Deprescribing for Community-Dwelling Older Adults: a Systematic Review and Meta-analysis

Hanna E. Bloomfield, MD, MPH[1,2,3], Nancy Greer, PhD[1,4], Amy M. Linsky, MD, MSc[5], Jennifer Bolduc, PharmD[1], Todd Naidl, PharmD[1], Orly Vardeny, PharmD, MS[1,2,4], Roderick MacDonald, MS[1,4], Lauren McKenzie, MPH[1,4], and Timothy J. Wilt, MD, MPH[1,2,4]

[1]Minneapolis VA Health Care System, Minneapolis, USA; [2]University of Minnesota School of Medicine, Minneapolis, USA; [3]Minneapolis VA Medical Center (151), 1 Veterans Drive, Minneapolis, MN, USA; [4]Minneapolis VA Center for Care Delivery and Outcomes Research, Minneapolis, USA; [5]VA Boston Healthcare System and Boston University School of Medicine, Boston, USA.

BACKGROUND: Polypharmacy and use of inappropriate medications have been linked to increased risk of falls, hospitalizations, cognitive impairment, and death. The primary objective of this review was to evaluate the effectiveness, comparative effectiveness, and harms of deprescribing interventions among community-dwelling older adults.

METHODS: We searched OVID MEDLINE Embase, CINAHL, and the Cochrane Library from 1990 through February 2019 for controlled clinical trials comparing any deprescribing intervention to usual care or another intervention. Primary outcomes were all-cause mortality, hospitalizations, health-related quality of life, and falls. The secondary outcome was use of potentially inappropriate medications (PIMs). Interventions were categorized as comprehensive medication review, educational initiatives, and computerized decision support. Data abstracted by one investigator were verified by another. We used the Cochrane criteria to rate risk of bias for each study and the GRADE system to determine certainty of evidence (COE) for primary outcomes.

RESULTS: Thirty-eight low and medium risk of bias clinical trials were included. *Comprehensive medication review* may have reduced all-cause mortality (OR 0.74, 95% CI: 0.58 to 0.95, $I^2 = 0$, $k = 12$, low COE) but probably had little to no effect on falls, health-related quality of life, or hospitalizations (low to moderate COE). Nine of thirteen trials reported fewer PIMs in the intervention group. *Educational interventions* probably had little to no effect on all-cause mortality, hospitalizations, or health-related quality of life (low to moderate COE). The effect on falls was uncertain (very low COE). All 11 education trials that included PIMs reported fewer in the intervention than in the control groups. Two of 4 *computerized decision support* trials reported fewer PIMs in the intervention arms; none included any primary outcomes.

DISCUSSION: In community-dwelling people aged 65 years and older, medication deprescribing interventions may provide small reductions in mortality and use of potentially inappropriate medications.

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KEY WORDS: deprescribing; polypharmacy; comprehensive medication review; older populations.

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INTRODUCTION

More than 40% of people in the USA aged ≥65 years take 5 or more prescription medications on a regular basis to control or prevent disease symptoms and complications.[1] Exposure to multiple medications, known as polypharmacy, is associated with increased risk of undesirable outcomes, such as falls, cognitive impairment and other geriatric syndromes, hospitalizations, and death.[2,3] The number of medications a person is taking may be the single most important predictor of adverse drug effects.[3] Furthermore, approximately half of older adults take one or more potentially inappropriate medications (PIMs), which includes duplicative medications and those with known risks or without a clear indication.[4]

Efforts have been underway for more than 30 years to develop and test interventions to mitigate the adverse effects of polypharmacy and inappropriate medication use. Initially, drug discontinuation efforts were focused on stopping specific medications considered to be problematic in older adults.[5,6] This has evolved into a more holistic approach, called "deprescribing," that considers medications in the context of the individual's comorbidities, functional status, treatment goals, and life expectancy.[1,5] Deprescribing has been defined as "the clinically supervised process of stopping or reducing the dose of medications when they cause harm or no longer provide benefit."[1,5,7]

Several systematic reviews on deprescribing have been recently published.[8,9] However, to our knowledge, none has focused on the comparative effectiveness of different deprescribing interventions for community-dwelling older adults. This gap in the literature may be an obstacle to implementation of

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deprescribing initiatives within clinics and healthcare systems.[10] We conducted this systematic review to determine the effectiveness, comparative effectiveness, and harms of deprescribing interventions in community-dwelling older adults.

METHODS

This manuscript is based on a Department of Veterans Affairs (VA) Evidence-based Synthesis Program report prepared for the VA Center for Medication Safety in Aging and available at https://www.hsrd.research.va.gov/publications/esp/. The purpose of the report, which was also supported by the VA Pharmacy Benefits Management and the Geriatrics and Extended Care Services, was to inform implementation of deprescribing within VA. These services collaborate within VA to identify deprescribing best practices to improve the health of Veterans.

