# Deprescribing for Older Veterans: A Systematic Review

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# PREFACE

The VA Evidence Synthesis Program (ESP) was established in 2007 to provide timely and accurate syntheses of targeted healthcare topics of importance to clinicians, managers, and policymakers as they work to improve the health and healthcare of Veterans. These reports help:

- Develop clinical policies informed by evidence;
- Implement effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures; and
- Set the direction for future research to address gaps in clinical knowledge.

The program is comprised of four ESP Centers across the US and a Coordinating Center located in Portland, Oregon. Center Directors are VA clinicians and recognized leaders in the field of evidence synthesis with close ties to the AHRQ Evidence-based Practice Center Program and Cochrane Collaboration. The Coordinating Center was created to manage program operations, ensure methodological consistency and quality of products, and interface with stakeholders. To ensure responsiveness to the needs of decision-makers, the program is governed by a Steering Committee comprised of health system leadership and researchers. The program solicits nominations for review topics several times a year via the program website.

Comments on this evidence report are welcome and can be sent to Nicole Floyd, Deputy Director, ESP Coordinating Center at Nicole.Floyd@va.gov.

# ACKNOWLEDGMENTS

This topic was developed in response to a nomination by Kenneth Boockvar, MD, MS, for the purpose of identifying deprescribing practices, tools, and products that have the greatest potential to be implemented in the Veterans Health Administration. The scope was further developed with input from the topic nominators (*ie*, Operational Partners), the ESP Coordinating Center, the review team, and the technical expert panel (TEP).

In designing the study questions and methodology at the outset of this report, the ESP consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicting opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

The authors gratefully acknowledge the following individuals for their contributions to this project:

## Operational Partners

Operational partners are system-level stakeholders who have requested the report to inform decision-making. They recommend Technical Expert Panel (TEP) participants; assure VA relevance; help develop and approve final project scope and timeframe for completion; provide feedback on draft report; and provide consultation on strategies for dissemination of the report to field and relevant groups.

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## Technical Expert Panel (TEP)

To ensure robust, scientifically relevant work, the TEP guides topic refinement; provides input on key questions and eligibility criteria, advising on substantive issues or possibly overlooked areas of research; assures VA relevance; and provides feedback on work in progress. TEP members are listed below:

Mary Goldstein, MD
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**Peer Reviewers**

The Coordinating Center sought input from external peer reviewers to review the draft report and provide feedback on the objectives, scope, methods used, perception of bias, and omitted evidence. Peer reviewers must disclose any relevant financial or non-financial conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The Coordinating Center and the ESP Center work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

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# EVIDENCE REPORT

## INTRODUCTION

More than 40% of people in the United States age ≥65 years take 5 or more prescription medications on a regular basis to control and/or prevent disease symptoms and complications.[1,2] Exposure to multiple medications, known as polypharmacy, is associated with increased risk of negative outcomes, such as falls, cognitive impairment and other geriatric syndromes, hospitalizations, and death.[3,4] The number of medications a person is taking may be the single most important predictor of adverse drug effects.[4] Furthermore, about 50% of older adults are taking 1 or more potentially inappropriate medications (PIMs), including those without a clear indication, duplicative medications, and medications known to pose risks in the elderly.[5]

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. This has evolved into a more holistic approach, called "deprescribing," that considers medications in the context of the individual's co-morbidities, functional status, treatment goals, and life expectancy. Deprescribing has been defined as "the clinically supervised process of stopping or reducing the dose of medications that could cause harm or that no longer provide benefits that outweigh potential risks".[1,6,7]

The Center for Medication Safety in Aging, a VA Patient Safety Center of Inquiry, was charged with development and implementation of deprescribing approaches in VA settings. The purpose of this evidence review, commissioned by the National Center for Patient Safety and endorsed by the VHA Pharmacy Benefits Management and the Geriatrics and Extended Care Services, is to inform that work.

The key questions for the review were as follows:

KQ1:   What are the effectiveness, comparative effectiveness, and harms of deprescribing interventions among adults age 65 and older?

   KQ1a: What are the identified elements/components that contribute the most to the effectiveness of deprescribing interventions?

   KQ1b: Do the effectiveness, comparative effectiveness, and harms of deprescribing interventions vary by patient population, provider factors, or setting?

KQ2:   What are the identified facilitators and barriers that impact the implementation of deprescribing interventions within large-scale health systems such as VA?

The intervention and outcomes of interest are depicted on the analytic framework (Figure 1).

**Figure 1. Analytic Framework**
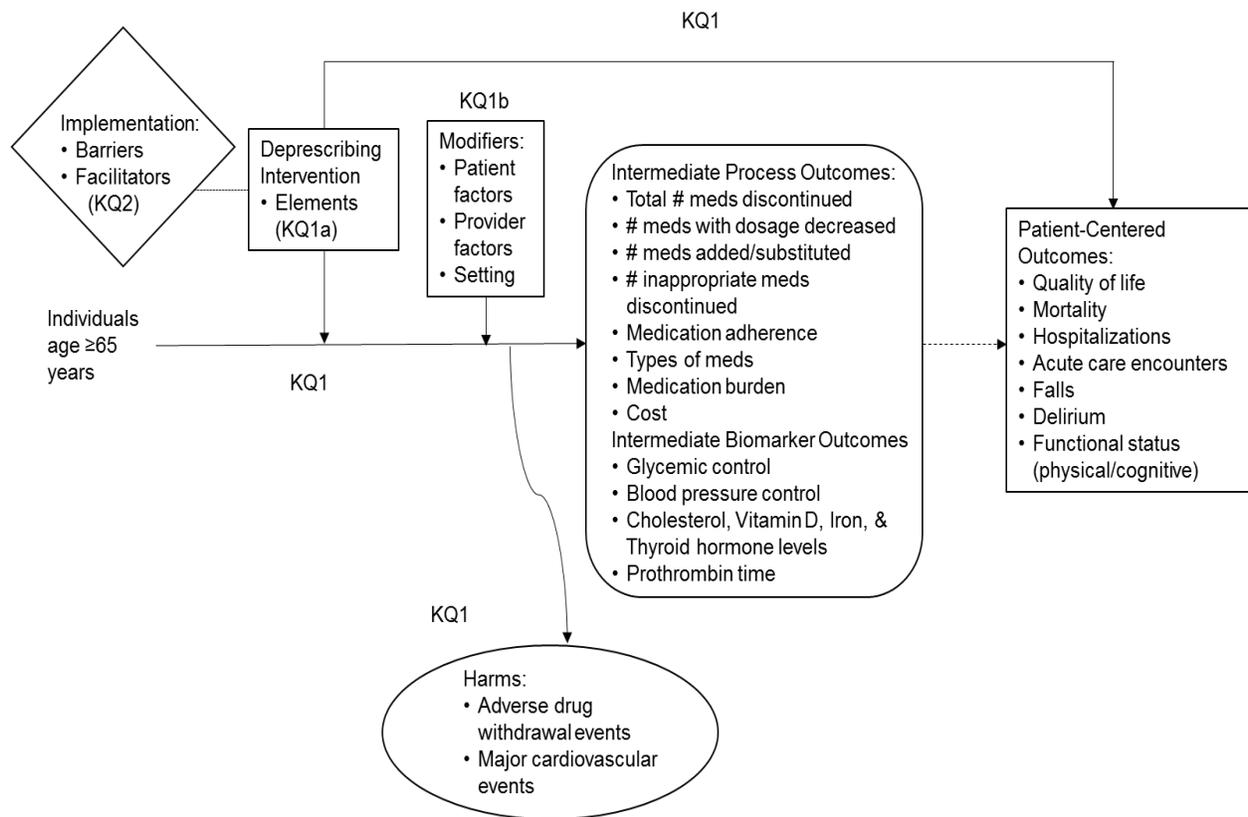
# METHODS

## TOPIC DEVELOPMENT

The key questions and scope of this review were developed with input from the Operational Partners, Technical Expert Panel, and content experts from out project team.

## SEARCH STRATEGY

We searched MEDLINE from 1990 to February 2019 using Medical Subject Headings (MeSH) and key words for deprescribing, medication review, 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. We did a supplemental search from 1990 to July 2019 of the same databases focused on identifying studies pertaining to barriers and facilitators of implementation using MeSH terms and key words for qualitative research, implementation, barriers, and facilitators (Appendix A).

## STUDY SELECTION

Citations were entered into Distiller SR (Evidence Partners). Titles and abstracts were reviewed independently by 2 reviewers with a citation moving to full-text review if either reviewer considered the citation eligible. At full-text review, agreement of 2 reviewers was needed for study inclusion or exclusion. Disputes were resolved by discussion with input from a third reviewer, if needed.

For Key Question 1, we included trials comparing implementation of a deprescribing intervention to usual care or another intervention among individuals age 65 years and older and reporting outcomes of interest. Outcomes included patient-centered outcomes, intermediate process outcomes, and intermediate biomarker outcomes as well as harms, as shown on the analytic framework (Figure 1).

For Key Question 2, we included trials, observational studies, and qualitative research reporting barriers and facilitators associated with implementation of a deprescribing intervention. Most of the included studies interviewed prescribers or intervention staff following implementation of the intervention in a population of individuals age 65 years and older.

Study exclusion criteria were as follows:

- Not a population of interest (*eg,* children or adults <65 years or mean age <65 years);

- No intervention;

- Not an intervention of interest (*eg*, intervention to reduce opioid use);

- No concurrent comparator group (Key Question 1 only);

- No outcomes of interest;

- Not a study design of interest:

    o KQ1: study design other than randomized controlled trial (RCT), cluster randomized controlled trial (CRCT), or controlled clinical trial (CCT)

    o KQ2: study design other than trials, observational studies, or qualitative research

    o Narrative reviews, case report/case series, editorials, letters (other than "Research Letters"), theses/dissertations are excluded;

- Full text of article not available in English.

## DATA ABSTRACTION

For Key Question 1, we completed full data abstraction from eligible studies conducted in community or primary care settings. From those studies, we abstracted study design and demographic data from eligible studies including study inclusion and exclusion criteria, description of intervention and control arms, and age, gender, race/ethnicity, comorbidity status, physical status, cognitive status, and baseline number of medications. We also abstracted outcomes data for outcomes and harms depicted in Figure 1. Data were abstracted by 1 investigator or research associate and verified by a second. Data abstraction tables were organized by intervention category – comprehensive medication review (CMR), education, computer decision support, or hybrid/other.

For studies conducted in nursing home, hospital, emergency department, or palliative care settings, we abstracted data to prepare an evidence map with key features of the eligible studies. Included data points were country or region where the study was conducted, setting, study design, number enrolled, intervention category, length of follow-up, primary outcome, and outcome categories reported. Information was abstracted by 1 investigator or research associate and verified by a second, Outcomes were grouped as medication change, resource utilization/cost, clinical, or functional status/quality of life/patient satisfaction outcomes. Specific outcomes within each category are presented in Table 1.

For Key Question 2, we abstracted information about the study setting, inclusion criteria for participants, data collection methods, response rates, and participant characteristics. We also abstracted barriers and/or facilitators reported.

**Table 1. Outcome Categories for Evidence Map**

**Medication Changes**
  Total number of Medications Discontinued
  Number of Medications with Dosages Decreased
  Number of Medications Added or Substituted
  Number of Inappropriate Medications Discontinued
  Adherence to Medications
  Types of Medications
  Medication Burden
**Resource Utilization and Costs**
  Hospitalizations
  Acute Care Encounters
  Costs
**Clinical Outcomes**
  Falls
  Delirium
  Major Adverse Cardiovascular Events
  Adverse Drug Withdrawal Events
  All-cause Mortality
  Biomarkers (Glycemic Control; Blood Pressure Control; Cholesterol, Vitamin D, Iron, Thyroid Hormone Levels; Prothrombin Time; Other)
**Functional Status, Quality of Life, & Patient Satisfaction**

## RISK OF BIAS ASSESSMENT

Risk of bias was assessed for community or primary care setting studies included for Key Question 1. Risk of bias of each study was rated by 1 co-investigator or research associate and verified by a second. Overall risk of bias for a study was rated as low, medium, or high after consideration of elements based on the Cochrane risk of bias criteria for randomized trials and cluster randomized trials including sequence generation, allocation concealment, recruitment bias, baseline imbalance, blinded outcome assessment, incomplete cluster data, incomplete outcome data, and selective outcome reporting.[8]

## DATA SYNTHESIS

For studies from community or primary care settings (Key Question 1), we pooled results if the studies were deemed low or moderate risk of bias and outcomes measures 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 (CI). Magnitude of statistical heterogeneity was assessed with the $I^2$ statistic ($I^2 > 75\%$ may indicate substantial heterogeneity).[9] Standardized mean differences (SMDs) between 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.[10] For studies reporting categorical outcomes that were not pooled due to differences in study design and/or definition of the

outcome we calculated absolute effects (risk differences) with corresponding 95% CIs for individual trials.

