Effectiveness of Deprescribing Interventions in Older Adults: An Overview of Systematic Reviews

Shiyun Chua

A thesis

submitted in partial fulfillment of the

requirements for the degree of

Master of Public Health

University of Washington

2021

Committee:

Beth Devine

Shelly Gray

Jeffrey Harris

Program Authorized to Offer Degree:

Health Services

University of Washington

Abstract

Effectiveness of Deprescribing Interventions in Older Adults: An Overview of Systematic Reviews

Shiyun Chua

Chair of the Supervisory Committee:

Jeffrey Harris

Department of Health Services, School of Public Health

Potentially inappropriate medications and unnecessary polypharmacy are associated with poor outcomes. Despite numerous systematic reviews examining deprescribing in recent years, rigorous evidence to guide deprescribing is limited, and priorities for deprescribing practice are still unclear. We aim to synthesize results from systematic reviews (SRs) addressing the effectiveness of deprescribing interventions in older adults. 11 databases were searched without language restrictions from January 2005 to October 2020. Inclusion criteria were developed a priori, using a conceptual framework and included SRs comparing deprescribing interventions to a control group, reporting on 18 outcomes of interest. Article selection, data extraction and quality assessment of included articles using a validated tool were conducted in duplicate, and conflicts resolved by consensus. Data synthesis was performed at three levels – at Level 1, we report SRs' authors' conclusions; at Level 2, results of SRs not including narrative of primary studies not of relevance and at Level 3 relevant primary studies. 2335 unique citations were

retrieved, of which 93 full-text SRs were assessed for eligibility and 21 SRs and 13 meta-analyses included. SRs scored low or critically low in quality assessment. At Level 1, all SRs reported on benefits, while ten made conclusions regarding harm, only two found harm associated with deprescribing. At Level 2, majority of SRs found that deprescribing can reduce the number of medications: 16 (52%) found positive effects and nine (29%) found mixed positive effects. The majority of studies reporting on mortality and patient-centered outcomes reported mixed positive or no effects. Only seven SRs reported effects that were considered harmful across all outcome themes. Few SRs reported on cost outcomes or results according to pre-specified subgroups of interest. At Level 3, regardless of intervention type, deprescribing interventions were associated with positive or no effect on outcomes. In older adults, deprescribing interventions can successfully result in medication withdrawal, and appear safe, but have demonstrated little impact on mortality, patient-centered outcomes or adverse effects. Few SRs examined utilization and cost outcomes, or focused on subgroups. Future research should focus on special populations

Title: Effectiveness of Deprescribing Interventions in Older Adults: An Overview of Systematic Reviews

Shiyun Chua MD[1], Beth Devine MBA PharmD PhD,[1] Adam Todd PhD FRPharmS SFHEA,[2], Yuhan Huang MHS[1], Stephen Hughes BPharm MPhil PhD[2], Zizi Elsisi BPharm MS[1], Andrew Husband PhD FRPharmS PFHEA[2], Shelly Gray PharmD MS[1]

[1] University of Washington, Seattle WA, [2] Newcastle University, Newcastle-upon-Tyne, UK

Introduction

Over 40% of older adults aged 75 years and older in OECD countries are prescribed five or more medications on a regular basis[1]. Use of multiple medications, or polypharmacy, is associated with increased risk of poor outcomes[2-4]. These harms appear to be amplified in vulnerable subgroups[5], such as those with frailty[6, 7] or dementia[8]. Moreover, approximately 50% of older adults are estimated to receive at least one unnecessary, or potentially inappropriate medication (PIM)[9]. Previous interventions to address polypharmacy have examined medicines optimization, while recent efforts have focused on deprescribing, defined as 'the process of withdrawal of an inappropriate medication, supervised by a health care professional with the goal of managing polypharmacy and improving outcomes'[10].

Numerous studies and systematic reviews (SRs) have examined a variety of strategies to deprescribe in older adults, with varying levels of success[11, 12]. Despite this progress, rigorous evidence to guide deprescribing is limited, and priorities for deprescribing practice are still unclear. Challenges contributing to the heterogeneity of evidence have included the lack of a consistent definition of deprescribing[10] and wide variation in study design[4]. While SRs are widely recognized as a robust way to appraise and synthesize available evidence, existing SRs on deprescribing have often focused on single medication classes[13], or specific patient populations[12]. A broad and comprehensive review of deprescribing interventions is needed to understand which areas of deprescribing are likely to yield the greatest benefit, in improving outcomes and therefore direct limited healthcare resources and research funding. An overview of SRs[14] is an established way to examine a broader scope and elucidate key findings from a field with a rapid increase in number of diverse SRs. We undertake the first overview of SRs to investigate whether deprescribing interventions lead to a difference in outcomes amongst older adults. We will synthesize results according to the focus of the interventions (single medication classes or reduction in polypharmacy and/or PIMs). We will also examine the effectiveness of deprescribing interventions on subgroups of older age (75+), dementia status, frailty/multimorbidity status, intervention type and setting.

Methods (150-250 words)

Search and Eligibility Criteria

The protocol was registered with PROSPERO (CRD42020178860)[15] and the overview was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[16].

A search strategy was developed by investigators in collaboration with a trained information specialist, and conducted in Medline, Embase, Cumulative Index to Nursing and Allied Health Literature (CINAHL) Complete, American Psychological Association (APA) PsycInfo, Scopus, Web of Science Core Collection, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment, National Health Service Economic Evaluation Database (NHS EED), and Epistemonikos. The search was conducted without language restrictions; databases were searched from January 1st 2005 to October 23rd 2020 to reflect the relatively new evidence base of deprescribing (deprescribing was first introduced by Woodward[17] in 2003). Search terms were tailored to the specific host site, with a combination of free keywords and MeSH terms (eAppendix). Reference lists of relevant articles were hand searched for potentially relevant systematic reviews.

Following standard evidence synthesis approaches, the inclusion criteria were determined *a priori* by using the PICOS (Population, Intervention, Comparison, Outcome and Study design) framework. A conceptual framework (Figure 1) of interventions and outcome themes was developed to guide this process. The Cochrane Effective Practice and Organization of Care (EPOC) taxonomy of health system interventions[18] was used to describe and organize the broad range of **deprescribing interventions**. Through an iterative process, we identified two main domains (delivery and implementation arrangements) and six main subcategories (education, comprehensive case management, medication reviews, disease management, targeted medication withdrawal and targeted medication substitution). Personnel involved in delivering and receiving these interventions were added as an additional dimension. Subgroup analyses were planned according to **patient characteristics** that may modify the effectiveness of interventions. **Outcomes** of interest were adapted from the core outcome set for polypharmacy[19].

***Population**:* Older adults aged 60 years and older. Systematic reviews including participants younger than 60 years were eligible if subgroup analyses for participants with mean age 60 years and older were available.