Data Sources

We searched MEDLINE from 1990 to February 2019 using Medical Subject Headings (MeSH) and key words for deprescribing, medication therapy management, decision support systems, geriatric assessment, electronic health records, medical order systems, polypharmacy, aged population, and Veterans (Appendix A). We searched Embase, the Cumulative Index of Nursing and Allied Health (CINAHL), and the Cochrane Library using search strategies based on the MEDLINE strategy. Citations were entered into DistillerSR (Evidence Partners). The full search strategy is available in Appendix A.

Study Selection

We included randomized and cluster randomized controlled trials and controlled clinical trials that evaluated any deprescribing intervention for community-dwelling adults aged ≥ 65 years and reported one or more of our outcomes of interest. We categorized deprescribing interventions based on their dominant component: comprehensive medication review (CMR), education and feedback, or computerized decision support. Two investigators independently evaluated each abstract, which moved to full-text review if either reviewer considered the citation eligible. At full-text review, agreement of 2 reviewers was required for study inclusion. Disputes were resolved by discussion with input from a third reviewer, if needed. We excluded articles not published in English.

Data Abstraction and Quality Assessment

Data were abstracted by one investigator or research associate and verified by a second. Abstracted data included study design, inclusion and exclusion criteria, description of intervention and control arms, subject characteristics (e.g., age, gender, race/ethnicity, comorbidities, physical and cognitive status), select laboratory values, and baseline number of medications. Our a priori primary outcomes were quality of life, all-cause mortality, hospitalizations, falls, adverse drug withdrawal events, major adverse cardiac events, and delirium; none of the included studies reported the latter 3 outcomes. In addition, we report potentially inappropriate medications (PIMs), the most commonly reported medication outcome in the included studies. Polypharmacy has been defined in many ways;[11] in this review, we accepted authors' definitions.

Each study's risk of bias was rated by one co-investigator or research associate and verified by a second. Overall risk of bias for a study was rated as low, medium, or high based on the Cochrane risk of bias criteria for randomized trials and cluster randomized trials: sequence generation, allocation concealment, recruitment bias, baseline imbalance, blinded outcome assessment, incomplete cluster data, incomplete outcome data, and selective outcome reporting.[12] High risk of bias studies were excluded from the analyses.

Data Synthesis and Analysis

We pooled results if studies were deemed low or medium risk of bias and outcome measures, populations, interventions, and study designs were comparable. Data were analyzed in Comprehensive Meta-Analysis version 3 (Biostat). Categorical outcomes data were pooled using the Peto odds ratio (Peto OR) method or risk ratios (RR) with corresponding 95% confidence intervals (CIs). Magnitude of statistical heterogeneity was assessed with the I^2 statistic ($I^2 > 75\%$ may indicate substantial heterogeneity).[13] Standardized mean differences (SMDs) between the intervention and control groups, with corresponding 95% CIs, were calculated for continuous efficacy outcomes and were interpreted by applying Cohen's definition of small (0.2), medium (0.5), and large (0.8) effects.[14] For studies reporting categorical outcomes that were not pooled due to differences in study design or outcome definition, we calculated absolute effects (risk differences) with corresponding 95% CIs for individual trials. Cluster randomized controlled trials were not pooled with randomized controlled trials if they did not report adjustment for clustering.

Certainty of evidence, our confidence in the estimates of effect, for primary efficacy outcomes was rated using GRADE software (GRADEpro GDT: GRADEpro Guideline Development Tool [Software] McMaster University and Evidence Prime, Inc. 2015. Ontario, Canada). Certainty of evidence was graded for each outcome as high, moderate, low, or very low by evaluating 4 critical domains (risk of bias, consistency, directness, precision). High certainty indicates high confidence that the estimate of effect reflects the true effect while very low certainty indicates that evidence is either unavailable or does not permit a conclusion. Discrepancies in certainty of evidence ratings were resolved by discussion with final determination arrived through consensus.

Role of the Funding Source

The funding source (Department of Veterans Affairs, Office of Research and Development, Health Services Research and

Development Service) assigned the topic and reviewed the protocol but was not involved in data collection, analysis, manuscript preparation, or submission.

RESULTS

As shown in Figure 1, 44 of the 278 full-text articles reviewed for eligibility met inclusion criteria.[15–67] Six were rated high risk of bias and are not included in the analyses.[62–67] Of the remaining 38, 12 were randomized controlled trials and 26 were cluster randomized controlled trials. Included studies were similar with respect to study population (older adults taking multiple medications and living in the community) and setting (outpatient primary care clinics). Most interventions focused on general deprescribing, although some studies targeted medication classes (e.g., psychotherapeutic) or specific goals (e.g., falls reduction). We report results by the type of intervention studied: CMR ($k = 22$), educational interventions ($k = 12$), or computerized decision support ($k = 4$). For more detailed information on the included studies, see Appendix B.