CRCTs were not pooled with RCTs if the adjustment for clustering was not indicated. The unit of randomization for a CRCT is at the cluster level rather than independent individuals and pooling RCTs and CRCTs with inappropriate or unclear adjustment for clustering can lead to misinterpretation of the results.[11]

For intervention studies in settings other than community or primary care and for Key Question 2 findings, results were narratively synthesized.

## RATING THE BODY OF EVIDENCE

For the community- or primary care-based intervention studies, we evaluated overall certainty of evidence for critical outcomes (mortality, hospitalization, quality of life, falls, delirium, adverse drug withdrawal events, and major adverse cardiovascular events) using methods developed by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) group.(GRADEpro 2015 accessed at www.gradepro.org).[12,13] The following domains were used to assess certainty of evidence: 1) risk of bias; 2) consistency; 3) directness; and 4) precision. Certainty of evidence ranges from high (indicating high confidence that the true effect lies close to that of the estimate of the effect) to very low (indicating very little confidence in the effect estimate and that the true effect is likely to be substantially different from the estimate of effect).

## PEER REVIEW

A draft version of this report was reviewed by content experts as well as clinical leadership. Reviewer comments and our responses are presented in Appendix B and the report was modified as needed.

# RESULTS

## LITERATURE FLOW

From the overall literature search (Key Questions 1 and 2), we identified 2,049 records after removing duplicates (Figure 2). Of those, 1,773 were excluded at the abstract level leaving 276 articles for full-text review. Two additional articles were identified from a recent systematic review. We excluded 170 articles and included 102 representing 86 trials.[14-115] An additional 6 trials met eligibility criteria but were rated high risk of bias and not included in analyses.[116-121]

For the focused search for barriers and facilitators of implementation, we re-reviewed 30 references identified in the overall search along with citations from the focused search resulting in a total of 1,325 records (Figure 3). After excluding 1,222 at the abstract level, we did a full-text review of 103 articles. We included 9 studies reported in 10 papers.[122-131]