Intervention: Any intervention with a primary focus on deprescribing. We included SRs that focused on deprescribing and those that focused on optimizing polypharmacy, because the latter often include elements of deprescribing. However, individual primary studies within each review, hereinafter referred to as *relevant* primary studies, needed to meet our definition of deprescribing to be included in Levels 2 and 3 data extraction and synthesis. Systematic reviews that did not contain at least two relevant primary studies were excluded.

Comparison: Systematic reviews including studies of 'usual care' and medication continuation.

***Outcomes**:* Eight outcome themes consisting of 18 individual outcomes of interest were identified (Table 1). Of these, two outcome themes (measure of medication reduction and other medication-related outcomes) will be referred to as intermediate outcomes, while the remaining six will be referred to as downstream outcomes.

Study design: Systematic reviews containing any of the following study designs: randomized trials, non-randomized trials, controlled before-after studies, interrupted time series studies and repeated measures studies. Following the methods of previous overviews[20, 21], we excluded records that did not meet the quality standard (≥4 DARE criteria)[22] for a systematic review.

Setting: Any health care setting in any country

Data Extraction and Assessment of Methodologic Quality

The titles and abstracts of returned studies were screened for eligibility for inclusion by three reviewers (YH, SC and NS). The software DistillerSR was used to measure agreement between reviewers; the kappa

statistic was 0.79. Full texts identified as potentially relevant were independently reviewed by two reviewers (YH and SC), with disagreements resolved by discussion to consensus with a third reviewer (SLG).

Data from each SR was independently extracted into Excel® by three reviewers (YH, SC and ZE) using a bespoke data extraction form. All data were extracted in duplicate; disagreements were resolved with the wider review group consensus. Data extraction and synthesis were conducted iteratively at three levels (Figure 2). At Level 1, we extracted data from the conclusions of SR authors. In the process of extracting data from full-text review, we recognized that not all primary studies within each SR were relevant to our key questions. Therefore, at Level 2, we further extracted aggregated narrative results from SRs that combined both relevant and non-relevant primary studies, excluding narrative results focusing solely on primary studies deemed not relevant. Extracted data included review characteristics, interventions, including whether they focused on single medication class or polypharmacy, outcome themes and available subgroup data. At Level 3, we extracted intervention type and outcomes of interest from relevant primary studies reported within SRs.

The quality of each SR was independently assessed in duplicate by four reviewers (YH, SC, ZE, SH) using the Assessment of Multiple Systematic Reviews: AMSTAR 2[23] criteria. Disagreements were resolved by discussion and consensus within the wider review group. No reviews were excluded following quality assessment. We report overlap of relevant primary studies in a citation matrix[24]. The degree of study overlap was calculated using the Corrected Coverage Area Index, a new measure developed by Pieper *et al*[24] that can better account for overlapping primary studies in more than two SRs.

Data Synthesis

Due to the heterogeneity of data, we performed separate data synthesis at the three levels (Figure 2). At Level 1, we focused on conclusions made by authors of included SRs, based on their reviews of the evidence and their definitions of harm and benefit, according to the focus of the SR (e.g. single medication classes versus polypharmacy or PIMS). If conclusions regarding harm were not made, we determined from

their objectives if they intended to evaluate harm. We also synthesized results of meta-analyses. At Level 2, we synthesized results into 6 mutually exclusive categories by outcome themes. In addition, a narrative synthesis of outcomes was conducted according to the subgroups of the very old (75+), dementia status, frailty/multimorbidity status and setting. At Level 3, since few SRs examined outcomes according to intervention type, we performed a narrative synthesis of deduplicated relevant primary studies (disaggregated from SRs), organized by intervention types as set out in Figure 1.

To increase validity and rigor, we adopted a reflexive approach to explicitly challenge and minimize the unconscious biases and assumptions that shape individual and collective decisions[25]. Reflective discussions were included in weekly research meetings and an interprofessional expert advisory panel was formed for external consultation.

Results

Study selection and characteristics

A total of 3949 articles were retrieved, resulting in 2335 unique citations. 93 were assessed in full text (eFigure 1). Reasons for exclusion at the full text stage are detailed in eTable 1. In total, 21 systematic reviews and 13 meta-analyses were included in our review. Eighteen SRs had a distinct deprescribing focus[11-13, 26-40]. The remaining sixteen had broader scopes of reducing PIMs[41-48], improving prescribing quality[49-53], improving appropriate polypharmacy[54, 55] or examining outcomes of medication reviews[56]. Twelve SRs focused on specific medication classes, including antihyperglycemics[26, 28], anticholinergics[27], antihypertensives[40], antipsychotics[29, 30, 34, 36, 42, 50, 53] and proton-pump inhibitors[31]. Nine SRs focused on specific disease states or patient characteristics– dementia[42, 52], type 2 diabetes[26, 28], frailty[35], history of falls[38], hypertension[40] and limited life expectancy[12, 32]. Most (n=27) SRs included multiple settings for interventions , while some specified inpatient[44, 45, 52], community-dwelling[36, 37, 46, 56] and long-term care facilities[34, 42, 49, 53]. The remaining seven did not state the setting of interest[27, 29, 32, 38, 39, 41, 51]. The majority (n=25) of SRs specified multiple outcomes of interest (eTable 2); 25 SRs[12, 27, 29-31, 33, 35-39, 41-48, 50-55] specified intermediate outcomes as their primary outcome(s).

Level 1: Results from SRs' Authors' Conclusions and Meta-analyses

All SRs (eTable 3) made conclusions regarding benefits in outcomes associated with deprescribing interventions, however, only ten SRs (29.4%) made conclusions regarding harm. Evidence was found in eight reviews to suggest deprescribing interventions were not associated with harm in outcomes including HbA1c levels, falls, recurrence of symptoms and adverse events. Only Thio *et al*[33] suggested evidence of harm after deprescribing due to relapse of symptoms. In terms of benefits, the majority of SRs found that deprescribing interventions reduced medication count or improved polypharmacy (intermediate outcomes) – 20 studies reported positive effects, while eight reported mixed effects. Few SRs (n=11) reported on downstream outcomes; most of these concluded there was limited or no evidence that deprescribing improved downstream outcomes. Only two SRs[11, 37] found evidence suggesting deprescribing reduced mortality.

In examining conclusions according to the focus of the SR, four of twelve studies and four of 22 studies concluded that deprescribing interventions were not associated with harm. Likewise, six of twelve studies focusing on single medication class and 14 of 22 studies focusing on polypharmacy concluded that deprescribing interventions resulted in benefits.

Thirteen SRs included a meta-analysis; eight reported only on intermediate outcomes, two reported only on downstream outcomes and three reported on both intermediate and downstream outcomes. There was heterogeneity in outcomes synthesized in meta-analyses, which precluded our summary of the meta-analysis results, except for mortality. All five reviews which reported on downstream outcomes included mortality; two[11, 37] reported some evidence for improvement in mortality while three[30, 48, 55] reported no effect.