Comprehensive Medication Review

Twenty-two trials evaluated the effect of comprehensive medication review (CMR) compared with a control group, most often usual care.[15–17,19,20,25,27–29,31–39,41–45,54,58–61] Generally the CMR interventions were conducted by a pharmacist ($k = 16$) and included a chart review, in-person patient interview, and provider consultation, culminating in recommendations for medication regimen changes. Eight studies also included a follow-up intervention with patients to reinforce the recommendations, such as 1 to 3 home care visits by nurses or telephone calls by pharmacists over the 2- to 12-month follow-up period. Five trials were conducted in the USA, one in Canada, one in Malaysia, and 15 in Europe. We judged the risk of bias to be low in 5 trials and medium in 17. Studies enrolled 9482 patients, with study sample sizes ranging from 25 to 1403. Certainty of evidence for primary outcomes is summarized in Table 1.

All-Cause Mortality. All-cause mortality was reported in 12 trials enrolling 4875 patients with follow-up ranging from 1 to 12 months.[15–17,19,20,27–29,36–39,44,45,59,61] Compared with

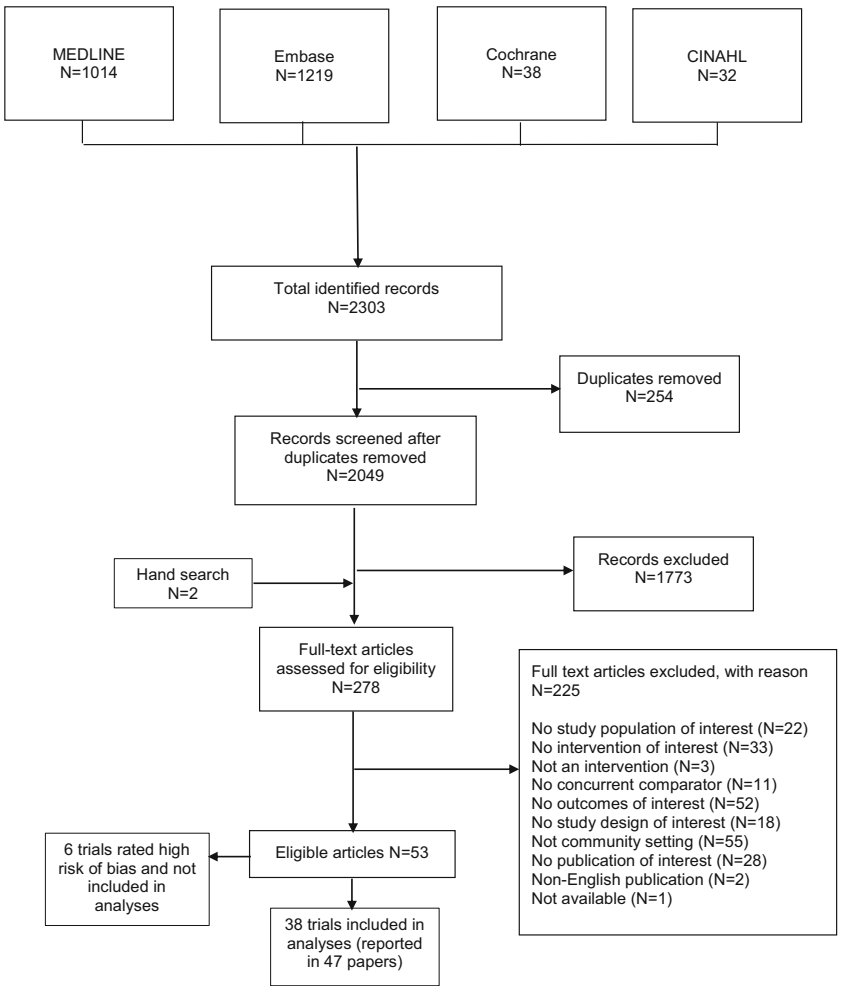


Figure 1 Literature search and selection.

Table 1 Certainty of Evidence for Comprehensive Medication Review for Deprescribing Compared with Usual Care in Elderly Populations