**Figure 2: Literature Flow Chart – Key Question 1**

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┌──────────────┐  ┌──────────────┐  ┌──────────────┐  ┌──────────────┐
│   MEDLINE    │  │    Embase    │  │   Cochrane   │  │    CINAHL    │
│   N=1014     │  │   N=1219     │  │    N=38      │  │    N=32      │
└──────────────┘  └──────────────┘  └──────────────┘  └──────────────┘
```

Total identified records
N=2303

Duplicates removed
N=254

Records screened after
duplicates removed
N=2049

Records excluded
N=1773

Hand search
N=2

Full-text articles
assessed for eligibility
N=278

Full text articles excluded, with reason
N=170

No study population of interest (N=22)
No intervention of interest (N=33)
Not an intervention (N=3)
No concurrent comparator (N=11)
No outcomes of interest (N=52)
No study design of interest (N=18)
No publication of interest (N=28)
Non-English publication (N=2)
Not available (N=1)

Articles also
identified for KQ 2
N=30

Included articles N=108
Included trials N=86
(+6 trials not analyzed due to
high risk of bias)

**Figure 3: Literature Flow Chart – Key Question 2**
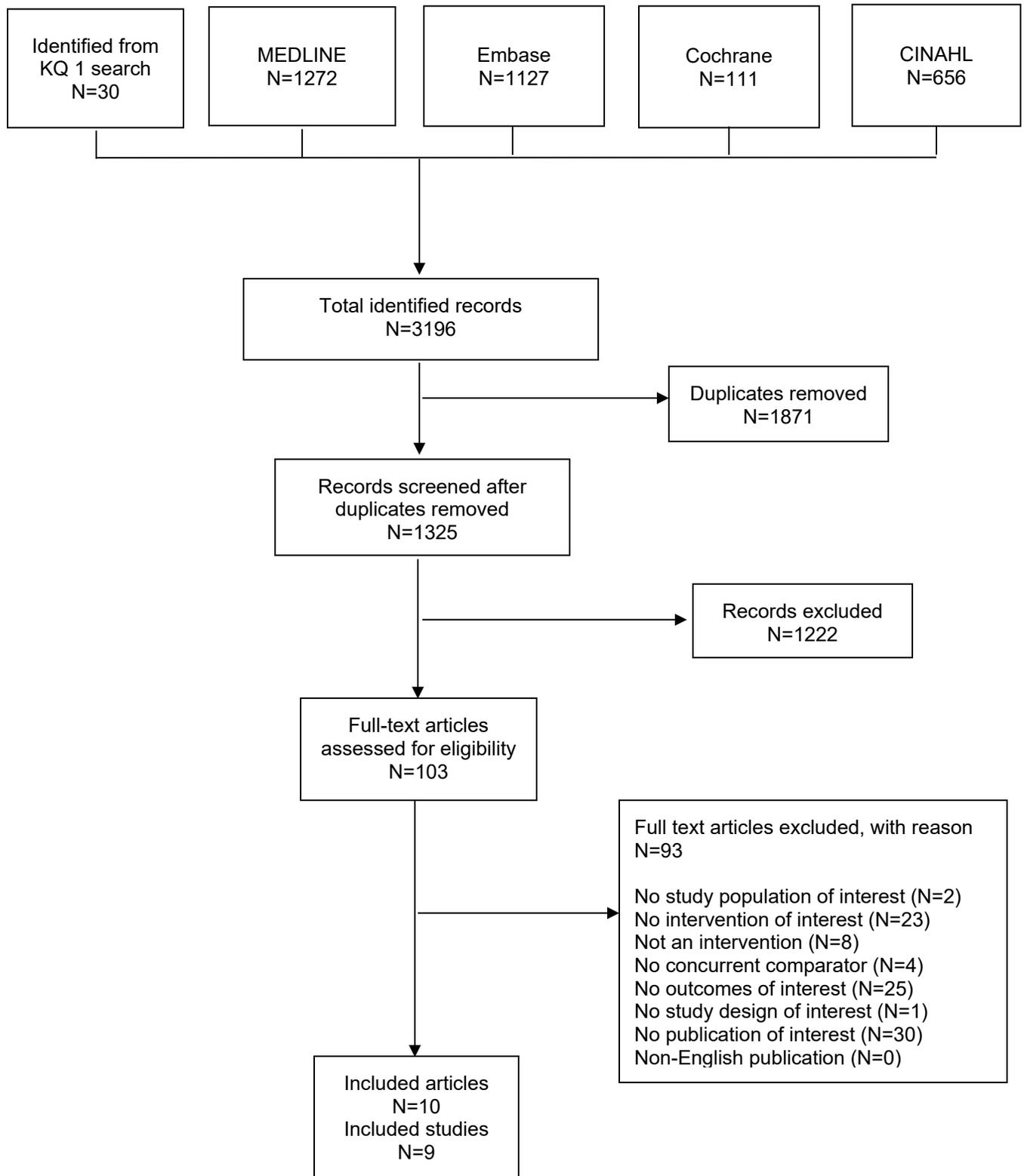
## KEY QUESTION 1: What are the effectiveness, comparative effectiveness, and harms of deprescribing interventions among adults age 65 and older?

We focus our review of effectiveness, comparative effectiveness, and harms on studies conducted in community or primary care settings. An evidence map summarizing studies from nursing home, hospital, emergency department, and palliative care settings is presented in Appendix C.

We identified 44 trials in 53 papers that met our inclusion criteria for KQ1. Six of these were rated high risk of bias and were not included in the analyses. Of the remaining 38, 12 were RCTs and 26 were CRCTs. Included studies were very similar with respect to patient population (older adults taking multiple medications and living in the community) and setting (primary care clinics). Most interventions focused on general deprescribing though some studies targeted particular medication classes (*eg*, benzodiazepines) or specific goals (*eg,* falls reduction). We found considerable variation in description of medication changes and reporting of outcomes.

Our primary outcomes were quality of life/ functional status, all-cause mortality, hospitalizations, falls, adverse drug withdrawal events (ADWE), major adverse cardiovascular events, and delirium. Secondary outcomes included total number of medications discontinued, number of medications with dosage decreased, number of potentially inappropriate medications (PIMs) discontinued, number of medications added or substituted, adherence to medications, types of medications discontinued, medication burden, and cost. We classified interventions into the following categories: Comprehensive Medication Review (CMR), Education (Provider or Patient Directed), Computer Decision Support, and Hybrid/Other. In this narrative summary, we focus on frequently reported outcomes; information about other outcomes is presented in Appendix D.

*Key Messages:*

- Comprehensive Medication Review may reduce all-cause mortality (low certainty of evidence), potentially inappropriate medications, and costs compared to usual care.

- Education (Provider or Patient Directed)

  - A direct-to-consumer patient engagement program with targeted educational material provided directly to patients may reduce PIMs.

  - Provider education without feedback had no significant effect on outcomes; however, when coupled with patient-specific feedback to the provider, it may reduce PIMs.

- Computer Decision Support, such as with electronic health record alerts and other clinical decision support systems, may reduce PIMs.

- Hybrid/Other Interventions may reduce falls and PIMs.

- There was no evidence of harms (adverse drug withdrawal events, worsening of medical conditions, or increased mortality, hospitalizations, or major adverse cardiovascular events) associated with any of the deprescribing interventions.

- No studies addressed the comparative effectiveness of the deprescribing interventions either within or across categories.

- Most studies were not designed to assess mortality, hospitalizations, delirium, falls, or major adverse cardiovascular events, and no studies reported on biomarker measures such as glycemic or blood pressure control.

## Comprehensive Medication Review (CMR) (k=21)

*Summary*

Comprehensive medication review (CMR) programs may reduce all-cause mortality, potentially inappropriate medications, and health care costs. The trials either did not report or did not significantly improve health related quality of life, or reduce falls, MACE, delirium, hospitalizations, or acute care visits. No adverse drug withdrawal events were reported.

Fourteen of the 21 trials that compared a CMR intervention to usual care reported that the intervention resulted in at least 1 favorable outcome. Compared to the 7 trials that did not report an intervention effect, these trials were more likely to have follow-up times of less than 1 year (64% vs 43%) and to have included an additional intervention (*eg,* patient call or visit) during follow-up (50% vs 14%). Otherwise there did not appear to be any systematic differences between the positive and negative studies with respect to country, sample size, risk of bias, or characteristics of the enrollees or the interventions.

*Overview of Studies*

Twenty-one trials evaluated the effect of CMR compared to a control group, most often usual care.[14,20,24,25,34,46,47,50,53,54,56,60,62,63,67,70-73,92,96,105,107,110,114] For the most part, the CMR interventions were led by a pharmacist and included a chart review, patient interview, and provider consultation, culminating in recommendations for medication regimen changes to a physician. Nine studies also included a follow-up intervention with patients to reinforce the recommendations, such as home-care visits by nurses or telephone calls by pharmacists. Six trials were conducted in the US, 1 in Canada, 1 in Malaysia, and 13 in Europe. Demographic characteristics of the enrolled patients are shown in Appendix D Table 1. We judged the risk of bias to be low in 5 trials and medium in 16 (Appendix D, Table 2). Outcomes were reported on about 8700 patients, with study sample sizes ranging from 25 to 1403.

*Primary Outcomes*

The primary outcomes reported were all-cause mortality, falls, hospitalizations and health-related quality of life/functional status/patient satisfaction metrics (Appendix D, Tables 3-5).

*All-cause mortality:* All-cause mortality was reported in 11 RCTs enrolling 3875 patients with follow-up ranging from 1-12 months. Compared to usual care, CMR resulted in a 21% relative risk reduction (OR 0.79, 95% CI: 0.58 to 1.08, $I^2$=0) corresponding to a <1 percentage point

absolute reduction (95% CI: -1.9 to 0.4) in all-cause mortality (Figure 4). Results were not statistically significant, perhaps due to the low number of events.

**Figure 4. All-cause Mortality – CMR Studies**

| Study name | Statistics for each study | | | Events / Total | | Peto odds ratio and 95% CI |
|---|---|---|---|---|---|---|
| | Peto odds ratio | Lower limit | Upper limit | Deprescribing | Usual care | |
| Allard 2001 (RCT) | 0.40 | 0.16 | 1.00 | 6 / 136 | 14 / 130 | |
| Boẏe 2016* (RCT) | 0.47 | 0.05 | 4.54 | 1 / 319 | 2 / 293 | |
| Campins 2017 (RCT) | 1.17 | 0.39 | 3.50 | 7 / 252 | 6 / 251 | |
| Haag 2016 (RCT) | 0.92 | 0.05 | 15.64 | 1 / 13 | 1 / 12 | |
| Hanlon 1996 (RCT) | 0.67 | 0.25 | 1.80 | 7 / 105 | 10 / 103 | |
| Kwint 2011 (RCT) | 0.87 | 0.12 | 6.36 | 2 / 63 | 2 / 55 | |
| Lenaghan 2007 (RCT) | 1.15 | 0.37 | 3.58 | 7 / 68 | 6 / 66 | |
| Olesen 2013 (RCT) | 1.45 | 0.71 | 2.93 | 19 / 253 | 14 / 264 | |
| Olsson 2012† (RCT) | 0.80 | 0.29 | 2.24 | 12 / 99 | 7 / 48 | |
| van der Meer 2018 (RCT) | 1.09 | 0.07 | 17.70 | 1 / 75 | 1 / 82 | |
| Zermansky 2001 (RCT) | 0.57 | 0.30 | 1.07 | 15 / 608 | 25 / 580 | |
| | 0.79 | 0.58 | 1.08 | | | |

$I^2 = 0\%$
* 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

*Falls:* Four trials reported fall outcomes. Two were specifically designed to assess falls.[20,107] Only 1 study found a difference between the intervention and control groups; this study enrolled 620 adults >age 70 from a healthcare system in Pennsylvania and focused on medications that might increase the 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 groups in total number of medications or number of psychoactive medications at follow-up.[107]

Results from the other 3 trials are summarized in Figure 5. In the IMPROveFALL trial that enrolled 612 older adults who had visited an emergency room because of a fall, there was no difference between intervention and control groups at 12 months in either the number of falls (37% vs 34%; absolute risk difference 4%, 95% CI: -4 to 12), number of Fall-Risk-Increasing-Drugs, or the number of falls requiring medical attention.[20]

There was no difference in incidence of falls in the other 2 trials, neither of which had designated falls as the primary outcome and both of which had very short lengths of follow-up. One trial

enrolled 259 participants and followed them for 6 to 12 weeks.[67] The second was designed to decrease the anticholinergic sedative load in 157 older adults. After 3 months of follow-up there was no difference between the 2 groups in the number of falls.[105]

**Figure 5. Absolute Risk Differences in Falls – CMR Studies**

| Study name | Statistics for each study | | | Events / Total | | Risk difference and 95% CI |
|---|---|---|---|---|---|---|
| | Risk difference | Lower limit | Upper limit | Deprescrib | Usual Care | |
| Boýe 2016 (RCT) | 0.04 | -0.04 | 0.12 | 115 / 308 | 91 / 272 | |
| Meredith 2002 (RCT) | 0.01 | -0.06 | 0.09 | 17 / 140 | 15 / 137 | |
| van der Meer 2018 (RCT) | 0.11 | -0.04 | 0.26 | 18 / 59 | 15 / 77 | |

-0.50   -0.25   0.00   0.25   0.50

Favors deprescrib   Favors usual care
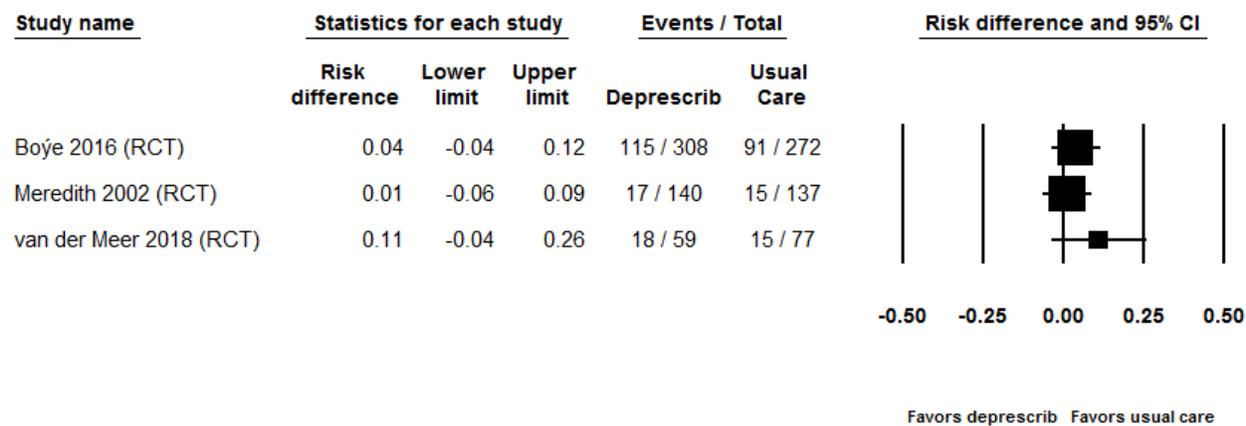
*Hospitalizations:* Hospitalizations over a wide range of follow-up durations were reported in 12 studies with a combined enrollment of 5672 participants. None of these studies reported a difference between the intervention and control groups with respect to number of participants with 1 or more hospitalizations during follow-up.[24,25,46,47,50,54,56,60,62,63,71,72,92,105,110,114] In the 6 RCTs that could be pooled, 20.4% of people in the deprescribing group were hospitalized versus 19.8% in usual care for an absolute risk difference of 0.6% (95% CI: -2.3 to 3.5) (Figure 6). The remaining 6 studies could not be included in the pooled analysis due to the varying definitions of hospitalization,[46,50,54,62,63,71] or because outcomes were not reported separately for intervention and control groups.[47,56,92]

**Figure 6. Hospitalizations Following Deprescribing – CMR Studies (RCTs)**

| Study name | Statistics for each study | | | Events / Total | | Risk ratio and 95% CI |
|---|---|---|---|---|---|---|
| | Risk ratio | Lower limit | Upper limit | Deprescrib | Usual Care | |
| Campins 2017 (RCT) | 0.92 | 0.68 | 1.26 | 57 / 245 | 63 / 250 | |
| Lenaghan 2007 (RCT) | 0.92 | 0.55 | 1.54 | 20 / 68 | 21 / 66 | |
| Olesen 2014 (RCT) | 1.10 | 0.84 | 1.44 | 77 / 253 | 73 / 264 | |
| Touchette 2012 (RCT) 3-6 m* | 1.59 | 0.95 | 2.65 | 55 / 373 | 17 / 183 | |
| van der Meer 2018 (RCT) | 0.44 | 0.12 | 1.54 | 3 / 59 | 9 / 77 | |
| Zermansky 2001 (RCT) | 1.14 | 0.88 | 1.46 | 110 / 579 | 92 / 550 | |
| | 1.07 | 0.92 | 1.26 | | | |

0.1 0.2   0.5   1   2   5   10

Favors depresrib   Favors usual care

$I^2$ = 12%
* Data from 3-6 month follow-up with basic and enhanced CMR arms combined

*Health-related Quality of Life, Functional Status, and Patient Satisfaction:* Eleven studies reported quality of life.[20,24,25,47,50,53,54,60,62,63,70,71,73,92,105] Three of these also reported functional status[47,71,92,105] and 2 reported a patient satisfaction outcome.[47,71,92]

Health-related quality of life was measured in all 11 studies with either the EuroQual Quality of Life scale (EQ-5D) (N=5), the Short Form Health Survey (SF-12/36) (k=5), or both (k=1). Nine studies reported no difference between the intervention and control groups in health-related quality of life at study end. The IMPROveFALL trial reported an improvement in the intervention compared to control group on the EQ-5D score, although not on either of physical or mental health component scores of the SF-12.[20,80] The conSIGUE trial reported improved quality of life in the intervention vs the control group on both the EQ-5D and EQ-5D visual analog scale (VAS) as shown in Figure 7.[50,62,63]

Three studies reported a variety of functional status measures other than the EQ-5D or the SF-12/36 component scores.[47,71,92,105] None found any differences between intervention and control groups on any metric. Neither of the studies reporting a patient satisfaction score found any differences between intervention and control group.[47,71,92]