Level 2: Results from Systematic Reviews

Table 2 summarizes evidence (by outcome theme) according to the categories of effect. The most commonly reported outcome themes were measures of medication reduction (n=30), adverse effects (n=20) and patient-centered outcomes (n=18). Only one review reported on cost outcomes. Evidence from Table 2 suggest that deprescribing can reduce the number of medications and improve other medication-related outcomes without causing harm, though there was little evidence of impact on downstream outcomes.

Of the 30 SRs reporting on measures of medication reduction, 24 (80%) reported a reduction in the number of medications: 16 (53%) found positive effects and eight (26.7%) found mixed positive effects, where mixed positive outcomes indicate reviews reported both positive and no effect outcomes. Of the remaining six, three found no effect, two found negative effects and one found mixed effects, which indicate reviews reported a combination of positive, negative and no effect outcomes. Likewise, 7 of 11 SRs reported improvement in other medication-related outcomes: six reported positive effects and two reported mixed positive effects. Adverse events or harms were reported in 20 reviews, with the majority reporting reduced risk of harms: five (25%) reported positive effects, five (25%) reported mixed positive effects and seven (35%) reported no effect. For mortality and patient-centered outcomes, the majority of studies reported effects that were considered beneficial, with most reporting mixed positive or no effects. Across all downstream outcome themes, seven SRs reported effects that were considered harmful.

Subgroup analysis

Few (n=11) studies[11, 29, 30, 35-37, 39, 41, 42, 46, 53] broadly examining deprescribing reported results by intervention type; the majority of these found beneficial effects in intermediate outcomes for all interventions, e.g. patient education[29], psychological support[30] and medication reviews[46]. There was little evidence on effectiveness of these interventions on downstream outcomes, except one review[37], which found that comprehensive medication reviews may reduce mortality. Two SRs[43, 44] focusing on computerized decision support tools found improvement in potentially inappropriate prescribing, but did not examine downstream outcomes. One review[13] focusing on targeted medication withdrawal found that specific classes of medications *e.g.* psychotropics and diuretics can be withdrawn without harm.

It was not possible to examine outcomes in terms of subgroups of setting, older age, dementia status, frailty and multimorbidity status, because only one SR[11] conducted a subgroup analysis. Of studies looking at a mixture of settings, analyses were not performed according to setting. Only one SR[42] focused on people with dementia, one other SR[11] conducted subgroup analysis for people with dementia and one SR[35] included frailty as an eligibility criterion for a larger group of patients, but SRs rarely completed subgroup analyses for specific vulnerable populations.

Level 3: Results of Relevant Primary Studies

The percentage of relevant primary studies in each SRs ranged from 11.5 to 100%. Of the 172 deduplicated primary studies, 57 evaluated targeted medication withdrawal; 41 evaluated medication reviews; 26 evaluated educational interventions; 20 examined comprehensive case management; one evaluated disease management and 27 evaluated a combination of up to two interventions (Figure 3).

Evidence from primary studies suggest that regardless of intervention type, deprescribing interventions were associated with positive or no effect on outcomes. Negative outcomes were rare, reported in only 13 (8%) primary studies, in 8 different outcomes.

Overall, where there were sufficient studies reporting an outcome within each intervention type, intervention types achieved comparable results. For instance, of the 60 studies reporting on change in number of medications prescribed, 24 (40%) demonstrated positive effects, 16 (27%) had no effect, one (2%) demonstrated negative effects while 17 (28%) were reported without statistical significance. Examining these studies by intervention type, medication reviews, education and comprehensive case management all reported similar findings. Positive effects were seen in 12 of 26 studies of medication reviews (46%), 5 of 11 studies of education (45%) and 6 of 13 studies of comprehensive case management (46%). Similarly, no effect was seen in 8 of 26 studies of medication reviews (31%), 3 of 11 studies of education (27%) and

4 of 13 studies of comprehensive case management (31%). A single study of medication review showed harm.

Risk of Bias Assessment

Assessment with AMSTAR-2 revealed that four SRs[28, 40, 42, 54] rated 'low', while 30 rated 'critically low' in overall confidence in results. Four SRs[28, 40, 42, 54] had one critical weakness; 11 [11, 26, 27, 31, 33, 34, 43, 44, 46, 47, 52] had two critical weaknesses; six [12, 30, 32, 45, 48, 50] had three critical weaknesses; three [37, 38, 51] had four critical weaknesses; nine [13, 29, 35, 39, 41, 49, 53, 55, 56] had five critical weaknesses and one [36] had seven critical weaknesses (eTable 4). Four domains – questions four, seven, 10 and 15 – were poorly scored across the included SRs, with fewer than six studies demonstrating strength. Of these, questions four, seven and 15 were proposed critical domains that affected overall confidence rating.

Overlap of Primary Studies

45% of relevant primary studies were reported in ≥1 SR (eTable 5). However, the corrected coverage area, which only considers the number of relevant primary studies, was 2.3%, representing marginal overlap in relevant primary studies. This further motivated our method of synthesizing at three different levels.

Discussion

This is the first overview of systematic reviews examining deprescribing interventions in older adults. While all reviews made conclusions about the benefits of deprescribing for intermediate outcomes, only 30% of reviews made conclusions regarding harm, or downstream outcomes. Where evidence is present, deprescribing interventions may result in reduced medication use with little indication of harm. However, there was less evidence suggesting beneficial effects on mortality and patient-centered outcomes or a reduced risk of adverse effects. There was a lack of evidence to indicate a specific intervention type is more successful. Further, outcomes evaluated were heterogeneous, and few studies examined utilization and

cost outcomes, or focused on subgroups of vulnerable patients including older people, or those with dementia, frailty or multimorbidity.

Our findings reflect prior research[11] and widespread consensus[57] that deprescribing can be achieved successfully, and is likely safe. As previously suggested by Reeve *et al*.[4], given the question over whether harms associated with polypharmacy are reversible, it could be argued that deprescribing inappropriate medications without causing worsening outcomes should be considered a benefit in itself. Hence, in Table 2, we identified benefit in downstream outcomes to encompass effects ranging from positive effects to no effects.

Importantly, we identified gaps in current evidence that we consider essential in advancing deprescribing in clinical practice. Firstly, we found that the majority of deprescribing SRs did not include harms in their aims. Exploring potential harms of deprescribing is important in facilitating increased deprescribing, as qualitative studies examining barriers to and enablers of deprescribing have consistently identified patients' fears of being without their medications[58]. This concern for the safety of deprescribing has also been identified in qualitative studies of healthcare professionals[59].

We also identified a dearth of research on downstream outcomes, including patient-centered outcomes such as quality of life, as well as healthcare utilization and cost. In many older adults, such factors are valued over mere longevity, reflected concisely in the 5Ms of geriatrics[60] – mind, mobility, medications, multi-complexity and what matters most. This dearth is partly a methodological challenge faced by deprescribing intervention trials, since clinical outcomes are dependent on the success of the interventions, which have been small, and length of follow-up is often insufficient for evaluating effects on downstream outcomes. Studies may also not be powered to find differences in these downstream outcomes.