Outcome* No. of participants (studies)	Relative effect (95% CI)	Absolute effects			Certainty	What happens
		Usual care	Deprescribing—medication review	Difference (95% CI)		
All-cause mortality Follow up: range 1 to 24 months No. of participants: 4495 (12 trials; 12 RCTs pooled $n = 4875$; 1 CRCT $n = 620$)	*RCT* **Peto OR 0.74** (0.58 to 0.95)	6.3%	**4.9%**	RCT **−1.4%** (−2.7 to −0.1)	⊕⊕○○ Low[a,b]	Comprehensive medication review may result in a slight reduction in all-cause mortality.
	*CRCT*** **Peto OR 0.57** (0.27 to 1.23)	6.8%	**4.1%**	*CRCT* −2.6% (−6.6 to 1.3)		
Hospitalizations (≥ 1 admission) Follow-up: range 3 to 24 months No. of participants: 2989 (6 RCTs pooled)	**RR 1.07** (0.92 to 1.26)	19.8%	**20.4%**	**0.6%** (−2.3 to 3.5)	⊕⊕⊕○ Moderate[a]	Comprehensive medication review likely results in little to no difference in hospitalizations.
Quality of life measures (QoL) Assessed with: EQ-5D, SF-12/36 PCS and MCS follow-up: range 3 to 12 months No. of participants: 3893 (11 trials)	-	-	-	Most trials reported no differences between groups in QoL measures	⊕⊕○○ Low[a,c]	Comprehensive medication review may result in little to no difference in quality of life measures.
Falls Follow-up: range 3 to 15 months No. of participants: 1613 (4 trials; 3 RCTs $n = 993$; 1 CRCT $n = 620$)	*RCT* NA *CRCT* OR 0.38 (CI NR)	Range 11–33% Ranges over time intervals 10–19%	Range 12–37% Ranges over time intervals 9–15%	Risk differences (range) 1 to 11% Risk differences (range) −7 to 1%	⊕⊕○○ Low[a,b]	Comprehensive medication review may result in a slight reduction to no difference in falls.

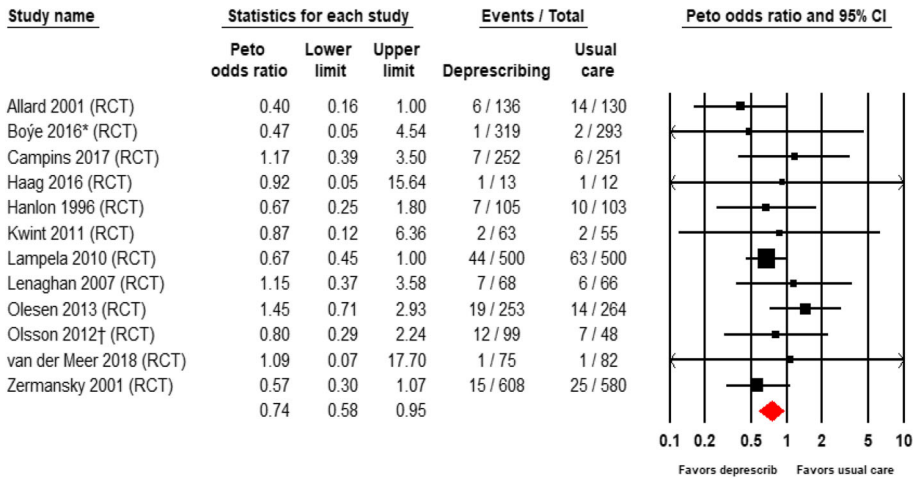
GRADE Working Group grades of evidence
High certainty: *We are very confident that the true effect lies close to that of the estimate of the effect*
Moderate certainty: *We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different*
Low certainty: *Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect*
Very low certainty: *We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect*
CI, confidence interval; OR, odds ratio; RR, risk ratio
[a]*Downgraded for study limitations (medium risk of bias)*
[b]*Downgraded for imprecision*
[c]*Although nearly all trials reported no significant difference between groups the estimated standardized mean differences exhibited wide confidence intervals*
**Three primary outcomes (adverse drug withdrawal events, major adverse cardiac events, and delirium) were not reported*
***Not adjusted for cluster design, estimate of the intracluster correlation coefficient (ICC) not provided by trial*

usual care, CMR resulted in a 26% relative risk reduction (OR 0.74, 95% CI: 0.58 to 0.95, $I^2 = 0$) corresponding to a 1.4 percentage point absolute reduction (95% CI: −2.7 to −0.1) in all-cause mortality (Fig. 2). Overall, CMR may result in a small reduction in all-cause mortality (low certainty).

Hospitalizations. Hospitalizations over a wide range of follow-up durations were reported in 12 studies with a combined enrollment of 5672 participants.[19,20,27–29,31–33,35,36,39,43,44,58,59,61] None of these studies reported a difference between the intervention and control groups with respect to the number of participants with one or more hospitalizations during follow-up. In the 6 RCTs that could be pooled,[19,20,39,44,58,59,61] 20.4% of people in the deprescribing group were hospitalized vs 19.8% in usual care for an absolute risk difference of 0.6% (95% CI: −2.3 to 3.5) over follow-up durations ranging from 3 to 24 months (Fig. 3). Overall CMR probably results in little to no reduction in hospitalizations (moderate certainty).

Health-Related Quality of Life. Health-related quality of life was reported in 11 studies measured with either the EuroQual Quality of Life scale (EQ-5D or EQ-5D VAS) ($k = 5$), the Short Form Health Survey (SF-12/36 or physical, mental subscales) ($k = 5$), or both ($k = 1$).[16,17,19,20,28,29,31–35,39,42,43,45,59] Nine studies reported no difference between the intervention and control groups in health-related quality of life at study end. Overall, CMR may result in little to no improvement in health-related quality of life scores (low certainty).

