the likelihood of adverse events, such as antiepileptics for the prevention of seizures. The recurrence of seizures could have significant consequences for individuals. When used for other indications Family members and front-line caregivers often have different priorities when it comes to managing behavioural and psychological symptoms of dementia (BPSD) with antiepileptics, particularly in balancing the relief of caregiver burden with improving the patient's quality of life. Physicians may view symptomatic benefits reported by patients or	Perspective taken: When used for BPSD Individual values and preferences determine the deprescribing approaches. Values and preferences of family members and front-line caregivers providing care for persons with dementia will also be important in cases of antiepileptics used for BPSD. When used for epilepsy Despite guidelines suggesting withdrawal for patients with epilepsy who have been seizure-free for at least two years, the "optimum timing" needs to be individualised to consider other personal life factors. Sources of values and preferences: 1) Consultation with patient and carer representatives 2) Non-systematic review of evidence Source of variability, if any: Difficult to determine the extent of variability; high variability for patient preferences. Method for determining values satisfactory for this recommendation? Yes ☑ No ☐ Yes, but would be improved with direct patient input

	their caregivers, as well as antiepileptics prescribed by another physician, as significant barriers to deprescribing. The decision to prescribe or deprescribe involves a complex interplay of physical, societal, environmental, psychosocial, and physiological factors. In both home and care settings, there is a fine line between effectively managing behaviours and ensuring the safety of both the patient and others. When considering medication reduction, it is essential to assess the management plan thoroughly and monitor behaviours closely to avoid detrimental effects. Staff training in care facilities is crucial, as is careful monitoring of withdrawal symptoms to ensure that any risks are captured and managed appropriately within the care plan. When it comes to pain management, patients may favour reducing the dose gradually, as long as their pain remains under control and manageable. Many patients initiate the conversation about discontinuing medicine themselves, prompted by the presence of side effects.	
Resources Are the resources worth the expected net benefit? Yes ☑ No ☐	A comprehensive economic evaluation was outside the scope of the current review. However, potential cost and resource implications related to deprescribing interventions and continuation of medications are discussed below._ <u>When used for BPSD</u> Cost implications: There is little evidence on the overall cost implications of long-term antiepileptics exposure. The cost-effectiveness analysis of continuation and discontinuation may be difficult to estimate due to the complexity of health outcomes,	Feasibility: Is this intervention generally available? Yes ☑ No ☐ Opportunity cost: Is this intervention and its effects worth withdrawing or not allocating resources from other interventions? Yes ☑ No ☐ Economic and preventive benefits for harms: Is there a lot of variability in resource requirements across settings? Yes ☐ No ☑

the types of deprescribing intervention and the rate of successful implementation. Antiepileptics may be a cheaper alternative to behavioural therapy. However, the serious adverse effects of antiepileptics and potentially wasted ineffective treatment may result in costs that far outweigh the cost of behavioural interventions. On the other hand, deprescribing of antiepileptics is likely to impose more requirements on caregivers. It is challenging to precisely estimate the amount of time (lost work time, transportation) and both physical and psychological stress of BPSD on caregivers of persons with dementia. Caregivers may require additional clinical and societal support in providing care. For persons with dementia living at home, this may involve costs of home visits for community-based interventions. For those who cannot be managed at home or in less restrictive settings, the cost of institutionalisation may be substantial. Additional training and resources are likely required in aged care organisations to develop specific expertise and skills in caring for people with severe BPSD, including the use of behavioural strategies, electing a program coordinator, and a regular audit of the care provided to people with dementia. Investing in behavioural interventions may result in lower long-term costs and better outcomes for patients with dementia.

Physician implications:
Physicians will need to closely monitor patients for dose tapering and to assess the impact of deprescribing on ongoing BPSD. Additional clinic visits and extended consultation time are likely required to reassess the person's BPSD and discuss

	practical strategies with the person and carer/health care team regularly and adjust as BPSD changes. In addition, weaning off antiepileptics may bring significant anxiety to the individual as well as their carers for which psychosocial support will be needed. <u>When used for epilepsy</u> Cost implications: There is a lack of evidence on the cost implications and cost-effectiveness analysis of deprescribing antiepileptics used for seizures. The direct medical costs and indirect costs such as loss of productivity from seizure recurrence can create a considerable economic burden to individuals and society. On the other hand, there are costs related to managing significant side effects of the continuation of antiepileptics such as cognitive impairment, fatigue, weight gain, or mood changes. Physician implications: Physicians will need to closely monitor patients for dose tapering and to assess the impact of deprescribing on the ongoing risk of seizure recurrence. Additional clinic visits and extended consultation time are likely required to explain the ongoing risk and benefit to patients. Physicians will need to monitor the therapeutic response and adverse effects of concomitant medications more closely following antiepileptics deprescribing due to potential drug-drug interactions. In addition, weaning off antiepileptics may bring significant anxiety to the individual for which psychosocial support will be needed.	
Equity What would be the impact of	The social determinants of health equity are complex and multifaceted. The impact of deprescribing on health equity is inadequately explored in the literature. By reducing medication burdens, lowering costs, and simplifying medicine regimens, deprescribing may enhance access to care and improve health outcomes. If deprescribing leads to better	

deprescribing on health inequities? ☑ Uncertain	management of BPSD through more appropriate or effective treatments, it could improve overall quality of life and support equitable care. However, for epilepsy, inadequate management of the deprescribing process could lead to a loss of seizure control, which may disproportionately affect individuals with less access to healthcare services or follow-up care. In addition, ensuring equitable implementation and addressing potential challenges faced by people with varying health literacy and access disparities is crucial to maximising these benefits. Culturally and linguistically diverse populations, Aboriginal and Torres Strait Islander populations, people with low socioeconomic status, and those living in rural or remote areas may require additional support or considerations when implementing deprescribing intervention, including the ongoing monitoring process.
Acceptability Is the option of deprescribing acceptable to key stakeholders? ☑ Probably yes	Healthcare practitioners: Deprescribing is likely acceptable to most healthcare practitioners, especially when supported by clinical practice guidelines and a shared decision-making process with patients. The term deprescribing may be new to healthcare practitioners but the concept is not. Healthcare practitioners are very familiar with discontinuing ineffective medications or those causing adverse effects worse than the condition being treated. Patients, their caregivers and family members: Many are open to deprescribing if they understand the potential benefits and risks. Policymakers and health systems: From a broader perspective, deprescribing can be seen as a way to reduce healthcare costs and improve patient outcomes. However, the short-term impacts on patient care and the resources required to implement effective deprescribing strategies may be a concern.
Overall judgment	There is a lack of quality evidence for deprescribing to inform evidence-based recommendations.

Abbreviation: BPSD behavioural and psychological symptoms of dementia

27. Levodopa

27.1 Overview of studies targeted levodopa

Article	Drug/Class	Study design	Sample size	Follow-up (months)	Withdrawal schedule
Tse 2008 [217]	Levodopa	RCT	11	1	Levodopa was tapered by 1 tablet, or 100 mg every 3 days until the medication was completely withdrawn
Hauser 2000 [218]	Levodopa with carbidopa and bromocriptine	Before and after study	31	0.5	Not described

27.2 Evidence for deprescribing of levodopa

Study	Specific outcome	Odds ratio (95% CI)	Mean difference (95% CI)
1. Mortality			
No available evidence			
2. Adverse drug withdrawal events (ADWEs)			
Tse 2008	Severity and progression of Parkinson's disease, measured by Unified Parkinson's Disease Rating Scale (UPDRS)		-11.99 (-39.98, 16.00)
3. Health outcomes			
No available evidence			
4. Cognitive function			
Tse 2008	Cognition, measured by Mini-Mental State Examination		3.20 (-7.80, 14.20)
5. Quality of life			
No available evidence			
6. Effect on medication regimen			
No available evidence			

27.3 Evidence for deprescribing of levodopa (non-controlled outcomes)

Study	Specific outcome	Result
1. Mortality		
No available evidence		
2. Adverse drug withdrawal events (ADWEs)		
Hauser 2000	Adverse drug withdrawal effects (other than recurrent of the underlying symptoms)	0%
Hauser 2000	United Parkinson's Disease Rating Scale at 15 days where higher scores indicate a greater symptom severity	7.4 ± 1.5, p<0.0001
3. Health outcomes		
No available evidence		
4. Cognitive function		
No available evidence		
5. Quality of life		
No available evidence		
6. Effect on medication regimen		
No available evidence		

27.4 GRADE evidence profile (critical or important but not critical outcomes only)

Question: In older people, what are the effects of deprescribing (i.e. dose reduction or complete discontinuation) long-term levodopa on mortality, adverse drug withdrawal events, health-related outcomes, cognitive function, and quality of life?

Certainty assessment							Number of participants		Effect	Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Depres cribing	Contin uation			
1. Mortality											
No available evidence											
2. Adverse drug withdrawal events (ADWEs)											
1 [217]	RCT	Serious[1]	Not serious	Not serious	Serious[2]	Not serious	5	3	Severity and progression of Parkinson's disease, measured by Unified Parkinson's Disease Rating Scale (UPDRS) -11.99 (-39.98, 16.00)		6
1 [218]	Non-controlled study	Serious[3]	Not serious	Not serious	Serious[2]	Not serious	31	N/A	Adverse drug withdrawal effects (other than recurrent of the underlying symptoms), 0% United Parkinson's Disease Rating Scale at 15 days where higher scores indicate a greater symptom severity, 7.4 ± 1.5, p<0.0001		6
3. Health outcomes											
No available evidence											
4. Cognitive function											
1 [217]	RCT	Serious[1]	Not serious	Not serious	Serious[2]	Not serious	6	5	Cognition, measured by Mini-Mental State Examination 3.20 (-7.80, 14.20)		7
5. Quality of life (QoL)											
No available evidence											

[1] The randomisation method was not described, and the study was not blinded. Potential for unmeasured confounding factors. The authors stated the other subcomponents of the Unified Parkinson's Disease Rating were not assessed, as these all involve assessment of symptomatology by history, which could not be reliably obtained in this severely cognitively impaired population. There was also no mention of doses of levodopa was made. The rate of tapering was constant (100mg every 3 days), but the starting point may have been variable. It is possible that tapering at this speed could produce neuroleptic malignant syndrome, which would manifest as a fever and stiffness. These are the very symptoms that the patients showed after withdrawal.
[2] Very small sample size and wide confidence intervals in the estimates of effect
[3] Potential biases including confounding bias as this study lacks a comparator group.

27.5 Evidence-to-Decision Table

Question: In older people, what are the effects of deprescribing (i.e. dose reduction or complete discontinuation) long-term levodopa on mortality, adverse drug withdrawal events, health-related outcomes, cognitive function, and quality of life?

Decision domain	Summary of reason for decision	Subdomains influencing decision
Certainty of evidence Is there a high or moderate certainty of evidence? Yes ☐ No ☑	The certainty of evidence for the benefits of deprescribing is low to very low. The certainty of evidence for the harms of deprescribing is low to very low.	Key reasons for downgrading: Risk of bias, imprecision Are all critical outcomes measured? Yes ☐ No ☑ There is a lack of evidence on critical outcomes including mortality, health outcomes, and quality of life.
Benefits and harms Is there certainty that the benefits of deprescribing outweigh the harms? Yes ☐ No ☑	The effects of deprescribing levodopa have been tabulated in Appendix B (GRADE evidence profile table) with an overview provided in the guideline document (a narrative overview and GRADE summary of findings table). Below is a summary according to the study designs. <u>Summary of outcomes</u> Randomised controlled trial: No significant difference in adverse drug withdrawal events and cognition Non-controlled trial: Increased severity of Parkinsonian symptoms <u>Summary of withdrawal schedules:</u> Randomised controlled trial: (Low certainty evidence) Levodopa was tapered by 1 tablet, or 100 mg every 3 days until the medication was completely withdrawn (study=1, n=11) Non-controlled trial: (Very low certainty evidence) Not described (study=1, n=31)	Is the baseline risk for benefits and harms of deprescribing similar across subgroups? Yes ☐ No ☑ Evidence at this time suggests that the benefits of deprescribing may be more pronounced in patients with advanced parkinsonism than in early Parkinson's disease. Should there be separate recommendations for subgroups? Yes ☑ No ☐ The guideline development group acknowledges that certain subgroups may have factors that could impact the balance of benefits and risks from deprescribing (e.g. severity of the condition, symptom control, concomitant medications, presence of adverse drug events, social aspects, emotional elements, and personal factors). However, the available evidence is insufficient to justify distinct evidence-based recommendations.

Values and preferences Is there confidence in the estimate of the relative importance of outcomes and individual preferences? Yes ☑ No ☐	Patients with Parkinson's disease have diverse perspectives on deprescribing medications, reflecting their unique experiences and priorities. Some people fear that reducing or stopping therapy could lead to a worsening of symptoms (e.g. tremors, rigidity) which would negatively affect their quality of life. Quality of life is central to how patients view their treatment. Many prefer interventions that minimise embarrassment and preserve their dignity, as Parkinson's symptoms, such as tremors or mobility challenges, can often lead to feelings of vulnerability. On the other hand, some patients may be hesitant about initiating levodopa, viewing it as a last-resort treatment. This cautious approach often stems from concerns about the side effects of medicines. Patients also emphasise the importance of personalised care that balances symptom relief with the potential for side effects. They value regular reviews of their medicine regimens to ensure appropriate dosing and avoid unnecessary risks, especially as the disease progresses and new health concerns arise. For example, patients with dementia associated with Parkinson's disease often advocate for treatment plans that consider their overall health profile and prioritise comfort and safety over aggressive symptom management. Patients also express concerns about medication interactions, such as those between Parkinson's drugs and antipsychotics, and appreciate when clinicians actively review and adjust their prescriptions to avoid inappropriate prescribing cascades. Overall, patients seek a collaborative approach to their care, valuing open discussions with clinicians that address both the physical and emotional dimensions of living with Parkinson's disease. Their preferences are often centred on maintaining independence, minimising side effects, and	Perspective taken: The lack of evidence for serious harm as a result of deprescribing and evident benefits related to reduced medication burden and costs. Individual values and preferences determine the deprescribing approaches. Sources of values and preferences: 1) Consultation with patient and carer representatives 2) Non-systematic review of evidence Source of variability, if any: Difficult to determine the extent of variability; high variability for patient preferences. Method for determining values satisfactory for this recommendation? Yes ☑ No ☐ Yes, but would be improved with direct patient input

	ensuring that treatment aligns with their individual goals and evolving needs. For healthcare providers, the decision to start or discontinue treatment largely relies on the patient's preference, symptom severity, presence of comorbidities and other sociodemographic factors such as occupation, age and presence of comorbidities.	
Resources Are the resources worth the expected net benefit? Yes ☑ No ☐	A comprehensive economic evaluation was outside the scope of the current review. However, potential cost and resource implications related to deprescribing interventions and continuation of medications are discussed below. Cost implications: Add-on therapies to control emerging symptoms are relatively common as over time motor fluctuations and levodopa-induced dyskinesia develop. Deprescribing of levodopa may lead to worsening of symptoms which may subsequently contribute to a greater burden to the health care system through increased emergency department visits and hospitalisation. On the other hand, levodopa is sometimes prescribed as a result of a prescribing cascade for drug-induced parkinsonism. Inappropriate use of levodopa can lead to increased costs due to medication-related harms. Physician implications: There is a lack of robust data informing the cost of the intervention and subsequently, cost-effectiveness. Most clinicians believe that deprescribing is a complex process, with barriers to resources commonly reported (e.g. suboptimal deprescribing organisational environment that included competing workloads, staffing issues, and limited financial support).	Feasibility: Is this intervention generally available? Yes ☑ No ☐ Opportunity cost: Is this intervention and its effects worth withdrawing or not allocating resources from other interventions? Yes ☑ No ☐ Economic and preventive benefits for harms: Is there a lot of variability in resource requirements across settings? Yes ☐ No ☑
Equity	The social determinants of health equity are complex and multifaceted. The impact of deprescribing on health equity is	

What would be the impact of deprescribing on health inequities? ☑ Uncertain	inadequately explored in the literature. Effective deprescribing of levodopa requires regular monitoring and follow-up appointments. Patients with limited access to healthcare services might face challenges in adhering to monitoring requirements, which could lead to inequities if they are unable to follow the deprescribing plan effectively. Ensuring equitable implementation and addressing potential challenges faced by people with varying health literacy and access disparities is crucial to maximising these benefits. Culturally and linguistically diverse populations, Aboriginal and Torres Strait Islander populations, people with low socioeconomic status, and those living in rural or remote areas may require additional support or considerations when implementing deprescribing intervention, including the ongoing monitoring process.
Acceptability Is the option of deprescribing acceptable to key stakeholders? ☑ Probably yes	Healthcare practitioners: Deprescribing is likely dependent on the preference of the patient and/or their caregiver. Patients, their caregivers and family members: There is a wide variability in the symptoms of Parkinson's disease. No two people experience Parkinson's disease the same way. Deprescribing may be more likely to be acceptable in advanced Parkinson's disease, particularly if medicines are no longer effective or if they increase the risk of adverse outcomes without substantial benefits. In early stages where the motor and non-motor disability are less severe and the related impairment in quality of life is low, deprescribing may be preferred If medicines are causing adverse effects that impact the quality of life. Policymakers and health systems: From a broader perspective, deprescribing can be seen as a way to reduce healthcare costs and improve patient outcomes. However, the short-term impacts on patient care and the resources required to implement effective deprescribing strategies may be a concern.
Overall judgment	There is a lack of quality evidence for deprescribing to inform evidence-based recommendations.

28. Antipsychotics

28.1 Overview of studies targeted antipsychotics

Article	Drug/Class	Study design	Sample size	Follow-up (months)	Withdrawal schedule
Ruths 2004 [219]	Antipsychotics (Haloperidol, olanzapine, risperidone)	RCT	30	1	Abrupt discontinuation
Van Reekum 2002 [220]	Antipsychotics	RCT	33	6	Week 1: half the original dose Week 2: a quarter of the original dose Week 3: cease
Bridges-Parlet 1997 [221]	Antipsychotics	RCT	36	1	Abrupt discontinuation if dose <50mg chlorpromazine equivalent daily. If >50mg chlorpromazine, titration was to halve the dose in week 1 and stop in week 2.
Devanand 2011 [222]	Typical antipsychotics (Haloperidol)	RCT	20	44	Patients on 4 mg daily: Week 1: 2 mg daily, Week 2: 1 mg daily, Week 3: Placebo Patients on 2-3 mg daily: Week 1 & 2: 1 mg daily, Week 3: Placebo Patients on 0.5-1 mg: Directly to placebo
Devanand 2012 [223]	Antipsychotics (risperidone)	RCT	110	11	Not described
Ballard 2008, 2009 [224, 225]	Antipsychotics (risperidone, haloperidol, trifluoperazine, chlorpromazine)	RCT	165	3	Not described
Ballard 2004 [226]	Antipsychotics	RCT	100	12	Not described
Cohen-Mansfield 1999 [227]	Typical antipsychotics (haloperidol, thioridazine)	RCT – crossover	58	5	Tapered over 3 weeks, then ceased
Somani 1996 [228]	Typical antipsychotics (Haloperidol, loxapine, chlorpromazine)	Before and after study	57	8	Tapered by 25% of daily dose each month for 4 months (based upon availability of suitable dosage forms) with a goal of discontinuation at 4

					months
Thapa 1994 [229]	Typical antipsychotics	Prospective cohort study	271	6	Not described
Azermai 2013 [230]	Antipsychotics	Before and after study	40	1	Abrupt discontinuation
Bach 2017 [231]	Antipsychotics	Before and after study	20	4	Gradual dose reduction
Bravo-Jose 2019 [232]	Antipsychotics	Before and after study	35	6	Gradual tapering of antipsychotic treatment according to the standardized deprescription guideline for the study
Brodaty 2018 [233]	Antipsychotics	Before and after study	93	12	Halving the dose every two weeks and then ceasing after two weeks on the minimum dose, one drug at a time
Bergh and Engedal 2008 [234]	Antipsychotics	Before and after study	12	6	Tapered over one week
Horwitz 1995 [235]	Typical antipsychotic	Before and after study	53	12	Not described
Fernandez 2005 [236]	Atypical antipsychotic (quetiapine, clozapine)	Before and after study	6	Not stated	Weaned over 2-8 weeks
Westbury 2018 [237]	Antipsychotics	Before and after study	83	6	Not described

28.2 Evidence for deprescribing antipsychotics

Study	Specific outcome	Odds ratio (95% CI)	Mean difference (95% CI)
1. Mortality			
Ballard 2004	Mortality at 3 months	1.19 (0.23, 6.18)	
Ballard 2008	Mortality at 6 months	0.51 (0.28, 0.96)	
Devanand 2012	Mortality at 4 months	0.38 (0.03, 4.44)	
Ruths 2004	Mortality at 1 month	3.38 (0.33, 34.65)	
Van Reekum 2002	Mortality at 6 months	0.44 (0.04, 5.36)	
2. Adverse drug withdrawal events (ADWEs)			
Exacerbation/return of underlying condition			
Somani 1996	Withdrawal dyskinesia	32.14 (1.67, 617.16)	
Somani 1996	Exacerbation/return of underlying condition	21.12 (1.18, 379.52)	
Bridges-Parlet 1997	At least one exacerbation/return of underlying condition	3.54 (0.16, 79.29)	
Devanand 2012	At least one exacerbation/return of underlying condition	3.07 (1.37, 6.86)	
Ruths 2004	At least one exacerbation/return of underlying condition	2.16 (0.18, 25.32)	
Van Reekum 2002	At least one exacerbation/return of underlying condition	1.33 (0.25, 7.17)	
3. Health outcomes			
Movement disorders			
Ballard 2008	Extrapyramidal symptoms	1.00 (0.54, 1.84)	
Thapa 1994	Involuntary movements, measured using the Abnormal Involuntary Movement Scale (AIMS)		2.37 (-1.57, 6.31)
Somani 1996	Dyskinesias, measured using the Dyskinesia Identification System Condensed User Scale (DISCUS) Instrument		0.10 (-1.35, 1.55)
Ballard 2008	Modified unified Parkinson's disease rating scale (8-point scale)		0.00 (-1.33, 1.33)
Behavioural and psychological symptoms			
Thapa 1994	Behavioural problems, measured using the Nursing Home Behaviour		-1.26 (-4.08, 1.56)

	Problem Scale (NHBPS)		
Bridges-Parlet 1997	Aggression, measured by episodes of physically aggressive behaviour in one week		-3.23 (-8.19, 1.73)
Thapa 1994	Psychiatric symptoms, measured using the Brief Psychiatric Rating Scale		-0.36 (-0.59, -0.13)
Thapa 1994	Depression, measured using the Geriatric Depression Scale		1.24 (-1.77, 4.25)
Ballard 2004	Neuropsychiatric Index		3.00 (-3.69, 9.69)
Ballard 2008	Neuropsychiatric Index		1.60 (-2.63, 5.83)
Ruths 2004	Neuropsychiatric Index		3.00 (0.16, 5.84)
Ballard 2004	Change in Neuropsychiatric Inventory-Nursing Home (NPI-NH)		-1.50 (-6.13, 3.13)
Cohen-Mansfield 1999	Brief Psychiatric Rating Scale (daytime) (typical antipsychotics and benzodiazepines)		-0.20 (-0.48, 0.08)
Cohen-Mansfield 1999	Physical aggression, measured using the Cohen-Mansfield Agitation Inventory (typical antipsychotics and benzodiazepines)		0.05 (-0.17, 0.27)
Falls			
Somani 1996	Number of participants who fell at least once	0.42 (0.13, 1.29)	
Physical function			
Thapa 1994	Activities of daily living, measured using the Lawton's Physical Self-Maintenance Scale		-0.02 (-0.48, 0.44)
Ballard 2008	Activities of daily living, measured using the Bristol ADL		-1.60 (-4.68, 1.48)
Clinical Global Impression Scale			
Cohen-Mansfield 1999	Clinical Global Impression Scale (typical antipsychotics and benzodiazepines)	0.18 (-0.19, 0.55)	
4. Cognitive function			
Thapa 1994	Cognition, measured using the Mini-Mental State Examination		0.04 (-2.09, 2.17)
Ballard 2008	Change in cognition, measured using the standardised Mini-Mental State Examination		-0.80 (-2.47, 0.87)
Ballard 2008	Change in verbal fluency, measured using the Verbal Fluency Task		-3.80 (-6.91, -0.69)
Ballard 2008	Verbal fluency in receptive language, measured using the STALD		-0.20 (-1.07, 0.67)
Ballard 2008	Verbal fluency in expressive language, measured using the Sheffield Test for Acquired Language Disorders (STALD)		-0.80 (-1.79, 0.19)
Ballard 2008	Severe Impairment Battery		2.00 (-4.81, 8.81)
Cohen-Mansfield	Mini-Mental Status Exam (typical antipsychotics and benzodiazepines)		1.60 (-0.28, 3.48)