Thirdly, we found that available evidence suggested intervention types were equivocal in effectiveness, but there was a lack of comparative effectiveness trials. Several interventions have been used in deprescribing studies, and it is important to understand if there are differences in efficacy. Further, there was also a lack

of standardization of outcomes, making comparisons across studies a challenge. We propose the need for development of a core outcome set for use in trials examining effectiveness of deprescribing intervention.

Finally, scant evidence focused on deprescribing in vulnerable subgroups, including patients with dementia, frailty and multimorbidity. We echo prior narrative reviews[4] that stated opportunities for deprescribing are being missed in these special populations, and should be focused on in future research, particularly where the effectiveness of interventions might differ by patient characteristics. Frail older adults with diabetes and hypertension are more likely to have adverse effects from treatment[61-63], however, these individuals are often not the targets of deprescribing trials. Those with dementia are also more sensitive to psychotropic medications[64]. Leveraging the multidisciplinary groups within nascent deprescribing networks, such as the US Deprescribing Network[65] and Australian Deprescribing Network[66], would be crucial in catalyzing the development of such research, and translating findings into clinical practice.

We conducted a comprehensive review using established methods[20, 67]. Of the 34 included SRs, 26 (76%) were published in the past 5 years, highlighting the unique gap that we fill with this review of reviews. Given the heterogeneous nature of this field, we categorized interventions *a priori* based on a peer-reviewed intervention taxonomy, allowing for standardization. We also established outcomes of interest from a core outcome set on polypharmacy that was developed rigorously[19]. We presented the multiple layers of evidence graphically in a novel way, allowing for clear communication of complex findings.

Despite these strengths, we acknowledge several limitations of this review. As is the case with other overviews in this field, we were limited by the lack of standardization of definitions of deprescribing, as well as inconsistency in instruments used for outcomes of interest, such as PIMs and cognitive function. Second, we included for synthesis only English language publications due to lack of proficiency with other languages – only one SR ended up being excluded for this reason. Further, as a review of reviews, consistent with prior established methods[20], we did not search for, extract from, or assess the quality of the original primary studies. Our information was dependent on reporting by authors of SRs, which varied in quality and style. Further, reviews were of low or critically low confidence ratings based on AMSTAR-2. It is of our opinion

that AMSTAR-2 remains a blunt tool for assessing quality of SRs. The 'floor effect' of AMSTAR-2 has been pointed out in prior studies[68, 69], with strict criteria in some critical domains highlighted in our results. Finally, as a review of reviews, we were only able to extract downstream outcomes regardless of whether those deprescribing interventions showed positive effects in intermediate outcomes. We were unable to estimate the association between success in deprescribing outcomes and its impact on downstream outcomes.

Conclusions

In summary, deprescribing interventions may be achieved successfully and likely safely. However, there was little to no evidence suggesting beneficial effects on mortality, patient-centered outcomes and adverse effects. Few studies examined utilization and cost outcomes, or focused on subgroups. Future research should utilize a standardized set of outcome measures, which include patient-centered, utilization and cost outcomes. Researchers should also focus on the effect of deprescribing on specific subgroups such as frail and multimorbid older adults and older age.

Tables

Table 1: Outcome themes and corresponding outcomes of our interest in systematic reviews, adapted from the core outcome set for improving appropriateness of polypharmacy[19]

	Outcome Themes	Definition	Outcomes of Interest
Intermediate Outcomes	Medication reduction	Any measure of medication discontinuation or dose reduction as defined within each systematic review	1. The number of medications prescribed, pre- and post-intervention 2. Change in dose of a medication 3. Measure of discontinuation
	Other medication-related outcomes	An outcome related to the process of prescribing medications, the quality of prescribing medications, or are direct consequences of medication use	4. Potentially inappropriate medications (*e.g.* as measured by screening tool of older person's prescriptions (STOPP) criteria) 5. Medication appropriateness (*e.g.* as measured by medication appropriateness index (MAI)) 6. Adherence
Downstream Outcomes	Adverse effects or harms	An unexpected event or effect of treatment or intervention	7. Falls 8. Adverse drug reactions and adverse drug withdrawal reactions
	Surrogate biomarkers outcomes	A logical and established biochemical or clinical measurement on an established disease pathway that functions as an indicator of disease management	9. HbA1c control 10. Blood pressure control
	Mortality	The death of a patient	11. Mortality
	Patient-centered outcomes	An outcome focusing attention on a patient's beliefs, preferences and needs[70]	12. Cognitive function 13. Quality of life 14. Patient perception of treatment burden 15. Other health/patient-centered outcomes
	Healthcare utilization	Any measure of healthcare use	16. Hospitalizations
	Cost outcomes	Any measure of healthcare costs	17. Hospitalization costs 18. Emergency department costs

Abbreviations: STOPP=Screening Tool of Older Persons' Prescriptions; START=Screening Tool to Alert to Right Treatment; MoCA=Montreal Cognitive Assessment

Table 2: Impact of deprescribing interventions on outcome themes, as reported by systematic reviews after excluding narrative results of primary studies not meeting criteria (Level 2)

INTERMEDIATE OUTCOMES						
	Beneficial		***Uncertain***	***No Effect***	***Not Beneficial***	
	+ effect	**+ or ↔ effect[a]**	**+, ↔, or – effect[b]**	**↔ effect**	**- or ↔ effect[c]**	**- effect**
Medication reduction	26, 28, 30, 31, 34, 36, 44, 50 11, 12, 13, 33, 38, 39, 48, 55	27, 29, 42, 53 35, 41, 46, 49	45	43, 47, 51		40[d], 56[e]
Other medication -related outcomes[f]	27 41, 45, 47, 52, 56	37, 46	54, 55			
DOWNSTREAM OUTCOMES						
Adverse Events Outcomes						
	Beneficial		***Mixed or No Effect***		***Harmful***	
	↓ risk	**↓ or ↔ risk**	**↓, ↔, or ↑ risk**	**↔ risk**	**↑or ↔ risk**	**↑ risk**
Adverse effects or harms[g]	27, 29, 44 41, 51	30 12, 37, 45, 49	13, 33	40, 50, 53 11, 38, 54, 55		52
Other Downstream Outcomes						
	Beneficial				***Harmful***	
	+ effect	**+ or ↔ effect[a]**	**+, ↔, or - effect[b]**	**↔ effect**	**- or ↔ effect[c]**	**- effect**
Surrogate biomarkers outcomes			33	26, 28	13	40 11
Mortality[h]		11, 12, 37	33	26, 28, 40, 44, 53 39, 45, 49, 52, 55		
Patient-centered outcomes[i]		30 11, 12, 32, 45, 48, 55	54, 56	26, 27, 28, 40 37, 49	34, 50	46
Healthcare utilization		34 52, 54, 55		40, 44, 53 32, 37, 39, 45, 49		
Costs		49				

This table captures results reported by systematic reviews, organized by outcome themes defined a priori according to the core outcome set for polypharmacy developed by Rankin et al. Individual sentences within the systematic reviews reporting on primary studies deemed not relevant are not included in this table. Empty cells denote that no studies reported that outcome effect for that specific outcome. Citations highlighted in red represent studies focusing on single medication class, while those in black represent studies focusing on polypharmacy.