Falls. Four trials reported fall outcomes,[16,17,41,59,60] only one of which found a difference between the intervention and control groups. This study (medium risk of bias) enrolled 620 adults ≥ 70 years old and focused on medications that might increase risk of falls. The intervention group had a 62% decrease in fall-related diagnoses during the 1-year study (OR 0.38, $P < .01$, CI not reported) despite no difference between



$I^2 = 0\%$

* These participants who died were reported in the study flow chart but were not included in the analyses. An unspecified number of participants also died but were included in the analyses.

† Intervention arms combined

Figure 2 All-cause mortality for comprehensive medication review randomized controlled trials.

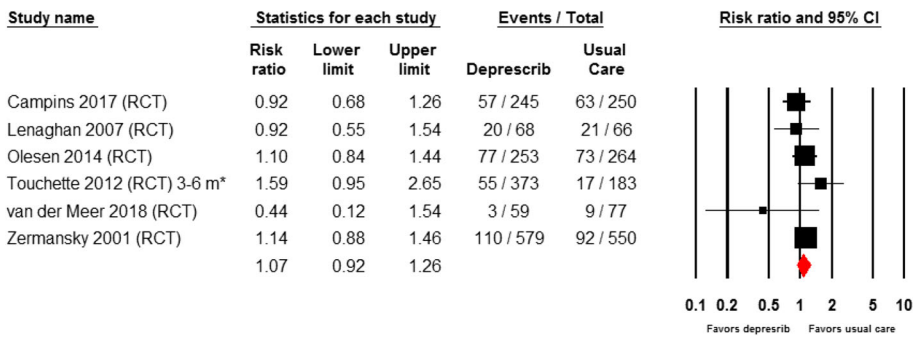
groups in the total number of medications or number of psychoactive medications at follow-up.[60]

The IMPROveFALL trial (medium risk of bias) enrolled 612 older adults who had visited an emergency room because of a fall; there was no difference between the intervention and control groups at 12 months in the number of falls (37% vs 34%; absolute risk difference 4%, 95% CI: − 4 to 12).[16,17] The other 2 trials did not designate falls as a primary outcome, had small sample sizes ($N = 259$ and 157), and had short lengths of follow-up (less than 3 months).[41,59] Overall, CMR may result in little to no reduction in falls (low certainty).

Reduction in Potentially Inappropriate Medications. Nine of thirteen trials that reported a potentially inappropriate medication outcome found fewer PIMs in the intervention group than in the control group; the difference was statistically significant in 7 studies (Table 3).[16,17,25,28,29,34,41,42,54] The variability in outcome definitions precluded pooling of results. However, we calculated standardized mean differences for the five trials that reported the Medication Appropriateness Index.[15,28,29,34,42,43] In these trials, the intervention effect, as measured by Cohen's *d*, was less than small in two,[15,43] small in one,[34] and moderate in two[28,29,42] (see Appendix C).

Educational Interventions

We identified 12 trials[18,21–24,30,40,46,47,50–53,55,57] that evaluated the effect of various educational interventions: provider education with feedback ($k = 5$); provider education without feedback ($k = 2$); patient education ($k = 3$); patient and provider education ($k = 1$); or patient and provider education with provider feedback ($k = 1$). The control groups were assigned



$I^2 = 12\%$

** Data from 3-6 month follow-up with basic and enhanced CMR arms combined*

Figure 3 Hospitalizations for comprehensive medication review randomized controlled trials.

Table 2 Certainty of Evidence for Educational Interventions for Deprescribing Compared with Usual Care in Elderly Populations

Outcome* No. of participants (studies)	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
		Usual care	Deprescribing—medication review	Difference		
All-cause mortality Follow-up: range 6 to 24 months No. of participants: 121,320 (6 CRCTs)	-	Range 1–16%	Range 0.6–16%	Risk differences (range) −1 to 5% Largest study (n = 119,910) reported a 0.1% (95% CI −0.1 to 0.6)	⊕⊕⊕○ Moderate[a]	Educational interventions likely result in little to no difference in all-cause mortality.
Hospitalizations (≥1 admission) Follow-up: range 9 months No. of participants: study 1 n = 119,910 (CRCT); study 2 n = 196 (CRCT). 1 other trial (n = 169) reported >1 hospitalization in frail high-risk participants (NS between group)	NA	Study 1 12.6% Study 2 1.6 mean inpatient admissions	Study 1 12.8% Study 2 1.9 mean inpatient admissions	Study 1 0.2% (95% CI −0.8 to 1.2) Study 2 0.3 admissions (95% −1.8 to 2.4)	⊕⊕⊕○ Moderate[a]	Educational interventions likely result in little to no difference in hospitalization.
Quality of life measures (QoL) Assessed with: EQ-5D Follow-up: range 12–15 months No. of participants: 1364 (3 CRCTs)	-			SMD 0.09 (95% CI −0.05 to 0.22)	⊕⊕○○ Low[a,b]	Educational interventions may result in little to no difference in quality of life measures.
Falls Follow-up: range 12 to 24 months No. of participants: 1018 (2 CRCTs)		Study 1 Ranges over time intervals 36–38%	Study 1 Ranges over time intervals 44%	Risk differences (range) −6 to −8% (NS between groups)	⊕○○○ Very low[a,b]	It is uncertain if educational interventions result in a reduction or an increase in falls.
		Study 2 30%	Study 2 20%	−10% (95% CI −17 to −4)		