1999			
5. Quality of life			
Ballard 2004	Quality of life, measured using the Dementia Care Mapping (DCM)		-0.53 (-1.42, 0.36)
6. Effect on medication regimen			
Somani 1996	Unsuccessful deprescribing, medicine reinstated	19.80 (1.01, 388.43)	
Ballard 2008	Deprescribing successful	0.64 (0.32, 1.29)	
Bridges-Parlet 1997	Deprescribing successful	0.61 (0.15, 2.43)	
Curtin 2020	Deprescribing successful	0.08 (0.01, 0.92)	
Devanand 2011	Deprescribing successful	6.00 (0.81, 44.35)	
Ruths 2004	Deprescribing successful	0.10 (0.00, 7.36)	
Cohen-Mansfield 1999	Deprescribing successful (typical antipsychotics and benzodiazepines)	0.01 (0.00, 0.10)	

28.3 Evidence for deprescribing antipsychotics (non-controlled outcomes)

Study	Specific outcome	Result
1. Mortality		
Azermai 2013	Mortality at 1 month	2/40 (5%)
2. Adverse drug withdrawal events (ADWEs)		
Exacerbation/return of underlying condition		
Fernandez 2005	Recurrence of the underlying condition of psychosis in people with comorbid dementia and Parkinson's Disease while continuing levodopa therapy	83%
ADWEs		
Azermai 2013	Mild adverse drug withdrawal effect after abrupt withdrawal	72%
Azermai 2013	Mild physical adverse drug withdrawal symptoms (e.g. nausea, emesis, diarrhoea, vertigo, altered appetite, dyskinesia, parageusia)	15%
Azermai 2013	Mild psychological adverse drug withdrawal symptoms (e.g. agitation, insomnia, anxiety, hallucinations)	67%
3. Health outcomes		
Health service use		
Brodaty 2018	Change in hospital admissions	-10%, p=0.14
Falls		
Brodaty 2018	Change in falls	-14%, p=0.32
Brodaty 2018	Change in number of participants who fell at least once	-10%, p not stated
Movement disorders		
Fernandez 2005	Change in Parkinson's Disease severity (measured using Unified Parkinson's Disease Rating Scale)	44.5 vs. 43.8; p=0.36
Bergh and Engedel 2008	Severity and progression of Parkinson's disease, measured using the Unified Parkinson's Disease Rating Scale (UPDRS)	3.9 ± 2.8 to 2.8 ± 1.6, p not stated
Behavioural and psychological symptoms		
Azermai 2013	Mean difference in Neuropsychiatric Index (NPI) score from baseline to endpoint for those who were successfully deprescribed, higher NPI score indicates more severe neuropsychiatric symptoms	-5.7, p=0.003
Azermai 2013	Mean difference in NPI score from baseline to endpoint for those who were not successfully deprescribed	-3.5, p=0.345

Brodaty 2018	Change in total NPI-NH score	-1.0 point, p=0.58
Bergh and Engedal 2008	NPI score after 24 weeks	33.4 ± 23.9 to 32.0 ± 30.9, p not stated
Bravo-Jose 2019	NPI score after 6 months	12.9 ± 12.8 to 13.8 ± 16.7, p=0.124
Westbury 2018	Agitation/aggression, as measured using the total Cohen-Mansfield Agitation Inventory score for each 10 % reduction in the antipsychotic dose	-0.73 point, p=0.210
Westbury 2018	Behavioural and psychological symptoms for each 10 % reduction in the antipsychotic dose, as measured using the Neuropsychiatric Inventory-Nursing Home version (NPI-NH)	-0.13 point, p=0.782
Westbury 2018	Social withdrawal for each 10 % reduction in the antipsychotic dose, as measured using the Multidimensional Observation Scale for Elderly Subjects-withdrawal subscale (MOSES-withdrawal subscale)	-0.16 point, p=0.192
Bergh and Engedal 2008	Depression, measured using the Cornell score after 24 weeks	7.6 ± 5.8 to 6.7 ± 6.4, p not stated
Brodaty 2018	Agitation/aggression, as measured using the total Cohen-Mansfield Agitation Inventory score	-1.7 point, p=0.37
Brodaty 2018	Social withdrawal	+0.27 point, p=0.52
4. Cognitive function		
Bergh and Engedal 2008	Cognition (measured with the severe impairment battery, which has a scale of 0 to 100) after 24 weeks	49.9 ± 35.2 to 60.3 ± 19.5, p not stated
Brodaty 2018	Cognition (measured with the Psychogeriatric Assessment-Cognitive Impairment Scale (PAS-CIS))	+0.22 points, p=0.56
5. Quality of life		
Westbury 2018	Assessment of Quality of Life-4D (AqoL-4D) utility score for each 10 % reduction in the antipsychotic dose	+0.01 point, p=0.124
6. Effect on medication regimen		
Brodaty 2018	Successfully deprescribed after 3 months	86%
Brodaty 2018	Successfully deprescribed after 6 months	79%
Brodaty 2018	Successfully deprescribed at 12 months	82%
Visser 2021	Successfully withdrawn	80%
Horwitz 1995	Successful deprescribing after 6 months in participants whose doctor	95%

	thought they could be successfully deprescribed	
Horwitz 1995	Successful deprescribing after 12 months in participants where the investigators rather than the person's doctor initiated the withdrawal	50%
Azermai 2013	Successful deprescribing at one month	85%
Westbury 2018	Successfully withdrawn completely or dose reduced after 6 months	39%
Brodaty 2018	Unsuccessful deprescribing (i.e. medicine reinstated)	22%
Bravo-Jose 2019	Antipsychotics reduced to a minimum effective dose	20%
Bach 2017	Residents on antipsychotics	-7%
Westbury 2018	Antipsychotic use	22%
Brodaty 2018	Use of PRN benzodiazepines at 12 months	30%
Westbury 2018	Change in mean chlorpromazine equivalent dose at 4 months, per resident per day	41.2 ± 57.7 mg to 35.3 ± 64.5 mg, p<0.001
Westbury 2018	Change in mean chlorpromazine equivalent dose at 6 months, per resident per day	22.9 ± 174.4 mg to 20.2 ± 151.9 mg, p<0.001

28.4 GRADE evidence profile (critical or important but not critical outcomes only)

Question: In older people, what are the effects of deprescribing (i.e. dose reduction or complete discontinuation) long-term antipsychotics on mortality, adverse drug withdrawal events, health-related outcomes, cognitive function, and quality of life?

Certainty assessment							Number of participants		Effect	Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Depres cribing	Contin uation			
1. Mortality											
5 [219, 220, 223, 225, 226]	RCTs	Serious [1,2]	Not serious	Serious [3]	Serious [4]	Not serious	212	213	OR 0.62 (0.37, 1.05)		8
1 [230]	Non-controlled study	Serious [5,6]	Not serious	Serious [3]	Serious [4]	Not serious	40	N/A	2/40 (5%)		8
2. Adverse drug withdrawal events (ADWEs)											
Exacerbation/return of underlying condition											
4 [219-221, 223]	RCTs	Serious [1,2]	Not serious	Serious [3]	Serious [4]	Not serious	106	128	At least one exacerbation/return of the underlying condition 2.62 (1.33, 5.16)		6
1 [228]	Non-randomised study	Serious [7]	Not serious	Not serious	Serious [4]	Not serious	35	22	Exacerbation/return of the underlying condition 21.12 (1.18, 379.52) [228]		6
1 [236]	Non-controlled study	Serious [5,8]	Not serious	Serious [3]	Serious [4]	Not serious	6	N/A	Recurrence of the underlying condition of psychosis in people with comorbid dementia and Parkinson's Disease while continuing levodopa therapy 83% [236]		6
ADWEs											
1 [228]	Non-randomised study	Serious [7]	Not serious	Not serious	Serious [4]	Not serious	35	22	Withdrawal dyskinesia 32.14 (1.67, 617.16) [228]		6
1 [230]	Non-controlled study	Serious [5,6]	Not serious	Serious [3]	Serious [4]	Not serious	40	N/A	Mild adverse drug withdrawal effect after abrupt withdrawal 72% - Physical adverse drug withdrawal		6

									symptoms (e.g. nausea, emesis, diarrhoea, vertigo, altered appetite, dyskinesia, parageusia) 15% - Psychological adverse drug withdrawal symptoms (e.g. agitation, insomnia, anxiety, hallucinations) 67%		
3. Health outcomes											
Physical function											
1 [225]	RCT	Not serious	Not serious	Serious [3]	Serious [4]	Not serious	52	54	Activities of daily living (ADL), measured using the Bristol ADL -1.60 (-4.68, 1.48)		6
1 [229]	Non-randomised study	Serious [9]	Not serious	Not serious	Serious [4]	Not serious	64	207	Activities of daily living, measured using the Lawton's Physical Self-Maintenance Scale -0.02 (-0.48, 0.44)		6
Clinical Global Impression Scale											
1 [227]	RCTs (typical antipsychotics and benzodiazepine)	Serious [10]	Not serious	Serious [11]	Serious [4]	Not serious	35	35	Clinical Global Impression Scale with higher score indicates more severe illness 0.18 (-0.19, 0.55)		4
Health service use											
1 [233]	Non-controlled study	Serious [5,6,12]	Not serious	Not serious	Serious [4]	Not serious	93	N/A	When considering only participants who had their antipsychotics deprescribed, -10%, p=0.14		5
Falls											
1 [228]	Non-randomised study	Serious [7]	Not serious	Not serious	Serious [4]	Not serious	35	22	Number of participants who fell at least once OR 0.42 (0.13, 1.29)		5
1 [233]	Non-controlled study	Serious [5,6,12]	Not serious	Not serious	Serious [4]	Not serious	93	N/A	When considering only participants who had their antipsychotics deprescribed, were mobile and completed the study, there were no significant differences in falls (reduced from 56.3% to 42.4%, p=0.32). The proportion of participants who fell at least once reduced from 54.2% to 44.7% from pre- to post-intervention (p not stated).		5
Movement disorders											
1 [225]	RCT	Not serious	Not serious	Serious [3]	Serious [4]	Not serious	83	83	Extrapyramidal symptoms OR 1.00 (0.54, 1.84)		5

									Modified unified Parkinson's disease rating scale (8-point scale) MD 0.00 (-1.33, 1.33)		
2 [228, 229]	Non-randomised studies	Serious [7,9]	Not serious	Not serious	Serious [4]	Not serious	99	229	Involuntary movements, measured using the Abnormal Involuntary Movement Scale (AIMS) MD 2.37 (-1.57, 6.31) [229] Dyskinesias, measured using the Dyskinesia Identification System Condensed User Scale (DISCUS) Instrument MD 0.10 (-1.35, 1.55) [228]		5
2 [234, 236]	Non-controlled studies	Serious [5,8,13]	Not serious	Serious [3]	Serious [4]	Not serious	18	N/A	Change in Parkinson's Disease severity (measured using Unified Parkinson's Disease Rating Scale) 44.5 vs. 43.8; p=0.36 [236] Severity and progression of Parkinson's disease, measured using the Unified Parkinson's Disease Rating Scale (UPDRS) 3.9 ± 2.8 to 2.8 ± 1.6 [234]		5
Behavioural and psychological symptoms											
5 [219, 221, 225-227]	RCTs	Serious [1,10]	Not serious	Serious [3,11]	Serious [4]	Not serious	164	155	Deprescribing of antipsychotics was not associated with a significant change in the number of episodes of physically aggressive behaviour in one week (MD -3.23, 95% CI -8.19, 1.73, study = 1, n =36) [221], neuropsychiatric symptoms measured using the Neuropsychiatric Inventory-Nursing Home (MD -1.50, 95% CI -6.13, 3.13, study = 1, n = 82) [226], daytime psychiatric symptoms measured using the Brief Psychiatric Rating Scale (MD -0.20, 95% CI -0.48, 0.08, study = 1, n = 70) [227], or physical aggression measured using the Cohen-Mansfield Agitation Inventory (MD 0.05, 95% CI -0.17, 0.27, study = 1, n = 70) [227]. However, the Neuropsychiatric Inventory score increased significantly in a meta-analysis of three studies (MD 2.61, 95% CI 0.39, 4.84, studies = 3, n = 213), with a higher score indicating more severe symptoms [219, 225, 226].		6

1 [229]	Non-randomised study	Serious [9]	Not serious	Not serious	Serious [4]	Not serious	64	207	Deprescribing of antipsychotics was not associated with a significant change in the behavioural problems measured using the Nursing Home Behaviour Problem Scale (MD -1.26, 95% CI -4.08, 1.56) or depression measured using the Geriatric Depression Scale (MD 1.24, 95% CI -1.77, 4.25). However, psychiatric symptoms appeared to be improved when assessed using the Brief Psychiatric Rating Scale (MD -0.36, 95% CI -0.59, -0.13).		6
5 [230, 232-234, 237]	Non-controlled studies	Serious [14]	Not serious	Serious [3]	Serious [4]	Not serious	254	N/A	In one study, the mean difference in Neuropsychiatric Index (NPI) score from baseline to endpoint for those who were successfully deprescribed was -5.7 (p = 0.003, n = 31) whereas for those who were not successfully deprescribed, the mean difference was -3.5 (p = 0.345, n = 6) [230]. Similarly, the total NPI-NH score improved by -1.0 points (p=0.58, n = 93) in one study [233], and another study, it improved from 33.4 ± 23.9 to 32.0 ± 30.9 (n = 12) [234]. In contrast, one study reported a slight increase in NPI score from 12.9 ± 12.8 at baseline to 13.8 ± 16.7 at 6 months (p = 0.124, n = 35) [232]. For each 10 % reduction in the chlorpromazine daily dose equivalent, behavioural and psychological symptoms improved by 0.13 points (p = 0.782, study = 1, n = 83) on a Neuropsychiatric Inventory-Nursing Home version (NPI-NH) scale, agitation/aggression improved by 0.73 points (p = 0.210, study = 1, n = 83) on a total Cohen-Mansfield Agitation Inventory scale, and social withdrawal improved by 0.16 points (p = 0.192, study = 1, n = 83) on a Multidimensional Observation Scale for Elderly Subjects-withdrawal subscale (MOSES-withdrawal subscale) [237]. Similarly, in a study by Brodaty 2018, agitation/aggression improved by 1.7 points (p		6

									= 0.37, study = 1, n = 93) on a total Cohen-Mansfield Agitation Inventory scale. However, social withdrawal worsened by 0.27 points (p = 0.52, study = 1, n = 93) on a Multidimensional Observation Scale for Elderly Subjects-withdrawal subscale (MOSES-withdrawal subscale). [233] In a study by Bergh and Engedel 2008, depression improved after 24 weeks of deprescribing of antipsychotics when assessed using the Cornell score (from 7.6 ± 5.8 to 6.7 ± 6.4, n = 12) [234].		
4.	Cognitive function										
2 [225, 227]	RCTs	Serious [10]	Not serious	Serious [3,11]	Serious [4]	Not serious	79	75	In a study, deprescribing of either antipsychotics or benzodiazepine (haloperidol, thioridazine, lorazepam) was not associated with a significant change in cognition measured using the standardised Mini-Mental State Examination (MD -0.80, 95% CI -2.47, 0.87), verbal fluency in receptive language (MD -0.20, 95% CI -1.07, 0.67) and expressive language (MD -0.80, 95% CI -1.79, 0.19) measured using the Sheffield Test for Acquired Language Disorders (STALD) as well as Severe Impairment Battery score (MD 2.00, 95% CI -4.81, 8.81) [225]. However, verbal fluency measured using the Verbal Fluency Task deteriorated (MD -3.80, 95% CI -6.91, -0.69) [225]. In another cross-over RCT, deprescribing of antipsychotics was not associated with a significant change in cognition measured using Mini-Mental Status Exam (MD 1.60, 95% CI -0.28, 3.48) [227].		7
1 [229]	Non-randomised study	Serious [9]	Not serious	Not serious	Serious [4]	Not serious	64	207	Cognition, measured using the Mini-Mental State Examination 0.04 (-2.09, 2.17) [229]		7
2 [233, 234]	Non-controlled studies	Serious [5,6,12,13]	Serious [14]	Serious [3]	Serious [4]	Not serious	105	N/A	Two studies reported conflicting results. One study stated cognition deteriorated by 0.22 points (p = 0.56, n = 93) on the		7

									Psychogeriatric Assessment-Cognitive Impairment Scale (PAS-CIS) when not on regular antipsychotics [233] whereas the other study stated cognition improved from 49.9 ± 35.2 to 60.3 ± 19.5 (n = 12) when evaluated using the Severe Impairment Battery after 24 weeks [234].		
5.	Quality of life (QoL)										
1 [226]	RCT	Not serious	Not serious	Serious [3]	Serious [4]	Not serious	36	46	Deprescribing of antipsychotics was not associated with a significant change in well-being (MD -0.53, 95% CI -1.42, 0.36) evaluated using the Dementia Care Mapping (DCM) tool.		7
1 [237]	Non-controlled study	Serious [5,15]	Not serious	Not serious	Not serious	Not serious	83	N/A	For each 10 % reduction in the chlorpromazine daily dose equivalent, quality of life deteriorated by 0.01 points (p = 0.124) on an Assessment of Quality of Life-4D (AqoL-4D) utility scale [237].		7

[1] Ruths 2004 – study combined data from typical and atypical antipsychotics could potentially blur the outcomes. This study assumes that the three antipsychotics studied are equal and that the non-psychotic reasons for prescription are equal. The differences between drugs are substantial. Analysis between drugs should have been done. Reasons for prescription should also be discriminated against. Potential selection bias in patient recruitment and short study duration (4 weeks)
[2] Van Reekum 2002 – High dropout rates and it appears that those who dropped out of the study were excluded from the analysis other than to assess if the two groups were similar in their dropout rates. Potential reporting bias as a few outcomes were not reported.
[3] Potential indirectness - One or more studies included exclusively patients with dementia, Alzheimer's disease, or cognitive impairment which limits the generalisability.
[4] Small sample size
[5] Lack of a true concurrent control group (in one or more studies, the comparison group was those who had failed withdrawal).
[6] Potential detection bias due to the use of non-validated checklists to assess withdrawal and neuropsychiatric symptoms. Potential for confounding factors, such as altered perceptions and attitudes among healthcare staff, but no explicit control for these factors in the analysis.
[7] Somani 1996 – a non-randomised study, group allocation was performed as a joint decision of the attending physician and the physician co-investigator. The criteria for choosing groups are not stated and could introduce selection bias. The study was single-blinded, however, the method to blind the outcome assessors is not described. Moreover, the interrater reliability between the two nurse raters was moderate (correlation coefficient of 0.59), which could introduce some measurement bias.
[8] Fernandez 2005 – this study investigated the deprescribing of antipsychotics in people taking dopamine for Parkinson's Disease. The study was aborted prematurely due to ethical reasons so there was a high risk of confounding.
[9] Non-randomised study - potential for selection bias.
[10] Cohen-Mansfield 1999 - A cross-over study hence carryover effects may be confounded with direct intervention effects. A large number of participants (23/58, 40%) withdrew from the study prematurely. Most of them withdrew before the cross-over stage. However, there was no statistically significant difference in the characteristics of those who discontinued the study compared to those who completed it.
[11] Potential indirectness - Cohen-Mansfield 1999 study included participants taking either haloperidol, thioridazine or lorazepam for agitation. The results from each of the two drug classes could not be differentiated.
[12] Brodaty 2018 - Potential selection bias as the study used a convenience sample of nursing homes and residents/limited control for confounding factors. Potential attrition bias: high attrition rate (33%).
[13] Potential attrition bias in one study (Bergh and Engedal 2008) due to a high dropout rate (13 out of 23 patients)

[14] Heterogeneous outcomes were reported using different measures.
[15] Potential for selection bias as participation was based on nominations by two large national residential aged care facility (RACF) organisations.

28.5 Evidence-to-Decision table

Question: In older people, what are the effects of deprescribing (i.e. dose reduction or complete discontinuation) long-term antipsychotics on mortality, adverse drug withdrawal events, health-related outcomes, cognitive function, and quality of life?

Decision domain	Summary of reason for decision	Subdomains influencing decision
Certainty of evidence Is there a high or moderate certainty of evidence? Yes ☐ No ☑	The certainty of evidence for the benefits of deprescribing is low to very low. The certainty of evidence for the harms of deprescribing is very low.	Key reasons for downgrading: Risk of bias, imprecision Are all critical outcomes measured? Yes ☑ No ☐
Benefits and harms Is there certainty that the benefits of deprescribing outweigh the harms? Yes ☐ No ☑	The effects of deprescribing antipsychotics have been tabulated in Appendix B (GRADE evidence profile table) with an overview provided in the guideline document (a narrative overview and GRADE summary of findings table). Below is a summary according to the study designs. <u>Summary of outcomes</u> Randomised and non-randomised controlled trials: • No significant difference in mortality, activities of daily living, Clinical Global Impression Scale, falls, movement disorders, depression, cognition, and quality of life • Increased withdrawal effects (e.g. withdrawal dyskinesia) • Increased psychosis or behavioural symptoms Deterioration in verbal fluency Neuropsychiatric symptoms appeared to significantly increase on antipsychotic withdrawal in a meta-analysis of three studies, but other studies reported no significant difference. One non-randomised study reported neuropsychiatric symptoms improved on	Is the baseline risk for benefits and harms of deprescribing similar across subgroups? Yes ☐ No ☑ There is no evidence at this time that the benefits or harms of deprescribing differ based on subgroups. However, there will be some groups at a higher risk depending on the indications for use. Should there be separate recommendations for subgroups? Yes ☑ No ☐ The guideline development group acknowledges that certain subgroups may have factors that could impact the balance of benefits and risks from deprescribing. These include the specific type of antipsychotics, indication for use, symptom severity, concurrent medications, comorbidities, functional and cognitive status, adverse drug events, patient care setting, and the availability and feasibility of non-pharmacological strategies to manage behavioural and psychological symptoms (including BPSD). However, the available evidence is insufficient to justify distinct evidence-based recommendations.

antipsychotic withdrawal.

Non-controlled trials:

- No change in physical function
- Reduced hospitalisations
- Reduced falls
- Improved symptoms of movement disorders
- Improved agitation and aggression
- Mortality (5%) (2/40 participants who had their antipsychotic deprescribed)
- Recurrence of psychosis in people with comorbid dementia and Parkinson's Disease (83%)
- Increased physical withdrawal effects (15%)
- Increased psychological withdrawal effects (67%)
- Worsening quality of life

Inconsistent findings across studies for neuropsychiatric symptoms and cognition, most likely due to the different measures used.

Summary of withdrawal schedules:
Randomised controlled trials: (very low certainty evidence)
Week 1: Dose halved, Week 2: Dose quartered, Week 3: Cease (study=1, n=34),
Abrupt discontinuation or titration based on the baseline dose (studies=2, n=80, low certainty evidence),
Abrupt discontinuation (study=1, n=30),
Tapered for 3-weeks then ceased (study=1, n=58),
Not described (studies=4, n=375, n unstated in one study)

	Non-randomised controlled trials: (very low certainty evidence) Tapered at a rate of 25% of the daily dose each month for four months (based upon the availability of suitable dosage forms) with a goal of discontinuation after a maximum of four months (study=1, n=57), Not described (study=1, n=271) Non-controlled trials: (very low certainty evidence) Not described (study=1,n=53), Individualised titration schedule over two to eight weeks (study=1,n=6), Individualised (study=1, n=12157), Abrupt discontinuation (study=1,n=40), Gradual dose reduction or abrupt discontinuation (study=1,n=20), Gradual tapering of antipsychotic treatment according to the standardized deprescription guideline for the study (study=1,n=35), Halving the dose every two weeks and then ceasing after two weeks on the minimum dose, one drug at a time (study=1,n=139)	
Values and preferences Is there confidence in the estimate of the relative importance of outcomes and individual preferences? Yes ☑ No ☐	Patients often have mixed views on antipsychotic use for various indications. While many report symptom relief, side effects that impact their quality of life, work, and social interactions can be an issue. Awareness of the side effects of antipsychotics, such as weight gain, cardiovascular issues, and sexual dysfunction, is a growing concern among patients. They often advocate for individualised treatment plans that weigh the risks and benefits based on their specific circumstances. While patients value guidelines as a foundation for care, they stress the importance of personalised care that reflects their unique health profiles and preferences.	Perspective taken: Individual values and preferences determine the deprescribing approaches. The availability of healthcare professionals to conduct regular monitoring and close observation, and provide non-pharmacological strategies are also important considerations to be able to cease antipsychotics when they are ineffective or they bring more harm than benefit. Sources of values and preferences: 1) Consultation with patient and carer representatives 2) Non-systematic review of evidence Source of variability, if any: Difficult to determine the extent of variability; high variability for patient preferences. Method for determining values satisfactory for this

	Concerns about the administration of chemical restraints and inadequate informed consent processes are another issue, particularly in dementia care, leaving families feeling excluded from decisions about treatment. Overall, patients prioritise maintaining their quality of life and autonomy in treatment decisions. They seek a collaborative approach that ensures their voices, and those of their families, are heard and respected throughout their care journey. Physicians believe symptomatic benefits reported by the patients or their caregivers and antipsychotics being prescribed by another physician are important barriers to attempting deprescribing. Additionally, physical, societal, environmental, psychosocial and physiological factors are all important determinants of a decision to prescribe or deprescribe	recommendation? Yes ☑ No ☐ Yes, but would be improved with direct patient input
Resources Are the resources worth the expected net benefit? Yes ☑ No ☐	A comprehensive economic evaluation was outside the scope of the current review. However, potential cost and resource implications related to deprescribing interventions and continuation of medications are discussed below. Cost implications: There is little evidence on the overall cost implications of long-term antipsychotic exposure. The cost-effectiveness analysis of continuation and discontinuation may be difficult to estimate due to the complexity of clinical indications, health outcomes, the types of deprescribing intervention and the rate of successful implementation. Antipsychotics may be a cheaper alternative to behavioural therapy. However, the serious adverse effects of antipsychotics when used for behavioural and psychological symptoms of	Feasibility: Is this intervention generally available? Yes ☑ No ☐ Opportunity cost: Is this intervention and its effects worth withdrawing or not allocating resources from other interventions? Yes ☑ No ☐ Economic and preventive benefits for harms: Is there a lot of variability in resource requirements across settings? Yes ☐ No ☑

dementia (BPSD) may result in costs that far outweigh the cost of behavioural interventions. On the other hand, deprescribing of antipsychotics for persons with dementia may impose more requirements on caregivers. It is challenging to precisely estimate the amount of time (lost work time, transportation) and both physical and psychological stress on caregivers of persons with dementia. Caregivers may require additional clinical and societal support in providing care. For persons with dementia living at home, this may involve costs of home visits for community-based interventions. For those who cannot be managed at home or in less restrictive settings, the cost of institutionalisation may be substantial. Additional resources are likely in aged care organisations to develop specific expertise and skills in caring for people with severe symptoms, including the use of behavioural strategies, electing a program coordinator, and a regular audit of the care provided to people with dementia. Investing in behavioural interventions may result in lower long-term costs and better outcomes for patients with dementia.