## Figure 7. Standardized Mean Differences for Quality of Life – CMR Studies

| Study name | Std diff in means | Lower limit | Upper limit | Deprescrib | Usual care | Std diff in means and 95% CI |
|---|---|---|---|---|---|---|
| Boýe 2016 EQ-5D (RCT) | 0.22 | 0.06 | 0.38 | 285 | 263 | |
| Boýe 2016 SF-12 PCS (RCT) | 0.15 | -0.02 | 0.32 | 283 | 258 | |
| Boýe 2016 SF-12 MCS (RCT) | -0.01 | -0.18 | 0.16 | 283 | 258 | |
| Jódar-Sánchez 2015 EQ-5D (CRCT) | 2.40 | 2.26 | 2.54 | 627 | 671 | |
| Jódar-Sánchez 2015 EQ-5D VAS (CRCT) | 0.39 | 0.28 | 0.50 | 627 | 671 | |
| Köberlein-Neu 2016 SF-12 Phys (CRCT) | -0.02 | -0.15 | 0.11 | 142 | 142 | |
| Köberlein-Neu 2016 SF-12 Psych (CRCT) | -0.07 | -0.20 | 0.06 | 142 | 142 | |
| Lenaghan 2007 EQ-5D (RCT) | -0.33 | -0.71 | 0.05 | 56 | 49 | |
| Lenaghan 2007 EQ-5D VAS (RCT) | -0.26 | -0.66 | 0.14 | 44 | 48 | |
| Moga 2017 SF-36 PCS (RCT) | -0.18 | -0.73 | 0.37 | 25 | 24 | |
| Moga 2017 SF-36 MCS (RCT) | 0.51 | -0.04 | 1.06 | 25 | 24 | |
| Muth 2018 EQ-5D (CRCT) | 0.12 | -0.09 | 0.33 | 222 | 214 | |
| Olsson 2012 EQ-5D VAS Group B (RCT) | 0.18 | -0.27 | 0.63 | 39 | 34 | |
| Olsson 2012 EQ-5D VAS Group C (RCT) | 0.06 | -0.39 | 0.51 | 33 | 34 | |
| van der Meer 2018 EQ-5D VAS (RCT) | -0.13 | -0.45 | 0.19 | 65 | 80 | |

Favors usual care    Favors deprescrib

*Secondary Outcomes: Medication Changes*

Nineteen studies reported at least 1 medication outcome. Outcomes included frequency of drug-related problems (k=3), reduction in total number of medications (k=10), and improvement in medication regimen appropriateness (k=12) (Appendix D, Tables 6 and7).

*Reduction in Drug-related Problems (k=3):* All trials reporting drug-related problems found that the CMR intervention was more effective than usual care.[54,56,114] A Dutch trial enrolled 125 patients from community pharmacies and reported that at 6 months, the mean number of drug changes was higher in the intervention group compared with the wait-list group (2.2 vs 1.0, P=.02) and the number of drug-related problems leading to a recommendation for a change was lower in the intervention compared to the control group (29% reduction in drug-related problems in the intervention group vs 5% in the control group, P<.01).[56]

A trial in the UK that enrolled 332 people age ≥65 taking at least 4 medications reported that at 3 months, the intervention group had a higher percentage of resolved "pharmaceutical care issues" compared to control subjects (78.8% vs 39.3%, P<.0001).[54]

A US trial randomized 637 people age ≥65 with ≥3 chronic conditions and ≥6 prescription medications to either usual care, basic CMR including patient interview only, and enhanced CMR including a medical record synopsis and patient interview. At 3 months, the average number of drug-related problems in the enhanced CMR group was lower than in the basic CMR group (OR: 0.43, 95% CI: 0.37 to 0.49, P<.001).[114]

*Reduction in Total Number of Medications (k=10):* Six of the 10 trials that reported reduction in total number of medications found no difference between intervention and control groups.[14,46,47,71,73,92,107] In 3 of the 4 trials reporting a difference, the mean difference was less than 1 medication and of uncertain clinical significance (Table 2).[24,25,60,110 50,62,63]

*Reduction in Potentially Inappropriate Medications (k=12):* Twelve trials reported inappropriate medication use; 5 of these included the Medication Appropriateness Index (MAI; scores range from 0=completely appropriate prescription to 18=completely inappropriate prescription).[47,92] Six trials found no difference between intervention and control groups.[14,20,46,71,73,105] However, the study by Haag[46] was very small and short term, the trial by Allard had a nearly 2-fold increase in the number of patients not being on a PIM,[14] and the study by Boyé[20] noted a decrease in the percentage of individuals on PIMs. Six other trials found significant reductions in PIMs, duplication medications, or MAI scores. Results are summarized in Table 3.

## Table 2. Reduction in Total Number of Medications – CMR Studies

| Author<br>Number enrolled<br>Length of follow-up | Findings |
| --- | --- |
| Allard, 2001[14]<br> n=266<br>12 months | Difference in mean number (SD) of drugs prescribed baseline to follow-up: Intervention: 0.24 (2.15); Control :0.13 (1.67) |
| Campins, 2017, 2019[24,25]<br>n=503<br>12 months | % of enrollees with 1 or more fewer medications at follow-up: 85% in intervention vs 75% in control group; OR:1.85, 95% CI: 1.17 to 2.9, P=.008 |
| Haag, 2016[46]<br>n=25<br>1 month | Intervention: median number of medications: 17 (IQR 12-20) at baseline to 18 (12-20) at follow-up; Control: 15.5 (13-18.5) to 17 (13-18) at follow-up |
| Hanlon, 1996, Schmader 1997[47,92]<br>n=208<br>3, 12 months | Mean number of VA-prescribed medications at 12 months: Intervention: 6.9 (2.6), Control: 7.9 (3.3), P=.83 |
| Jodar-Sanchez, 2015[50]<br>Malet-Larrea 2016, 2017[62,63]<br>n=1403<br>6 months | Difference in mean number of prescribed medications in the intervention vs control group: - 0.21 drugs, 95% CI: -0.092 to -0.335, P=.001 |
| Lenaghan, 2007[60]<br>n=136<br>6 months | Difference in mean number of prescribed medications in the intervention vs control group: -0.87 drugs, 95% CI: -1.66 to -0.08, P=0.03 |
| Muth, 2018[71]<br>n=505<br>9 months | Adjusted mean difference in number of medications between 2 groups: 1.0 (1.0 to 1.1) |
| Olsson, 2012[73]<br>n=150<br>12 months | Median number of drugs at baseline/follow-up: Control: 8.0/9.0; Intervention 1: 10.0/11.0; Intervention 2: 10.0/10.0 |
| Weber, 2008[107]<br>n=620<br>15 months | Mean number of medications from baseline to end of study: Intervention 7.65 to 7.88; Control: 7.46 to 7.62 |
| Zermansky, 2001[110]<br>n=1188<br>12 months | Increase in number of medications in intervention vs control groups: 0.2 vs 0.4, P=.01 |

CI=confidence interval; SD=standard deviation; IQR=interquartile range; OR=odds ratio; VA=Veterans Affairs
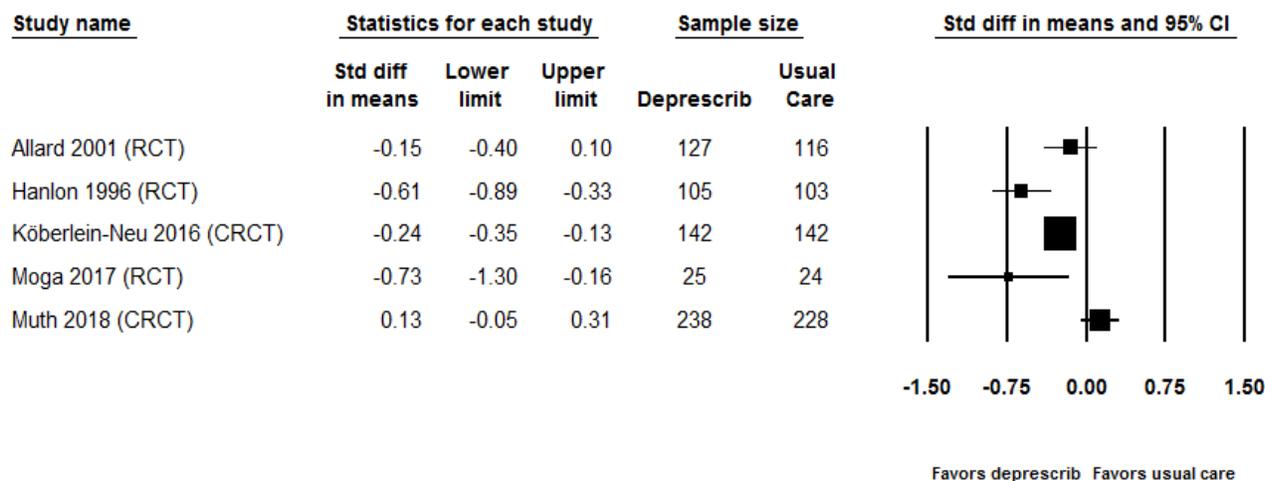
**Table 3. Potentially Inappropriate Medications – CMR Studies**

| Author<br>Number enrolled<br>Length of follow-up | Findings |
|---|---|
| Allard, 2001[14]<br>n=266<br>12 months | Reduction in PIMs/patient: 0.24 (Intervention) vs 0.15 (Control), P=.13; odds of NOT being on a PIM at study's end in the intervention group was 1.83 (95% CI: 0.94 to 3.57) |
| Boyé 2017,[20] 2017<br>n=612<br>12 months | % using ≥ 3 fall risk increasing medications went from 72% to 75% from baseline to 1 year in control group and stayed at 70% in intervention group; % with decreased PIMs: 37% (Intervention) vs 19% (Control) |
| Denneboom, 2007[34]<br>n=738<br>6 months | % of recommendations leading to a medication change:<br>Case conference group: 29.8% vs 17.2% in written feedback group, P=.02;<br>% of maintained medication change at 6 months: 25.5% vs 14.8%, P=.03 |
| Haag, 2016[46]<br>n=25<br>1 month | No difference between groups in any of multiple measure of PIMs |
| Hanlon 1996, Schmader 1997[47,92]<br>n=208<br>3, 12 months | MAI scores improved by 24% in the intervention group compared to 6% in the control group (adjusted change score -4.3 compared to -1.1, P=.0006) at 3 months and persisted through 12 months |
| Köberlein-Neu, 2016[53]<br>n=142<br>15 months | MAI scores were lower (*ie,* better) in the intervention phase compared to the 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) |
| Meredith, 2002[67]<br>n=259<br>6-12 weeks | Intervention resulted in a decrease in therapeutic duplications (71% intervention vs 24% control, P=.003) and "more appropriate" cardiovascular medication regimens (55% vs 18% in controls, P=.02); no effect on either psychotropic or NSAID use |
| Moga, 2017[70]<br>n=50<br>8 weeks | MAI score improved in the intervention compared to control (change score: -3.6 +/- 1.1 for intervention vs 1.0 +/- 0.9 for control, P=.04) |
| Muth, 2018[71]<br>n=505<br>9 months | Adjusted mean difference between groups at 6 months: MAI score 0.7 (95% CI: -0.2 to 1.6) |
| Olsson, 2012[73]<br>n=150<br>12 months | Change from baseline in % of patients on PIMs was not significant in any of the 3 groups |
| Shim, 2018[96]<br>n=160<br>6 months | MAI scores were lower (*ie,* better) in intervention group compared to control group (median score 8.0 [IQR 9.0] vs 20.0 [IQR 16.0], P<.001) |
| van der Meer, 2018[105]<br>n=157<br>3 months | Odds of a decrease in Drug Burden Index ≥0.5 in intervention vs control: 1.09 (95% CI: 0.45 to 2.63) |

CI=confidence interval; IQR=interquartile range; MAI=Medication Appropriateness Index; NSAID=non-steroidal anti-inflammatory drugs; PIM=Potentially inappropriate medications

We were able to calculate standardized mean differences from 5 trials that reported a measure of PIMs,[14,53,70,71] as shown in Figure 8.[47,92] In 2 of the 5 trials the intervention effect, as measured by Cohen's d,[10] was less than small,[14,71] in 1 it was small,[53] and in 2 it was moderate.[47,70,92]

**Figure 8. Standardized Mean Differences in Medication Appropriateness Index (MAI) or Potentially Inappropriate Medications (PIMs) Outcomes\* – CMR Studies**

| Study name | Statistics for each study | | | Sample size | | Std diff in means and 95% CI |
|---|---|---|---|---|---|---|
| | Std diff in means | Lower limit | Upper limit | Deprescrib | Usual Care | |
| Allard 2001 (RCT) | -0.15 | -0.40 | 0.10 | 127 | 116 | |
| Hanlon 1996 (RCT) | -0.61 | -0.89 | -0.33 | 105 | 103 | |
| Köberlein-Neu 2016 (CRCT) | -0.24 | -0.35 | -0.13 | 142 | 142 | |
| Moga 2017 (RCT) | -0.73 | -1.30 | -0.16 | 25 | 24 | |
| Muth 2018 (CRCT) | 0.13 | -0.05 | 0.31 | 238 | 228 | |



-1.50   -0.75   0.00   0.75   1.50

Favors deprescrib   Favors usual care

\* Definitions of outcomes
Allard 2001: Mean reduction in the number of PIMs
Hanlon 1996: Mean change in MAI scores
Köberlein-Neu 2016: Mean difference in MAI scores
Moga 2017: Mean change in MAI scores for anticholinergic medication
Muth 2018: Mean change in MAI scores

*Secondary Outcomes: Acute Care Visits and Costs*

*Acute Care Visits:* Acute care visits were reported in 4 studies with a combined enrollment of 2543.[20,24,25,46,50,62,63] Three studies (2 medium, 1 low risk of bias) reported no intervention effect. The largest (medium risk of bias) reported a significant difference between groups in mean number of emergency department (ED) visits per patient per 6 months[50,62,63] as shown in Table 4.

**Table 4. Acute Care Visits – CMR Studies**

| Author Number enrolled Length of follow-up | Findings |
|---|---|
| Boyé, 2017[20] n=612 12 months | Number with fall-related ED visits: Intervention:16 (5%) Control: 21 (8%), P=.22 |
| Campins, 2017, 2019[24,25] n=503 12 months | Mean number of ED visits per patient: Intervention: 0.9 (1.5) Control: 1.1 (1.5), P=.06 |
| Haag, 2016[46] n=25 1 month | 1 person in each group with an ED visit |
| Jodar-Sanchez, 2015[50] Malet-Larrea 2016, 2017[62,63] (CONSIGUE) n=1403 6 months | Mean number of ED visits per patient (decreased in both groups): Intervention: 0.43 (0.83) baseline, 0.19 (0.51) during study; difference 0.24 Control: 0.55 (1.55) baseline, 0.42 (1.21) during study; difference 0.13 |

ED=emergency department; SD=standard deviation

◀◀    ◀    ▶

*Costs:* Seven studies, all medium risk of bias, reported a comparison of medication costs between the intervention and control groups[20,24,25,34,50,54,62,63,80,107,110]; in 2 studies this was the only cost data reported.[54,107] Three studies also reported costs of the intervention (*eg,* time spent by health care professionals to implement the intervention)[24,25,34,110] and 2 reported more extensive cost-utility and/or cost-benefit analyses.[20,50,62,63,80]

*Medication Costs Only:* Neither of these trials reported significant differences between intervention and control groups in average monthly costs of medications per patient.[54,107]

*Medication Costs and Intervention Costs:* In a study of 1188 patients in 4 general practices in the UK, increased costs were reported for both intervention and control groups, but the net increase per patient per month was significantly smaller in the intervention group (difference between groups -4.72 GBP [95% CI: -7.04 to -2.41], P=.0001).[110] The Spanish trial of 502 participants found decreased costs in both intervention and control group over 1 year but the decrease was greater in the intervention than the control group (-14.3% vs -7.7%, P=.04). The authors estimated that the intervention resulted in an annual reduction in expenditures of 64 euros per patient.[24,25] The third study, conducted in the Netherlands with 738 participants followed for 9 months, found no net differences in costs between intervention and control groups.[34]

*Cost Utility and Cost-Benefit Analyses:* In a cost-utility analysis, the IMPROveFALL trial reported that the intervention did not result in a reduction in total fall-related health care costs.[20,80] The conSIGUE trial conducted a detailed cost-benefit analysis in which health benefits were estimated by assigning a monetary value to quality-adjusted life years gained. The analysis indicated that the intervention saved 97 euros per patient over 6 months.[50,62,63]