GRADE Working Group grades of evidence
High certainty: *We are very confident that the true effect lies close to that of the estimate of the effect*
Moderate certainty: *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 certainty: *Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect*
Very low certainty: *We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect*
CI, confidence interval; NS, not significant; OR, odds ratio; RR, risk ratio
[a]*Downgraded for study limitations (medium risk of bias)*
[b]*Downgraded for imprecision*
**Three primary outcomes (adverse drug withdrawal events, major adverse cardiac events, and delirium) were not reported*

either usual care (k = 10) or a sham intervention (i.e., targeting drugs that were not of interest, k = 2). Two trials were conducted in the USA, 3 in Canada, 6 in Europe, and 1 in Australia. We judged the risk of bias to be low in 6 trials and medium in the other 6. Outcomes were reported on a total of 3463 patients in the 9 smaller trials and on 252,684 in the 3 larger trials. Certainty of evidence for each primary outcome is summarized in Table 2.

All-Cause Mortality. All-cause mortality was reported in 6 trials (n = 121,314).[18,21–24,30,40,53] None of the trials reported a difference between the intervention and control groups, and the data were not suitable for pooling due to heterogeneity of study interventions. Overall, educational interventions probably had no effect on all-cause mortality (moderate certainty).

Hospitalizations. Four of the 5 trials that reported hospitalizations found no difference between the intervention and control groups.[21–24,40,53,57] Overall, education interventions probably do not reduce hospitalizations (moderate certainty).

Health-Related Quality of Life. Health-related quality of life was reported in 4 trials, none of which found a difference between the intervention and control groups.[21–24,47,52] Overall, education interventions may have little to no effect on HRQoL (low certainty).

Falls. Two medium risk of bias trials reported falls and came to opposite conclusions. A US trial that randomized 169 people aged ≥65 at high risk for hospitalization or functional decline to enrollment in a chronic care clinic program or usual care. There was no difference in incidence of falls at 12 months between the 2 groups (43.5% vs 35.6%; P = .35).[24] The second was an Australian trial that randomized 22 general practitioners to a provider education with feedback intervention or usual care.[47] The physicians recruited 849 patients aged ≥65. At 12 months, the

Table 3 Effect of Deprescribing Interventions on Potentially Inappropriate Medication (PIM) Use