Physician implications:
Physicians will need to closely monitor patients for dose tapering and to assess the impact of deprescribing on ongoing BPSD. Additional clinic visits and extended consultation time are likely required to reassess the person's BPSD and discuss practical strategies with the person and carer/health care team regularly and adjust as BPSD changes. In addition, weaning off antipsychotics may bring significant anxiety to the individual as well as their carers for which psychosocial support will be needed.

Equity What would be the impact of deprescribing on health inequities? ☑ Uncertain	The social determinants of health equity are complex and multifaceted. The impact of deprescribing on health equity is inadequately explored in the literature. Older people affected by the inappropriate use of antipsychotics are likely to derive substantial benefits in terms of health equity from deprescribing. By reducing medication burdens, lowering costs, and simplifying medicine regimens, deprescribing may enhance access to care and improve health outcomes for this vulnerable population. There is a risk that deprescribing antipsychotics could lead to relapse or worsening of symptoms if not managed carefully. This could disproportionately affect vulnerable populations who may have less access to mental health support and crisis intervention services. Exploration of non-pharmacological treatments, such as cognitive behavioural therapy, may be costly and not accessible to all patients. If deprescribing antipsychotics leads to the need for more expensive or less accessible alternatives, it could exacerbate disparities, particularly for those with limited financial resources. Ensuring equitable implementation and addressing potential challenges faced by people with varying health literacy and access disparities is crucial to maximising these benefits. Culturally and linguistically diverse populations, Aboriginal and Torres Strait Islander populations, people with low socioeconomic status, and those living in rural or remote areas may require additional support or considerations when implementing deprescribing intervention, including the ongoing monitoring process.
Acceptability Is the option of deprescribing acceptable to key stakeholders? ☑ Probably yes	Healthcare practitioners: Deprescribing is likely acceptable to most healthcare practitioners, especially when supported by clinical practice guidelines and a shared decision-making process with patients. The term deprescribing may be new to healthcare practitioners but the concept is not. Healthcare practitioners are very familiar with discontinuing ineffective medications or those causing adverse effects worse than the condition being treated. Patients, their caregivers and family members: Many are open to deprescribing if they understand the potential benefits and risks, especially when given the option to restart medications when necessary. Policymakers and health systems: From a broader perspective, deprescribing can be seen as a way to reduce healthcare costs and improve patient outcomes. However, the short-term impacts on patient care and the resources required to implement effective deprescribing strategies may be a concern.
Overall judgment	There is a lack of quality evidence for deprescribing to inform evidence-based recommendations.

Abbreviation: BPSD behavioural and psychological symptoms of dementia

29. Benzodiazepine derivatives used as anxiolytics

29.1 Overview of studies targeted benzodiazepine derivatives used as anxiolytics

Article	Drug/Class	Study design	Sample size	Follow-up (months)	Withdrawal schedule
Habraken 1997 [238]	Benzodiazepines	RCT	55	12	Withdrawn over 5 weeks: 25% reduction per week for weeks 1-3; 12.5% reduction for weeks 4 and 5
Cohen-Mansfield 1999 [227]	Benzodiazepine (lorazepam)	RCT – crossover	58	5	Tapered over 3 weeks, then ceased
Tannenbaum 2014 [239]	Benzodiazepines	Cluster RCT	303	12	21-week tapering protocol
Gnjidic 2019 [240]	Benzodiazepines	RCT	42	1	Not described
Navy 2018 [241]	Benzodiazepine (alprazolam)	RCT	314	6	Individualised
Carr 2019 [242]	Benzodiazepines	Before and after study	12	3	Individualised
Del Giorno 2018 [243]	Benzodiazepines	Before and after study	45597	36	Not described
Fernandes 2022 [244]	Benzodiazepines	Before and after study	64	12	Switched all benzodiazepines into diazepam prior to initiating gradual tapering
Javelot 2018 [245]	Benzodiazepines	Before and after study	31	12	Decrease initial dose by 25% in the first week, continue reducing over 4-10 week
Mendes 2018 (study 1) [246]	Benzodiazepines	Before and after study	3896	9-24	Tapered for up to 12 weeks or ceased abruptly
Westbury 2018 [237]	Benzodiazepines	Before-and-after study	118	6	Not described
da Silva 2022 [247]	Benzodiazepine (clonazepam)	Before and after study	129	2.5	Dose reduced by 25% fortnightly

Chae 2024 [248]	Benzodiazepines (for insomnia and anxiety)	Before and after study	25	12	A tapering plan based on previously published clinical guidelines
Salzman 1992 [249]	Benzodiazepines	Prospective cohort study	25	12	Individualised with gradual tapering over 2 weeks without obvious discomfort
Mendes 2018 (study 2) [246]	Benzodiazepines	Retrospective cohort study	2632	12	Tapered for up to 12 weeks or ceased abruptly
Allary 2024 [250]	Benzodiazepines and Z-drugs	Before and after study	45	12	Gradual dose reductions using a study-specific withdrawal grid over 16 weeks (self-withdrawal or supervised by a physician)

29.2 Evidence for deprescribing benzodiazepine derivatives used as anxiolytics

Study	Specific outcome	Odds ratio (95% CI)	Mean difference (95% CI)
1. Mortality			
Habraken 1997	Mortality at 12 months	0.10 (0.01, 1.93)	
2. Adverse drug withdrawal events (ADWEs)			
No available evidence			
3. Health outcomes			
Behavioural and psychological symptoms			
Cohen-Mansfield 1999	Brief Psychiatric Rating Scale (daytime) (typical antipsychotics and benzodiazepines)		-0.20 (-0.48, 0.08)
Cohen-Mansfield 1999	Physical aggression, measured using the Cohen-Mansfield Agitation Inventory (daytime) (typical antipsychotics and benzodiazepines)		0.05 (-0.17, 0.27)
Physical function			
Habraken 1997	Change in daily functioning, measured using the geriatrics behavioural observational scale		-7.60 (-14.28, -0.92)
Clinical Global Impression Scale			
Cohen-Mansfield 1999	Clinical Global Impression Scale (typical antipsychotics and benzodiazepines)		0.18 (-0.19, 0.55)
4. Cognitive function			
Cohen-Mansfield 1999	Mini-Mental Status Exam (typical antipsychotics and benzodiazepines)		1.60 (-0.28, 3.48)
Salzman 1992	Memory, measured using the WAIS-R digit span test		-1.90 (-3.40, -0.40)
5. Quality of life			
No available evidence			
6. Effect on medication regimen			
Gnjidic 2019	Deprescribing successful	1.46 (0.26, 8.05)	
Tannenbaum 2014	Deprescribing successful	0.13 (0.06, 0.30)	
Navy 2018	Number of participants who discontinued alprazolam	0.57 (0.27, 1.17)	
Navy 2018	Number of participants with >50% alprazolam dose reduction	1.21 (0.58, 2.55)	
Mendes 2018 (study 2)	Benzodiazepines discontinuation	0.70 (0.61, 0.81)	
Salzman 1992	Successful deprescribing at 12 months	21.67 (1.06, 442.04)	

Cohen-Mansfield 1999	Deprescribing successful (typical antipsychotics and benzodiazepines)	0.01 (0.00, 0.10)

29.3 Evidence for deprescribing benzodiazepine derivatives used as anxiolytics (non-controlled outcomes)

Study	Specific outcome	Result
1. Mortality		
No available evidence		
2. Adverse drug withdrawal events (ADWEs)		
Carr 2019	At least one withdrawal symptom	6/11 (55%)
Fernandes 2022	At least one withdrawal symptom	31/66 (47%)
3. Health outcomes		
Falls		
Javelot 2018	Change in the number of falls	2.3 ± 0.6 vs. 0.5 ± 0.2, p = 0.01
Behavioural and psychological symptoms		
Westbury 2018	Behavioural and psychological symptoms for each 10 % reduction in the benzodiazepine dose, as measured using the Neuropsychiatric Inventory-Nursing Home version (NPI-NH)	-0.38 points, p=0.153
Westbury 2018	Agitation/aggression, as measured by total Cohen-Mansfield Agitation Inventory score for each 10 % reduction in the benzodiazepine dose	-0.49 points, p=0.078
Westbury 2018	Social withdrawal for each 10 % reduction in the benzodiazepine dose, as measured using the Multidimensional Observation Scale for Elderly Subjects-withdrawal subscale (MOSES-withdrawal subscale)	+0.04 points, p=0.590
Sleep quality		
Allary 2024	Association between a change in benzodiazepine and Z-drug use and the change in sleep quality between baseline and 12 months after discontinuation	0.208, non-statistically significant (Unstandardised regression coefficient, p-value)
Depressive symptoms		
Allary 2024	Association between a change in benzodiazepine and Z-drug use and the intensity of depressive symptoms change between baseline and 12 months after discontinuation	0.879, p < .01 (Unstandardised regression coefficient, p-value) which translates to reduced depressive symptoms with reduced benzodiazepine or Z-drug use
Worry intensity		

Allary 2024	Association between a change in benzodiazepine and Z-drug use and the change in worry intensity between baseline and 12 months after discontinuation	0.312, non-statistically significant (Unstandardised regression coefficient, p-value)
4. Cognitive function		
No available evidence		
5. Quality of life		
No available evidence		
6. Effect on medication regimen		
Carr 2019	Successfully withdrawn	6/11 (55%)
Fernandes 2022	Successfully withdrawn	11/31 (35%)
Javelot 2018	Successfully withdrawn	38/66 (59%)
Fernandes 2022	Successfully deprescribed at 12 months	85%
Chae 2023	Successfully deprescribed at 12 months	64%
Del Giorno 2018	Change in new benzodiazepine prescriptions initiated, monthly	-1.70%, p<0.001
Da Silva 2022	Successfully withdrawn completely or dose reduced	82%
Mendes 2018 (study 1)	Dose reduced	47%
Mendes 2018 (study 1)	Dose tapered and then discontinued	12%
Mendes 2018 (study 1)	Discontinued immediately without tapering	12%
Mendes 2018 (study 1)	Dose increased	15%
Mendes 2018 (study 1)	Dose remained	14%
Westbury 2018	Successfully withdrawn completely or dose reduced after 6 months	39%
Westbury 2018	Benzodiazepine use	18%
Westbury 2018	Change in mean diazepam equivalent dose at 6 months, per resident per day	1.4 ± 5.6 mg to 1.1 ± 8.4, p<0.001
Westbury 2018	Change in mean diazepam equivalent dose at 4 months, per resident per day	5.1 ± 5.5 mg to 4.3 ± 6.1, p<0.001

29.4 GRADE evidence profile (critical or important but not critical outcomes only)

Question: In older people, what are the effects of deprescribing (i.e. dose reduction or complete discontinuation) long-term benzodiazepine derivatives used as anxiolytics on mortality, adverse drug withdrawal events, health-related outcomes, cognitive function, and quality of life?

Certainty assessment							Number of participants		Effect	Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Deprescribing	Continuation			
1. Mortality											
1 [238]	RCT	Serious [1,2]	Not serious	Not serious	Serious [3]	Not serious	27	28	0.10 (0.01 to 1.93)	⨁◯◯◯	8
2. Adverse drug withdrawal events (ADWEs)											
ADWEs											
2 [242, 244]	Non-controlled studies	Serious [4]	Not serious	Not serious	Serious [3]	Not serious	77	N/A	At least one withdrawal symptoms: • 6/11 (55%), presented as worsening anxiety symptoms and withdrawal symptoms [242] • 31/66 (47%), presented as insomnia and anxiety [244]	⨁◯◯◯	6
3. Health outcomes											
Behavioural and psychological symptoms											
1 [227]	RCT (typical antipsychotics and benzodiazepine)	Serious [5]	Not serious	Serious [6]	Serious [3]	Not serious	35	35	Brief Psychiatric Rating Scale (daytime) where a higher score indicates more severe psychiatrically impairment MD -0.20 (-0.48, 0.08) Physical aggression, measured using the Cohen-Mansfield Agitation Inventory (daytime) where a higher score indicates more pronounced agitation MD 0.05 (-0.17, 0.27)	⨁◯◯◯	6
1 [237]	Non-controlled study	Serious [4]	Not serious	Not serious	Serious [3]	Not serious	118	N/A	For each 10 % reduction in the diazepam daily dose equivalent, behavioural and psychological symptoms improved by 0.38 points (p=0.153) on a Neuropsychiatric Inventory-Nursing Home version (NPI-NH) scale, agitation/aggression improved by 0.49 points (p=0.078) on a total Cohen-Mansfield Agitation Inventory scale, and social withdrawal worsened by 0.04 points (p=0.590) on a Multidimensional Observation Scale for Elderly Subjects-withdrawal subscale	⨁◯◯◯	6

									(MOSES-withdrawal subscale).		
Physical function											
1 [238]	RCT	Serious [1,2]	Not serious	Not serious	Serious [3]	Not serious	15	18	Change in daily functioning, measured using the Geriatrics Behavioural Observational Scale where a higher score indicates better functioning MD -7.60 (-14.28, -0.92)		6
Clinical Global Impression Scale											
1 [227]	RCT (typical antipsychotics and benzodiazepine)	Serious [5]	Not serious	Serious [6]	Serious [3]	Not serious	35	35	Clinical Global Impression Scale where a higher score indicates more severe illness MD 0.18 (-0.19, 0.55)		4
Falls											
1 [245]	Non-controlled study	Serious [4,7]	Not serious	Not serious	Serious [3]	Not serious	11	N/A	Change in the number of falls 2.3 ± 0.6 vs. 0.5 ± 0.2, p = 0.01		5
Sleep quality											
1 [250]	Non-controlled study	Serious [4,10,11]	Not serious	Not serious	Serious [3]	Not serious	45	N/A	Unstandardised regression coefficient 0.208 (a non-statistically significant improvement in sleep quality associated with reduced benzodiazepine or Z-drug use		6
Depressive symptoms											
1 [250]	Non-controlled study	Serious [4,10,11]	Not serious	Not serious	Serious [3]	Not serious	45	N/A	0.879, p < .01 (Unstandardised regression coefficient, p-value) which translates to reduced depressive symptoms with reduced benzodiazepine or Z-drug use		6
Worry intensity											
1 [250]	Non-controlled study	Serious [4,10,11]	Not serious	Not serious	Serious [3]	Not serious	45	N/A	Unstandardised regression coefficient 0.312 (a non-statistically significant improvement in worry intensity associated with reduced benzodiazepine or Z-drug use		6
4. Cognitive function											
1 [227]	RCT (typical antipsychotics and benzodiazepine)	Serious [5]	Not serious	Serious [6]	Serious [3]	Not serious	35	35	Cognition, measured using Mini-Mental Status Exam MD 1.60 (-0.28, 3.48)		7
1 [249]	Non-randomised study	Serious [8,9]	Not serious	Not serious	Serious [3]	Not serious	13	12	Memory, measured using WAIS-R digit span test MD -1.90 (-3.40, -0.40)		7
5. Quality of life (QoL)											
No available evidence											

[1] Potential attrition bias - approximately one-third of subjects in both study groups withdrew from the study with the reasons for dropouts likely related to intervention.
[2] Lorazepam was chosen as the standardized benzodiazepine. This is an inherent methodological design flaw as lorazepam has a relatively short half-life compared to other benzodiazepines and is more likely to cause withdrawal symptoms than diazepam for instance.
[3] Small sample size and/or wide confidence intervals in the estimates of effect
[4] Non-controlled study; potential for selection and detection biases
[5] Potential biases - Cohen-Mansfield 1999 was a cross-over study hence carryover effects may be confounded with direct intervention effects. A large number of participants (23/58, 40%) withdrew from the study prematurely. Most of them withdrew before the cross-over stage. However, there was no statistically significant difference in the characteristics of those who discontinued the study compared to those who completed it.
[6] Potential indirectness - Study included participants taking either haloperidol, thioridazine or lorazepam for agitation. The results from each of the two drug classes could not be differentiated.
[7] Potential of selection, performance, detection, attrition, and reporting bias
[8] Non-randomised study and study was not blinded, which could introduce performance bias. Other potential confounding factors (e.g., concomitant medications, cognitive impairment) could also introduce bias.
[9] Potential for selection bias - residents were allocated based on their physician's recommendation, hence it was based on the medical practitioner's opinion of whether the benzodiazepine could be withdrawn safely and feasibly. Those patients more likely to suffer adverse effects in the opinion of their prescriber were excluded from the study.
[10] Potential attrition bias – in one study (Allary 2024), approximately 40% of participants (n=28/75) did not have follow-up data at 12-months.
[11] The study included people taking benzodiazepine or Z-drug. It was stated that "To simplify reading, the term BZD will include Z-drugs in this research". It was unclear the proportion of participants taking each drug and changes in anxiety symptoms were not measured which could potentially limit the generalisability of the findings given that benzodiazepines are indicated for the management of anxiety.

29.5 Evidence-to-Decision table

Question: In older people, what are the effects of deprescribing (i.e. dose reduction or complete discontinuation) long-term benzodiazepine derivatives used as anxiolytics on mortality, adverse drug withdrawal events, health-related outcomes, cognitive function, and quality of life?

Decision domain	Summary of reason for decision	Subdomains influencing decision
Certainty of evidence Is there a high or moderate certainty of evidence? Yes ☐ No ☑	The certainty of evidence for the benefits of deprescribing is low to very low. The certainty of evidence for the harms of deprescribing is very low.	Key reasons for downgrading: Risk of bias, imprecision Are all critical outcomes measured? Yes ☐ No ☑ There is a lack of evidence on quality of life.
Benefits and harms Is there certainty that the benefits of deprescribing outweigh the harms? Yes ☐ No ☑	The effects of deprescribing benzodiazepine derivatives used as anxiolytics have been tabulated in Appendix B (GRADE evidence profile table) with an overview provided in the guideline document (a narrative overview and GRADE summary of findings table). Below is a summary according to the study designs. <u>Summary of outcomes</u> Randomised and non-randomised controlled trials: • No significant difference in mortality, physical aggression, psychiatric symptoms, and Clinical Global Impression Scale • Improved daily functioning Inconsistent findings across studies for cognitive function where a randomised controlled trial showed no difference in cognition, but a non-randomised controlled trial showed improved memory. Non-controlled trials: • Improved behavioural and psychological symptoms, agitation, aggression • Improved depressive symptoms	Is the baseline risk for benefits and harms of deprescribing similar across subgroups? Yes ☐ No ☑ Evidence at this time suggests that the benefits of deprescribing may be more pronounced in people who have a decline in daily functioning. Should there be separate recommendations for subgroups? Yes ☑ No ☐ The guideline development group acknowledges that certain subgroups may have factors that could impact the balance of benefits and risks from deprescribing (e.g. type of benzodiazepines, indication for use, severity of symptoms, concomitant medications, other important comorbidities, functional status, cognitive status, and presence of adverse drug events). However, the available evidence is insufficient to justify distinct evidence-based recommendations.

	• Reduced falls • Worsening social withdrawal • Worsening symptoms (47-55%) • No change in worry intensity or sleep quality <u>Summary of withdrawal schedules:</u> Randomised controlled trials: 25% reduction per week for first three weeks, then 12.5% reduction for the final two weeks (study=1, n=55, low certainty evidence), Titrated over 21 weeks (study=1, n=303, low certainty of evidence), Individualised (study=1, n=314, very low certainty), Tapered for 3-weeks then ceased (study=1, n=58, very low certainty), Not described (study=1, n=42), Non-randomised controlled trials: (very low certainty) Tapered for up to 12 weeks or ceased abruptly (studies=2, n=6528), Individualised with gradual tapering of the benzodiazepine over two weeks (study=1, n=25) Non-controlled trials: (very low certainty) Individualised (studies=2, n=12169), Not described (study=1, n=45597), Switched all benzodiazepines into diazepam prior to initiating gradual tapering (study=1, n=64), Decrease initial dose by 25% in the first week, continue reducing over 4-10 weeks (study=1, n=31), Tapering plan based on previously published clinical guidelines (study=1, n=25), Dose reduced by 25% (study=1, n=129), Gradual dose reduction for up to 16 weeks (study=1, n=45 very low certainty).	
Values and preferences Is there	Many patients report a lack of counselling regarding benzodiazepine use. Patients often are unaware that benzodiazepines are recommended for short-term	Perspective taken: Individual values and preferences determine the deprescribing approaches. The availability of healthcare professionals to conduct regular monitoring and close

confidence in the estimate of the relative importance of outcomes and individual preferences? Yes ☑ No ☐	use only, and there is a high risk of dependence which can present challenges during discontinuation. Patients value appropriate counselling before initiating benzodiazepines and prefer a clear education about the risks of harm and potential benefits from their healthcare providers. If deprescribing is to be attempted, patients prefer adequate support systems and stress the importance of monitoring withdrawal symptoms, which may sometimes be attributed to other underlying conditions rather than deprescribing itself. Many patients are also concerned about the significant gap in the transition of care. They value a collaborative care coordination approach among healthcare providers to ensure continuous support, clear communication and shared decision-making throughout their care journey. Physicians are aware of the potential side effects of benzodiazepines. Some physicians believe chronic use is justified if their patients feel better without any adverse events, with some believing that benzodiazepines are more effective than available alternatives. Patient resistance is commonly cited as a major barrier to deprescribing benzodiazepines.	observation is also an important consideration to be able to cease benzodiazepines when they are ineffective or bring more harm than benefit. Sources of values and preferences: 1) Consultation with patient and carer representatives 2) Non-systematic review of evidence Source of variability, if any: Difficult to determine the extent of variability; high variability for patient preferences. Method for determining values satisfactory for this recommendation? Yes ☑ No ☐ Yes, but would be improved with direct patient input
Resources Are the resources worth the expected net benefit? Yes ☑ No ☐	A comprehensive economic evaluation was outside the scope of the current review. However, potential cost and resource implications related to deprescribing interventions and continuation of medications are discussed below. Cost implications: The adverse drug reactions and societal impact of benzodiazepines have been linked to many avoidable healthcare costs. Cost-effectiveness studies showed a direct reduction in	Feasibility: Is this intervention generally available? Yes ☑ No ☐ Opportunity cost: Is this intervention and its effects worth withdrawing or not allocating resources from other interventions? Yes ☑ No ☐ Economic and preventive benefits for harms: Is there a lot of variability in resource requirements across settings? Yes ☐ No ☑

	medication costs after deprescribing benzodiazepines, and other related healthcare utilisation costs related to adverse events (e.g. hospitalisations, emergency department and outpatient visits associated with benzodiazepine-related fall injuries). However, it is crucial to take into consideration the costs associated with non-pharmacological methods to manage ongoing symptoms, and additional support needed such as psychological interventions following deprescribing of benzodiazepines. Physician implications: Physicians will need to closely monitor patients for dose tapering and to assess the impact of deprescribing on ongoing symptoms. Additional clinic visits and extended consultation time are likely required to reassess the person's symptoms, discuss practical strategies with the person and carer/health care team regularly and adjust as symptoms change. In addition, weaning off benzodiazepines may bring significant anxiety to the individual for which psychosocial support will be needed.	
Equity What would be the impact of deprescribing on health inequities? ☑ Uncertain	The social determinants of health equity are complex and multifaceted. The impact of deprescribing on health equity is inadequately explored in the literature. Older people affected by the inappropriate use of benzodiazepines are likely to derive substantial benefits in terms of health equity from deprescribing. By reducing medication burdens, lowering costs, and simplifying medicine regimens, deprescribing may enhance access to care and improve health outcomes for this vulnerable population. However, there may be people with limited access to mental health services or specialists who can appropriately manage and monitor the deprescribing process. Exploration of non-pharmacological treatments, such as cognitive-behavioural therapy (CBT) may be costly and not accessible to all patients. If deprescribing benzodiazepines leads to the need for more expensive or less accessible alternatives, it could exacerbate disparities, particularly for those with limited financial resources. Ensuring equitable implementation and addressing potential challenges faced by people with varying health literacy and access disparities is crucial to maximising these benefits. Culturally and linguistically diverse populations, Aboriginal and Torres Strait Islander populations, people with low socioeconomic status, and those living in rural or	

	remote areas may require additional support or considerations when implementing deprescribing intervention, including the ongoing monitoring process. On the other hand, successful deprescribing of benzodiazepines can help reduce the stigma associated with their use, which can be important for patients in marginalized communities who may already face stigma related to mental health conditions.
Acceptability Is the option of deprescribing acceptable to key stakeholders? ☑ Probably yes	Healthcare practitioners: Deprescribing is likely acceptable to most healthcare practitioners, especially when supported by clinical practice guidelines and a shared decision-making process with patients. The term deprescribing may be new to healthcare practitioners but the concept is not. Healthcare practitioners are very familiar with discontinuing ineffective medications or those causing adverse effects worse than the condition being treated. Patients, their caregivers and family members: Many are open to deprescribing if they understand the potential benefits and risks, especially when given the option to restart medications when necessary. Policymakers and health systems: From a broader perspective, deprescribing can be seen as a way to reduce healthcare costs and improve patient outcomes. However, the short-term impacts on patient care and the resources required to implement effective deprescribing strategies may be a concern.
Overall judgment	There is a lack of quality evidence for deprescribing to inform evidence-based recommendations.