[a] Mixed positive outcomes indicate reviews reported both positive outcomes and outcomes with no effects

[b] Mixed outcomes indicate reviews reported a combination of positive, negative and no effect outcomes

[c] Mixed negative outcomes indicate reviews reported both outcomes with no effect and negative outcomes.

[d] Some studies found that instead of withdrawal of medications, deprescribing interventions was associated with a higher risk of medications being continued.
[e] Some studies found that instead of withdrawal of medications, medications were started in both control and intervention groups. More medications were started in control groups.
[f] Castelino et al.[51] reported other medication-related outcomes that were not statistically significant, and was not included in this table.
[g] In this outcome theme, positive effects on adverse effects or harms refer to deprescribing interventions reducing risk of adverse effects e.g. adverse drug reactions or falls, while negative effects refer to deprescribing interventions increasing risk of adverse effects.
[h] Hoyle et al.[34] reported mortality outcomes that were not statistically significant, and was not included in this table.
[i] Earl et al.[39] reported patient-centered outcomes that were not statistically significant, and was not included in this table.

Figures

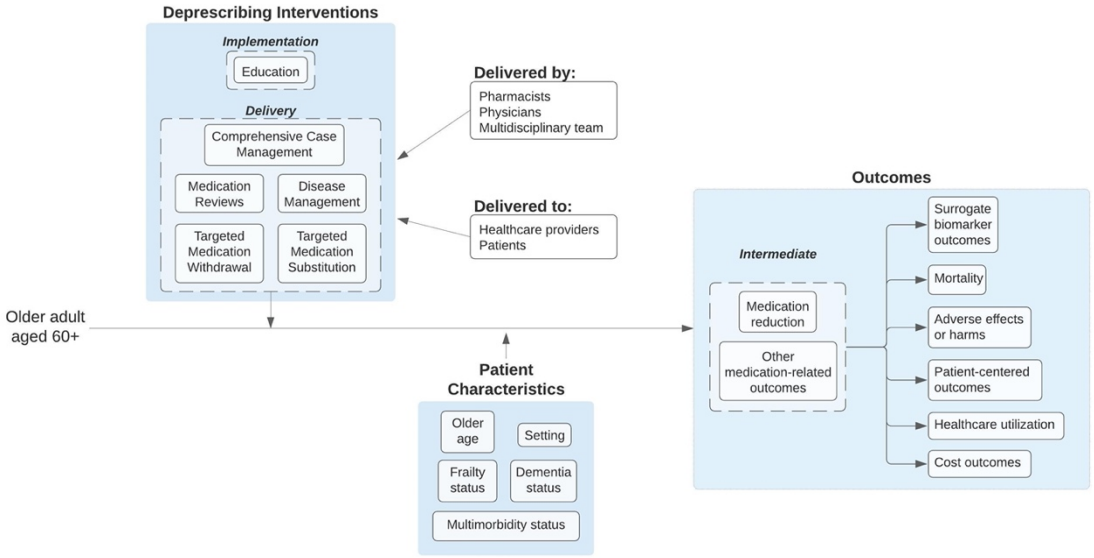

Figure 1: A conceptual framework of deprescribing interventions, modifying patient characteristics and outcomes of interest

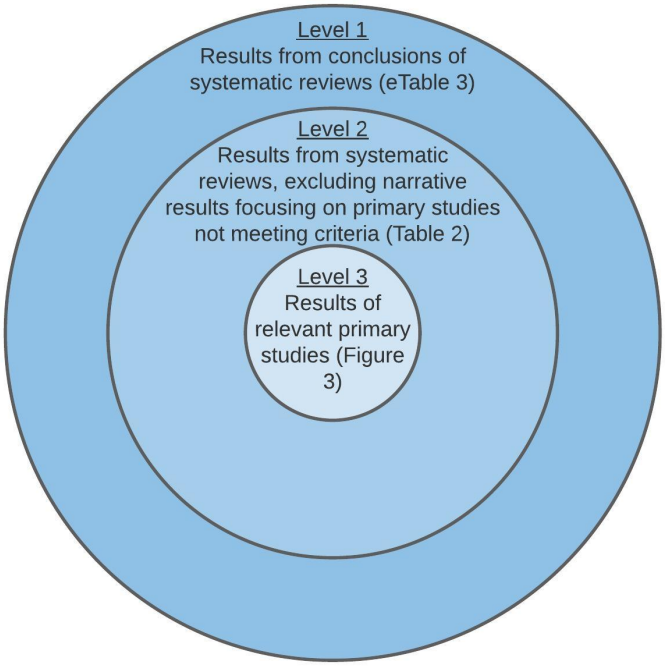

Figure 2: Levels of data extraction and synthesis of systematic reviews and relevant primary studies.
In Level 1, we extracted data from conclusions of systematic reviews and synthesized it by medication class. In Level 2, we further extracted aggregated narrative results from SRs that combined both relevant and non-relevant primary studies, but did not include narrative results focusing solely on primary studies deemed not relevant. We synthesized this by outcome themes, and according to prespecified subgroups. In Level 3, we extracted data from relevant primary studies as reported by SRs, and synthesized by intervention type.