Author Number enrolled.	Findings
Comprehensive medication review	
Allard, 2001[15] $n = 266$	Odds of NOT being on a PIM at *12 months* in the intervention group: 1.83 (95% CI: 0.94 to 3.57)
Boyé, 2017[16] Polinder, 2016[17] $n = 612$	% with decreased PIMs at *12 months*: 37% (intervention) vs 19% (control) ($P < .0001$, calculated)
Denneboom, 2007[25] $n = 738$	% of clinically relevant recommendations leading to a medication change: 29.8% (intervention) vs 17.2% (control) ($P = .02$) % maintained at *6 months*: 25.5% (intervention) vs 14.8% (control) ($P = .03$) % maintained at *9 months*: 23.9% (intervention) vs 15.1% (control) ($P = .08$)
Haag, 2016[27] $n = 25$	No difference between groups in any of multiple measure of PIMs at 1 month
Hanlon, 1996[28] Schmader, 1997[29] $n = 208$	Improvement in MAI scores *3 months*: 24% (intervention) vs 6% (control); adjusted change score −4.3 vs −1.1 ($P = .0006$) *12 months*: 28% (intervention) vs 5% (control); adjusted change score −4.9 vs −0.9 ($P = .0002$)
Köberlein-Neu, 2016[34] $n = 142$	MAI scores lower (i.e., better) at *3 months* in intervention phase compared with control phase (mean difference −4.51, 95% CI −6.66 to −2.36, $P < .001$) Mean difference in PIMs: −0.04 (95% CI: −0.09 to 0.01)
Lampela, 2010[37] Rikala, 2011[38] $n = 644$	% of patients taking inappropriate drugs or dosages at *12 months*: 18% (intervention) vs 24% (control) ($P = .08$, calculated)
Meredith, 2002[41] $n = 259$	Therapeutic duplications discontinued at *6–12 weeks*: 71% (intervention) vs 24% (control) ($P = .003$) "More appropriate" cardiovascular medication regimen: 55% (intervention) vs 18% (control) ($P = .02$) No effect on either psychotropic or NSAID use
Moga, 2017[42] $n = 50$	Improvement in MAI at *8 weeks* (change score, mean (SD)): −3.6 (1.1) (intervention) vs −1.0 (0.9) (control) ($P = .04$)
Muth, 2018[43] $n = 505$	MAI score-adjusted mean difference between groups at *9 months*: 0.6 (95% CI: −0.5 to 1.7) ($P = .27$)
Olsson, 2012[45] $n = 150$	Change from baseline to *12 months* in % of patients on PIMs was not significant in intervention or control groups
Shim, 2018[54] $n = 160$	MAI scores lower (i.e., better) in intervention group at *6 months*: median score 8.0 (IQR 9.0) (intervention) vs 20.0 (IQR 16.0) (control) ($P < .001$)
van der Meer, 2018[59] $n = 157$	Odds of a decrease in Drug Burden Index ≥0.5 at *3 months* in intervention vs control: 1.09 (95% CI: 0.45 to 2.63)
Educational interventions	
Bregnhoj, 2009[18] $n = 212$	5-point reduction (i.e., improvement) in MAI in combined intervention group at *12 months* (95% CI: −7.3 to −2.6); no change in other groups
Clyne, 2015, 2016[21,22] Gillespie, 2017[23] $n = 190$	Intervention group less likely to be taking a PIM than control group at intervention completion (*4–6 months*) (OR 0.32, 95% CI: 0.15 to 0.70, $P = .02$) and *12 months* (OR 0.28, 95% CI: 0.11, 0.76, $P = .01$)
Coleman, 1999[24] $n = 169$	Mean number of high-risk medications at *24 months*: intervention: 1.86, control: 2.54 ($P = .17$)
Jager, 2017[30] $n = 273$	Risk difference between groups in number of subjects with ≥1 PIM per year (assessed at *9 months*): 0.9 (0.4 to 2.0) ($P = .81$)
Martin, 2018[40] $n = 489$	Complete cessation of fills for targeted drugs at *6 months*: intervention: 43%, control: 12% (risk difference 31%, 95% CI: 23 to 38).
Pimlott, 2003[46] $n = 374$	Change in number of benzodiazepine prescriptions at *6 months*: intervention: −0.7%, control: +1.1% ($P = .036$)
Pit, 2007[47] $n = 849$	Odds of improved medication use composite score in intervention group compared with control at *4 months*: OR 1.86, 95% CI: 1.21 to 2.85 (composite score reflected use of benzodiazepines, NSAIDs, and thiazide diuretics)
Rognstadt, 2013[51] Rognstadt, 2018[50] $n = 81,810$	PIMs per 100 patients decreased at *12 months* by 12% (95% CI: 16.8 to 6.9%), intervention vs control
Schmidt-Mende, 2017[53] $n = 119,910$	Risk difference in number on ≥10 medications at *9 months*: −0.1 (95% CI: −0.5 to 0.3)
Simon, 2006[55] $n = 50,924$	Decrease of 19.7 medications per 10,000 members (intervention) vs 13.0 (control) over *18 months* ($P = .52$)
Tannenbaum, 2014[57] $n = 303$	Benzodiazepine discontinuation at *6 months*: intervention: 27%, control: 5% (risk difference 23%, 95% CI: 14 to 32%).
Computerized decision support	
Fried, 2017[26] $n = 128$	Proportion of reconciliation errors corrected at *90 days*: 48.4% (intervention) vs 14.3% (control) ($P < .001$)
Price, 2017[48] $n = 81,905$	Change in PIM rates from baseline at *16 weeks*: 0.1% (intervention), 0.1% (control) ($P = .80$)
Raebel, 2007[49] $n = 59,680$	Percentage of patients newly dispensed ≥1 PIM over *12 months*: 1.8% (intervention), 2.2% (control) ($P = .002$)
Tamblyn, 2003[56] $n = 12,560$	Percentage of patients given PIMs during over *13 months*: 16% (intervention), 20% (control) (RR 0.82, 95% CI: 0.69, 0.98)

CI, confidence interval; IQR, interquartile range; MAI, Medication Appropriateness Index; NSAID, non-steroidal anti-inflammatory drugs; OR, odds ratio; PIM, potentially inappropriate medication; RR, relative rate; SD, standard deviation

intervention group had lower odds of falls (OR: 0.61, 95% CI: 0.41 to 0.91; 20% vs 30%), injury (OR: 0.56, 95% CI: 0.32 to 0.96, 10% vs 18%), and injury requiring medical attention (OR: 0.46, 95% CI 0.30 to 0.70; 6% vs 13%). Overall, the effect of educational interventions on the risk of falls is not known (very low certainty).