Abbreviation: BPSD behavioural and psychological symptoms of dementia

30. Hypnotics and sedatives

30.1 Overview of studies targeted hypnotics and sedatives

Article	Drug/Class	Study design	Sample size	Follow-up (months)	Withdrawal schedule
Bourgeois 2014 [251]	Benzodiazepines and Z-drugs	Before and after study	38	8	Not strictly set but researchers suggested a 25% reduction every 1 to 2 weeks.
Lui 2021 [252]	Benzodiazepines and Z-drugs	Before and after study	111	6	Individualised (stop or taper)
Fixen 2022 [253]	Benzodiazepines or non-benzodiazepine sedative hypnotics	Before and after study	93	9	Not described
Wilson 2018 [254]	Benzodiazepines or non-benzodiazepine sedative hypnotics	Before and after study	62	1	Not described
Kuntz 2019 [255]	Non-benzodiazepine sedative hypnotics (Z drugs)	RCT	149	6	Individualised
Tabloski 1998 [256]	Sedative hypnotics	RCT	20	1.25	Dose reduced by half over one week, then cease
Kosto 2023 [257]	Sedative hypnotics (Benzodiazepines and Z-drugs)	Retrospective cohort study	215	3	Drug-specific ‘tapering down table’
Puustinen 2014 [258]	Benzodiazepines (zopiclone, zolpidem and temazepam)	Retrospective cohort study	89	6	Withdrawn over one month by replacing either with melatonin or a placebo
Gemelli 2016 [259]	Sedative hypnotics	Before and after study	36	4	Gradual dose reductions or abrupt discontinuation
Ragan 2021 [260]	Sedative hypnotics	Before and after study	155 prescribers (participant numbers unknown)	36	Not described
Fung 2024	Benzodiazepines and Z-drugs	Before and	176	6	Gradual dose reductions

[261]	(lorazepam, alprazolam, clonazepam, temazepam, and/or zolpidem)	after study			
Gardner 2024 [262]	Sedative hypnotics (Benzodiazepines and Z-drugs) excluding other sedatives	RCT	565	6	Not described
Allary 2024 [250]	Benzodiazepines and Z-drugs	Before and after study	45	12	Gradual dose reductions using a study-specific withdrawal grid over 16 weeks (self-withdrawal or supervised by a physician)
Van der Linden 2023 [263]	Sedative hypnotics (Benzodiazepines and Z-drugs)	Before and after study	173	1	Standardised tapering regimen, abrupt discontinuation, or “any attempt”
Chae 2024 [248]	Benzodiazepines (for insomnia and anxiety)	Before and after study	25	12	A tapering plan based on previously published clinical guidelines
Curran 2003 [264]	Benzodiazepines (temazepam, nitrazepam, alprazolam)	RCT	138	12	Dose titration regime devised to minimise the risk of withdrawal, according to each patient’s original dose and benzodiazepine
Petrovic 2002 [265]	Benzodiazepines (lormetazepam)	RCT	40	12	One week of 1mg lormetazepam, which was less than half the average daily benzodiazepine dose
Tham 1989 [266]	Benzodiazepines (temazepam)	RCT	36	Unstated	Abrupt withdrawal group: switched straight to a placebo for 10 days Gradual withdrawal group: 5mg temazepam for 4 days, 2mg temazepam for 4 days, placebo for 2 days
Tsunoda 2010 [267]	Benzodiazepines (brotizolam, flunitrazepam, etizolam, quazepam, estazolam, nitrazepam, flurazepam, diazepam)	Before and after study	30	2	Weekly reduction of 25% from baseline for 3 weeks

30.2 Evidence for deprescribing hypnotics and sedatives

Study	Specific outcome	Odds ratio (95% CI)	Mean difference (95% CI)
1. Mortality			
Curran 2003	Mortality at 12 weeks	0.29 (0.01, 7.32)	
2. Adverse drug withdrawal events (ADWEs)			
Petrovic 2002	ADWEs, number of participants who experienced at least one exacerbation	0.21 (0.02, 2.08)	
Gardner 2024	ADWEs, number of participants who experienced adverse drug withdrawal event	1.58 (0.54, 4.66)	
Curran 2003	ADWEs, measured using the Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ)		1.50 (-6.09, 9.09)
3. Health outcomes			
Health service use			
Kuntz 2019	Hospitalisations, average per participant	-0.10 (-0.16, -0.04)	
Kuntz 2019	Emergency room presentation, rate	0.00 (-0.17, 0.17)	
Sleep			
Tabloski 1998	Sleep latency, minutes		-13.70 (-26.95, -0.45)
Tabloski 1998	Total sleep time, hours		1.43 (0.88, 1.97)
Tabloski 1998	Wakefulness after sleep onset		-28.50 (-45.60, -11.40)
Tabloski 1998	Number of wakes		0.30 (-0.54, 1.14)
Tabloski 1998	Longest sleep duration, minutes		28.00 (14.90, 41.10)
Tham 1989	Total sleep time, hours		0.00 (-0.83, 0.83)
Kosto 2023	Sleep quality, measured by the Pittsburgh Sleep Quality Index (PSQI)		-3.30 (-5.09, -1.51)
Van der Linden 2023	Sleep quality, measured by the Pittsburgh Sleep Quality Index (PSQI)		-0.17 (-1.27, 0.93)
Behavioural and psychological symptoms			
Curran 2003	Depression, measured using the Geriatric Depression Scale		0.30 (-0.85, 1.45)
Delirium			
Van der Linden 2023	Delirium	1.14 (0.44, 2.96)	

Falls			
Van der Linden 2023	Number of participants who fell at least once	0.86 (0.31, 2.38)	
4. Cognitive function			
No available evidence			
5. Quality of life			
Curran 2003	Quality of life, measured using the Short Form-36		0.00 (-12.97, 12.97)
6. Effect on medication regimen			
Curran 2003	Deprescribing successful	0.26 (0.00, 13.35)	
Petrovic 2002	Deprescribing successful	0.25 (0.06, 1.02)	
Kosto 2023	Deprescribing successful	0.05 (0.01, 0.22)	
Kuntz 2019	Deprescribing successful	0.28 (0.13, 0.59)	
Van der Linden 2023	Deprescribing successful	0.46 (0.24, 0.90)	
Gardner 2024	Benzodiazepines discontinuation at 6 months	0.27 (0.15, 0.48)	
Gardner 2024	Benzodiazepines dose reduction at 6 months	0.70 (0.42, 1.15)	
Van der Linden 2023	Benzodiazepines discontinuation	0.05 (0.01, 0.24)	
Van der Linden 2023	Z-drugs discontinuation	1.27 (0.39, 4.10)	
Van der Linden 2023	Emergency antipsychotic use	0.41 (0.04, 4.00)	
Van der Linden 2023	Emergency hypnotics use	1.07 (0.35, 3.34)	
Kuntz 2019	Number of Z drugs dispensing	-0.90 (-1.44, -0.36)	

30.3 Evidence for deprescribing hypnotics and sedatives (non-controlled outcomes)

Study	Specific outcome	Result
1. Mortality		
Bourgeois 2014	Death at 8 months (benzodiazepines and Z-drugs)	1/38 (3%)
2. Adverse drug withdrawal events (ADWEs)		
Bourgeois 2014	Benzodiazepine Withdrawal Symptom Questionnaire (benzodiazepines and Z-drugs)	3.9 ± 2.8 to 4.1 ± 2.6, p = 0.865
Fixen 2022	Adverse drug withdrawal events (benzodiazepines or non-benzodiazepine sedative hypnotics)	19%
Tsunoda 2010	Recurrence of underlying condition	13%
Fung 2024	Insomnia Severity Index, with lower scores indicate lower severity of insomnia	Masked taper group: Difference from baseline to 6 months, −6.41, 95% CI −7.87 to −4.95 (P < .001) Unmasked taper group: Difference from baseline to 6 months, −6.57, 95%CI −8.00 to −5.14 (P < .001)
Allary 2024	Association between a change in benzodiazepine and Z-drug use and the change in sleep quality between baseline and 12 months after discontinuation	0.208, non-statistically significant (Unstandardised regression coefficient, p-value)
3. Health outcomes		
Body stability		
Tsunoda 2010	Stability of body (measured by the total length of the trunk motion with eyes closed)	-1.5cm, p=0.002
Tsunoda 2010	Stability of body (measured by the range of the trunk motion with both the eyes open)	-0.02cm, p=0.046
Tsunoda 2010	Stability of body (measured by the range of the trunk motion with both the eyes closed)	-1.51cm, p=0.01

Falls		
Fung 2024	Falls that led to the discontinuation of the intervention or hospitalisation/emergency department presentation	3/176 (2%)
Depressive symptoms		
Allary 2024	Association between a change in benzodiazepine and Z-drug use and the intensity of depressive symptoms change between baseline and 12 months after discontinuation	0.879, p < .01 (Unstandardised regression coefficient, p-value) which translates to reduced depressive symptoms with reduced benzodiazepine or Z-drug use
Worry intensity		
Allary 2024	Association between a change in benzodiazepine and Z-drug use and the change in worry intensity between baseline and 12 months after discontinuation	0.312, non-statistically significant (Unstandardised regression coefficient, p-value)
4. Cognitive function		
Tsunoda 2010	Cognitive function (Repeatable Battery for the Assessment of Neuropsychological Status score where a higher score indicates a better cognitive function) in the domain of immediate memory	+10.3, p<0.001
Tsunoda 2010	Cognitive function (Repeatable Battery for the Assessment of Neuropsychological Status score where a higher score indicates a better cognitive function) in the domain of visuospatial	+6.1, p=0.036
Tsunoda 2010	Cognitive function (Repeatable Battery for the Assessment of Neuropsychological Status score where a higher score indicates a better cognitive function) in the domain of language	+5.2, p=0.007
Tsunoda 2010	Cognitive function (Repeatable Battery for the Assessment of Neuropsychological Status score where a higher score indicates a better cognitive function) in the domain of attention	+13.8, p<0.001
Tsunoda 2010	Cognitive function (Repeatable Battery for the Assessment of Neuropsychological Status score where a higher score indicates a better cognitive function) in the domain of delayed memory	+7.8, p=0.015
Tsunoda 2010	Central fatigue (measured using the critical flicker fusion test where a lower score is associated with higher levels of central fatigue)	+2.1, p<0.001
5. Quality of life		
Bourgeois 2014	Quality of life measured with the EuroQol-5D (benzodiazepines and Z-drugs)	0.439 to 0.456, p = 0.879

6. Effect on medication regimen		
Lui 2021	Successfully withdrawn completely or dose reduced (benzodiazepines and Z-drugs)	64%
Lui 2021	Successfully deprescribed after 6 months (benzodiazepines and Z-drugs)	72%
Fung 2024	Successfully deprescribed after 6 months (benzodiazepines and Z-drugs)	66%
Chae 2023	Successfully deprescribed at 12 months	64%
Fixen 2022	Successfully withdrawn (benzodiazepines or non-benzodiazepine sedative hypnotics)	40%
Wilson 2018	Successfully withdrawn (benzodiazepines or non-benzodiazepine sedative hypnotics)	64%
Gemelli 2016	Successfully withdrawn completely or dose reduced	53%
Ragan 2021	Prevalence of benzodiazepines	-23%, p<0.001
Ragan 2021	Prevalence of benzodiazepine receptor agonists	-15%, p<0.001
Ragan 2021	New benzodiazepine prescriptions	-54%, p<0.001
Ragan 2021	New benzodiazepine receptor agonist prescriptions	-53%, p<0.001
Ragan 2021	Use of alternative medicines for insomnia	+23%, p<0.001
Puustinen 2014	Successfully deprescribed from benzodiazepines after 6 months	38%
Puustinen 2014	Successfully reduced dose from regular to as-required use of benzodiazepines after 6 months	49%

30.4 GRADE evidence profile (critical or important but not critical outcomes only)

Question: In older people, what are the effects of deprescribing (i.e. dose reduction or complete discontinuation) long-term sedative hypnotics on mortality, adverse drug withdrawal events, health-related outcomes, cognitive function, and quality of life?

Certainty assessment							Number of participants		Effect	Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Deprescribing	Continuation			
1. Mortality											
1 [264]	RCT	Serious [1]	Not serious	Not serious	Serious[2]	Not serious	55	49	0.29 (0.01, 7.32)		8
1 [251]	Non-controlled study	Serious [3,4]	Not serious	Serious [5]	Serious[2]	Not serious	38	N/A	This study investigated the deprescribing of benzodiazepines and Z-drugs (most commonly lormetazepam and lorazepam). Death at 8 months was 1/38 (3%).		8
2. Adverse drug withdrawal events (ADWEs)											
ADWEs											
3 [262, 264, 265]	RCTs	Serious [1,6,18]	Not serious	Serious [7]	Serious[2]	Not serious	453	256	There was no significant association between the deprescribing of sedative hypnotics and the number of participants who experienced at least one exacerbation (OR 0.21, 95% CI 0.02. 2.08) [265], ADWEs (OR 1.58, 95% CI 0.54, 4.66) [262], or ADWEs measured using the Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ) (MD 1.50, 95% CI -6.09, 9.09) [264].		6
5 [250, 251, 253, 261, 267]	Non-controlled studies	Serious [3,416,19]	Not serious	Serious [5]	Serious[2]	Not serious	326	N/A	the Benzodiazepine Withdrawal Symptom Questionnaire score increased non-significantly from 3.9 ± 2.8 to 4.1 ± 2.6, p = 0.865 after discontinuation, with higher scores indicating more withdrawal symptoms and the maximum score is 40 [251]. Fixen 2022 investigated deprescribing of benzodiazepines or non-benzodiazepine sedative hypnotics. Among the 37 participants who discontinued the medication, 76% were prescribed the medication for symptoms of insomnia. The other indications were anxiety, insomnia and anxiety, muscle spasms,		6

									essential tremors, and fear of flying. Adverse drug withdrawal events, specifically anxiety was reported by 7 out of 37 participants who discontinued the medication (19%) [253]. Recurrence of the underlying condition, specifically insomnia occurred in 4 out of 30 (13%) participants [267]. Insomnia Severity Index, with lower scores indicate lower severity of insomnia [261] • Masked taper group: Difference from baseline to 6 months, −6.41, 95% CI −7.87 to −4.95 (P < .001) • Unmasked taper group: Difference from baseline to 6 months, −6.57, 95%CI −8.00 to −5.14 (P < .001) [261] Unstandardised regression coefficient 0.208 (a non-statistically significant improvement in sleep quality associated with reduced benzodiazepine or Z-drug use		
3. Health outcomes											
Health service use											
1 [255]	RCT	Serious [8]	Not serious	Not serious	Serious[2]	Serious[9]	99	50	Deprescribing led to a significant reduction in the number of hospitalisations per participant in the intervention group (MD -0.10, 95% CI -0.16, -0.04) but there was no change in the rate of emergency room presentation (MD 0.00, 95% CI -0.17, 0.17).		5
Sleep											
2 [256, 266]	RCT	Serious [10]	Not serious	Serious [11]	Serious[2]	Not serious	46	41	Deprescribing of sedative hypnotics (diphenhydramine, lorazepam, flurazepam, nortriptyline, triazolam) was not associated with a significant difference in the number of wakes (MD 0.30, 95% CI -0.54, 1.14) [256]. The intervention group had a significantly reduced sleep latency (MD -13.70 minutes, 95% CI -26.95, -0.45), and reduced wakefulness after sleep onset (MD -28.50, 95% CI -45.60, -11.40). Control group participants reported longer total sleep time in hours (MD 1.43, 95%		4

									CI 0.88, 1.97) and sleep duration (MD 28.00, 95% CI 14.90, 41.10) [256]. Deprescribing of temazepam was not associated with a significant change in the total sleep time in hours (MD 0.00, 95% CI -0.83, 0.83) [266].		
2 [257, 263]	Non-randomised study	Serious [12,13]	Serious [14]	Not serious	Serious[2]	Not serious	132	210	Change in Pittsburgh Sleep Quality Index MD -1.65 (-4.72, 1.41)		4
Behavioural and psychological symptoms											
1 [264]	RCT	Serious [1]	Not serious	Not serious	Serious[2]	Not serious	48	43	Depression, measured using the Geriatric Depression Scale MD 0.30 (-0.85, 1.45)		6
Body stability											
1 [267]	Non-controlled study	Serious [15]	Not serious	Not serious	Serious[2]	Not serious	26	N/A	Change from baseline to endpoint • Total length of the trunk motion with eyes closed, -1.5cm, p=0.002 • Range of the trunk motion with both eyes open, -0.02cm, p=0.046 • Range of the trunk motion with both eyes closed, -1.51cm, p=0.01		4
Falls											
1 [263]	Non-randomised study	Serious [12]	Not serious	Not serious	Serious[2]	Not serious	77	96	OR 0.86 (0.31, 2.38)		5
1 [261]	Non-controlled study	Serious [16]	Not serious	Not serious	Serious[2]	Not serious	176	N/A	Falls that led to the discontinuation of the intervention or hospitalisation/emergency department presentation 3/176 (2%) [261]		5
Delirium											
1 [263]	Non-randomised study	Serious [12]	Not serious	Not serious	Serious[2]	Not serious	77	96	OR 1.14 (0.44, 2.96)		5
Depressive symptoms											
1 [250]	Non-controlled study	Serious [3,19]	Not serious	Not serious	Serious[2]	Not serious	45	N/A	0.879, p < .01 (Unstandardised regression coefficient, p-value) which translates to reduced depressive symptoms with reduced benzodiazepine or Z-drug use		6
Worry intensity											
1 [250]	Non-controlled	Serious [3,19]	Not serious	Not serious	Serious[2]	Not serious	45	N/A	Unstandardised regression coefficient 0.312 (a non-statistically significant improvement in		6

	study								worry intensity associated with reduced benzodiazepine or Z-drug use		
4.	Cognitive function										
1 [267]	Non-controlled study	Serious [15]	Not serious	Not serious	Serious[2]	Not serious	26	N/A	Cognitive function (Repeatable Battery for the Assessment of Neuropsychological Status score where a higher score indicates a better cognitive function) • Immediate memory, +10.3, p<0.001 • Visuospatial, +6.1, p=0.036 • Language, +5.2, p=0.007 • Attention, +13.8, p<0.001 • Delayed memory, +7.8, p=0.015 • Total scale index score, +8.8, p<0.001 Central fatigue (measured using the critical flicker fusion test where a lower score is associated with higher levels of central fatigue), +2.1, p<0.001		7
5.	Quality of life										
1 [264]	RCT	Serious [1]	Not serious	Not serious	Serious[2]	Not serious	48	43	Quality of life, measured using the Short Form-36 MD 0.00 (-12.97, 12.97)		7
1 [251]	Non-controlled study	Serious [3,4,17]	Not serious	Serious [5]	Serious[2]	Not serious	38	N/A	Quality of life measured with the EuroQol-5D increased non-significantly from 0.439 to 0.456, p = 0.879 after discontinuation, with higher scores indicating better health.		7

[1] Potential selection bias in one study (Curran 2003) – patients wishing to discontinue were chosen to participate, hence might introduce bias toward the outcome assessed (e.g. successful discontinuation or self-reported outcomes).
[2] Small sample size and/or wide confidence intervals in the estimates of effect
[3] Non-controlled studies. Potential detection bias caused by reliance on self-reported outcomes.
[4] Potential selection bias – in one study (Bourgeois 2014), the decision to initiate discontinuation was left to the general practitioner in the study, so not uniform and subject. It was based on the general practitioner's judgement for deprescribing.
[5] Potential indirectness - One study (Bourgeois 2014) only considered benzodiazepines and Z-drugs and not other sedative hypnotics such as sedating antihistamines.
[6] Potential reporting bias - In one study (Petrovic 2002), not all stated outcomes were reported for both control and intervention groups.
[7] Potential indirectness - In one study (Petrovic 2002), the participants should have been stratified for diagnosis. As it was, the authors found a difference when anxiety was part of the patient's profile, in which a quarter (10/40) of the participants were primarily taking the benzodiazepine which could limit the generalisability of the findings.
[8] Randomisation method not described. Potential imbalance in the study groups.
[9] This study appears to be a quality improvement activity which later became a research project. Ethics was granted retrospectively.
[10] Potential biases in both studies. In one study (Tabloski 1998), the sleep measures of the two groups were not comparable at baseline. There was no blinding in this study as the participants in the intervention group were told very precisely that there was only sugar in the small placebo capsules instead of their sleeping pills. The study also involved

a very brief follow-up duration. In another study (Tham 1989), Thioridazine 12.5mg could be given if the participant became agitated but its use was not clearly reported. This could be a major confounding factor as this drug could be used for insomnia.

[11] Potential indirectness - Only females were included in one study (Tabloski 1998).

[12] Potential selection, performance, and detection biases due to the non-randomised study design.

[13] Kosto 2023 controlled for several potential confounding factors through randomisation and baseline characteristic comparisons, but the control arm was retrospective. Potential confounding bias within the retrospective control arm was not adjusted.

[14] Significant variability in the study outcome. Sleep quality improved significantly in one study (Kosto 2023) but no change in another study (Van der Linden 2023).

[15] Non-controlled study. Potential attrition bias - 4 participants (13%) withdrew from the study prematurely due to worsening insomnia and thus failed to do the end-point assessment.

[16] The study was an RCT with participants randomised to either masked taper plus cognitive behavioural therapy (CBT) (n=92) or standard CBT plus unmasked tapering. However, for analysis purposes, we combined the outcomes as both groups would have received the intervention to have their benzodiazepines discontinued using two different mechanisms for tapering. Potential reporting biases as participants were aware of group allocation on completing the baseline interview and reported their sleep parameters over the past seven days via a telephone assessment at six months. Fall-related injuries were also self-reported by participants.

[17] Quality of life was assessed with the descriptive part of the EQ-5D-3L and was self-reported by the participants.

[18] Potential selection bias (Gardner 2024) – the majority of participants had previously attempted to stop benzodiazepines and/or Z-drugs.

[19] Potential attrition bias – in one study (Allary 2024), approximately 40% of participants (n=28/75) did not have follow-up data at 12-months.

30.5 Evidence-to-Decision table

Question: In older people, what are the effects of deprescribing (i.e. dose reduction or complete discontinuation) long-term sedative hypnotics on mortality, adverse drug withdrawal events, health-related outcomes, cognitive function, and quality of life?