## Educational Interventions (k=10)

*Summary*

Nine of 10 trials of educational interventions directed at providers, patients, or both either did not report or did not have a significant effect on 6 of the primary outcomes: all-cause mortality, falls, MACE, delirium, health-related quality of life/functional status, or adverse drug withdrawal events. One trial reported fewer hospitalizations in the intervention group.

Nine trials reported potentially inappropriate medications (PIMs). Six found that compared to control, the intervention was associated with fewer PIMs at the end of the study. The interventions used in these 6 studies were: a direct-to-consumer patient engagement program with targeted educational material provided directly to patients (k=2 low risk of bias trials); provider education plus feedback (k=2, 1 low, 1 medium risk of bias); and a patient education with a provider education plus feedback intervention (k=2, 1 low, 1 medium risk of bias). The 2 studies testing provider education alone did not report an effect on PIMs.

*Overview of Studies*

We identified 10 trials that evaluated the effect of educational interventions directed at either patients (k=1), providers (k=5), or both (k=4).[21,28,64,77,89,91,95,97,112,115] The control groups were assigned either usual care (k=8) or a sham intervention (*ie,* targeting drugs that were not of interest, k=2). Two trials were conducted in the US, 3 in Canada, and 5 in Europe. Demographic characteristics of the enrolled patients are shown in Appendix D, Table 8. We judged the risk of
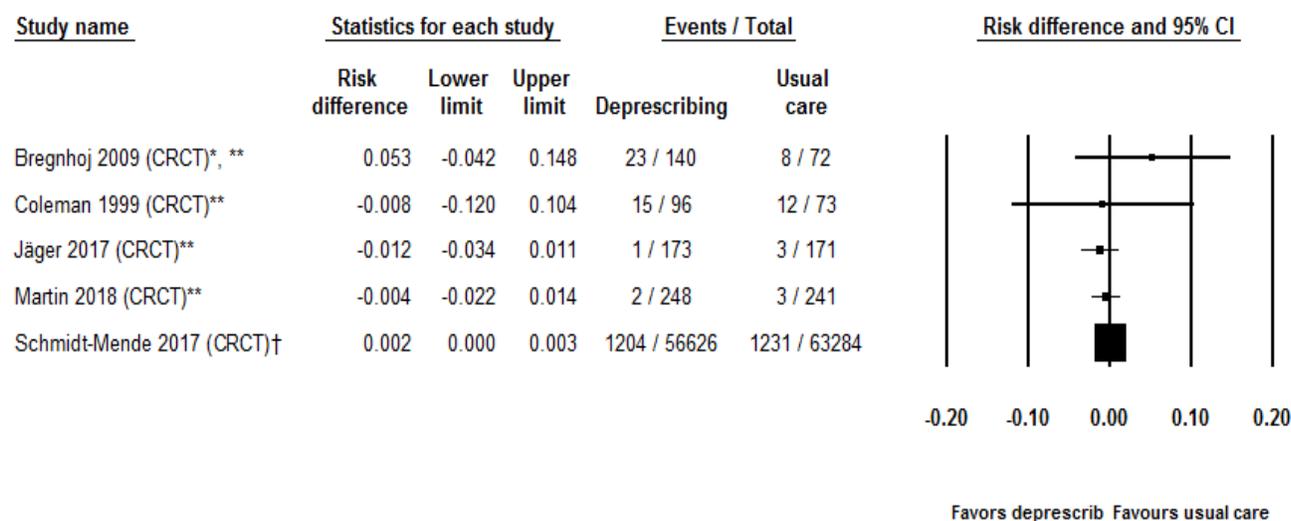
bias to be low in half the trials and medium in the other half (Appendix D, Table 9). Outcomes were reported on a total of 2424 patients in the 7 smaller trials and on 252,684 in the 3 larger trials.

*Primary Outcomes*

The outcomes reported were all-cause mortality, falls, hospitalizations, and quality of life/functional status (Appendix D, Tables 10-12).

*All-cause Mortality:* Reported in 5 trials, there was no difference in all-cause mortality between the intervention and control groups (Figure 9).

**Figure 9. Risk Differences in Mortality – Education Studies**

| Study name | Statistics for each study | | | Events / Total | | Risk difference and 95% CI |
|---|---|---|---|---|---|---|
| | Risk difference | Lower limit | Upper limit | Deprescribing | Usual care | |
| Bregnhoj 2009 (CRCT)*, ** | 0.053 | -0.042 | 0.148 | 23 / 140 | 8 / 72 | |
| Coleman 1999 (CRCT)** | -0.008 | -0.120 | 0.104 | 15 / 96 | 12 / 73 | |
| Jäger 2017 (CRCT)** | -0.012 | -0.034 | 0.011 | 1 / 173 | 3 / 171 | |
| Martin 2018 (CRCT)** | -0.004 | -0.022 | 0.014 | 2 / 248 | 3 / 241 | |
| Schmidt-Mende 2017 (CRCT)† | 0.002 | 0.000 | 0.003 | 1204 / 56626 | 1231 / 63284 | |



-0.20   -0.10   0.00   0.10   0.20

Favors deprescrib   Favours usual care

* Intervention arms combined
** Not adjusted for cluster design, estimate of the intracluster correlation coefficient (ICC) not provided by trial
† The post-intervention analysis in the publication reported a non-significant difference 0.1 (−0.1 to 0.6). Clustering was accounted for.

*Falls:* Only 1 trial reported falls outcomes. This medium risk of bias US trial enrolled 169 people age ≥65 at high risk for hospitalization or functional decline. The intervention was enrollment in a chronic care clinic program. There was no difference between intervention and control group in incidence of falls "over past 12 months": 35.6% versus 43.5%, P=.35.[28]

*Hospitalizations:* Four trials reported hospitalizations. A low risk of bias cluster randomized trial conducted at 55 primary care practices in Germany that enrolled 604 people age 65 to 84 with at least 3 chronic conditions reported a reduction in days spent in hospital in the intervention compared to the control group (-3.07, 95% CI: -5.25 to -0.89), despite no change in the trial's primary outcome, number of medications. The intervention was described as narrative medicine-based and consisted of four 4-hour training sessions for the physicians and three 30-minute physician-patient dialog sessions over the 1-year study.[91]

The other 3 trials found no difference in hospitalizations between intervention and control groups. One was a medium risk of bias cluster randomized trial with 9 months of follow-up that tested a provider education and feedback intervention in 69 clinics in Sweden and enrolled

119,910 people age ≥65. Risk difference between intervention and control for 1 or more hospitalizations was 0.2 (95%CI: -0.8 to 1.2).[95] The second was a medium risk of bias US CRCT that enrolled 169 people age ≥65 at high risk for hospitalization or functional decline. The intervention was enrollment in a half day multidisciplinary chronic care clinic. At 2 years, 34.3% of control vs 36.5% of intervention enrollees had >1 hospitalization, P=.77.[28]

The third study (D-PRESCRIBE) was a low risk of bias trial focused on sedative-hypnotics, first-generation antihistamines, glyburide, and non-steroidal anti-inflammatory drugs (NSAIDs). Sixty-nine pharmacies (489 patients) were randomized to either usual care or a patient and provider educational intervention. The patients were sent educational brochures describing harms of the targeted medications, alternatives, and, for those on sedative-hypnotics, a visual tapering protocol. Their providers were sent a "pharmaceutical opinion", which is a legal and reimbursable action in Quebec. The study states: "No adverse effects requiring hospitalization were reported".[64]

*Health-related Quality of Life, Functional Status, and Patient Satisfaction (k=2):* 1 study, described above, reported no difference between intervention and control group at 24 months, in SF-36 physical function (mean of 37.5 in both groups); Center for Epidemiologic Studies Depression Scale (CES-D) (mean of 14.8 vs 12.4, P=.11); or patient satisfaction with overall medical care (25.3 % vs 40% rated it excellent, P=.13).[28] The second study, also described above, reported no difference in health-related quality of life as measured on the EQ-5D between the intervention and control group at 12 months of follow-up: mean score: 0.68 versus 0.70, P=.5.[91]

*Secondary Outcomes – Medication Changes*

*Medication Changes (k=10)* All 10 trials reported 1 or more medication outcomes (Appendix D, Tables 13 and 14). Three reported on total medications[21,91,95] and 9 reported on inappropriate medications.[21,28,64,77,89,95,97,112,115]

*Reduction in Total Number of Medications (k=3):* Only 1 of the 3 studies reported a reduction in total number of medications at follow-up (Table 5).

**Table 5. Number of Medications at Follow-up – Education Studies**

| Author<br>Number enrolled<br>Length of follow-up | Intervention | Risk of Bias | Total Number of Medications at Follow up |
|---|---|---|---|
| Bregnhoj, 2009[21]<br>n=212<br>12 months | Provider education or provider education plus feedback vs usual care | Medium | The mean change in total medications in the education plus feedback group vs the other 2 groups combined, was -1.03 (95% CI: -1.7 to -0.3) |
| Schaefer, 2018[91]<br>n=604<br>12 months | Narrative medicine-based physician-patient dialog sessions | Low | Intervention: 7.3,<br>Control: 6.8, P=.09 |
| Schmidt-Mende, 2017[95]<br>n=119,910<br>9 months | Provider and nurse education/feedback | Medium | Risk difference: number of subjects on ≥ 10 medications: -0.1 (95% CI: -0.5 to 0.3) |

CI=confidence interval

*Reduction in Potentially Inappropriate Medications (k=9):* As shown in Table 6, 9 trials reported potentially inappropriate medications (PIMs) using the MAI or pre-defined lists. Six trials found a significant reduction in PIMs due to education and provider feedback as measured by varying definitions of PIM reduction.

**Table 6. Potentially Inappropriate Medications at Follow-up – Education Studies**

| Author Number enrolled Length of follow-up | Intervention | Risk of Bias | PIMs at Follow-up |
|---|---|---|---|
| Bregnhoj, 2009[21] n=212 12 months | Provider education or provider education plus feedback vs usual care | Medium | 5-point reduction (*ie,* improvement) in MAI in combined intervention group (95% CI: -7.3 to -2.6); no change in other groups |
| Coleman, 1999,[28] n=169 24 months | Patient education in chronic care clinic | Medium | Mean number of high-risk medications at 24 months: Intervention: 1.86, Control: 2.54, P=.17 |
| Jager, 2017[112] n=273 9 months | Patient education and provider education/feedback | Low | Risk difference between groups in number of subjects with ≥1 PIM per year: 0.9 (0.4 to 2.0) |
| Martin, 2018[64] n=489 6 months | In-person or mailed brochures on harms of targeted medications and for sedative-hypnotics, a visual tapering protocol; providers received a "pharmaceutical opinion" | Low | Complete cessation of fills for targeted drugs: Intervention: 43%, Control: 12% (risk difference 31%, 95% CI: 23 to 38). |
| Pimlott,2003[77] n=374 6 months | Provider education/feedback focus on benzodiazepines | Medium | Change in number of benzodiazepine prescriptions: Intervention: -0.7%, Control: +1.1%, P=.036 |
| Rognstadt, 2013[89] n=81,810 12 months | Provider education and feedback | Low | PIMs per 100 patients decreased by 12% (95% CI: 16.8% to 6.9%), intervention vs control |
| Schmidt-Mende, 2017[95] n=119,910 9 months | Provider and nurse education/feedback | Medium | Risk difference in number on ≥10 medications: -0.1 (95% CI: -0.5 to 0.3) |
| Simon, 2006[97] n=50,924 18 months | Provider education and EHR alerts vs alerts alone | Medium | Decrease of 19.7 medications per 10,000 members (Intervention) vs 13.0 (Control), P=.52 |
| Tannenbaum, 2014[115] n=303 6 months | Mailed personalized information to patients on the harms of benzodiazepines and a recommendation for tapering | Low | Benzodiazepine discontinuation: Intervention: 27%, Control: 5% (risk difference 23%, 95% CI: 14% to 32%). |

CI=confidence interval; EHR=electronic health record; MAI=Medication Appropriateness Index; PIM=potentially inappropriate medication

*Secondary Outcomes – Acute Care Visits and Costs*

*Acute Care Visits:* Neither of the 2 studies that reported frequency of acute care encounters found any difference between intervention and control groups.[28,95]

*Costs:* The only study to report costs found no difference between intervention and control groups in total health care costs per year.[28]

## Computer Decision Support Interventions (κ=4)

*Summary of Findings*

None of the 4 trials reported primary outcomes.

Two of the 4 trials reported that the intervention resulted in fewer PIMs. The 2 negative studies may have been underpowered to detect a difference; both had shorter duration of follow-up (13 weeks and 16 weeks) than the positive studies (12 and 13 months).

*Overview of Studies*

We included 4 trials that evaluated the effect of a computer decision support intervention.[37,83,84,100] Two trials were conducted in the US[37,84] and 2 in Canada.[83,100] Sample sizes ranged from 128 to 59,680 patients and study periods ranged from 90 days to 13 months. Demographic characteristics of the enrolled patients are shown in Appendix D, Table 15. All 4 trials were considered medium risk of bias (Appendix D, Table 16). In all 4 trials reduction in potentially inappropriate prescriptions was the only outcome reported (Appendix D, Tables 17 and 18).

*Primary Outcomes*

None reported.

*Secondary Outcomes – Medication Changes*

Two of the 4 trials reported a reduction of PIMs in the intervention compared to the control group.

A Canadian cluster randomized trial tested an EHR-based alert system that notified primary care physicians (n=28) providing office-based care to patients age ≥65 of potentially inappropriate prescriptions. The control group was usual care. At 16 weeks of follow-up, there was no difference in frequency of PIMs between intervention and control groups: 0.1% increase in number of PIMs in both groups.[83]

A trial conducted in the VA Connecticut Health Care system enrolled 156 people age ≥65 taking 7 or more medications. The intervention was an HER-based system called Tool to Reduce Inappropriate Medications (TRIM) that identifies PIMs from standard EHR data and input from a telephonic patient assessment; it then generates a patient-specific feedback report and sends it to the prescribing physician. One control group received the intervention *without* the patient-specific feedback report and another control group was usual care. The primary outcome of the study was a patient assessment of the quality of both communication and shared decision-making between patient and provider. At 90 days there was no difference between the intervention and control group in the number of prescribed medications (13.3 vs 13.8, P=.65).[37]

A Canadian cluster randomized controlled trial included 107 primary care physicians and 12,560 of their patients age >65 years. The intervention was a computer decision support system which