Potentially Inappropriate Medications. All 11 trials that reported potentially inappropriate medications (PIMs) reported fewer PIMs in the intervention group than in the control group; the difference was statistically significant in 7 studies (Table 3).[18,21–24,30,40,46,47,50,51,53,55,57]

Computerized Decision Support

We identified 4 trials that evaluated the effect of computerized decision support.[26,48,49,56] The interventions in these trials generally included electronic medical record alerts to pharmacists or providers identifying a PIM, sometimes with additional features such as a recommendation for a substitute medication. Two trials were conducted in the USA and 2 in Canada. Samples sizes ranged from 128 to 59,680 patients and study periods from 90 days to 13 months. All were considered medium risk of bias. In all 4 trials, reduction in PIMs was the only outcome reported (Table 3). Two reported a significant reduction of PIMs in the intervention group compared with the control group[49,56] and 2 reported no intervention effect.[26,48]

DISCUSSION

We conducted this systematic review to evaluate the efficacy of deprescribing interventions in community-dwelling persons aged 65 or older. Study interventions included comprehensive medication review, provider and/or patient education, or computerized decision support. We found that deprescribing based on comprehensive medication review may reduce mortality and that all 3 types of interventions may reduce the number of PIMs. The evidence did not indicate that deprescribing either reduced or increased falls, hospitalizations, or health-related quality of life.

Although, to our knowledge, this is the first SR of controlled clinical trials that specifically addresses the comparative effectiveness of different deprescribing interventions in community-dwelling older adults, our findings are generally consistent with other recent reviews. A 2018 Cochrane review focused on older adults taking four or more medications in the community, hospital, or nursing home setting. The review, which included RCTs and non-randomized trials, controlled before and after studies and interrupted time series, concluded that it "was uncertain whether the interventions reduced the number of PIMs … and likely led to little or no difference in QOL or hospital admissions."[8] A systematic review of 116 experimental and observational studies of deprescribing interventions in older adults in any setting reported that compared with the control conditions, deprescribing reduced the number of inappropriate medications (mean difference −0.49, 95% CI: −0.7 to −0.28, $k = 3$, $N = 839$), but had no demonstrable effect on quality of life or falls risk.[9]

Exploratory analysis of our data suggested some hypotheses that might be tested in future research. First, comprehensive medication reviews may reduce healthcare costs in addition to the reduction in mortality and PIMs reported here (see http://www.hsrd.research.va.gov/publications/esp/). Furthermore, follow-up interventions, such as phone calls or clinic visits with patients, may improve the effectiveness of comprehensive medication reviews. Second, provider education-only interventions are not effective. However, direct-to-consumer patient engagement programs with targeted educational material may be an efficient mechanism for reducing use of specific potentially inappropriate medications on a large scale. From the small group of computerized decision support trials, we were unable to identify any insights into which intervention components were most promising.

We acknowledge several limitations of this review. First, we included only English language publications. Second, the possibility of selective reporting and publication bias may have affected our findings. Third, this review was limited to the community setting; the effects of deprescribing for people in hospitals or long-term care facilities may differ. Fourth conclusions from the review are constrained by limitations of the available data, including the absence of data on major adverse cardiac events, adverse drug withdrawal events, and delirium and lack of standardized definitions of PIMs and other outcomes of interest. Finally, we identified no trials comparing two or more different active interventions with each other. Despite the evidence that polypharmacy is associated with increased risk of undesirable outcomes, such as falls, cognitive impairment, hospitalizations, medication burden, and costs among older adults, deprescribing has not been widely embraced.[2] This may reflect patients' concerns about the impact of medication discontinuation on their health and on their relationship with the prescribing providers, and providers' concerns about meeting quality metrics, increased workload, patient acceptance, and overturning the prescribing decisions of colleagues.[68] It might also reflect the lack of comparative effectiveness trials that would inform implementation efforts. Recent efforts to develop and disseminate evidence-based guidelines may facilitate broader adoption of deprescribing programs in healthcare systems.[69]

In conclusion, comprehensive medication review may result in a reduction in mortality and use of PIMs. Educational initiatives may reduce use of PIMs but have uncertain effects on quality of life and rates of hospitalizations and falls. Computer decision support interventions may reduce PIMs but have not reported clinical outcomes. We did not identify any studies that assessed the comparative effectiveness of the different deprescribing approaches. Future research should include well-

designed comparative effectiveness trials conducted in a variety of settings, employing a uniform set of outcome measures and including process evaluations to guide subsequent implementation of effective interventions.

Corresponding Author: *Hanna E. Bloomfield, MD, MPH; Minneapolis VA Medical Center (151), 1 Veterans Drive, Minneapolis, MN 55417, USA (e-mail: hanna.bloomfield@va.gov).*

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