Decision domain	Summary of reason for decision	Subdomains influencing decision
Certainty of evidence Is there a high or moderate certainty of evidence? Yes ☐ No ☑	The certainty of evidence for the benefits of deprescribing is low to very low. The certainty of evidence for the harms of deprescribing is low to very low.	Key reasons for downgrading: Risk of bias, imprecision Are all critical outcomes measured? Yes ☑ No ☐
Benefits and harms Is there certainty that the benefits of deprescribing outweigh the harms? Yes ☐ No ☑	The effects of deprescribing sedative hypnotics have been tabulated in Appendix B (GRADE evidence profile table) with an overview provided in the guideline document (a narrative overview and GRADE summary of findings table). Below is a summary according to the study designs. <u>Summary of outcomes</u> Randomised and non-randomised controlled trials: • No significant difference in mortality, exacerbation, adverse drug withdrawal events, emergency room presentation, sleep quality, severity of insomnia, depression, falls, delirium, and quality of life • Significant reduction in the number of hospitalisations per participant • Shorter time to fall asleep • Reduced wakefulness after sleep onset • Longer sleep duration • No significant difference in the number of wakes • Shorter sleep duration Inconsistent findings across studies for the total sleep time where one study stated no change, but another study reported shorter sleep time following deprescribing.	Is the baseline risk for benefits and harms of deprescribing similar across subgroups? Yes ☐ No ☑ There is no evidence at this time that the benefits or harms of deprescribing differ based on subgroups. However, there will be some groups at a higher risk. Should there be separate recommendations for subgroups? Yes ☑ No ☐ The guideline development group acknowledges that certain subgroups may have factors that could impact the balance of benefits and risks from deprescribing (e.g. types of sedative hypnotics, indication for use, the severity of symptoms, concomitant medications, other important comorbidities, functional status, cognitive status, and presence of adverse drug events). However, the available evidence is insufficient to justify distinct evidence-based recommendations.

Non-controlled trials:

- Improved body stability
- Improved quality of life
- Improved cognitive functions
- Improved central fatigue
- Mortality (3%)
- Increased withdrawal symptoms (13-19%)
- Falls (2%)
- Improved depressive symptoms
- No change in worry intensity or sleep quality

Summary of withdrawal schedules:
Randomised controlled trials:
Individualised (study=1, n=149, low certainty evidence), Individualised dose titration regime according to each patient's original dose and benzodiazepine to minimise the risk of withdrawal (study=1, n=138, moderate certainty evidence), Dose halved for one week then cease (study=1, n=20, very low certainty evidence), Titrated using one week of 1mg lormetazepam (study=1, n=40, very low certainty evidence), Abrupt discontinuation or gradual withdrawal (study=1, n=36, very low certainty evidence). The method not described in one RCT (n=565, very low certainty) [262]

Non-randomised controlled trials: (very low certainty evidence)
Drug-specific 'tapering down table' (study=1, n=215), Standardised tapering regimen, abrupt discontinuation, or "any attempt" (study=1, n=173)

Non-controlled trials: (very low certainty evidence)
25% reduction either every 1 week or every 2 weeks (study=1, n=38), Not described (studies=3, n=357, n unstated in one study), Individualised (study=1, n=111), Gradual dose reductions or abrupt discontinuation (study=1, n=36), Weekly

	reduction of 25% of the regular daily dose from baseline each week for 3 weeks (study=1, n=30), Withdrawn over 1 month by replacing either with melatonin or a placebo (study=1, n=89), Tapering plan based on previously published clinical guidelines (study=1, n=25), Gradual dose reduction (study=2, n=249, very low certainty) [250, 261]	
Values and preferences Is there confidence in the estimate of the relative importance of outcomes and individual preferences? Yes ☑ No ☐	Some patients firmly believe in the necessity of effective treatment for their insomnia and are less concerned about the potential risks associated with these medications. However, other patients express reluctance to use sedative-hypnotics, such as benzodiazepines or Z-drugs, for insomnia. A primary motivator for this is the concern over dependence on sleeping pills. These patients prioritise non-pharmacological approaches, such as improving sleep hygiene and adopting lifestyle changes. They often view medicines as a last resort and prefer exploring alternative remedies and support options before turning to medicines. Patients are aware of the risks of dependence, leading them to seek more sustainable treatment options. When attempting deprescribing, patients prefer a collaborative approach where decisions about continuing or discontinuing medicines are made with careful consideration of their evolving needs and preferences. Physicians believe a lack of treatment choices for insomnia is an important barrier to deprescribing sedative hypnotics. Physicians believe they are limited in providing options for patients with insomnia who may not favour non-drug approaches such as cognitive behavioural therapy, sleep hygiene practices, and lifestyle changes due to various factors. The lack of supporting institutional structures and resources, the attitudes and practices of previous clinicians, and patient-related factors such as dependence are also often cited as important barriers.	Perspective taken: Individual values and preferences determine the deprescribing approaches. The availability of healthcare professionals to conduct regular monitoring and close observation is also an important consideration to be able to cease sedative hypnotics when they are ineffective or bring more harm than benefit. Sources of values and preferences: 1) Consultation with patient and carer representatives 2) Non-systematic review of evidence Source of variability, if any: Difficult to determine the extent of variability; high variability for patient preferences. Method for determining values satisfactory for this recommendation? Yes ☑ No ☐ Yes, but would be improved with direct patient input
Resources Are the resources	A comprehensive economic evaluation was outside the scope of the current review. However, potential cost and resource	Feasibility: Is this intervention generally available? Yes ☑ No ☐

worth the expected net benefit? Yes ☑ No ☐	implications related to deprescribing interventions and continuation of medications are discussed below. Cost implications: The adverse drug reactions of sedative hypnotics have been linked to many avoidable healthcare costs. Cost-effectiveness studies showed a direct reduction in medication costs after deprescribing sedative hypnotics, and other related healthcare utilisation costs related to adverse events (e.g. hospitalisations, emergency department and outpatient visits associated with falls and fractures). However, it is crucial to take into consideration the costs associated with non-pharmacological methods to manage ongoing symptoms, and additional support needed such as cognitive behavioural therapy. An economic evaluation in the United States showed cognitive behavioural therapy to be the most cost-effective (lowest cost with greater quality-adjusted life years) compared to sedative hypnotics and no treatment. Although the result was sensitive to the baseline risk of falling for an older person. Assuming a willingness to pay US$50,000, the net monetary benefit was positive for cognitive behavioural therapy (US$10,287) and negative for sedative hypnotics (-US$4,851) and no treatment (-US$7,993). Physician implications: Physicians will need to closely monitor patients for dose tapering and to assess the impact of deprescribing on ongoing symptoms. Additional clinic visits and extended consultation time are likely required to reassess the symptoms, discuss practical strategies with the person and carer/health care team regularly and adjust as symptoms change. In addition, weaning off sedative hypnotics may lead to disrupted sleep for the individual for which patient education and cognitive behavioural therapy referral will be required.	Opportunity cost: Is this intervention and its effects worth withdrawing or not allocating resources from other interventions? Yes ☑ No ☐ Economic and preventive benefits for harms: Is there a lot of variability in resource requirements across settings? Yes ☐ No ☑
Equity	The social determinants of health equity are complex and multifaceted. The impact of deprescribing on health equity is	

What would be the impact of deprescribing on health inequities? ☑ Uncertain	inadequately explored in the literature. Older people affected by the inappropriate use of benzodiazepines are likely to derive substantial benefits in terms of health equity from deprescribing. By reducing medication burdens, lowering costs, and simplifying medicine regimens, deprescribing may enhance access to care and improve health outcomes for this vulnerable population. However, there may be people with limited access to mental health services or specialists who can appropriately manage and monitor the deprescribing process. Exploration of non-pharmacological treatments, such as cognitive-behavioural therapy (CBT) may be costly and not accessible to all patients. If deprescribing benzodiazepines leads to the need for more expensive or less accessible alternatives, it could exacerbate disparities, particularly for those with limited financial resources. Ensuring equitable implementation and addressing potential challenges faced by people with varying health literacy and access disparities is crucial to maximising these benefits. Culturally and linguistically diverse populations, Aboriginal and Torres Strait Islander populations, people with low socioeconomic status, and those living in rural or remote areas may require additional support or considerations when implementing deprescribing intervention, including the ongoing monitoring process. On the other hand, successful deprescribing of benzodiazepines can help reduce the stigma associated with their use, which can be important for patients in marginalized communities who may already face stigma related to mental health conditions.
Acceptability Is the option of deprescribing acceptable to key stakeholders? ☑ Probably yes	Healthcare practitioners: Deprescribing is likely acceptable to most healthcare practitioners, especially when supported by clinical practice guidelines and a shared decision-making process with patients. The term deprescribing may be new to healthcare practitioners but the concept is not. Healthcare practitioners are very familiar with discontinuing ineffective medications or those causing adverse effects worse than the condition being treated. Patients, their caregivers and family members: Many are open to deprescribing if they understand the potential benefits and risks, especially when given the option to restart medications when necessary. Policymakers and health systems: From a broader perspective, deprescribing can be seen as a way to reduce healthcare costs and improve patient outcomes. However, the short-term impacts on patient care and the resources required to implement effective deprescribing strategies may be a concern.
Overall judgment	There is a lack of quality evidence for deprescribing to inform evidence-based recommendations.

31. Antidepressants

31.1 Overview of studies targeted antidepressants

Article	Drug/Class	Study design	Sample size	Follow-up (months)	Withdrawal schedule
Bergh 2012 [268]	Antidepressants (SSRIs)	RCT	128	6	Not described
Ulfvarson 2003 [269]	Antidepressants (SSRIs)	RCT	70	12	Halving the dose for a few days before cessation
Lindström 2007 [270]	Antidepressants (SSRIs)	Before and after study	119	Unclear, perhaps up to 28 weeks	Tapered gradually, and ceased after six to eight weeks
Bergh and Engedal 2008 [234]	Antidepressants (SSRIs)	Before and after study	11	6	Tapered over one week
Flint and Rifat 1999 [271]	Antidepressants (nortriptyline/phenelzine, with or without adjunctive lithium)	Before and after study	21	24	Antidepressant medication and, when applicable, adjunctive lithium withdrawn over a period of 8 weeks
Fahy & Lawlor 2001 [272]	Lithium augmentation (for depression)	Case-control study	21	19.5	Tapered gradually over a period of 2 to 12 weeks
Hardy 1997 [273]	Lithium augmentation (for depression)	RCT	12	24	Dose reduced by 150mg daily each week until completely replaced with matching placebo

31.2 Evidence for deprescribing antidepressants

Study	Specific outcome	Odds ratio (95% CI)	Mean difference (95% CI)
1. Mortality			
Bergh 2012	Mortality at 6 months	1.04 (0.34, 3.14)	
Ulfvarson 2003	Mortality at 12 months	1.29 0.32 , 5.28)	
2. Adverse drug withdrawal events (ADWEs)			
Bergh 2012	Depression, measured using Cornell Scale		1.61 (-0.39, 3.61)
Ulfvarson 2003	Depression, measured using Montgomery-Asberg depression rating scale		-0.80 (-2.87, 1.27)
Hardy 1997	ADWEs, number of participants who experienced at least one exacerbation	1.0 (0.09, 11.03)	
3. Health outcomes			
Adverse drug events			
Ulfvarson 2003	Adverse effects symptoms (scale of 0 to 100, where a higher score indicates greater side effects of depression or SSRI drug)		3.13 (-0.33, 6.59)
Ulfvarson 2003	Frequency of Medication Side Effects, measured on a 0–52point scale		1.40 (-0.55, 3.34)
Movement disorders			
Bergh 2012	Severity and progression of Parkinson's disease, measured using the Unified Parkinson's Disease Rating Scale (UPDRS)		-0.13 (-1.70, 1.44)
Falls			
Bergh 2012	Change in the number of falls per day		0.00 (-0.01, 0.01)
Physical function			
Bergh 2012	Physical self-maintenance scale		-0.35 (-2.77, 2.07)
Ulfvarson 2003	Global assessment of functioning		-3.42 (-7.74, 0.90)
Behavioural and psychological symptoms			
Bergh 2012	Neuropsychiatric Index		7.80 (1.10, 14.50)
Weight			
Bergh 2012	Weight		-4.05 (-10.38, 2.28)
Thyroid stimulating hormone			

Hardy 1997	Thyroid stimulating hormone		0.56 (-0.08, 1.20)
Creatinine			
Hardy 1997	Creatinine		13.30 (0.47, 26.13)
4. Cognitive function			
Bergh 2012	Cognition, measured using the Severe Impairment Battery (higher scores indicating less impairment)		-5.38 (-19.35, 8.59)
5. Quality of life			
Ulfvarson 2003	Quality of life, measured using the Health Index		1.72 (0.11, 3.33)
Bergh 2012	Quality of life, measured using the QoL-AD, caregiver rating		-0.78 (-3.42, 1.86)
Bergh 2012	Quality of life, measured using the QoL-AD patient rating		3.07 (-0.50, 6.64)
6. Effect on medication regimen			
Bergh 2012	Rescue medicine used in mg		-0.09 (-0.33, 0.15)
Bergh 2012	Total number of psychotropic medicines		-0.10 (-0.53 to 0.33)

31.3 Evidence for deprescribing antidepressants (non-controlled outcomes)

Study	Specific outcome	Result
1. Mortality		
No available evidence		
2. Adverse drug withdrawal events (ADWEs)		
Flint and Rifat 1999	Recurrence of the underlying symptom	57%
Flint and Rifat 1999	The recurrence of underlying symptoms responded to the re-introduction of medicine	92%
Flint and Rifat 1999	Time for response to re-introduction of treatment	4.5 weeks ± 1.8
Bergh and Engedal 2008	Depression (measured using Cornell score) after 24 weeks	6.9 ± 4.5 to 3.3 ± 3.4
Fahy & Lawlor 2001	Relapse	11/21 (52.4%)
3. Health outcomes		
Movement disorders		
Bergh and Engedal 2008	Movement disorders measured using the Unified Parkinson's Disease Rating Scale	6.4 ± 4.2 to 4.5 ± 3.4
Behavioural and psychological symptoms		
Bergh and Engedal 2008	Neuropsychiatric Index after 24 weeks	29.2 ± 20.2 to 17.3 ± 21.4
4. Cognitive function		
Bergh and Engedal 2008	Cognition after 24 weeks (measured with the severe impairment battery, which has a scale of 0 to 100, with higher scores indicating less impairment)	50.1 ± 22.5 to 28.0 ± 20.3
5. Quality of life		
No available evidence		
6. Effect on medication regimen		
Lindström 2007	Successful deprescribing	53%
Flint and Rifat 1999	Successful deprescribing	43%

31.4 GRADE evidence profile (critical or important but not critical outcomes only)

Question: In older people, what are the effects of deprescribing (i.e. dose reduction or complete discontinuation) long-term antidepressants on mortality, adverse drug withdrawal events, health-related outcomes, cognitive function, and quality of life?

Certainty assessment							Number of participants		Effect	Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Depresscribing	Continuation			
1. Mortality											
2 [268, 269]	RCTs (SSRIs)	Serious [1,2]	Not serious	Serious [3,4]	Serious[5]	Not serious	98	100	1.13 (0.47, 2.69)	⨁◯◯◯	8
2. Adverse drug withdrawal events (ADWEs)											
ADWEs											
2 [268, 269]	RCTs (SSRIs)	Serious [1,2]	Not serious	Serious [3,4]	Serious[5]	Not serious	56	73	Deprescribing of selective serotonin reuptake inhibitors (SSRIs) was not associated with a significant change in the severity of depression measured using Cornell Scale for Depression in Dementia (MD 1.61, 95% CI -0.39, 3.61) [268] or Montgomery-Asberg depression rating scale (MD -0.80, 95% CI -2.87, 1.27) [269].	⨁◯◯◯	6
1 [273]	RCT (Lithium augmentation)	Not serious	Not serious	Serious [6]	Serious[5]	Not serious	6	6	OR 1.00 (0.09, 11.03)	⨁◯◯◯	6
2 [234, 271]	Non-controlled studies	Serious [7,8,9]	Not serious	Serious [10]	Serious[5]	Not serious	32	N/A	Recurrence of major depression was reported in 12 out of 21 participants (57%). Eleven participants agreed to restart their antidepressant and 10 out of them (92%) responded to reintroduction of the antidepressant. The average time taken to respond to the re-introduction of antidepressants was 4.5 weeks ± 1.8 [271]. In another study, the severity of depression reduced after 24 weeks of antidepressant discontinuation when measured using the Cornell's depression scale (from 6.9 ± 4.5 to 3.3 ± 3.4) [234].	⨁◯◯◯	6

Exacerbation/return of underlying condition										
1 [272]	Non-controlled study (Lithium augmentation)	Serious [11]	Not serious	Not serious	Serious[5]	Not serious	21	NA	11/21 (52.4%) relapsed	6
3. Health outcomes										
Adverse drug events										
1 [269]	RCT (SSRIs)	Serious [1]	Not serious	Serious [4]	Serious[5]	Not serious	25	27	Deprescribing of SSRIs was not associated with a significant change in the side effects of SSRIs (MD 3.13, 95% CI -0.33, 6.59), or symptoms of side effects of SSRI drug treatments (on a 0–52 point scale) (MD 1.40, 95% CI -0.55, 3.34).	5
Movement disorders										
1 [268]	RCT (SSRIs)	Serious [2]	Not serious	Serious [3]	Serious[5]	Not serious	35	46	Severity and progression of Parkinson's disease, measured using Unified Parkinson's Disease Rating Scale (UPDRS) MD -0.13 (-1.70, 1.44)	5
1 [234]	Non-controlled study (SSRIs)	Serious [7,8]	Not serious	Not serious	Serious[5]	Not serious	11	N/A	The severity of movement disorders reduced after 24 weeks of antidepressant discontinuation when measured using the Unified Parkinson's Disease Rating Scale (from 6.4 ± 4.2 to 4.5 ± 3.4).	5
Falls										
1 [268]	RCT (SSRIs)	Serious [2]	Not serious	Serious [3]	Serious[5]	Not serious	35	45	Change in the number of falls per day MD 0.00 (-0.01, 0.01)	5
Physical function										
2 [268, 269]	RCTs (SSRIs)	Serious [1,2]	Not serious	Serious [3,4]	Serious[5]	Not serious	45	58	Lawton and Brody's physical self-maintenance scale MD -0.35 (-2.77, 2.07) [268] Global assessment of functioning MD -3.42 (-7.74, 0.90) [269]	6
Behavioural and psychological symptoms										
1 [268]	RCT (SSRIs)	Serious [2]	Not serious	Serious [3]	Serious[5]	Not serious	35	46	Neuropsychiatric inventory, total score MD 7.80 (1.10, 14.50)	6
1 [234]	Non-controlled study	Serious [7,8]	Not serious	Not serious	Serious[5]	Not serious	11	N/A	Neuropsychiatric inventory 29.2 ± 20.2 to 17.3 ± 21.4	6

	(SSRIs)										
4.	Cognitive function										
1 [268]	RCT (SSRIs)	Serious [2]	Not serious	Serious [3]	Serious[5]	Not serious	23	37	Cognition, measured using the Severe Impairment Battery (higher scores indicating less impairment) MD -5.38 (-19.35, 8.59)		7
1 [234]	Non-controlled study (SSRIs)	Serious [7,8]	Not serious	Not serious	Serious[5]	Not serious	11	N/A	Cognition deteriorated after 24 weeks of antidepressant discontinuation when measured using the severe impairment battery (from 50.1 ± 22.5 to 28.0 ± 20.3).		7
5.	Quality of life (QoL)										
2 [268, 269]	RCTs (SSRIs)	Serious [1,2]	Not serious	Serious [3,4]	Serious[5]	Not serious	45	58	When using the Health Index as a measure, control group participants who continued using their selective serotonin reuptake inhibitors (SSRIs) reported improved health-related quality of life at 6 months whereas intervention group participants reported a deterioration (MD 1.72, 95% CI 0.11, 3.33) [269]. In another study that used the quality of life-Alzheimer's disease scale, deprescribing was not associated with a significant change when it was rated by the caregiver (MD -0.78, 95% CI -3.42, 1.86) or the patient (MD 3.07, 95% CI -0.50, 6.64) [268] at 6 months.		7

[1] One study (Ulfvarson, 2003 study) was not blinded and potential confounding factors were not controlled.
[2] Potential attrition bias and potential confounding factors were not controlled in one study (Bergh 2012). The grouping of "neuropsychiatric symptoms" together is a major weakness. Although schizophrenia was an exclusion criterion, the neuropsychiatric inventory includes many common psychotic symptoms that can be caused by many medical conditions besides depression. High dropout rate for patients in the discontinuation group who withdrew due to increased neuropsychiatric symptoms.
[3] Potential indirectness - one study (Bergh 2012) included participants with dementia and neuropsychiatric symptoms who had been prescribed Selective Serotonin Reuptake Inhibitors (SSRIs) for more than 3 months but excluded people with a history of depressive disorder. Considering that SSRIs are commonly indicated for depression, this seems to exclude a substantial cohort which limits the generalisability.
[4] Potential indirectness - one study (Ulfvarson 2003) included only patients without indications of depression, anxiety, or dementia who had received treatment with SSRI drugs which limits the generalisability.
[5] Small sample size and/or wide confidence intervals for some studies.
[6] Hardy 1997 only included elderly patients who received lithium augmentation for refractory unipolar depression. This study was fairly dated, with lithium now being used as the drug of choice for the prevention of manic or depressive episodes and treatment of acute mania in bipolar disorder. There was some risk of attrition bias (3/12). There was some potential for confounding from life events/medical conditions that occurred during the 2-year follow-up period.
[7] Lack of a control group in one study (Bergh and Engedal 2008).
[8] Potential attrition bias in one study (Bergh and Engedal 2008). High dropout rate (13 out of 23 patients).
[9] One study (Flint 1999) did not mention any blinding procedures and there is a lack of considerations for potential confounding factors.
[10] Potential indirectness - one study (Flint 1999) appeared to only target nortriptyline (with or without adjunctive lithium) or phenelzine.

[11] Fahy& Lawlor 2001 - This study lacks a true comparator group which introduces potential selection and confounding biases. Participants were those from a clinic who had their medication discontinued. There is a high risk of selection bias, as patients were selected based on clinical decisions to discontinue lithium. There is also potential reporting bias as it was a retrospective study and outcomes were not pre-specified. There was limited control for confounding factors.

31.5 Evidence-to-Decision Table

Question: In older people, what are the effects of deprescribing (i.e. dose reduction or complete discontinuation) long-term antidepressants on mortality, adverse drug withdrawal events, health-related outcomes, cognitive function, and quality of life?		
Decision domain	Summary of reason for decision	Subdomains influencing decision
Certainty of evidence Is there a high or moderate certainty of evidence? Yes ☐ No ☑	The certainty of evidence for the benefits of deprescribing is very low. The certainty of evidence for the harms of deprescribing is very low.	Key reasons for downgrading: Risk of bias, indirectness, imprecision Are all critical outcomes measured? Yes ☑ No ☐
Benefits and harms Is there certainty that the benefits of deprescribing outweigh the harms? Yes ☐ No ☑	The effects of deprescribing antidepressants have been tabulated in Appendix B (GRADE evidence profile table) with an overview provided in the guideline document (a narrative overview and GRADE summary of findings table). Below is a summary according to the study designs. <u>Summary of outcomes</u> Randomised and non-randomised controlled trials of selective serotonin reuptake inhibitors (SSRIs): • No significant difference in mortality, severity of depression, drug-related side effects, severity and progression of movement disorders, falls, physical function, and cognition • Deterioration in neuropsychiatric symptoms Inconsistent findings across studies for the quality of life, where one study reported deterioration and another study reported no change. Non-controlled trials of SSRIs: • No change in movement disorders • Improved neuropsychiatric symptoms • Reduced severity of depression • Worsening cognitive function	Is the baseline risk for benefits and harms of deprescribing similar across subgroups? Yes ☐ No ☑ Evidence at this time suggests that deprescribing is more likely to be successful in people without a current indication of depression. Should there be separate recommendations for subgroups? Yes ☑ No ☐ The guideline development group acknowledges that certain subgroups may have factors that could impact the balance of benefits and risks from deprescribing (e.g. antidepressant drug class, indication for use, severity of symptoms, concomitant medications, other important comorbidities, functional status, cognitive status, and presence of adverse drug events). However, the available evidence is insufficient to justify distinct evidence-based recommendations.