alerted the physician to any of 26 prescribing problems, including drug-drug interactions, drug-age contraindications, drug-disease contraindications, and therapeutic duplications. The control group providers were given the same computer hardware and software as the intervention providers, but the software did not generate alerts. At 13 months of follow-up, the number of new PIMs per 1000 visits was lower in the intervention than the control group (RR 0.82, 95%CI: 0.69 to 0.98).[100]

A US trial included 59,680 members of the Kaiser Permanente health care system age ≥65. The intervention was a triggered alert in the EHR when a patient was prescribed 1 of 11 medications considered potentially inappropriate for older adults. The control group was usual care. At 12 months of follow-up there were fewer newly dispensed prescriptions for the targeted medications in the intervention compared to the control group (1.8% vs 2.2%, P=.002).[84]

### Hybrid/Other Interventions (κ=3)

#### Overview of Studies

We included 3 trials in this category because they either included interventions from at least 2 of the 3 other categories or were not otherwise classifiable. In all 3 trials the comparison group was usual care. The trials were conducted in Finland,[57,87] Ireland,[26,27,41] and Australia.[78] A total of 1683 patients were followed for 12 months (Appendix D, Table 19). One trial was considered low risk of bias and 2 were considered medium risk (Appendix D, Table 20).

A low risk of bias cluster RCT (OPTI-SCRIPT) conducted in Ireland enrolled 190 people age ≥ 70 from 21 practices. The intervention combined CMR and a computer-based intervention. It included a 30-minute visit by a pharmacist with the physicians that focused on medication reviews and PIMs; a medication review by each physician with web-based pharmaceutical algorithms that identified PIMs and offered alternatives; and provision of patient information on the relevant PIMs and the alternatives.[26,27,41]

An Australian cluster RCT (medium risk of bias) enrolled 20 general practitioners and 849 patients age ≥65. The intervention included provider education and feedback delivered by a pharmacist at 2 meetings for which physicians were reimbursed; a medication risk assessment completed by patients; and a medication review checklist for at-risk patients for which physicians were compensated after completing 10 reviews. The primary outcome was a composite score reflecting the use of benzodiazepines, NSAIDs, and thiazides.[78]

A population-based medium risk of bias trial in Finland randomized 644 home-dwelling people age ≥75 to either a comprehensive geriatric assessment intervention or control. The geriatric assessment (a clinical examination, lab tests, and medication reviews) was conducted by 2 physicians, 2 nurses, 2 physiotherapists, and a nutritionist.[57,87]

#### Primary Outcomes

Primary outcomes reported were all-cause mortality, falls, and health-related quality of life (Appendix D, Table 21-22).

*All-cause Mortality:* Reported in 1 trial, there were 2 deaths in both the intervention and control groups at 6 months.[26,27,41]

*Falls:* The 1 trial that evaluated falls found that at 12 months of follow-up, the intervention group had fewer falls (20% vs 30%, OR 0.61, 95% CI: 0.41 to 0.91); fall-related injuries (10% vs 18%, OR 0.56, 95%CI: 0.32 to 0.96); and falls requiring medical attention (6% vs 13%, OR 0.46, 95% CI: 0.30 to 0.70).[78]

*Health-related Quality of Life:* The 2 trials that evaluated quality of life found no differences between intervention and control groups.[26,27,41,78]

*Secondary Outcomes – Medication Changes*

All 3 trials reported at least 1 medication outcome, and noted an improvement in medication prescribing, as summarized below (Table 7) (Appendix D, Tables 24 and 25).

**Table 7. Medication Change Outcomes – Hybrid/Other Studies**

| Author Number enrolled Length of follow-up | Findings |
|---|---|
| Clyne, 2015, 2016[26,27] n=190 12 months | Intervention group patients were less likely to be taking a PIM than control patients (OR 0.32, 95% CI: 0.15 to 0.70, P=.02) |
| Lampela, 2010[57] Rikala 2011[87] n=644 12 months | Subjects in the intervention group were more likely to have changes to their medication regimen (84%) than those in the control group (73%) (OR 1.9, 95% CI: 1.3 to 2.8) |
| Pit, 2007[78] n=849 4 months | The intervention group was more likely to have an improved medication use composite score compared to control (OR 1.86, 95% CI: 1.21 to 2.85) (composite score reflected use of benzodiazepines, NSAIDs, and thiazide diuretics) |

CI=confidence interval; NSAID=non-steroidal anti-inflammatory drug; OR=odds ratio; PIM=potentially inappropriate medication

*Certainty of Evidence for Key Question 1 – Community or Primary Care Studies*

Table 8 summarizes the certainty of evidence for critical outcomes in studies comparing CMR to usual care. We found moderate certainty of evidence that CMR interventions probably result in little to no difference in hospitalizations and low certainty of evidence that CMR interventions may reduce by a small amount or make no difference in all-cause mortality, a slight reduction to no difference in falls, and little to no difference in quality of life measures. Delirium, adverse drug withdrawal events, and major adverse cardiovascular events were not reported in the CMR studies.

For education interventions (Table 9), we found moderate certainty of evidence that the education interventions probably result in little to no difference in all-cause mortality or hospitalizations and low certainty of evidence that education intervention may result in little to no difference in quality of life measures or falls. Delirium, adverse drug withdrawal events, and major adverse cardiovascular events were not reported in the education studies.

We did not assess certainty of evidence for the computer decision support or hybrid interventions due to the small number of studies and heterogeneity of the interventions.

**Table 8. Certainty of Evidence for Comprehensive Medication Review Interventions Compared to Usual Care in Elderly Populations**

| Outcome № of participants (studies) | Relative effect (95% CI) | Anticipated absolute effects (95% CI) | | | Certainty | What happens |
|---|---|---|---|---|---|---|
| | | Usual Care | Deprescribing-Medication Review | Difference | | |
| **All-cause Mortality** follow-up: range 1 to 24 months № of participants: 4495 (12 trials; 11 RCTs pooled n=3875; 1 CRCT n=620) | *RCT* **Peto OR 0.79** (0.58 to 1.08) | 4.7% | **3.7%** (2.8 to 5) | RCT **0.9% fewer** (1.9 fewer to 0.4 more) | ⊕⊕◯◯ LOW [a,b] | Deprescribing interventions based on Medication Review may reduce by a small amount or make no difference in all-cause mortality. |
| | *CRCT\** **Peto OR 0.57** (0.27 to 1.23) | 6.8% | **4.8%** (1.9 to 8.2) | | | |
| **Hospitalizations** ( ≥1 admission) follow-up: range 3 to 24 months № of participants: 2411 (6 RCTs pooled). | **RR 1.07** (0.92 to 1.26) | 19.8% | **21.2%** (19 to 25.9) | **1.4% more** (1.6 fewer to 5.1 more) | ⊕⊕⊕◯ MODERATE [a] | Deprescribing interventions based on Medication Review probably result 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 № of participants: 3893 (11 trials) | | - | - | - | Most trials reported no differences between groups in QoL measures. | ⊕⊕◯◯ LOW [a,c] | Deprescribing interventions based on Medication Review may result in little to no difference in quality of life measures. |
| **Falls** follow-up: range 3 to 15 months № of participants: 1613 (4 trials; 3 RCTs n=993; 1 CRCT n=620) | *RCT* NA | Range 11-33% | Range 12-37% | Risk differences (range) 1% to 11% | ⊕⊕◯◯ LOW [a,b] | Deprescribing interventions based on Medication Review may result in a slight reduction to no difference in falls. |
| | *CRCT* OR 0.38 (CI NR) | Ranges over time intervals 10-19% | Ranges over time intervals 9-15% | Risk differences (range) - 7% to 1% | | |

**Delirium** - not reported

**Adverse Drug Withdrawal Events** - not reported

**Major Adverse Cardiovascular Events (MACE)** - not reported

**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
Explanations
a. Downgraded for study limitations (medium risk of bias)
b. Downgraded for imprecision (wide confidence intervals)
c. Although nearly all trials reported no significant difference between groups the estimated standardized mean differences exhibited wide confidence intervals
* Not adjusted for cluster design, estimate of the intracluster correlation coefficient (ICC) not provided by trial

**Table 9. Certainty of Evidence for Education Interventions Compared to Usual Care in Elderly Populations**

| Outcome № 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 № of participants: 121,124 (5 CRCTs) | - | Range 1-16% | Range 0.6-16% | Risk differences (range) -1% to 5% Largest study (n=119,910) reported 0.1% (95%CI -0.1 to 0.6) | ⊕⊕⊕◯ MODERATE a | Deprescribing interventions based on Education probably result in little to no difference in all-cause mortality. |
| **Hospitalizations** (≥1 admission) Follow-up: range 9 months № of participants: 119,910 (1 CRCT); 1 other trial (n=169) reported >1 hospitalization in frail high-risk participants (NS between group)) | NA | 12.6% | 12.8% | 0.2% (95%CI -0.8 to 1.2) | ⊕⊕⊕◯ MODERATE a | Deprescribing interventions based on Education probably result in little to no difference in hospitalization. |
| **Quality of Life Measures (QoL)** assessed with: EQ-5D Follow-up: range 15 months № of participants: 601 (1 CRCT) | - | 0.01 | -0.02 | SMD -0.10 (95% CI -0.26 to 0.06) | ⊕⊕◯◯ LOW a,b | Deprescribing interventions based on Education may result in little to no difference in quality of life measures. |
| **Falls** Follow-up: range 24 months № of participants: 169 (1 CRCT) | | Ranges over time intervals 36-38% | Ranges over time intervals 44% | Risk differences (range) 6% to 8% | ⊕⊕◯◯ LOW a,b | Deprescribing interventions based on Education may result in little to no difference in falls. |

**Delirium** - not reported

**Adverse Drug Withdrawal Events** - not reported

**Major Adverse Cardiovascular Events (MACE)** - not reported

**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
Explanations
a. Downgraded for study limitations (medium risk of bias)
b. Downgraded for imprecision

## KQ 1A: What are the identified elements/components that contribute the most to the effectiveness of deprescribing interventions?

We did not identify any studies that explicitly addressed this question. However, as described above, it appears that performance feedback to providers improves the effectiveness of educational interventions and that follow-up interventions such as phone calls or clinic visits may improve the effectiveness of comprehensive medication reviews.

## KQ 1B: Do the effectiveness, comparative effectiveness, and harms of deprescribing interventions vary by patient population, provider factors, or setting?

The included studies were very similar with respect to patient population (older adults taking multiple medications and living in the community) and setting (primary care clinics). Only 1 study explicitly analyzed the effect of provider factors on intervention effectiveness. This Norwegian study of a provider education and feedback intervention reported that physician factors associated with prescribing improvements included age 57-68 years, advanced training in primary care, and working in solo practices.[89,113]

Eleven studies reported the effect of the intervention on use of psychotropic medications, as shown in Table 10. None of the CMR studies (k=3) or the hybrid/other studies (k=3) found an intervention effect, but 4 of 5 trials of an educational intervention reported a reduction in psychotropic use at follow-up.

**Table 10. Deprescribing of Psychotropic Medications**

| Study Risk of bias/Number enrolled | Targeted Medications | Results: Intervention vs Control |
|---|---|---|
| *Comprehensive Medication Review* | | |
| Weber, 2008[107] Medium/620 | "psychotropics" | No difference in use at 15 months |
| Van der Meer, 2018[105] Medium/157 | "psycholeptics/ psychoanaleptics" | No difference in "anticholinergic/sedative load" at 3 months |
| Meredith, 2002[67] Low/259 | "psychotropics" | No difference at 6-12 weeks |

| Study Risk of bias/Number enrolled | Targeted Medications | Results: Intervention vs Control |
|---|---|---|
| *Education (Provider and Patient Directed)* | | |
| Martin, 2018[64] Low/489 | "sedatives/hypnotics" | At 6 months absolute risk difference was 34% (95% CI: 25 to 43%) favoring Intervention |
| Pimlott, 2003[77] Medium/374 | Benzodiazepines | % change in mean number of prescriptions at 6 months: Intervention: -0.7%, Control: +1.1%, P=.036. |
| Rognstad, 2013, 2018[89,113] Low/81,000 | Tricyclics, Antipsychotics, Benzodiazepines | Drug        Unadjusted % change (95% CI) <br> Tricyclics:      -17.1 (-19.3 to -14.9) <br> Antipsychotics:      -24.7 (-27.7 to -21.7) <br> Benzodiazepines: -5.7 (-6.7 to -4.7) |
| Simon, 2006[97] Medium/50,924 | Benzodiazepines, Tricyclics | "no apparent effect of the intervention on rates of target medication use" |