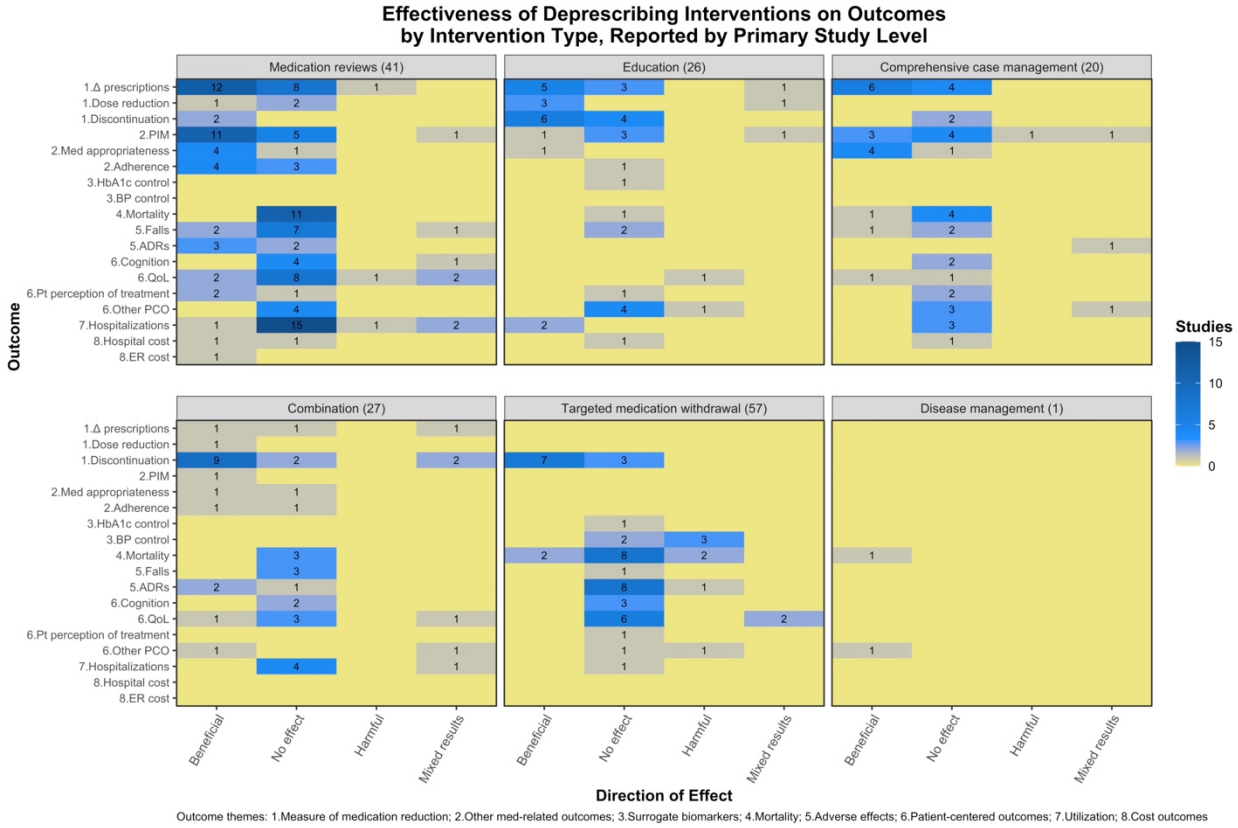

Figure 3: ***Heatmap of Results from Relevant Primary Studies (n=172), by Intervention Type (Level 3)****. In this figure, deprescribing interventions are grouped by intervention types as laid out in our conceptual model, with 'combination' representing multicomponent interventions*. Results are reported according to individual outcomes of interest, with prefixes representing the outcome theme. Outcomes can be beneficial, of no effect, harmful or mixed, which represents a mixture of beneficial / no effect / harmful results. Studies with outcomes that are not statistically significant are not included in this table.*

Within each cell, the number represents the number of unique relevant primary studies reporting that directionality for that outcome. The density of studies is represented by the color scale on the right.

** Combinations include: Comprehensive Case Management and Education; Medication Review and Education; Medication Review and Disease Management; Medication Review and Targeted Medication Withdrawal; Disease Management and Targeted Medication Withdrawal; Disease Management and Education; Education and Targeted Medication Withdrawal; Targeted Medication Withdrawal and Targeted Medication Substitution.*

References

1. Statistics OH. Health at a Glance 2019 : OECD Indicators. 2019.
2. Maher RL, Hanlon J, Hajjar ER. Clinical consequences of polypharmacy in elderly. *Expert Opin Drug Saf*. Jan 2014;13(1):57-65. doi:10.1517/14740338.2013.827660
3. Cahir C, Moriarty F, Teljeur C, Fahey T, Bennett K. Potentially inappropriate prescribing and vulnerability and hospitalization in older community-dwelling patients. *Ann Pharmacother*. Dec 2014;48(12):1546-54. doi:10.1177/1060028014552821
4. Reeve E, Thompson W, Farrell B. Deprescribing: A narrative review of the evidence and practical recommendations for recognizing opportunities and taking action. *Eur J Intern Med*. Mar 2017;38:3-11. doi:10.1016/j.ejim.2016.12.021
5. Lattanzio F, Landi F, Bustacchini S, et al. Geriatric conditions and the risk of adverse drug reactions in older adults: a review. *Drug Saf*. Jan 2012;35 Suppl 1:55-61. doi:10.1007/BF03319103
6. Benetos A, Petrovic M, Strandberg T. Hypertension Management in Older and Frail Older Patients. *Circ Res*. 03 2019;124(7):1045-1060. doi:10.1161/CIRCRESAHA.118.313236
7. Abdelhafiz AH, Koay L, Sinclair AJ. The effect of frailty should be considered in the management plan of older people with Type 2 diabetes. *Future Sci OA*. Mar 2016;2(1):FSO102. doi:10.4155/fsoa-2015-0016
8. Sakiris MA, Sawan M, Hilmer SN, Awadalla R, Gnjidic D. Prevalence of adverse drug events and adverse drug reactions in hospital among older patients with dementia: A systematic review. *Br J Clin Pharmacol*. Feb 2021;87(2):375-385. doi:10.1111/bcp.14417
9. Scott IA, Hilmer SN, Reeve E, et al. Reducing inappropriate polypharmacy: the process of deprescribing. *JAMA Intern Med*. May 2015;175(5):827-34. doi:10.1001/jamainternmed.2015.0324
10. Reeve E, Gnjidic D, Long J, Hilmer S. A systematic review of the emerging definition of 'deprescribing' with network analysis: implications for future research and clinical practice. *Br J Clin Pharmacol*. Dec 2015;80(6):1254-68. doi:10.1111/bcp.12732
11. Page AT, Clifford RM, Potter K, Schwartz D, Etherton-Beer CD. The feasibility and effect of deprescribing in older adults on mortality and health: a systematic review and meta-analysis. *Br J Clin Pharmacol*. 09 2016;82(3):583-623. doi:10.1111/bcp.12975
12. Shrestha S, Poudel A, Steadman K, Nissen L. Outcomes of deprescribing interventions in older patients with life-limiting illness and limited life expectancy: A systematic review. *Br J Clin Pharmacol*. Oct 2020;86(10):1931-1945. doi:10.1111/bcp.14113
13. Iyer S, Naganathan V, McLachlan AJ, Le Couteur DG. Medication withdrawal trials in people aged 65 years and older: a systematic review. *Drugs Aging*. 2008;25(12):1021-31. doi:10.2165/0002512-200825120-00004
14. Pollock M, Fernandes RM, Becker LA, Pieper D, Hartling L. Chapter V: Overviews of Reviews. *Cochrane handbook for systematic reviews of interventions*. Wiley-Blackwell; 2008:xxi, 649 pages.
15. Gray S, Devine B, Huang Y, et al. Deprescribing interventions in older adults: overview of systematic reviews. CRD42020178860. PROSPERO: National Institute for Health Research; 2020.
16. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. Jul 2009;339:b2535. doi:10.1136/bmj.b2535
17. Woodward M. Deprescribing: Achieving Better Health Outcomes for Older People through Reducing Medications. *Journal of Pharmacy Practice and Research*. 12/1/2003 2003;33:323-8. doi:10.1002/jppr2003334323
18. *(EPOC) EPaOoC*. EPOC Taxonomy. https://epoc.cochrane.org/epoc-taxonomy
19. Rankin A, Cadogan CA, In Ryan C, Clyne B, Smith SM, Hughes CM. Core Outcome Set for Trials Aimed at Improving the Appropriateness of Polypharmacy in Older People in Primary Care. *J Am Geriatr Soc*. 07 2018;66(6):1206-1212. doi:10.1111/jgs.15245
20. Thomson K, Hillier-Brown F, Walton N, Bilaj M, Bambra C, Todd A. The effects of community pharmacy-delivered public health interventions on population health and health inequalities: A review of reviews. *Prev Med*. 07 2019;124:98-109. doi:10.1016/j.ypmed.2019.04.003
21. Davies LE, Spiers G, Kingston A, Todd A, Adamson J, Hanratty B. Adverse Outcomes of Polypharmacy in Older People: Systematic Review of Reviews. *J Am Med Dir Assoc*. 02 2020;21(2):181-187. doi:10.1016/j.jamda.2019.10.022