	Non-controlled trial of nortriptyline/phenelzine (with or without adjunctive lithium): Harm 57% of participants had worsened depression with the majority of participants (92%) responding to the reintroduction of antidepressants. <u>Summary of withdrawal schedules:</u> Randomised controlled trials: The dose was halved for a few days before cessation (study=1, n=70, very low certainty evidence), Not described (study=1, n=128, very low certainty evidence), Lithium dose was reduced by 150mg daily each week until completely replaced with matching placebo (<u>Lithium augmentation</u>; study=1, n=12, low certainty evidence) Non-randomised controlled trial: (very low certainty evidence) Tapered gradually over a period of 2 to 12 weeks (Lithium augmentation; study=1, n=21) Non-controlled trials: (very low certainty evidence) Taper gradually and discontinued after 6-8 weeks (study=1, n=119), Tapered over one week (study=1, n=23), Titrated over a period of 8 weeks (study=1, n=21)	
Values and preferences Is there confidence in the estimate of the relative importance of	Older people often show resistance to taking antidepressants, primarily due to concerns about dependence, a reluctance to view depression as a medical issue, fears that antidepressants will suppress emotions and past negative experiences with depression medications. Many patients who are already	Perspective taken: Individual values and preferences determine the deprescribing approaches. Sources of values and preferences: 1) Consultation with patient and carer representatives 2) Non-systematic review of evidence

outcomes and individual preferences? Yes ☑ No ☐	taking antidepressants express a desire to stop their use but worry about the risk of relapse and withdrawal symptoms. Some have tried various types of antidepressants without finding one that is effective for their condition while avoiding severe side effects. Certain antidepressants can cause side effects so severe that patients prefer to discontinue them. Additionally, many patients also understand that underlying environmental factors contributing to depression, such as ongoing stressors, cannot be easily resolved with medicine alone. For older people experiencing grief, alternative coping mechanisms are often more appreciated than medicines. Many prefer non-pharmacological interventions, such as counselling or cognitive-behavioural therapy, to manage their symptoms. However, they also recognise that short-term use of antidepressants can be helpful in specific situations. Some patients would like to involve family members and caregivers in the decision-making process to ensure they receive comprehensive support. They also want to be provided with appropriate education and counselling about the use of antidepressants from the outset. Most physicians believe discontinuation of long-term antidepressants is a complex process, especially for older people living in nursing homes. Many prefer to maintain the status quo and are unwilling to take unpredictable risks without clear benefits. For older patients with a severe medical condition, the shift in treatment goals from prevention and cure to prioritising quality of life may present as a facilitator to deprescribing.	Source of variability, if any: Difficult to determine the extent of variability; high variability for patient preferences. Method for determining values satisfactory for this recommendation? Yes ☑ No ☐ Yes, but would be improved with direct patient input
Resources Are the resources	A comprehensive economic evaluation was outside the scope of the current review. However, potential cost	Feasibility: Is this intervention generally available? Yes ☑ No ☐

worth the expected net benefit? Yes ☑ No ☐	and resource implications related to deprescribing interventions and continuation of medications are discussed below. Cost implications: The use of antidepressants in Australia is one of the highest in the world which contributes to significant healthcare expenditures. However, there is little evidence on the overall cost implications of long-term antidepressant exposure. The cost-effectiveness analysis of continuation and discontinuation may be difficult to estimate due to the complexity of health outcomes, the types of deprescribing intervention and the rate of successful implementation. Although antidepressants may be viewed as a cheaper alternative to psychotherapy, the costs of managing adverse effects of antidepressants such as sexual dysfunction, weight change, anxiety, and insomnia could be substantial. On the other hand, deprescribing antidepressants would likely incur costs associated with non-pharmacological methods to manage ongoing symptoms and additional support needed such as psychological interventions. Patients may experience antidepressant withdrawal symptoms, which can last for weeks or months, with the severity and duration likely proportional to the duration of usage. It is challenging to precisely estimate the indirect economic burden associated with both physical and psychological aspects of major depressive disorder. Such costs may include loss of productivity, absenteeism, disability, and more important, suicide. Physician implications: Physicians will need to closely monitor patients for dose tapering and to assess the impact of deprescribing on ongoing symptoms. Additional clinic visits and extended consultation time	☐ Opportunity cost: Is this intervention and its effects worth withdrawing or not allocating resources from other interventions? Yes ☑ No ☐ Economic and preventive benefits for harms: Is there a lot of variability in resource requirements across settings? Yes ☐ No ☑

	are likely required to reassess the person's symptoms, discuss practical strategies with the person and carer/health care team regularly and adjust as symptoms change. In addition, weaning off antidepressants may bring significant anxiety to the individual. Physicians will likely need to refer patients to psychological therapy, social support, cognitive behaviour therapy, interpersonal therapy, supportive counselling, and physical activity.	
Equity What would be the impact of deprescribing on health inequities? ☑ Uncertain	The social determinants of health equity are complex and multifaceted. The impact of deprescribing on health equity is inadequately explored in the literature. There is a risk that deprescribing antidepressants could lead to relapse or worsening of symptoms if not managed carefully. This could disproportionately affect vulnerable populations who may have less access to mental health support and crisis intervention services. Exploration of non-pharmacological treatments, such as psychotherapy may be costly and not accessible to all patients. If deprescribing antidepressants leads to the need for more expensive or less accessible alternatives, it could exacerbate disparities, particularly for those with limited financial resources. Ensuring equitable implementation and addressing potential challenges faced by people with varying health literacy and access disparities is crucial to maximising these benefits. Culturally and linguistically diverse populations, Aboriginal and Torres Strait Islander populations, people with low socioeconomic status, and those living in rural or remote areas may require additional support or considerations when implementing deprescribing intervention, including the ongoing monitoring process.	
Acceptability Is the option of deprescribing acceptable to key stakeholders? ☑ Probably yes	Healthcare practitioners: Deprescribing is likely acceptable to most healthcare practitioners, especially when supported by clinical practice guidelines and a shared decision-making process with patients. The term deprescribing may be new to healthcare practitioners but the concept is not. Healthcare practitioners are very familiar with discontinuing ineffective medications or those causing adverse effects worse than the condition being treated. Patients, their caregivers and family members: Many are open to deprescribing if they understand the potential benefits and risks, especially when given the option to restart medications when necessary. Policymakers and health systems: From a broader perspective, deprescribing can be seen as a way to reduce healthcare costs and improve patient outcomes. However, the short-term impacts on patient care and the resources required to implement effective deprescribing strategies may be a concern.	
Overall judgment	There is a lack of quality evidence for deprescribing to inform evidence-based recommendations.	

Abbreviation: SSRI selective serotonin reuptake inhibitors

32. Anti-dementia medicines

32.1 Overview of studies targeted anti-dementia medicines

Article	Drug/Class	Study design	Setting	Sample size	Follow-up (months)	Withdrawal schedule
Minett 2003 [274]	Anticholinesterase (Donepezil)	Before and after study	Community	19	7.5	Abrupt discontinuation
Gaudig 2011 (study 1) [275]	Anticholinesterase (Galantamine)	Before and after study	Community	723	1.5	Not described
Gaudig 2011 (study 2) [275]	Anticholinesterase (Galantamine)	RCT	Community	118	1.5	Not described
Scarpini 2011 [276]	Anticholinesterase (Galantamine)	RCT	Community	139	36	Not described
Herrmann 2016 [277]	Anticholinesterases	RCT	Residential care	40	2	Tapered for 2 weeks, then ceased
Moo 2021 [278]	Anticholinesterases	RCT	Community	62	1.5	Dose halved for 3 weeks then replaced with a placebo for 3 weeks
García-García & Calleja-Hernández, 2022 [279]	Anticholinesterases	Before and after study	Residential care	23	3	Dose halved every week

32.2 Evidence for deprescribing of anti-dementia medicines

Study	Specific outcome	Odds ratio (95% CI)	Mean difference (95% CI)
1. Mortality			
Gaudig 2011 (study 1)	Mortality	0.51 (0.02, 12.66)	
Scarpini 2011	Mortality	0.47 (0.09, 2.49)	
2. Adverse drug withdrawal events (ADWEs)			
Exacerbation/return of underlying condition			
Herrmann 2016	Exacerbation/return of underlying condition	3.75 (0.36, 39.59)	
3. Health outcomes			
Adverse drug events			
Gaudig 2011 (study 1)	Adverse drug events, number of participants who experienced once	0.99 (0.66, 1.47)	
Gaudig 2011 (study 2)	Adverse drug events, number of participants who experienced once	0.61 (0.24, 1.58)	
Scarpini 2011	Adverse drug events, number of participants who experienced once	0.71 (0.34, 1.48)	
Serious adverse event			
Gaudig 2011 (study 1)	Serious adverse event	0.82 (0.05, 13.58)	
Gaudig 2011 (study 2)	Serious adverse event	0.73 (0.29, 1.86)	
Scarpini 2011	Serious adverse event	0.40 (0.12, 1.33)	
Neuropsychiatric symptoms			
Herrmann 2016	Change in Neuropsychiatric Inventory-Nursing Home (NPI-NH)		-4.70 (-11.53, 2.13)
Clinical Global Impressions of Change			
Herrmann 2016	Change in Clinical Global Impressions of Change (CGIC)		0.20 (-0.08, 0.48)
Agitation			
Herrmann 2016	Change in Cohen-Mansfield Agitation Inventory score		2.80 (-3.01, 8.61)
Activities of Daily Living			
Herrmann 2016	Change in Activities of Daily Living, measured by ADCS-ADL		0.10 (-2.14, 2.34)
Moo 2021	Change in Activities of Daily Living, measured by ADCS-ADL		2.02 (-16.32, 20.36)

Apathy			
Herrmann 2016	Change in Apathy Evaluation Scale score		1.50 (-2.65, 5.65)
4. Cognitive function			
Gaudig 2011 (study 1)	Cognition, measured by Alzheimer's Disease Assessment Scale-Cognitive scales		2.50 (1.18, 3.82)
Gaudig 2011 (study 2)	Cognition, measured by ADAS-cog		1.60 (-1.15, 4.35)
Herrmann 2016	Change in cognition, measured by standardised Mini-Mental State Examination		-1.70 (-3.91, 0.51)
Moo 2021	Change in cognition, measured by Six-item Screener		0.28 (-0.59, 1.15)
5. Quality of life			
Herrmann 2016	Change in quality of life, measured by Quality of Life in Late Stage of Dementia score (QUALID)		-0.40 (-3.12, 2.32)
6. Effect on medication regimen			
No available evidence			

32.3 Evidence for deprescribing of anti-dementia medicines (non-controlled outcomes)

Study	Specific outcome	Result
1. Mortality		
No available evidence		
2. Adverse drug withdrawal events (ADWEs)		
No available evidence		
3. Health outcomes		
Minett 2003	Neuropsychiatric Index after 6 weeks in participants living with Dementia from Parkinson's Disease	2.6, p=0.008
4. Cognitive function		
Minett 2003	MMSE in participants living with Dementia with Lewy Bodies	1.1, p = 0.229
Minett 2003	MMSE in participants living with Dementia from Parkinson's Disease	1.1, p = 0.221
5. Quality of life		
No available evidence		
6. Effect on medication regimen		
Minett 2003	Successfully deprescribed in participants living with Dementia with Lewy Bodies	50%
Minett 2003	Successfully deprescribed in participants living with Dementia from Parkinson's Disease	45%

32.4 GRADE evidence profile (critical or important but not critical outcomes only)

Question: In older people, what are the effects of deprescribing (i.e. dose reduction or complete discontinuation) long-term anti-dementia medicines on mortality, adverse drug withdrawal events, health-related outcomes, cognitive function, and quality of life?

Certainty assessment							Number of participants		Effect	Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Depresscribing	Continuation			
1. Mortality											
2 [275, 276]	RCTs	Serious [1]	Not serious	Serious [2]	Serious [3]	Serious [4]	261	382	OR 0.48 (0.11, 2.10)		8
2. Adverse drug withdrawal events (ADWEs)											
Exacerbation/return of underlying condition											
1 [277]	RCT	Not serious	Not serious	Serious [5]	Serious [2]	Not serious	21	19	OR 3.75 (0.36, 39.59)		6
3. Health outcomes											
Adverse drug events											
2 [275, 276]	RCTs	Serious [1]	Not serious	Serious [2]	Serious [3]	Serious [4]	102	108	OR 0.67 (0.38, 1.20)		5
1 [275]	Non-randomised study	Serious [1]	Not serious	Serious [2]	Serious [3]	Serious [4]	198	202	OR 0.99 (0.66, 1.47)		5
Serious adverse event											
2 [275, 276]	RCTs	Serious [1]	Not serious	Serious [2]	Serious [3]	Serious [4]	102	108	OR 0.44 (0.15, 1.32)		7
1 [275]	Non-randomised study	Serious [1]	Not serious	Serious [2]	Serious [3]	Serious [4]	198	202	OR 0.73 (0.29, 1.86)		7
Clinical Global Impressions of Change											
1 [277]	RCT	Not serious	Not serious	Serious [5]	Serious [2]	Not serious	21	19	MD 0.20 (-0.08, 0.48)		4
Agitation											
1 [277]	RCT	Not serious	Not serious	Serious [5]	Serious [2]	Not serious	21	19	MD 2.80 (-3.01, 8.61)		6
Apathy											
1 [277]	RCT	Not serious	Not serious	Serious [5]	Serious [2]	Not serious	21	19	MD 1.50 (-2.65, 5.65)		6
Neuropsychiatric symptoms											

1 [277]	RCT	Not serious	Not serious	Serious [5]	Serious [2]	Not serious	21	19	MD -4.70 (-11.53, 2.13)		6
1 [274]	Non-controlled study	Serious [7]	Not serious	Serious [8]	Serious [2]	Not serious	24	N/A	Neuropsychiatric Index after 6 weeks in participants living with Dementia from Parkinson's Disease Worsening, 2.6, p=0.008		6
Activities of Daily Living											
2 [277, 278]	RCTs	Serious [9]	Not serious	Serious [5,10]	Serious [2]	Not serious	45	57	MD 0.13 (-2.10, 2.36)		6
4. Cognitive function											
2 [277, 278]	RCTs	Serious [9]	Not serious	Serious [5,10]	Serious [2]	Not serious	47	55	Change in cognition, measured by standardised Mini-Mental State Examination, -1.70 (-3.91, 0.51) Change in cognition, measured by Six-item Screener, 0.28 (-0.59, 1.15)		7
1 [274]	Non-controlled study	Serious [7]	Not serious	Serious [8]	Serious [2]	Not serious	24	N/A	MMSE in participants living with Dementia with Lewy Bodies, 1.1, p = 0.229 MMSE in participants living with Dementia from Parkinson's Disease, 1.3, p = 0.221		7
5. Quality of life											
1 [277]	RCT	Not serious	Not serious	Serious [5]	Serious [2]	Not serious	18	15	Change in quality of life, measured by Quality of Life in Late Stage of Dementia score (QUALID) -0.40 (-3.12, 2.32)		7

[1] The pooled studies consisted of double-blind withdrawal RCTs (Gaudig 2011) and a randomised, double-blind, placebo-controlled withdrawal trial (Scarpini 2011), all with potential risk of bias. Gaudig 2011, Study 2 - the groups were inherited from the parent study, and this introduced a risk of selection bias. The discontinuation group included those who had been on the highest dose of galantine (24mg) whereas continued doses were 8mg and 16mg. Unclear why only the highest dose stopped. The study is very difficult to read, partly because there were two different methods of allocating patients. Very complicated design. Combined participants from two unequal studies. The reason for choosing which groups to deprescribe and continue is not described. Scarpini 2011 - There was a significant dropout, especially in the placebo group (potential of attrition bias). While the primary outcome showed statistically significant results, the ADAS-cog analysis was underpowered due to higher-than-expected dropouts, leading to imprecision. The study design and analysis appear to have adequately controlled for potential confounding factors. The overall quality of evidence is low, considering the study's strengths, including appropriate design and low risk of most biases, but the high dropout rate and underpowered ADAS-cog analysis reduce the overall quality. However, the results were consistent across studies, showing cognitive decline with galantamine withdrawal and maintained benefits with continued treatment.
[2] Potential indirectness as one or more studies only included people using anticholinesterase for mild to moderate Alzheimer's disease, thereby limiting the generalisability of the findings to other patient populations (such as those with Parkinson's Disease Dementia or dementia with Lewy bodies).
[3] Small sample size and/or wide confidence intervals in the estimates of effect.
[4] These studies (Gaudig 2011, Scarpini 2011) were funded by a pharmaceutical company.

[5] Potential indirectness as one study (Herrmann 2016) only included long-term care facility residents with moderate to severe Alzheimer Disease, thereby limiting the generalisability of the findings to other settings and patient populations (such as those with Parkinson's Disease Dementia or dementia with Lewy bodies).
[6] In one study (Gaudig 2011, Study 1), group allocation is not randomised. Patients had to elect to continue into the withdrawal study. This could introduce selection bias.
[7] Single-arm study with potential selection, confounding, and reporting biases. The stated outcomes are reported with varying levels of detail. Some large effects were observed, particularly in cognitive improvement (4-point increase in MMSE) and behavioural symptoms. The study design does not adequately control for confounding factors. The overall quality of evidence is very low due to the open-label design, small sample size, and lack of a control group.
[8] Potential indirectness – Minette 2003 only included people using anticholinesterase for probable dementia with Lewy bodies or Parkinson's disease who subsequently developed dementia, thereby limiting the generalisability of the findings to other patient populations (such as Alzheimer's disease).
[9] Moo 2021 – potential risk of selection bias due to the very low recruitment rate (<5% of eligible patients enrolled). Natural disease progression and fluctuations may have impacted outcomes, leading to a potential risk of confounding.
[10] Moo 2021 – potential indirectness as the study included a predominantly male veteran population.

32.5 Evidence-to-Decision table

Question: In older people, what are the effects of deprescribing (i.e. dose reduction or complete discontinuation) long-term anti-dementia medicines on mortality, adverse drug withdrawal events, health-related outcomes, cognitive function, and quality of life?

Decision domain	Summary of reason for decision	Subdomains influencing decision
Certainty of evidence Is there a high or moderate certainty of evidence? Yes ☑ No ☐	The certainty of evidence is moderate to very low.	Key reasons for downgrading: Risk of bias, imprecision, and other considerations (two industry-sponsored studies) Are all critical outcomes measured? Yes ☑ No ☐
Benefits and harms Is there certainty that the benefits of deprescribing outweigh the harms? Yes ☐ No ☑	The effects of deprescribing anti-dementia medicines have been tabulated in Appendix B (GRADE evidence profile table) with an overview provided in the guideline document (a narrative overview and GRADE summary of findings table). Below is a summary according to the study designs. <u>Summary of outcomes</u> Randomised and non-randomised controlled trials: • No significant difference in mortality, exacerbation/return of the underlying condition, adverse drug events, serious adverse events, Clinical Global Impressions of Change, agitation, apathy, neuropsychiatric symptoms, activities of daily living, cognitive function, and quality of life. Non-controlled trials: • No change in cognition when compared to baseline • Worsening neuropsychiatric symptoms in participants with dementia from Parkinson's Disease <u>Summary of withdrawal schedules:</u> Randomised controlled trials: Tapered for 2 weeks, then ceased (study=1, n=40, moderate certainty evidence), Dose halved for 3 weeks then	Is the baseline risk for benefits and harms of deprescribing similar across subgroups? Yes ☐ No ☑ There is limited evidence at this time that the benefits or harms of deprescribing differ based on subgroups. However, there will be some groups at a higher risk depending on the indications for use and severity of the condition. Should there be separate recommendations for subgroups? Yes ☑ No ☐ The guideline development group acknowledges that certain subgroups may have factors that could impact the balance of benefits and risks from deprescribing (e.g. severity of symptoms, concomitant medications, other important comorbidities, functional status, and presence of adverse drug events). However, the available evidence is insufficient to justify distinct evidence-based recommendations.

	replaced with a placebo for 3 weeks (study=1, n=62, very low certainty evidence), Not described (studies=2, n=257, very low certainty evidence) Non-randomised controlled trials: (very low certainty evidence) Dose halved every week (study=1, n=43), Not described (study=1, n=723) Non-controlled trial: (very low certainty evidence) Abrupt discontinuation (study=1, n=24)	
Values and preferences Is there confidence in the estimate of the relative importance of outcomes and individual preferences? Yes ☑ No ☐	In nursing homes, family/caregivers of the residents and dementia specialists have a significant influence on decisions about the use of anti-dementia medications. In general, the majority of patients and their families/caregivers are willing to have their medications deprescribed to reduce the medication load if suggested by their prescribers. Many carers and family members recognise the progressive nature of dementia and the absence of a cure, valuing a thoughtful, individualised approach to care that considers the patient's specific needs and goals. In aged care, family members and carers value regular medication reviews and monitoring of care plans to ensure decisions are timely and responsive. Recommendations in care plans must be actioned. They also view patient's advanced health directives as critical for preserving the dignity of their care recipients and ensuring their wishes are respected. Patients and their families want informed consent processes to prioritise their voices and the input of caregivers, who can provide valuable insights into their daily experiences and the care needs of the care recipients. However, some carers recognise that their judgment may be clouded by emotional factors and that they would defer their decisions to healthcare providers.	Perspective taken: The lack of evidence for serious harm following cholinesterase inhibitor withdrawal and the evident benefits related to reduced medication burden and costs could be important to certain populations. Individual values and preferences determine the deprescribing approaches. Sources of values and preferences: 1) Consultation with patient and carer representatives 2) Non-systematic review of evidence Source of variability, if any: Difficult to determine the extent of variability; high variability for patient preferences. Method for determining values satisfactory for this recommendation? Yes ☑ No ☐ Yes, but would be improved with direct patient input

	A gradual approach to deprescribing is preferred, allowing symptoms to stabilise and improvements in mobility and well-being to be observed. Patients also value thorough assessments and clear communication throughout the process, particularly when addressing concerns like aggression or behavioural changes to consider the source of triggers. Support for family members or caregivers is seen as essential, as they often play a key role in managing care and advocating for their loved ones. Overall, patients prioritise a collaborative and transparent process that aligns with their values and enhances their quality of life. Clinicians often consider patient and caregiver preference and the presence of severe side effects (e.g. gastrointestinal side effects including diarrhoea, anorexia, abdominal pain, dyspepsia) when considering deprescribing cholinesterase inhibitors. They generally do not rely on any single measure of cognition (such as the Mini-Mental State Examination), function and/or behaviour in their decision-making	
Resources Are the resources worth the expected net benefit? ☑ Uncertain	A comprehensive economic evaluation was outside the scope of the current review. However, potential cost and resource implications related to deprescribing interventions and continuation of medications are discussed below. Cost implications: A 2022 systematic review and meta-analysis of economic evidence revealed that cholinesterase inhibitors and memantine for Alzheimer's disease and other dementias were cost-effective in managing dementia-related symptoms. There was a trend of nonsignificant savings in societal cost, which could include reduced caregiver burden and delayed institutionalisation. However, the economic impact of these medicines on long-term healthcare costs remains a topic of further study. On the topic of deprescribing cholinesterase inhibitors and memantine,	Feasibility: Is this intervention generally available? Yes ☑ No ☐ Opportunity cost: Is this intervention and its effects worth withdrawing or not allocating resources from other interventions? Yes ☑ No ☐ Economic and preventive benefits for harms: Is there a lot of variability in resource requirements across settings? Yes ☑ No ☐ Resource requirements can vary significantly based on the care setting, level of support, and infrastructure available. More structured settings may have the

	evidence is currently lacking. Physician implications: There is a lack of robust data informing the cost of the intervention and subsequently, cost-effectiveness. Most clinicians believe that deprescribing is a complex process, with barriers to resources commonly reported (e.g. suboptimal deprescribing organisational environment that included competing workloads, staffing issues, and limited financial support).	advantage of closer monitoring and specialised care. In contrast, community or primary care settings may face greater challenges, requiring more resources for follow-up, caregiver education, and multidisciplinary involvement.
Equity What would be the impact of deprescribing on health inequities? ☑ Uncertain	The social determinants of health equity are complex and multifaceted. The impact of deprescribing on health equity is inadequately explored in the literature. By reducing medication burdens, lowering costs, and simplifying medicine regimens, deprescribing may enhance access to care and improve health outcomes. Effective deprescribing of anti-dementia medicines requires regular monitoring and follow-up appointments. Patients with limited access to healthcare services might face challenges in adhering to monitoring requirements, which could lead to inequities if they are unable to follow the deprescribing plan effectively. Ensuring equitable implementation and addressing potential challenges faced by people with varying health literacy and access disparities is crucial to maximising these benefits. Culturally and linguistically diverse populations, Aboriginal and Torres Strait Islander populations, people with low socioeconomic status, and those living in rural or remote areas may require additional support or considerations when implementing deprescribing intervention, including the ongoing monitoring process.	
Acceptability Is the option of deprescribing acceptable to key stakeholders? ☑ Probably yes	Healthcare practitioners: Deprescribing is likely dependent on the preference of the patient and/or their caregiver. Patients, their caregivers and family members: The acceptability of deprescribing anti-dementia medicines, such as cholinesterase inhibitors and memantine, to patients, caregivers, and family members can vary depending on several factors. While some patients and families are open to deprescribing, especially in cases where the medication is perceived as ineffective or the patient is in advanced stages of dementia, others may be more hesitant due to fears of symptom worsening. Policymakers and health systems: From a broader perspective, deprescribing can be seen as a way to reduce healthcare costs and improve patient outcomes. However, the short-term impacts on patient care and the resources required to implement effective deprescribing strategies may be a concern.	
Overall judgment	There is a lack of quality evidence for deprescribing to inform evidence-based recommendations.	