| Tannenbaum, 2014[115] Low/303 | Benzodiazepines | At 6 months, risk difference 23% (95% CI: 14% to 32%) favoring Intervention |
| *Hybrid/Other* | | |
| Clyne, 2015, 2016[26,27] Low/190 | Benzodiazepines | Use at 4-6 months in intervention vs control group: OR: 1.31 (95% CI:0.47 to 3.68) |
| Lampela, 2010[57] Rikala, 2011[87] Medium/644 | "psychotropics" | No difference between groups at 1 year |
| Pit, 2007[78] Medium/659 | Benzodiazepines | Use at 1 year in intervention vs control group: OR: 0.65 (95% CI: 0.27 to 1.57) |

CI=confidence interval; OR=odds ratio

## KEY QUESTION 2: What are the identified facilitators and barriers that impact the implementation of deprescribing interventions within large-scale health systems such as VA?

We identified 9 studies that reported on facilitators and barriers that impact implementation of deprescribing interventions in large-scale health systems (*eg*, VHA, other integrated care delivery organizations, government health authorities) (Appendix D, Table 27). Of these, 5 studies were from community/primary care settings[125,126,128-130] including 1 in VA,[129] 1 from a large integrated health care delivery system in the US,[126] 1 from primary care practices in Germany affiliated with a large health insurer,[130] and 2 from regional health authorities in Europe.[125,128] All of the deprescribing interventions in community/primary care settings focused on CMR. One study targeted non-benzodiazepine sedative-hypnotic medications (Z-drugs)[126] while the remaining studies focused on medications more broadly.

Three of the 9 identified studies were conducted in nursing homes in either Canada,[124] Europe,[122,127] or Australia.[123] Two of these involved educational interventions[122,124,127] and 1 involved CMR.[123] Two were focused on anti-psychotic medications.[122,124,127]

The ninth identified study was conducted in an Emergency Department setting within VA.[131] The intervention was multicomponent and included geriatric order sets.

Information on barriers and facilitators was collected via interviews, focus groups, or surveys with prescribers and staff members. Two studies also included patients/nursing home residents as respondents.[123,126] The number of individuals who participated in an interview, focus group, or survey pertaining to barriers/facilitators was fewer than 25 in 7 of the studies. Appendix Table 28 contains information on barriers and facilitators identified in each study.

## Patient Perspective

Two studies reported patient perspectives, a study from the US of a medication review intervention to encourage deprescribing of Z-drugs[126] and a nursing home study from Australia (Table 11).[123]

**Table 11. Patient-Reported Facilitators and Barriers to Implementing a Deprescribing Intervention in Primary Care**

| Facilitators | Barriers |
|---|---|
| <ul><li>Treat patients as individuals</li><li>Providing education about safer alternatives to current medication regimen</li><li>Improve quality of prescribing by addressing costs of medication and difficulties associated with taking medications (*eg*, size, texture, taste)</li></ul> | <ul><li>Patients did not identify with patient stories presented in education materials they received</li><li>Deprescribing not emphasized by providers</li><li>Not provided with alternatives to current medication regimen</li></ul> |

## Prescriber Perspective

*Comprehensive Medication Review*

Table 12 summarizes findings from 5 studies that assessed prescriber perspectives following implementation of CMR in primary care settings.[125,126,128-130] The 1 study conducted within VA obtained feedback following a quality improvement initiative in 4 rural outpatient clinics.[129] Another US-based study focused on inappropriate prescribing of Z-drugs.[126]

**Table 12. Prescriber-Reported Facilitators and Barriers to Implementation of Comprehensive Medication Review as a Deprescribing Intervention in Primary Care**

| Facilitators | Barriers |
|---|---|
| <ul><li>Development of work routines for implementing the intervention recommendations</li><li>Collaboration involving all key individuals (including patients and the public)</li><li>Better use of skills available within a practice (including optimal use of practice pharmacists)</li><li>Shared electronic medical records and prescribing tools</li><li>Shared learning with interprofessional team within a practice</li><li>Education (for prescribers) on geriatric prescribing</li><li>Shared evidence on inappropriate polypharmacy to increase awareness</li></ul> | <ul><li>Too many checklists and guidelines (feasibility, time, impede individual care for patient, 'question' provider competence)</li><li>Prescriber lack of knowledge</li><li>Prescriber difficulty attending outside workshops</li><li>Changes in trade names of medications</li><li>Lack of availability of clinical pharmacists</li><li>Lack of team (*ie*, multiprofessional collaboration)</li><li>Skepticism towards physician/pharmacist collaboration</li><li>Prescriber lack of belief in need for medication reviews (*ie,* prescribe correctly from the start)</li><li>Potentially providing too much information to patients on medications and side effects</li></ul> |

- Patient materials designed to improve self-management abilities
- Home visits for medication review consultations
- Templates for standardized medication lists
- Financial support to hire clinical pharmacists
- Financial support for research and innovation
- Protected time for polypharmacy medication review consultations
- Individualized feedback forms for prescribers with PIM prescribing information

- ('unsettling' for patients, counter to patient satisfaction goals)
- Patients reluctance to give up medications (dependence, long-term users don't identify with the safety concerns)
- Lack of continuity in healthcare
- Lack of institutional support and resources
- Inadequate time for medication review
- Inadequate time to access online resources
- Tools for medication review not integrated into practice software

An Australian study from nursing home settings identified inflexible work practices and legislative requirements, a 'plethora' of documentation, lack of standardized procedures, untrained or lack or qualified staff, time pressures, and the complexity of facility resident case mix and available medications as barriers to implementation of an intervention focused on quality use of medicines.[123] Teamwork, communication and effective information exchange, use of information technology, mutual respect and trust of others, qualified and educated staff, and continuing education were identified as facilitators of implementation.

### Education

Two nursing home-based studies, both focused on appropriate prescribing of anti-psychotic medications, reported on implementation of education interventions.[122,124,127] Both studies identified barriers related to time and resources. The study from the United Kingdom cited multiple levels of management contributing to communication problems, unclear expectations, and uncertainty about roles as well as confusion about the organizational aims when the program being implemented conflicts with other organizational elements.[122,127] The study from Canada similarly identified potential for competing priorities when deprescribing initiatives conflict with established care.[124] Both studies also noted external pressures in working with residents, families, and prescribers or with the public perception of deprescribing where the focus may be on adverse consequences of deprescribing. The skill of the individuals involved in introducing and implementing the intervention was cited by both studies as a facilitator. Critical skills included credibility (knowledge, understanding of context, confidence), listening, communication (team building, relationships with colleagues), and adaptability. The study from Canada also cited direct involvement of administrators, physicians, pharmacists, and front-line staff with implementation leaders as a facilitator.

### Computer Decision Support

A VA study of computer decision support in the emergency department identified several barriers to implementation including loss of autonomy (*ie*, desire to make prescribing decisions based on medical experience) and comfort level with existing order menus and prescribing reminders already posted in the facility.[131] Those actively using the system (including those who used computerized geriatric order sets at least once as well as those using order sets at least once per shift) reported that time needed to learn the system was a barrier and cited non-intuitive navigation and the need to change prescribing behavior. However, several facilitators were also identified, including potential for improved safety (*ie*, reducing the risk of adverse events) and

efficiency (*ie,* saving time). Some providers viewed the intervention as a resource for information and as a tool that would be useful for training other providers. Among active users of the system, the location of the geriatric order sets within the emergency department orders, the categorical organization, and the prepopulated fields were facilitating factors.

## Summary of Findings

Nine studies assessed barriers or facilitators of implementing a deprescribing intervention in a large health care system as part of the implementation process. All reported on provider perspectives; 2 reported patient perspectives. Barriers and facilitators of implementation included patient, provider, and system factors.

# SUMMARY AND DISCUSSION

This systematic review determined the effectiveness of deprescribing interventions designed to mitigate the adverse effects of polypharmacy and use of inappropriate medications in older community-dwelling Veterans. The results of this review are intended to inform the development and implementation of deprescribing initiatives within VA. We focus our discussion on the most commonly reported primary outcomes (falls, hospital admissions, health-related quality of life, all-cause mortality) and reduction in PIMs, a secondary outcome judged important to our nominators, technical panel members, and this review team.

Our 2 key questions were:

KQ1: What is the effectiveness, comparative effectiveness, and harms of deprescribing interventions among adults age 65 and older?

> KQ1a: What are the identified elements/components that contribute the most to the effectiveness of deprescribing interventions?

> KQ1b: Do the effectiveness, comparative effectiveness, and harms of deprescribing interventions vary by patient population, provider factors, or setting?

KQ2: What are the identified facilitators and barriers that impact the implementation of deprescribing interventions within large-scale health systems such as VA?

## SUMMARY OF EVIDENCE AND CERTAINTY OF EVIDENCE BY KEY QUESTION

### Key Question 1

We identified 38 trials (12 RCTs, 26 cluster RCTs) in community and primary care settings that met our inclusion criteria and were rated as low or medium risk of bias. We divided the trials into 4 intervention categories: comprehensive medication review (CMR) (k=21), education (k=10), computer-based (k=4), and hybrid/other (k=3). Almost all trials compared the intervention to a usual care control.

*Key Messages*:

- Comprehensive Medication Review may reduce all-cause mortality (low certainty of evidence), potentially inappropriate medications, and costs compared to usual care.

- Education (Provider and Patient Directed)

    o A direct-to-consumer patient engagement program with targeted educational material provided directly to patients may reduce PIMs.

    o Provider education without feedback had no significant effect on outcomes; however, when coupled with patient-specific feedback to the provider, it may reduce PIMs.

- Computer Decision Support, such as with electronic health record alerts and other clinical decision support systems, may reduce PIMs.

- Hybrid/Other Interventions may reduce falls and PIMs.

- There was no evidence of harms (adverse drug withdrawal events, worsening of medical conditions, or increased mortality, hospitalizations, or major adverse cardiovascular events) associated with any of the deprescribing interventions.

- No studies addressed the comparative effectiveness of the deprescribing interventions either within or across categories.

- Most studies were not designed to assess mortality, hospitalizations, delirium, falls, or major adverse cardiovascular events and no studies reported on biomarker measures such as glycemic or blood pressure control.

*Comprehensive Medication Review (CMR), k=21*

The CMR interventions were generally led by a pharmacist and included chart review, patient interview, and provider consultation, culminating in recommendations for medication regimen changes to a physician. Nine trials included a follow-up intervention with patients to reinforce the recommendations, such as home-care visits by nurses or telephone calls by pharmacists. We judged the risk of bias to be low in 5 trials and medium in 16. Outcomes were reported on about 8000 patients, with study sample sizes ranging from 25 to 1403.