22. Dissemination NCfRa. The Database of Abstracts of Reviews of Effects (DARE). Effectiveness Matters; 2002.
23. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ*. 09 2017;358:j4008. doi:10.1136/bmj.j4008
24. Pieper D, Antoine SL, Mathes T, Neugebauer EA, Eikermann M. Systematic review finds overlapping reviews were not mentioned in every other overview. *J Clin Epidemiol*. Apr 2014;67(4):368-75. doi:10.1016/j.jclinepi.2013.11.007
25. Bishop EC, Shepherd ML. Ethical reflections: examining reflexivity through the narrative paradigm. *Qual Health Res*. Sep 2011;21(9):1283-94. doi:10.1177/1049732311405800
26. Black CD, Thompson W, Welch V, et al. Lack of Evidence to Guide Deprescribing of Antihyperglycemics: A Systematic Review. *Diabetes Ther*. Feb 2017;8(1):23-31. doi:10.1007/s13300-016-0220-9
27. Nakham A, Myint PK, Bond CM, Newlands R, Loke YK, Cruickshank M. Interventions to Reduce Anticholinergic Burden in Adults Aged 65 and Older: A Systematic Review. *J Am Med Dir Assoc*. 02 2020;21(2):172-180.e5. doi:10.1016/j.jamda.2019.06.001
28. Seidu S, Kunutsor SK, Topsever P, Hambling CE, Cos FX, Khunti K. Deintensification in older patients with type 2 diabetes: A systematic review of approaches, rates and outcomes. *Diabetes Obes Metab*. 07 2019;21(7):1668-1679. doi:10.1111/dom.13724
29. Dou C, Rebane J, Bardal S. Interventions to improve benzodiazepine tapering success in the elderly: a systematic review. *Aging Ment Health*. 04 2019;23(4):411-416. doi:10.1080/13607863.2017.1423030
30. Reeve E, Ong M, Wu A, Jansen J, Petrovic M, Gnjidic D. A systematic review of interventions to deprescribe benzodiazepines and other hypnotics among older people. *Eur J Clin Pharmacol*. Aug 2017;73(8):927-935. doi:10.1007/s00228-017-2257-8
31. Wilsdon TD, Hendrix I, Thynne TR, Mangoni AA. Effectiveness of Interventions to Deprescribe Inappropriate Proton Pump Inhibitors in Older Adults. *Drugs Aging*. 04 2017;34(4):265-287. doi:10.1007/s40266-017-0442-1
32. Pruskowski JA, Springer S, Thorpe CT, Klein-Fedyshin M, Handler SM. Does Deprescribing Improve Quality of Life? A Systematic Review of the Literature. *Drugs Aging*. 12 2019;36(12):1097-1110. doi:10.1007/s40266-019-00717-1
33. Thio SL, Nam J, van Driel ML, Dirven T, Blom JW. Effects of discontinuation of chronic medication in primary care: a systematic review of deprescribing trials. *Br J Gen Pract*. Oct 2018;68(675):e663-e672. doi:10.3399/bjgp18X699041
34. Hoyle DJ, Bindoff IK, Clinnick LM, Peterson GM, Westbury JL. Clinical and Economic Outcomes of Interventions to Reduce Antipsychotic and Benzodiazepine Use Within Nursing Homes: A Systematic Review. *Drugs Aging*. 02 2018;35(2):123-134. doi:10.1007/s40266-018-0518-6
35. Tjia J, Velten SJ, Parsons C, Valluri S, Briesacher BA. Studies to reduce unnecessary medication use in frail older adults: a systematic review. *Drugs Aging*. May 2013;30(5):285-307. doi:10.1007/s40266-013-0064-1
36. Parr JM, Kavanagh DJ, Cahill L, Mitchell G, McD Young R. Effectiveness of current treatment approaches for benzodiazepine discontinuation: a meta-analysis. *Addiction*. Jan 2009;104(1):13-24. doi:10.1111/j.1360-0443.2008.02364.x
37. Bloomfield HE, Greer N, Linsky AM, et al. Deprescribing for Community-Dwelling Older Adults: a Systematic Review and Meta-analysis. *J Gen Intern Med*. Aug 2020;doi:10.1007/s11606-020-06089-2
38. Hart LA, Phelan EA, Yi JY, Marcum ZA, Gray SL. Use of Fall Risk-Increasing Drugs Around a Fall-Related Injury in Older Adults: A Systematic Review. *J Am Geriatr Soc*. Jun 2020;68(6):1334-1343. doi:10.1111/jgs.16369
39. Earl TR, Katapodis ND, Schneiderman SR, Shoemaker-Hunt SJ. Using Deprescribing Practices and the Screening Tool of Older Persons' Potentially Inappropriate Prescriptions Criteria to Reduce Harm and Preventable Adverse Drug Events in Older Adults. *J Patient Saf*. Sep 2020;16(3S Suppl 1):S23-S35. doi:10.1097/PTS.0000000000000747
40. Reeve E, Jordan V, Thompson W, et al. Withdrawal of antihypertensive drugs in older people. *Cochrane Database Syst Rev*. 06 2020;6:CD012572. doi:10.1002/14651858.CD012572.pub2