33. Medicines for obstructive airway diseases

33.1 Overview of studies targeted medicines for obstructive airway diseases

Article	Drug/Class	Study design	Sample size	Follow-up (months)	Withdrawal schedule
Choudhury 2007 [280]	Inhaled corticosteroids	RCT	260	12	Abrupt discontinuation
O'Brien 2001 [281]	Inhaled corticosteroids	RCT with cross-over	24	3	Not described
Borrill 2009 [282]	Fluticasone and salmeterol, inhaled	RCT	14	1.5	Not described
Adams 2009 [283]	Tiotropium, inhaled	Before and after study	921	0.7 (3 weeks)	Not described
Patel 2022 [284]	Inhaled corticosteroids	Before and after study	11093	9	Not described
Jarad 1999 [285]	Inhaled corticosteroids, as either beclomethasone dipropionate or budesonide	Prospective cohort study	272	2	Withdraw at own discretion during the next 7 days
Steeves 2023 [286]	Inhaled corticosteroids	Retrospective cohort study	75	12	Abrupt discontinuation or gradual tapering

33.2 Evidence for deprescribing medicines for obstructive airway diseases

Study	Specific outcome	Odds ratio (95% CI)	Mean difference (95% CI)
1. Mortality			
Choudhury 2007	Mortality at 12 months	0.14 (0.01, 2.65)	
2. Adverse drug withdrawal events (ADWEs)			
Choudhury 2007	Rate of exacerbations		0.21 (-0.47, 0.89)
Jarad 1999	Exacerbation/return of underlying condition	9.00 (3.93, 20.62)	
Borrill 2009	At least one exacerbation	9.00 (0.38, 210.39)	
O'Brien 2001	At least one exacerbation	7.45 (0.36, 156.28)	
O'Brien 2001	Dyspnoea, measured using the T Borg scale		0.85 (-0.45, 2.15)
3. Health outcomes			
Respiratory measures			
Adams 2009	Transition dyspnoea index focal score after 3 weeks		-0.19 (-0.70, 0.32)
O'Brien 2001	Forced expiratory volume		0.02 (-0.51, 0.55)
Adams 2009	Peak Expiratory Flow Rate AM [L/min] after 3 weeks		-0.20 (-17.47, 17.07)
Adams 2009	Peak Expiratory Flow Rate PM [L/min] after 3 weeks		-2.05 (-20.28, 16.18)
Exercise tolerance			
O'Brien 2001	Exercise tolerance, distance walked in feet		36.00 (-398.50, 470.50)
Fatigue			
O'Brien 2001	Fatigue		1.40 (-2.07, 4.87)
4. Cognitive function			
No available evidence			
5. Quality of life			
Adams 2009	St George's Respiratory Questionnaire total score after 3 weeks		-1.69 (-3.51, 0.13)
Adams 2009	St George's Respiratory Questionnaire impact score after 3 weeks		-1.12 (-3.24, 1.00)
O'Brien 2001	Emotional function, measured using the chronic respiratory disease questionnaire		1.80 (-3.12, 6.72)
O'Brien 2001	Mastery, measured using the chronic respiratory disease questionnaire (a measure of patient's feeling of control over the		0.90 (-2.08, 3.88)

	disease)		
6. Effect on medication regimen			
Choudhury 2007	Deprescribing successful	2.38 (1.41, 4.00)	
Adams 2009	Use of other medications to control the condition		0.01 (-0.42, 0.44)
Adams 2009	Rescue medicine use		-0.32 (-0.34, -0.30)

33.3 Evidence for deprescribing medicines for obstructive airway diseases (non-controlled outcomes)

Study	Specific outcome	Result
1. Mortality		
No available evidence		
2. Adverse drug withdrawal events (ADWEs)		
Patel 2022	Recurrence of the underlying symptom	31%
Patel 2022	Exacerbations of underlying condition, primary care recorded pneumonia episodes	13%
3. Health outcomes		
Health service use		
Patel 2022	Chronic Obstructive Pulmonary Disease (COPD)-related hospitalisation	11%
Steeves 2023	COPD-related hospitalisation	7%
Patel 2022	Hospitalised pneumonia episodes	7%
4. Cognitive function		
No available evidence		
5. Quality of life		
No available evidence		
6. Effect on medication regimen		
No available evidence		

33.4 GRADE evidence profile (critical or important but not critical outcomes only)

Question: In older people, what are the effects of deprescribing (i.e. dose reduction or complete discontinuation) long-term medicines for obstructive airway diseases on mortality, adverse drug withdrawal events, health-related outcomes, cognitive function, and quality of life?

Certainty assessment							Number of participants		Effect	Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Deprescribing	Continuation			
1. Mortality											
1 [280]	RCT	Not serious	Not serious	Serious [1]	Serious [2]	Not serious	132	128	OR 0.14 (0.01, 2.65)	⨁◯◯◯	8
2. Adverse drug withdrawal events (ADWEs)											
Exacerbation/return of underlying condition											
3 [280-282]	RCTs	Serious [3,4]	Not serious	Serious [5]	Serious [6]	Not serious	319	261	Deprescribing of inhaled corticosteroids (ICS) in people with COPD was not associated with a significant increase in the frequency of exacerbation (MD 0.21, 95% CI -0.47, 0.89, n = 260) [280]. In two studies, withdrawal of ICS (either alone or with a long-acting beta agonist) also was not associated with a significant increase in the number of participants having at least one exacerbation (OR 8.14, 95% CI 0.91, 72.87, n = 48) [281, 282]. There was no significant change in the T Borg scale assessment of dyspnoea following the withdrawal of inhaled steroids (MD 0.85, 95% CI -0.45, 2.15, n = 30) [281].	⨁◯◯◯	6
1 [285]	Non-randomised study	Serious [7]	Not serious	Serious [8]	Serious [6]	Not serious	160	112	One study reported a higher risk of exacerbation in participants who had their ICS discontinued compared with participants who were chronically untreated with ICS (OR 9.00, 95% CI 3.93, 20.62, n = 272) [285].	⨁◯◯◯	6
1 [284]	Non-controlled study	Serious [9]	Not serious	Not serious	Not serious	Not serious	11093	N/A	31% of the participants reported an exacerbation event and 13% had primary care recorded pneumonia episodes.	⨁◯◯◯	6
3. Health outcomes											
Respiratory measures											
1 [281]	RCT	Serious [4]	Not serious	Serious [5,10]	Serious [6]	Not serious	15	15	There was no significant change in mean forced expiratory volume during the placebo and ICS treatment periods (MD 0.02, 95% CI -0.51, 0.55).	⨁◯◯◯	4

1 [283]	Non-randomised study	Serious [7]	Not serious	Serious [10,11]	Not serious	Serious [12]	264	432	When compared to the placebo group, participants who had their tiotropium discontinued for 3 weeks had worsening Transition Dyspnoea Index focal score (MD -0.19, 95% CI -0.70, 0.32, n = 696), morning Peak Expiratory Flow Rate (MD -0.20, 95% CI -17.47, 17.07, n = 488), and evening Peak Expiratory Flow Rate (MD -2.05, 95% CI -20.28, 16.18, n = 409). However, none of these were significant.		4
Exercise tolerance											
1 [281]	RCT	Serious [4]	Not serious	Serious [5,10]	Serious [6]	Not serious	7	7	There was no significant change in distance walked during the 6-min walk test during the placebo and ICS treatment periods (MD 36.00, 95% CI -398.50, 470.50) in feet.		5
Fatigue											
1 [281]	RCT	Serious [4]	Not serious	Serious [5,10]	Serious [6]	Not serious	15	15	There was no significant change in the symptoms of fatigue assessed using the Chronic Respiratory Disease Questionnaire during the placebo and ICS treatment periods (MD 1.40, 95% CI -2.07, 4.87).		5
Health service use											
2 [284, 286]	Non-controlled studies	Serious [9]	Not serious	Not serious	Not serious	Not serious	11168	N/A	During the ICS-free period, 11% of the participants had a COPD-related hospitalisation and 7% experienced hospitalised pneumonia episodes [284]. In another study, 7% experienced a COPD exacerbation requiring an emergency department visit or hospitalisation within 12 months of ICS discontinuation [286].		5
4. Cognitive function											
No available evidence											
5. Quality of life (QoL)											
1 [281]	RCT	Serious [4]	Not serious	Serious [5]	Serious [6]	Not serious	15	15	There was no significant change in emotional function (MD 1.80, 95% CI -3.12, 6.72) and mastery (MD 0.90, 95% CI -2.08, 3.88) assessed using the Chronic Respiratory Disease Questionnaire during the placebo and ICS treatment periods.		7
1 [283]	Non-randomised study	Serious [7]	Not serious	Serious [10,11]	Not serious	Serious [12]	263	438	When compared to the placebo group, participants who had their tiotropium discontinued for 3 weeks reported greater improvement in the St George's Respiratory Questionnaire total score (MD -1.69, 95% CI -		7

									3.51, 0.13) although not significant. Although not significant, the placebo group had a slight deterioration in the St George's Respiratory Questionnaire impact score but participants who had their tiotropium discontinued had an improvement (MD -1.12, 95% CI -3.24, 1.00).		

[1] Study only included people with a history of smoking who had been prescribed ICS for at least six months.
[2] Small sample size and/or wide confidence intervals in the estimates of effect.
[3] One study (Borrill 2009) is an open-label study - potential selection, performance, and detection biases
[4] One study (O'Brien 2001) - potential attrition bias due to high dropout rate due to worsening of the primary outcome
[5] Potential indirectness - participants in one study (O'Brien 2001) were all male
[6] Small sample size and/or wide confidence intervals in the estimates of effect.
[7] Non-randomised controlled study, brief follow-up period
[8] Potential indirectness - One study (Jarad 1999) compared the discontinuation of ICS between participants who were chronically untreated with ICS and those previously treated with these drugs. None of the two groups would have received the drug for comparison. It is unclear if the outcome can be generalised in the absence of a true comparison group.
[9] Although the original study was randomised, this follow-up study was an observational single-arm study and there was no concurrent control group (Patel 2022). Steeves 2024 was also a single-arm observational study.
[10] Potential indirectness - respiratory measures/fatigue/exercise tolerance were all surrogate outcomes that serve as proxies for more direct measures of clinical benefit, such as symptom relief, reduced hospitalisation, or improved survival in patients with respiratory conditions.
[11] This study (Adams 2009) compared two groups. The first group had taken a placebo in the main study and then ceased. The second group had used the active drug in the main study and then ceased. Therefore, there is no opportunity to compare the cessation of active drugs with the continued active drugs to know if longer treatment durations are of increased benefit than shorter treatment durations.
[12] This study was sponsored by a pharmaceutical company and the sponsor had a role in the original study design and statistical analyses.

33.5 Evidence-to-Decision table

Question: In older people, what are the effects of deprescribing (i.e. dose reduction or complete discontinuation) long-term medicines for obstructive airway diseases on mortality, adverse drug withdrawal events, health-related outcomes, cognitive function, and quality of life?

Decision domain	Summary of reason for decision	Subdomains influencing decision
Certainty of evidence Is there a high or moderate certainty of evidence? Yes ☐ No ☑	The certainty of evidence is low to very low.	Key reasons for downgrading: Risk of bias, indirectness, imprecision Are all critical outcomes measured? Yes ☐ No ☑ There is a lack of evidence on cognitive function.
Benefits and harms Is there certainty that the benefits of deprescribing outweigh the harms? Yes ☐ No ☑	The effects of deprescribing medicines for obstructive airway diseases have been tabulated in Appendix B (GRADE evidence profile table) with an overview provided in the guideline document (a narrative overview and GRADE summary of findings table). Below is a summary according to the study designs. <u>Summary of outcomes</u> Randomised and non-randomised controlled trials: • No significant difference in mortality, respiratory measures, exercise tolerance, symptoms of fatigue and quality of life Inconsistent findings across studies for exacerbations where randomised controlled trials reported no significant change, whereas a non-randomised study reported a significant increase in exacerbations. However, the latter study lacked a true comparison group. Non-controlled trials: • Exacerbations (31%) • Primary care recorded pneumonia episodes (13%) • Chronic obstructive pulmonary disease (COPD)-related hospitalisation (7-11%) • Hospitalised pneumonia episodes (7%)	Is the baseline risk for benefits and harms of deprescribing similar across subgroups? Yes ☐ No ☑ There is no evidence for COPD at this time that the benefits or harms of deprescribing differ based on subgroups. However, there will be some groups at a higher risk. Should there be separate recommendations for subgroups? Yes ☑ No ☐ The guideline development group acknowledges that certain subgroups may have factors that could impact the balance of benefits and risks from deprescribing (e.g. severity of the disease, indication for corticosteroid use, the presence of adverse drug events, prior history of infection, blood eosinophil count, presence of asthma-COPD overlap, and history of exacerbations). However, the available evidence is insufficient to justify distinct evidence-based recommendations.

	<u>Summary of withdrawal schedules:</u> Randomised controlled trials: Not described (studies=2, n=38), Abrupt discontinuation (study=1, n=260, low certainty) Non-randomised controlled trials: Withdrew at participant's own discretion for seven days (study=1, n=272, very low certainty), Not described (study=1, n=921) Non-controlled trial: Not described (study=1, n=11093), Abrupt discontinuation or gradual tapering (study=1, n=75)	
Values and preferences Is there confidence in the estimate of the relative importance of outcomes and individual preferences? Yes ☑ No ☐	Patients' attitudes toward discontinuing inhaled corticosteroids vary significantly. While many are open to reducing or withdrawing these medications if recommended by their physician, others express concerns about the possibility of worsening symptoms after discontinuation. Reported side effects, such as oral candidiasis related to inhaled corticosteroid use, are also a significant issue for some patients, particularly when these infections become recurrent or systemic. Patients highlight the importance of non-pharmacological support, such as pulmonary rehabilitation to improve lung function. They value clear communication and education from their healthcare providers regarding the benefits, risks, and rationale for both initiating and discontinuing COPD medicines, enabling them to make informed decisions aligned with their health goals. A qualitative study exploring the perspectives of 17 patients with COPD on the proposed withdrawal of inhaled corticosteroids prescribed outside guidelines found that many patients had limited awareness of the medicine, its indication in COPD, and its potential side effects. This finding underscores the need for shared decision-making in	Perspective taken: Individual values and preferences determine the deprescribing approaches. Sources of values and preferences: 1) Consultation with patient and carer representatives 2) Non-systematic review of evidence Source of variability, if any: Difficult to determine the extent of variability; high variability for patient preferences. Method for determining values satisfactory for this recommendation? Yes ☑ No ☐ Yes, but would be improved with direct patient input

	deprescribing conversations. Most clinicians and pulmonologists agree that inhaled corticosteroids are over-prescribed in the primary care setting and are confident to discontinue when inhaled corticosteroids are no longer needed or ineffective. However, some physicians are reluctant to instil any change if the patient is doing well or if a pulmonologist is involved in the patient's care. In addition, several clinicians are not aware of the current evidence and recommendations for prescribing inhaled corticosteroids among patients with mild-to-moderate COPD. For instance, some clinicians are not aware of the increased risk of pneumonia in the long-term use of inhaled corticosteroids.	
Resources Are the resources worth the expected net benefit? Yes ☑ No ☐	A comprehensive economic evaluation was outside the scope of the current review. However, potential cost and resource implications related to deprescribing interventions and continuation of medications are discussed below. Cost implications: The use of medicines for obstructive airway diseases has significant cost implications. Overtreatment of COPD with inhaled corticosteroids was associated with significant costs related to medications and treating serious adverse events related to the use of inhaled corticosteroids such as pneumonia. For patients with a low risk of exacerbations, the use of low-value inhaled corticosteroids led to higher subsequent outpatient healthcare utilisation and costs. The overall cost-effectiveness evaluation of long-term inhaled corticosteroid exposure and discontinuation may be difficult to estimate due to the complexity of health outcomes, the types of deprescribing intervention and the rate of successful implementation. Physician implications: Healthcare providers will need to	Feasibility: Is this intervention generally available? Yes ☑ No ☐ Opportunity cost: Is this intervention and its effects worth withdrawing or not allocating resources from other interventions? Yes ☑ No ☐ Economic and preventive benefits for harms: Is there a lot of variability in resource requirements across settings? Yes ☐ No ☑

	closely monitor patients to assess the impact of deprescribing on ongoing disease severity. Dose tapering may involve additional clinic visits, laboratory tests and extended consultation time. However, it is likely to be feasible compared to the workload required for managing serious adverse drug reactions and periodic monitoring of infection risk.	
Equity What would be the impact of deprescribing on health inequities? ☑ Uncertain	The social determinants of health equity are complex and multifaceted. The impact of deprescribing on health equity is inadequately explored in the literature. Older people affected by the inappropriate use of medications are likely to derive substantial benefits in terms of health equity from deprescribing. By reducing medication burdens, lowering costs, and simplifying medicine regimens, deprescribing may enhance access to care and improve health outcomes for this vulnerable population. However, ensuring equitable implementation and addressing potential challenges faced by people with varying health literacy and access disparities is crucial to maximising these benefits. Culturally and linguistically diverse populations, Aboriginal and Torres Strait Islander populations, people with low socioeconomic status, and those living in rural or remote areas may require additional support or considerations when implementing deprescribing intervention, including the ongoing monitoring process.	
Acceptability Is the option of deprescribing acceptable to key stakeholders? ☑ Probably yes	Healthcare practitioners: Deprescribing is likely acceptable to most healthcare practitioners, especially when supported by clinical practice guidelines and a shared decision-making process with patients. The term deprescribing may be new to healthcare practitioners but the concept is not. Healthcare practitioners are very familiar with discontinuing ineffective medications or those causing adverse effects worse than the condition being treated. Patients, their caregivers and family members: Many are open to deprescribing if they understand the potential benefits and risks, especially when given the option to restart medications when necessary. Policymakers and health systems: From a broader perspective, deprescribing can be seen as a way to reduce healthcare costs and improve patient outcomes. However, the short-term impacts on patient care and the resources required to implement effective deprescribing strategies may be a concern.	
Overall judgment	There is a lack of quality evidence for deprescribing to inform evidence-based recommendations.	

Abbreviation: COPD chronic obstructive pulmonary disease

34. Corticosteroids (eye)

We were unable to identify a study that assessed deprescribing corticosteroids (eye) from the systematic search.

35. Antiglaucoma preparations and miotics

We were unable to identify a study that assessed deprescribing antiglaucoma preparations and miotics from the systematic search.

36. Ocular lubricants (other ophthalmologicals)

We were unable to identify a study that assessed deprescribing ocular lubricants from the systematic search.

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Appendix C. Study protocol for guideline development

Study Protocol for Developing Deprescribing Clinical Practice Guidelines: Evidence-based GRADE Methodology and a Delphi Consensus Method

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Abstract (<350 words)
Background: Deprescribing has emerged as a strategy to reduce the use of potentially inappropriate medicines, particularly in older people. Evidence-based deprescribing clinical practice guidelines are a key enabler in integrating deprescribing into routine care. This protocol outlines the development of deprescribing clinical practice guidelines targeting commonly prescribed medicines for older people, specifically focusing on applying the evidence-based Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology alongside a Delphi consensus-building process.

Methods: The guideline development process follows the World Health Organisation Handbook for Guideline Development, Australian National Health and Medical Research Council Guideline Development Methodology, and the Appraisal of Guidelines for Research & Evaluation (AGREE) II Instrument. This project is guided by a guideline development group that includes a multidisciplinary healthcare team, representatives from professional organisations, and patient or carer stakeholders. The development involves both evidence-deriving and consensus-building processes. A comprehensive systematic review and meta-analysis of the literature has been conducted, and evidence related to deprescribing in older people has been identified, with the certainty of evidence assessed using the GRADE framework. Where quality evidence is available, evidence-based recommendations will be formulated following the evidence-to-decision GRADE framework. For areas with insufficient evidence, consensus-based recommendations will be developed using a modified Delphi method. Additional practice points will be created where necessary to facilitate the practical application of these recommendations.

Discussion: Given the large scope of the currently proposed guidelines, the proposed approach discussed in this protocol is adapted based on several important considerations on the practical, operational, and resource issues. Given deprescribing is an emerging area and the limited availability of evidence for some drug classes, expert consensus and input from patient representatives offer a valuable alternative for recommendation development. The final guideline will provide broad guidance for deprescribing common medicines used in older people that complement existing single drug-class deprescribing guidelines and other treatment guidelines.

Trial Registration: Not applicable

Keywords: Aged, Delphi Technique, Drug Utilization, Geriatric Medicine, Clinical Decision-Making

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INTRODUCTION

Background

The ageing population presents a unique set of challenges that necessitate a careful approach to medication management. Older people are more likely to have comorbidities that prompt the use of multiple medicines to manage their complex medical conditions. As such, polypharmacy, defined as the concurrent use of five or more medicines, is prevalent in older people [1, 2]. A systematic review revealed that up to 93% of people aged 65 and over globally experience multimorbidity, with polypharmacy affecting as many as 87% of this population [3]. While polypharmacy has been associated with negative outcomes including falls, frailty, and mortality [4-6], the number of medicines does not necessarily indicate the appropriateness of a medication regimen [7, 8]. Medicines can play a crucial role in preventing future complications and providing symptomatic relief, thereby significantly enhancing a person's functioning and quality of life. Consequently, it is essential to distinguish between appropriate and inappropriate polypharmacy by applying careful clinical judgment. Inappropriate polypharmacy increases the risks of adverse drug events, medication non-adherence, hospitalisations, geriatric syndromes, and mortality [9, 10]. Older people, in particular, are more vulnerable to these negative consequences of potentially inappropriate medicines than younger people due to reduced physiological reserves. Medication optimisation is a process to ensure safe and effective use of medicines [11] and deprescribing forms a part of the process.

Deprescribing is a systematic process of tapering, stopping, discontinuing, or withdrawing one or more medicines with the goal of managing inappropriate polypharmacy and achieving improved outcomes [12-14]. Deprescribing has emerged as a critical component of patient-centred care and is viewed as an effective intervention to reduce the use of potentially inappropriate medicines [15, 16]. While deprescribing has been extensively explored in various contexts, its implementation in routine clinical practice has not been widely reported, with healthcare professionals consistently citing a lack of detailed guidance as a barrier to deprescribing [17, 18]. A scoping review indicated that only 29% of existing treatment guidelines incorporated at least one recommendation about deprescribing, with a primary focus on prescribing practice for disease management [19].

Evidence-based deprescribing guidelines are seen as a facilitator of deprescribing in clinical practice [20-22]. Clinical practice guidelines are ‘systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances’ [23]. As opposed to guides, clinical practice guidelines are formal documents developed through a rigorous and standardised process that involves systematic reviews of existing evidence and expert consensus.

A qualitative study has shown that evidence-based deprescribing guidelines increased clinicians' perceived self-efficacy in developing and implementing deprescribing plans for certain drug classes [24]. However, clinical practice guidelines for deprescribing currently exist for only a limited number of drug classes. Although more recently, an attempt has been made to develop a comprehensive guideline for common psychiatric medicines, this guide was developed using a different approach than standard clinical practice guidelines, which may require different critical appraisal methods [25]. Additionally, a study shows that deprescribing recommendations currently incorporated in treatment guidelines do not contain clear and actionable recommendations with a substantial variation in their content and format that may further confuse healthcare professionals [19]. Deprescribing is an area of practice requiring complex decision-making in partnership with patients, their carers, and family members. Hence, a specific clinical practice guideline targeting deprescribing may improve effective implementation in clinical practice. Current clinical practice guidelines for deprescribing exist for antipsychotics [26], benzodiazepine receptor agonists [27], proton-pump inhibitors [28], antihyperglycemics [29], opioid analgesics [30], as well as cholinesterase inhibitors and memantine [31]. The population for the systematic review conducted for these guidelines included people aged over 18, with most of the guidelines did not provide specific recommendations for older people. The models of care for older people and their care goals can be vastly different to those of younger people, especially for older people who are frail [32, 33]. Additionally, single drug class guidelines may have limited application in addressing inappropriate polypharmacy commonly seen in older people.

Objective

The increasing prevalence of preventable harms associated with inappropriate polypharmacy and potentially inappropriate medicines in older people [34] highlights the urgent need to promote judicious deprescribing in practice. Despite this pressing need, there is a notable lack of deprescribing guidelines for many commonly used medicines. To address this gap, we aim to develop a clinical practice guideline for deprescribing that encompasses medicines frequently prescribed to older people. The current protocol outlines the development of this guideline, specifically focusing on applying the evidence-based Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology alongside a Delphi consensus-building process.

METHODS

Study design

The development of this clinical practice guideline consists of evidence-deriving and consensus-building processes. For the first part, evidence will be derived using a systematic review and meta-analysis of the literature and a rigorous assessment of the quality of the evidence using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework. Systematic reviews and meta-analyses are considered the gold standard in evidence synthesis [35] whereas the GRADE framework is increasingly seen as the preferred approach for summarising findings in systematic reviews and rating the certainty of a body of evidence [36]. For the second part about the consensus-building process where evidence is insufficient or lacking, a modified Delphi approach will be used as it is well-suited for gathering

input from individuals across diverse professions and specialties, especially when there are expected differences in opinions [37, 38]. The traditional Delphi method involves generating qualitative data in the first round of data collection to guide the development of statements for the subsequent rounds. A modified method will be used that omits the first qualitative round and begins the series of rounds with a set of carefully selected statements derived from the literature, previous research, or existing clinical practice guidelines for treatment [39]. The modification was carefully considered to expedite the process, minimise participant fatigue and increase overall engagement throughout the subsequent iterative rounds without compromising the integrity of the consensus-building process [40]. We acknowledge the potential biases inherent in the Delphi approach. Nevertheless, the Delphi technique provides advantages particularly through the anonymity of responses during the survey rounds. This anonymity helps mitigate potential dominance effects, halo effects, and groupthink commonly encountered in other group settings such as a focus group [41]. Additionally, the iterative process allows for controlled feedback, ultimately facilitating the achievement of group consensus. We plan to include a diverse group of Delphi panel members and establish a predetermined cut-off response rate to mitigate potential selection and response biases.

The development of the clinical practice guideline follows the World Health Organisation Handbook for Guideline Development, Australian National Health and Medical Research Council (NHMRC) Guideline Development Methodology and the Appraisal of Guidelines for Research & Evaluation (AGREE) II Instrument and User's Manual [42-44]. In Australia, guidelines developed by groups external to NHMRC may be approved by NHMRC. While it is not mandatory for guidelines to obtain approvals, NHMRC offers step-by-step guidance to produce high-quality guidelines. Additionally, multiple tools have been developed for guideline appraisal among which the AGREE II instrument is the most commonly used and forms part of the process suggested by NHMRC [36]. Adhering to the processes detailed in the WHO handbook, NHMRC guidance and AGREE II instrument will ensure the guidelines meet the requirements for methodological rigour in the development and reporting of guidelines.

Purpose of the guideline

The guideline will provide guidance on the key aspects of deprescribing in people aged 65 years and over, which are to determine when, how, and for whom a medicine should be deprescribed, as well as identify monitoring requirements during deprescribing and the ongoing treatment needs as applicable.

Scope of the guideline

This guideline prioritises providing recommendations for medicines commonly prescribed and dispensed to older people as it is likely to have the largest impact on clinical practice. We leveraged data from the Australian PBS to identify the top 100 medicines as priorities for future deprescribing efforts. The PBS is routine administrative data that provides an accurate representation of common medicines used by the population. The Australian PBS subsidises the cost of most medicines in Australia for eligible residents, with over half (54%) of PBS-subsidised medicines dispensed to people aged 65 and over [45]. This guideline will be limited to medicines intended for regular use. Hence, medicines prescribed for short-term,

intermittent, as required, or acute use only (e.g. systemic or topical antibiotics) will not be included.

The guideline steering committee analysed the PBS data for people aged 65 or over who were dispensed PBS-listed medicines in 2023 to identify the top 100 medicines with the highest dispensing volumes or the largest number of unique persons dispensed, excluding non-regular medicines. The volume-based metric represents the total number of dispensing in a calendar year, while the person-based metric refers to the number of people who received the medicine in a calendar year. The person-based metric is included to account for medicines with less frequent dosing, such as denosumab, which is typically administered every six months. This methodology was previously adopted in a study investigating the inclusion of information about medication withdrawal and medicine use in older people [46]. A limitation of using the PBS data to estimate common medicines is the data does not include medicines available without a prescription, such as over-the-counter and complementary medicines, or medicines dispensed on private prescriptions. While the primary focus of this guideline will be common PBS-listed medicines, the guideline development group will review and consider on a case-by-case basis the inclusion of additional medicines where evidence for deprescribing is identified in the search. The rationale is to not exclude medicines simply because they are not listed on the PBS but to consider the potential risks of inappropriate use and the impact of deprescribing.

Stakeholder involvement

Guideline steering committee

The guideline steering committee (authors of the current protocol) has a primary role of guiding and overseeing the overall development of the guideline. Their responsibilities are to propose the topic and scope of the guidelines to the guideline development group, refine the key clinical questions, as well as plan and lead the development of high-quality, credible evidence-based and consensus-based recommendations. The steering committee will support the implementation of the guideline in clinical practice and actively take part in the dissemination process.

Guideline development group

The guideline steering committee will establish a guideline development group with members from each of the following categories: 1) physicians including general practitioners, geriatricians, clinical pharmacologists, and geriatric psychiatrists, 2) nurse practitioners 3) pharmacists, 4) statisticians, 5) policymakers, 6) allied health professionals (optometry, dental, podiatry, physiotherapy, physiotherapist), 7) methodologist with experience in guideline development, methodology or systematic reviews, 8) expert in implementation science or behavioural science, 9) pharmacoepidemiologist, 10) health economist, and 11) patients or carers with lived experience. Clinicians and pharmacists must be practising in the field of geriatric care or pharmacotherapy relevant to people aged 65 and over meeting one or more of the following selection criteria:

1. Demonstrable clinical experience in the field of geriatric and gerontology or specialised in providing pharmaceutical care for older people (e.g. practice-based experts who are practising or having practised in the field for at least five years)

2. Recognised as an expert in the field by peers (e.g. invitation to a relevant symposium, conference or other academic events as a speaker or presenter, or membership in an association or research group)
3. Recent publications as a first or last author on the relevant topic in peer-reviewed journals within the past five years
4. Post-graduate qualification or current credential relevant to geriatric pharmacotherapeutics (e.g. a geriatrician or a pharmacist credentialed with a certificate in geriatric pharmacy)

At least one member, regardless of profession, will be practising in each hospital, residential aged care facility and private practice settings and at least one member will be practising in a rural or remote area. Individual members may fulfil multiple criteria, such as a general practitioner practising in a hospital in a rural area.

All members of the guideline development group and steering committee will be required to declare any perceived or actual financial or non-financial competing interests. The guideline steering committee will record and manage potential conflicts of interest relevant to the guideline development. Members of the guideline development group will be identified through professional networks and snowball sampling. If there is a lack of relevant content expertise for a specific therapeutic area, the guideline steering committee will be responsible for recruiting additional clinical experts with relevant expertise and credentials based on their existing professional networks.

At least four members of the guideline development group will represent a specific panel consisting of at least one layperson, patient, and carer with lived experience. These individuals will be identified through the Western Australian Health Translation Network Consumer and Community Involvement Program. These individuals are invited to provide critical insights into the challenges and needs that are often overlooked in clinical practice, provide their input on draft deprescribing recommendations, and ensure that at every stage the views of patients and carers are prioritised. Layperson, patients and carers will be reimbursed for their time. By integrating their perspectives, we aim to create guidelines that resonate with the actual experiences and preferences of patients and the wider public, ensuring greater relevance and uptake in real-world settings.

All members of the guideline development group will contribute by reviewing draft recommendations. They will also be invited to take part in the modified Delphi study to establish consensus-based recommendations for common drug classes without evidence from the literature.

External experts

External experts will be individuals with the expertise and experience relevant to the methodology or the content of the guideline who have indicated a preference to provide external expert feedback independent from the guideline development group.

Rigour of guideline development

The development of the guideline comprises two main phases (Figure S1). Phase 1 involves synthesising evidence using a systematic review and meta-analysis

approach. Phase 2 will involve presenting draft recommendations to a guideline panel to determine consensus using a systematic modified Delphi method.

Figure S1. Guideline development process focusing on GRADE Methodology and a Delphi Consensus Method

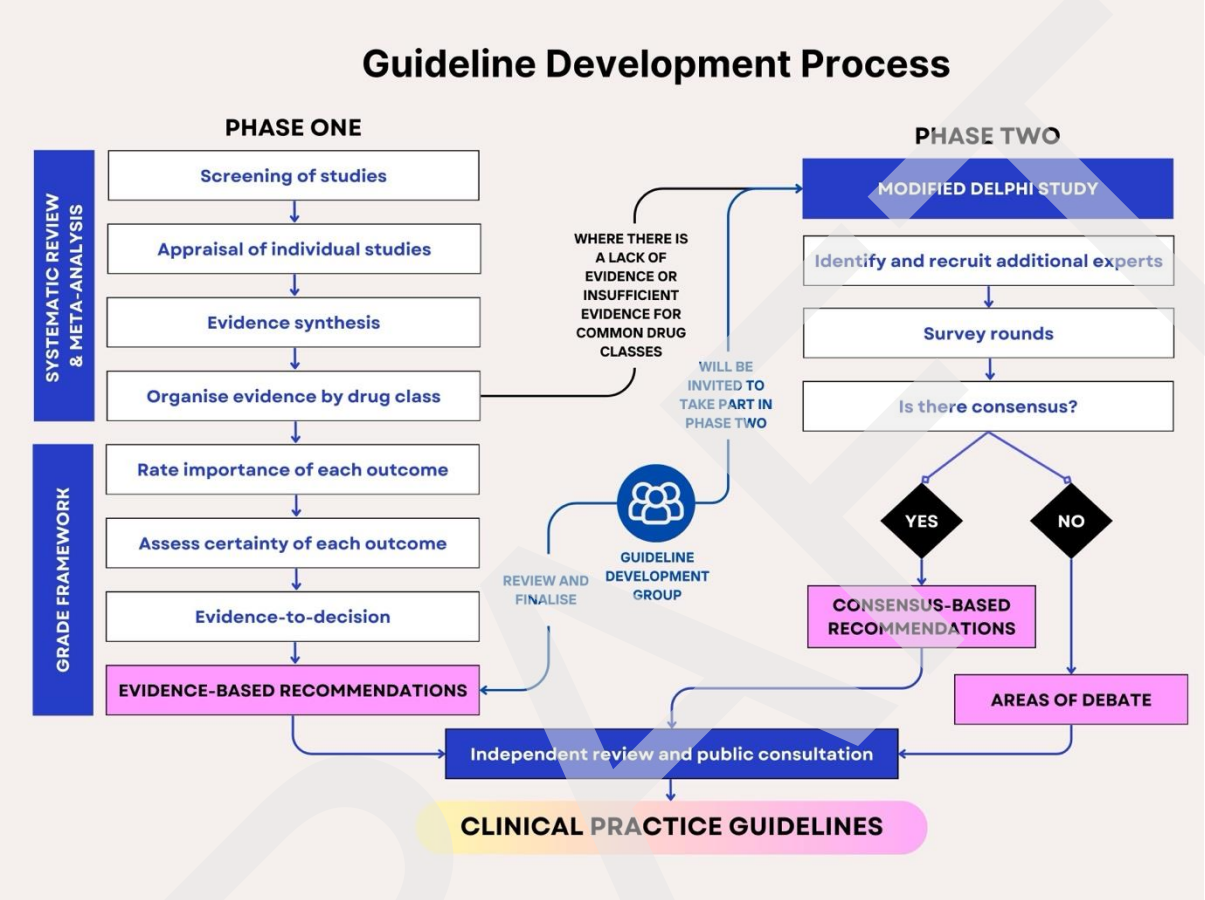

Figure legend: A two-phase process for developing clinical practice guidelines. Phase One involves systematic review and meta-analysis to synthesise evidence and recommendation development using the GRADE framework. Phase Two addresses areas where evidence is insufficient, inconclusive, or unavailable, aiming to develop consensus-based recommendations using a modified Delphi approach or identifying "Areas of Debate." The final recommendations will further undergo independent review and public consultation.

Phase 1: Synthesising evidence

Identifying relevant evidence

The guideline steering committee updated a 2016 systematic review and meta-analysis [47] assessing the effects of deprescribing in older people to capture new evidence that emerged since the original publication [48]. This systematic review and meta-analysis summarised comprehensive findings on the effects of deprescribing on mortality, physical health, cognitive function, quality of life, effect on medication regimen, and adverse drug withdrawal events. The process follows the Cochrane Handbook for Systematic Reviews of Interventions, which consists of an updated literature search, screening for study inclusion, data extraction, quality appraisal, data analysis and synthesis (meta-analysis), and interpretation of findings [49]. The methods have previously been described in a published protocol [50]. The updated systematic review and meta-analysis has since been published [51]. Briefly, the

review had broad selection criteria without limitations on study settings, patient sub-groups, or types of medicines targeted, aiming to capture all relevant studies related to deprescribing in older people. Electronic database searches were conducted in CINAHL, Medline, Embase, Scopus, Web of Science, and ProQuest (Dissertations and Theses Global) to identify relevant published studies up to April 2024 in which older people (aged 65 years and older) had at least one medicine deprescribed. Both experimental (randomised or non-randomised controlled trials) and observational studies with or without concurrent control groups (before-and-after, case-control or cohort studies) were included. Studies were grouped by study designs and targeted medicines for data analysis. The risk of bias was assessed using the Cochrane tool and the Newcastle-Ottawa tool. Odds ratios or mean differences were calculated as the effect measures using either the Mantel–Haenszel or generic inverse-variance method with fixed- or random-effects meta-analyses.

Formulating draft recommendations

The certainty of the evidence in the systematic review and meta-analysis will be rated using the GRADE approach. This structured and transparent approach will enable recommendations to be synthesised based on the evidence and its certainty, while also considering overall benefits and harms, patient values and preferences, resource implications, and the feasibility of implementation [52]. The GRADE approach has been adopted by national and international organisations as a preferred approach to rate the certainty of evidence in systematic reviews to develop and determine the strength of recommendations in clinical practice guidelines [53]. The key steps in developing recommendations using the GRADE approach are: 1) selecting and rating the importance of outcomes, 2) summarising the evidence, 3) determining the quality of evidence, and 4) moving from evidence to recommendations.

It is acknowledged that the importance of an outcome may only become known once evidence is reviewed, or the analyses were carried out (e.g. serious adverse effect). The search strategy for our systematic review and meta-analysis has thus included broad outcomes of mortality, physical health, cognitive function, quality of life, effect on medication regimen, and adverse drug withdrawal events. Initially, the guideline steering committee will organise the evidence of outcomes identified from the systematic review and meta-analysis by drug classes. Each outcome will be rated on its relative importance by the guideline development group for decision-making: critical, important but not critical, or low importance [54]. Outcomes rated as critical and important will be used to produce the GRADE evidence profile and GRADE summary of findings table which will bear on guideline recommendations.

Two researchers trained in the GRADE approach will independently assess the certainty of the evidence for each outcome by considering eight GRADE criteria (risk of bias, directness of evidence, consistency and precision of results, risk of publication bias, magnitude of the effect, dose-response gradient, and influence of residual plausible confounding). Outcomes will be rated as high, moderate, low, or very low certainty (Table 1), with discrepancies between the researchers resolved through discussion and consensus. These outcomes along with the certainty of the evidence will be included in the GRADE evidence profile and subsequently GRADE summary of findings table. The latter is intended to be a quick summary and will not contain details of the judgments about the certainty of the evidence.

The GRADE Evidence-to-Decision framework provides a structured and transparent framework to develop recommendations based on the relative importance and certainty of the evidence, while also considering the overall benefits and harms, patient values and preferences, implications for resource utilisation, equity, acceptability and feasibility of deprescribing [52]. The guideline steering committee will follow the GRADE Evidence-to-Decision framework to draft recommendations. Specifically, when considering the overall balance of benefits and harms, best estimates of the magnitude of effects on desirable and undesirable outcomes and the relative importance of outcomes based on estimated values and preferences will be considered. Patient values and preferences for each drug class will be investigated based on consultations with the layperson, patient, or carer representatives in the guideline development group as well as non-systematic reviews of the available literature, or clinicians' experience of interactions with their patients. Investigations on the implications of resources, equity, acceptability and feasibility of deprescribing will rely on non-systematic reviews of the available literature, expert opinions or individual experiences of the guideline development group members.

Draft recommendations will be presented to all members of the guideline development group along with the evidence for review presented in tables and as narrative reviews, and where appropriate including statistical data such as meta-analysis results. The group members will be briefed on the guideline development methodology and the GRADE framework so each member can independently apply their judgement in a consistent and systematic way. The guideline development group will ultimately determine the type of recommendation categorised based on the type and source of evidence that supports them (Table 2). For evidence-based recommendations, the strength (strong or weak) and direction (for or against) of recommendations will also be determined. The guideline steering committee will be responsible for revising the draft recommendations based on feedback from the development group ensuring all appropriate viewpoints are considered. Where the guideline development group identifies there is insufficient quality evidence or lack of evidence, they may choose not to make a recommendation. Alternatively, consensus methods (Phase 2) will be used to develop recommendations or practice points grounded in expert opinions and individual patient or carer experiences.

TABLE 1. GRADE CERTAINTY OF EVIDENCE RATINGS [54]

GRADE ratings	**Definitions**
⊕⊕⊕⊕ High	We are very confident that the true effect lies close to that of the estimate of the effect.
⊕⊕⊕◯ Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
⊕⊕◯◯ Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
⊕◯◯◯ Very low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

TABLE 2. TYPES OF GUIDELINE RECOMMENDATIONS

Recommendation types	Description
Evidence-based recommendation	Recommendation developed based on quality and consistent evidence identified from a systematic review and meta-analysis linking deprescribing to outcomes.
Consensus-based recommendation	Recommendation developed through Delphi panel consensus when evidence is insufficient, inconclusive, or unavailable, following a systematic review and meta-analysis approach to search for evidence. The purpose of consensus-based recommendation is to fill the knowledge gap.
Practice point	Guidance based on expert opinion and individual experience, outside the scope of the search strategy used to identify evidence from a systematic review and meta-analysis. The purpose of practice points is to support the implementation of recommendations.

Phase 2: Consensus-building process using a modified Delphi method

While peer-reviewed evidence has long been considered the gold standard for developing guideline recommendations [55], research is not always available to inform guideline recommendations. As deprescribing is a relatively new field, there is sparse evidence for patient-important outcomes, as shown in previous systematic reviews [47, 48]. In situations where there is insufficient information, consensus methods provide another means of synthesising information grounded in expert opinions and experiences.

For the second phase of guideline development, the guideline steering committee will use surveys to elicit opinions from leading experts and patients or carers to reach a consensus on core recommendations for deprescribing clinical practice guidelines to fill the knowledge gap (see Figure S 1).

Selection, identification and recruitment of the panel

All members of the guideline development group involved in Phase 1 will be invited to take part in the modified Delphi study to establish consensus-based recommendations for common drug classes with insufficient or a lack of evidence from the literature review. The criteria of the Delphi panel will follow the criteria of the guideline development group as described above. At a minimum, the panel members must include at least one member from each of the following healthcare professions: geriatrician, general practitioner, nurse practitioner, and consultant pharmacist. As the guideline steering committee drafted the recommendations, they will not be involved in the decisions made by the consensus panel.

Participants will be included if they are willing to participate in all Delphi rounds and declare ongoing conflicts of interest. While literature commonly suggests a panel size of 10 to 18 for a Delphi study, we plan to include a minimum of 20 participants to account for potential attrition [56]. If recruitment for additional panel members who were not previously involved in Phase 1 becomes necessary to meet the targeted sample size, the recruitment will primarily be based on a purposive sampling approach. A generic advertisement will be posted on social media to call for potential participants. We will endeavour to identify potential Australian expert panel members

by searching and cross-referencing recent publications in the field of geriatric pharmacotherapy. The experts identified will be sent a personalised email invitation to participate in the study. Additionally, we will identify practice-based experts through peers and professional organisations or scientific networks. A snowball sampling approach will also be used where the experts identified will be encouraged to nominate other colleagues in the field who may meet the eligibility criteria.

Delphi method

The online surveys will be administered using the Qualtrics software (Qualtrics, Provo, UT, USA. https://www.qualtrics.com) [57]. The content of the survey will include best practice statements about deprescribing that are specific to drug classes. The statements will be organised into the pre-defined aspects of deprescribing, as described above.

In each round, an online survey will be disseminated via email that prompts the panel members to review the statements provided based on their best judgment and experience. The response to each best practice statement in the survey will be binary, either agree or disagree, with an optional free-text comment section at the end of each drug class section. This is so we can capture any valuable insights that are not in the statements provided. We will not consider a round valid if the response rate falls below 70%, as it may give rise to non-response bias [58]. Survey responses will remain confidential and accessible only to the guideline steering committee responsible for data analysis. Participants will complete the survey independently, without direct interaction with other survey respondents.

The participants will be given 14 days to complete the survey. The survey will be designed to automatically save responses, enabling participants to resume and complete the survey at a later time, even if they exit the survey before submitting. A first reminder email will be sent on Day 7. If participants are unable to complete the survey by the original deadline, individual extensions will be granted for a reasonable duration to accommodate their schedules. For those who have not yet responded to any prior email prompts, a final email reminder will be sent on Day 21, which is seven days past the original deadline. To further maximise the retention rate, we will provide an email update to all participants about the study progress, including the anticipated date for the next survey round, so the participants are prepared [59]. After each round is concluded, we will summarise and anonymise the feedback. We will share a brief feedback report that summarises the response percentages for each question to the panel members who participated, and they will be thanked for their contribution to the study.

Definition of consensus

In theory, consensus is achieved when all panel members agree or disagree on the items. However, a full agreement is rarely achieved and likely not feasible in a Delphi study. The goal of consensus is to reach a mutually acceptable level of agreement. Although consensus is fundamental to Delphi studies, a systematic review revealed that it is often poorly defined and rarely reported [60]. It is recommended to pre-specify a threshold percentage for agreement [60]. In this study, we will define 75% or greater agreement as consensus, as this percentage of agreement is generally considered acceptable in literature [40, 60, 61].

Delphi rounds
We will conduct at least one survey round to allow feedback and revision of responses. The most common number of rounds to reach consensus in practice is typically two to three [62]. Statements where consensus has been achieved will be incorporated into clinical practice guidelines as consensus-based recommendations. If consensus has not been achieved, the statements will be presented to the panel members in the next round. The steering committee will modify the survey in the next round to include refined statements to capture the evolving consensus. If consensus is still not achieved after a reasonable number of rounds, we will identify these items in the clinical practice guideline under 'Areas of Debate', highlighting a lack of consensus for future research. In this regard, no recommendation will be made.

Data analysis
We will collect information about the participants' demographics, including name, email address, age, gender, and where relevant, the geographic location of their current primary work location, job title and number of years of experience. These data will be analysed descriptively [63]. As the focus of this study is on quantitative data collection and analyses for binary responses, the participants' responses for each statement will be aggregated and analysed in percentages to determine consensus. We anticipate optional free-text comments may include main insights, reasons for agreement or disagreement, and any suggestions for statement revisions. Qualitative data collected from the free-text comments will be analysed thematically to identify common themes and topics that emerge from the participants' responses.

Patient and public involvement
Independent review
Following Phases 1 and 2, we will invite at least two independent expert peer-reviewers who are not part of the guideline development group and the modified Delphi panel to review the guideline using the AGREE-II instrument. The independent review stage helps identify areas for improvement before the guidelines are finalised by assessing the methodological quality of guidelines against the AGREE II instrument. The independent reviewers will be identified by the guideline development group through existing networks. They will have the expertise and experience relevant to the content of the guideline as well as an understanding of the context in which the guideline will be implemented.

Public consultation
Prior to finalising the overall guideline, we will also conduct a public consultation process to seek input from the wider community on the draft recommendations. This will ensure that the guideline recommendations are aligned with the community's values and expectations. The public includes individuals, patient organisations, and professional organisations that will be involved in, or affected by, the implementation of the clinical recommendations of the guideline. We will notify the public of the opportunity to review the draft and share their written feedback via emails, social media, website notices, or directly emailing relevant stakeholders. As part of the public consultation process, we will make the draft guideline available for a period of 30 days on an online platform for public access. An extension of the consultation period may be considered if requests have been made from the public. Following the conclusion of the public consultation, we will prepare a public consultation report with

a summary of the process and the changes made to the guidelines as a result. All stakeholders who have made a submission will be formally acknowledged in the guideline, provided they have given consent to do so.

Discussion

The proposed approach discussed in this protocol is adapted based on several important considerations on the practical, operational, and resource issues while aiming to align with established guideline development frameworks to ensure methodological rigour and enhance credibility. The currently proposed guidelines present a large scope of targeted medicines. The option of including a systematic review and meta-analysis for each drug class was given deliberate and extensive consideration, and it was concluded that the length of time and resources rendered it inappropriate for the goal of this work. Instead, a comprehensive systematic review and meta-analysis were chosen that included evidence on deprescribing with broad inclusion criteria as detailed above. Given deprescribing is an emerging area and the limited availability of evidence for some drug classes, expert consensus and input from patient representatives offer a valuable alternative for recommendation development.

The final guideline will provide broad guidance for deprescribing common medicines used in older people, that complements existing single drug-class deprescribing guidelines and other treatment guidelines. The dissemination plan for the clinical practice guideline will be informed by the NHMRC approach and our ongoing knowledge of translation activities [64]. To ensure wide uptake across diverse healthcare settings, various channels will be used to disseminate the guideline including digital platforms (e.g. media release, social media channels, professional forums), professional networks (e.g. relevant societies, organisations, key target groups, and charities), and events (e.g. presentation at academic conferences, webinar). An impact log will be used to keep a record of the dissemination across various channels and to accumulate feedback using Google Analytics, Scopus, SciVal, Almetric Explorer, and Web of Science as appropriate. We anticipate the guideline to be implemented in a range of workplace settings, including but not limited to primary care clinics, hospitals, and residential aged care facilities where older people are cared for.

DECLARATIONS

Ethics approval and consent to participate

Ethics approval has been granted by the University of Western Australia Human Research Ethics Committee (reference: 2023/ET001118). Consent for participating in the study will be obtained prior to the commencement of the study.

Consent for publication

Not applicable

Availability of data and materials

The data and materials generated or analysed during the study will be made available upon reasonable request from the corresponding author.

Competing interests

The authors declare no competing interests.

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Author contributions

All authors shared the study conception. HWQ led the detailed protocol planning and drafted the manuscript. All authors critically reviewed the study protocol and assisted in the development and implementation of the study. All authors read, revised, and accepted the final draft.

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