41. Kaur S, Mitchell G, Vitetta L, Roberts MS. Interventions that can reduce inappropriate prescribing in the elderly: a systematic review. *Drugs Aging*. 2009;26(12):1013-28. doi:10.2165/11318890-000000000-00000
42. Thompson Coon J, Abbott R, Rogers M, et al. Interventions to reduce inappropriate prescribing of antipsychotic medications in people with dementia resident in care homes: a systematic review. *J Am Med Dir Assoc*. Oct 2014;15(10):706-18. doi:10.1016/j.jamda.2014.06.012
43. Monteiro L, Maricoto T, Solha I, Ribeiro-Vaz I, Martins C, Monteiro-Soares M. Reducing Potentially Inappropriate Prescriptions for Older Patients Using Computerized Decision Support Tools: Systematic Review. *J Med Internet Res*. 11 2019;21(11):e15385. doi:10.2196/15385
44. Dalton K, O'Brien G, O'Mahony D, Byrne S. Computerised interventions designed to reduce potentially inappropriate prescribing in hospitalised older adults: a systematic review and meta-analysis. *Age Ageing*. 09 2018;47(5):670-678. doi:10.1093/ageing/afy086
45. Thillainadesan J, Gnjidic D, Green S, Hilmer SN. Impact of Deprescribing Interventions in Older Hospitalised Patients on Prescribing and Clinical Outcomes: A Systematic Review of Randomised Trials. *Drugs Aging*. Apr 2018;35(4):303-319. doi:10.1007/s40266-018-0536-4
46. Clyne B, Fitzgerald C, Quinlan A, et al. Interventions to Address Potentially Inappropriate Prescribing in Community-Dwelling Older Adults: A Systematic Review of Randomized Controlled Trials. *J Am Geriatr Soc*. 06 2016;64(6):1210-22. doi:10.1111/jgs.14133
47. Hansen CR, O'Mahony D, Kearney PM, et al. Identification of behaviour change techniques in deprescribing interventions: a systematic review and meta-analysis. *Br J Clin Pharmacol*. 12 2018;84(12):2716-2728. doi:10.1111/bcp.13742
48. Almutairi H, Stafford A, Etherton-Beer C, Flicker L. Optimisation of medications used in residential aged care facilities: a systematic review and meta-analysis of randomised controlled trials. *BMC Geriatr*. 07 2020;20(1):236. doi:10.1186/s12877-020-01634-4
49. Verrue CL, Petrovic M, Mehuys E, Remon JP, Vander Stichele R. Pharmacists' interventions for optimization of medication use in nursing homes : a systematic review. *Drugs Aging*. 2009;26(1):37-49. doi:10.2165/0002512-200926010-00003
50. Sheehan R, Strydom A, Brown E, Marston L, Hassiotis A. Association of Focused Medication Review With Optimization of Psychotropic Drug Prescribing: A Systematic Review and Meta-analysis. *JAMA Netw Open*. 10 2018;1(6):e183750. doi:10.1001/jamanetworkopen.2018.3750
51. Castelino RL, Bajorek BV, Chen TF. Targeting suboptimal prescribing in the elderly: a review of the impact of pharmacy services. *Ann Pharmacother*. Jun 2009;43(6):1096-106. doi:10.1345/aph.1L700
52. Walsh KA, O'Riordan D, Kearney PM, Timmons S, Byrne S. Improving the appropriateness of prescribing in older patients: a systematic review and meta-analysis of pharmacists' interventions in secondary care. *Age Ageing*. Mar 2016;45(2):201-9. doi:10.1093/ageing/afv190
53. Nishtala PS, McLachlan AJ, Bell JS, Chen TF. Psychotropic prescribing in long-term care facilities: impact of medication reviews and educational interventions. *Am J Geriatr Psychiatry*. Aug 2008;16(8):621-32. doi:10.1097/JGP.0b013e31817c6abe
54. Rankin A, Cadogan CA, Patterson SM, et al. Interventions to improve the appropriate use of polypharmacy for older people. *Cochrane Database Syst Rev*. 09 2018;9:CD008165. doi:10.1002/14651858.CD008165.pub4
55. Johansson T, Abuzahra ME, Keller S, et al. Impact of strategies to reduce polypharmacy on clinically relevant endpoints: a systematic review and meta-analysis. *Br J Clin Pharmacol*. 08 2016;82(2):532-48. doi:10.1111/bcp.12959
56. Kallio SE, Kiiski A, Airaksinen MSA, et al. Community Pharmacists' Contribution to Medication Reviews for Older Adults: A Systematic Review. *J Am Geriatr Soc*. 08 2018;66(8):1613-1620. doi:10.1111/jgs.15416
57. Gnjidic D, Reeve E. Deprescribing: What do we know, and where to next? *Br J Clin Pharmacol*. Aug 2020;doi:10.1111/bcp.14525
58. Pickering AN, Hamm ME, Dawdani A, et al. Older Patient and Caregiver Perspectives on Medication Value and Deprescribing: A Qualitative Study. *J Am Geriatr Soc*. 04 2020;68(4):746-753. doi:10.1111/jgs.16370
59. Foley RA, Hurard LL, Cateau D, Koutaissoff D, Bugnon O, Niquille A. Physicians', Nurses' and Pharmacists' Perceptions of Determinants to Deprescribing in Nursing Homes Considering Three Levels of Action: A Qualitative Study. *Pharmacy (Basel)*. Feb 2020;8(1)doi:10.3390/pharmacy8010017

60. Tinetti M, Huang A, Molnar F. The Geriatrics 5M's: A New Way of Communicating What We Do. *J Am Geriatr Soc*. 09 2017;65(9):2115. doi:10.1111/jgs.14979
61. Liau SJ, Lalic S, Sluggett JK, et al. Medication Management in Frail Older People: Consensus Principles for Clinical Practice, Research, and Education. *J Am Med Dir Assoc*. Jan 2021;22(1):43-49. doi:10.1016/j.jamda.2020.05.004
62. Lipska KJ, Krumholz H, Soones T, Lee SJ. Polypharmacy in the Aging Patient: A Review of Glycemic Control in Older Adults With Type 2 Diabetes. *JAMA*. Mar 2016;315(10):1034-45. doi:10.1001/jama.2016.0299
63. Bromfield SG, Ngameni CA, Colantonio LD, et al. Blood Pressure, Antihypertensive Polypharmacy, Frailty, and Risk for Serious Fall Injuries Among Older Treated Adults With Hypertension. *Hypertension*. 08 2017;70(2):259-266. doi:10.1161/HYPERTENSIONAHA.116.09390
64. Hernández MH, Mestres C, Modamio P, et al. Adverse Drug Events in Patients with Dementia and Neuropsychiatric/Behavioral, and Psychological Symptoms, a One-Year Prospective Study. *Int J Environ Res Public Health*. 03 2019;16(6)doi:10.3390/ijerph16060934
65. Network UDR. US Deprescribing Research Network. https://deprescribingresearch.org
66. Network AD. Australian Deprescribing Network. https://australiandeprescribingnetwork.com.au
67. Becker LA, Oxman AD. Overviews of Reviews. In: Collaboration C, Higgins JPT, Green S, eds. *Cochrane book series: Cochrane handbook for systematic reviews of interventions*. Wiley-Blackwell; 2008:xxi, 649 pages:chap 22.
68. Matthias K, Rissling O, Pieper D, et al. The methodological quality of systematic reviews on the treatment of adult major depression needs improvement according to AMSTAR 2: A cross-sectional study. *Heliyon*. Sep 2020;6(9):e04776. doi:10.1016/j.heliyon.2020.e04776
69. Leclercq V, Beaudart C, Tirelli E, Bruyère O. Psychometric measurements of AMSTAR 2 in a sample of meta-analyses indexed in PsycINFO. *J Clin Epidemiol*. 03 2020;119:144-145. doi:10.1016/j.jclinepi.2019.10.005
70. Jayadevappa R. Patient-Centered Outcomes Research and Patient-Centered Care for Older Adults: A Perspective. *Gerontol Geriatr Med*. 2017 Jan-Dec 2017;3:2333721417700759. doi:10.1177/2333721417700759