*All-cause Mortality:* Pooled data on 3875 enrollees in 11 trials indicate that CMR may reduce all-cause mortality by about 20% (OR 0.79, 95% CI: 0.58 to 1.08, $I^2$ =0). Certainty of evidence was low.

*Falls*: Three of 4 studies reporting falls found no difference between the CMR intervention and the control group. The studies were not considered suitable for pooling. Certainty of evidence was low.

*Hospitalizations:* None of the 12 trials reporting hospitalizations found an intervention effect. Results of the 6 studies suitable for pooling showed that compared to control, the CMR interventions had no effect on number of participants with 1 or more unplanned hospital admission during follow-up (RR 1.07, 95% CI: 0.92 to 1.26, $I^2$=12%). Certainty of evidence was moderate.

*Health-related Quality of Life:* Nine of the 11 trials that reported a quality of life outcome found no differences between the CMR and the control intervention. The studies were not considered suitable for pooling. Certainty of evidence was low.

*Medication Changes:* Nineteen trials reported at least 1 medication change measure: 12 reported reduction in potentially inappropriate medication use; 2 in drug-related problems, and 5 in total number of medications. Twelve of the 19 trials (63%) found that, compared to control, the CMR intervention resulted in a reduction in 1 or more of these outcomes. The studies were not considered suitable for pooling. In the 5 trials in which standardized mean differences could be calculated, the intervention effect was moderate in 2, small in 1, and less than small in 2.

There were no differences between the negative and positive studies with respect to length of follow-up, risk of bias, enrollee demographics, or country. However, in 5 of the 12 positive studies (42%), the protocol included additional follow-up with the patient after the initial CMR. Only 2 of the 7 negative studies (29%) included such follow-up.

*Health Care Costs:* Of the 7 studies reporting a cost outcome, 3 reported no difference between intervention and control groups (2 of these studies reported medication costs only and 1 reported a cost-utility analysis); 1 reported a cost benefit analysis suggesting that the CMR intervention was cost-effective. The other 3 studies evaluated both medication costs and costs of implementing the CMR intervention: 1 reported no net difference in costs between intervention and control groups; 1 reported that costs increased in both intervention and control groups, but the net increase was smaller in the intervention group; and 1 reported that the costs decreased in both groups but the net decrease was larger in the intervention group.

*Education Interventions, k=10*

We identified 10 trials that evaluated the effect of educational interventions directed at either patients (k=1), providers (k=5), or both (k=4). The control groups were assigned either usual care (k=8) or a sham intervention (*ie,* targeting drugs that were not of interest, k=2). We judged the risk of bias to be low in half the trials and medium in the other half. Outcomes were reported on a total of 2424 patients in the 7 smaller trials and on 252,684 in the 3 larger trials.

*All-cause mortality:*  All-cause mortality was reported in 5 trials (n=121,124). None of the trials reported a difference between intervention and control groups. The data were not suitable for pooling. Certainty of evidence was moderate.

*Falls:* In the only trial that reported falls, there was no difference between intervention and control groups. Certainty of evidence was low.

*Hospitalizations:* Three of the 4 trials that reported hospitalizations found no difference between intervention and control groups. The data were not considered suitable for pooling. Certainty of evidence was moderate.

*Health-related Quality of Life:* The 2 trials that reported a quality of life measure found no difference between intervention and control groups. Certainty of evidence was low.

*Medication Changes:* Nine trials reported potentially inappropriate medications (PIMs). Six found that compared to control, the intervention was associated with fewer PIMs at the end of the study. The interventions used in these 6 studies were: a direct-to-consumer patient engagement program with targeted educational material mailed directly to patients (k=2 low risk of bias trials); provider education plus feedback (k=2, 1 low, 1 med risk of bias); and patient education with provider education plus feedback (k=2, 1 low, 1 med risk of bias). The 2 studies testing provider education alone did not report an effect on PIMs.

*Computer Decision Support Interventions k=4*

We identified 4 trials that evaluated the effect of a computer-based intervention. Samples sizes ranged from 128 to 59,680 patients and study periods ranged from 90 days to 13 months. All 4

trials were considered medium risk of bias. In all 4 trials reduction in potentially inappropriate prescriptions was the only outcome reported.

Two of the 4 trials reported that the intervention resulted in fewer PIMs. The negative studies may have been underpowered to detect a difference; both had shorter duration of follow-up (13 weeks and 16 weeks) than the positive studies (12 and 13 months).

*Hybrid/Other Interventions k=3*

We classified 3 trials as hybrid because they included interventions from at least 2 of the 3 other categories. In all 3 trials the comparison group was usual care. A total of 1683 patients were followed for 12 months. One trial was considered low risk of bias and 2 were considered medium risk. All 3 studies focused on psychotropic medications.

*All-cause Mortality:* All-cause mortality was reported in 1 trial: there were 2 deaths in both the intervention and control groups.

*Falls:* The only trial that evaluated falls found that at 12 months of follow-up, the intervention group had significantly fewer falls, fall-related injuries, and falls requiring medical attention. The multicomponent intervention in this medium risk of bias Australian trial included provider education and feedback, comprehensive medication review, and physician reimbursement.

*Health-related Quality of Life:* The 2 trials that evaluated quality of life found no differences between intervention and control groups.

*Medication Changes:* All 3 trials reported medication regimen improvements in the intervention compared with the control groups.

## KQ1a: What are the identified elements/components that contribute the most to the effectiveness of deprescribing interventions?

We did not identify any studies that explicitly addressed this question. However, as described above, it appears that patient-specific performance feedback to providers improves the effectiveness of educational interventions and that follow-up interventions such as phone calls or clinic visits with patients may improve the effectiveness of comprehensive medication reviews.

## KQ1b: Do the effectiveness, comparative effectiveness, and harms of deprescribing interventions vary by patient population, provider factors, or setting?

The included studies were very similar with respect to patient population (older adults taking multiple medications and living in the community) and setting (primary care clinics). Only 1 study explicitly analyzed the effect of provider factors on intervention effectiveness. This Norwegian study of a provider education and feedback intervention reported that physician factors associated with prescribing improvements included age 57-68, advanced training in primary care, and working in solo practices**.**

Eleven studies reported the effect of the intervention on use of psychotropic medications. None of the CMR studies (k=3) or the hybrid/other studies (k=3) found an intervention effect, but 4 of 5 trials of an educational intervention reported a reduction in psychotropic use at follow-up.

Fourteen of the 21 trials that compared a CMR intervention to usual care reported that the intervention resulted in at least 1 favorable outcome. Compared to the 7 trials that did not report an intervention effect, these trials were more likely to have follow-up times of less than 1 year (64% vs 43%) and to have included an additional intervention (*eg,* patient call or visit) during follow-up (50% vs 14%). Otherwise there did not appear to be any systematic differences between the positive and negative studies with respect to country, sample size, risk of bias, or characteristics of the enrollees or the interventions.

## Recent Systematic Reviews

None of the systematic reviews we identified used the same inclusion/exclusion criteria or reported results by the intervention categories that we used. Nevertheless, most of these reviews reported results generally consistent with our findings.

*All-cause Mortality:* A recent systematic review of observational and experimental studies (k=132) evaluated the effect of any type of deprescribing intervention in people age ≥65 in any setting. The review's primary outcome was all-cause mortality. Deprescribing was associated with decreased mortality in both randomized (OR 0.82, 95% CI: 0.61 to 1.11) and non-randomized studies (OR 0.32, 95% CI: 0.17 to 0.60). Interventions that were patient-specific were more effective than generalized educational programs.[132] Another review of RCTs and CCTs that evaluated any deprescribing intervention in any setting reported an OR of 1.02 (95% CI: 0.84 to 1.23).[133] The effect size and confidence intervals from these reviews are very similar to what we found in our CMR trials.

*Falls:* In the systematic review described above, Page et al reported that deprescribing did not have a significant effect on risk of 1 or more falls (OR 0.65, 95% CI: 0.40 to 1.05).[132] This was based on pooled results from 5 RCTs; half the participants were nursing home residents.

*Hospitalizations:* At least 3 other systematic reviews reported the effect of deprescribing interventions on hospital admissions. A Cochrane review that included several different study designs (trials, controlled before-after, and interrupted time-series) concluded, based on data from 12 studies, that "pharmaceutical care [*ie,* CMR] may make little or no difference in hospital admissions".[134] A systematic review that included RCTs and CCTs of any deprescribing intervention in any setting was unable to pool hospitalization outcomes; most of the identified studies found no intervention effect.[133]

A very recent systematic review of 4 RCTs that evaluated community pharmacist-led medication review programs reported that the intervention had a significant impact on emergency department visits (RR 0.68, 95% CI: 0.48 to 0.96) and may have led to fewer hospitalizations (RR 0.88, 95% CI: 0.78 to 1.00). Only 1 of these 4 studies was included in the present review.[135]

*Health-related Quality of Life:* The Cochrane review concluded that "pharmaceutical care may make little or no difference" in quality of life based on 12 studies that were not deemed suitable for pooling.[134] The review of the 4 RCTs of community pharmacist-led medication review programs found mixed results among the 3 trials that reported quality of life outcomes.[135] Page et al reported that only 1 of 18 trials reported an intervention effect on quality of life.[132]

*Medication Changes:* The Cochrane review reported number of enrollees on 1 or more PIMs at the end of the study (k=11) and concluded that subjects in the deprescribing interventions group were less likely to be on a PIM than the control group (RR 0.79 95% CI: 0.61 to 1.02, $I^2$=85%).[134] Page et al reported pooled results from 3 studies with 839 subjects; compared to the control conditions, deprescribing reduced the number of inappropriate medications (mean difference -0.49, 95% CI: -0.7 to -0.28).[132]

## Key Question 2: What are the identified facilitators and barriers that impact the implementation of deprescribing interventions within large-scale health systems such as VA?

We included 9 studies that assessed barriers and facilitators of implementing a deprescribing intervention in a large health care system as part of the implementation process. Five of the studies were from community/primary care settings, 3 from nursing homes, and 1 from an emergency department. Interventions included CMR (6 studies), education (2 studies), and computer decision support (1 study). In most studies, fewer than 25 prescribers or others involved with the intervention were interviewed following implementation. Two studies also sought input from either patients or nursing home residents.

### *Key Messages*

- Few studies assessed barriers or facilitators of implementation meeting eligibility for inclusion in our review. The perspective of patients/nursing home residents or family members was only assessed in 2 of 9 studies.

- Barriers and facilitators of implementation of CMR, educational, and computer decision support deprescribing interventions included patient (*eg,* concerns about safety of alternative medication regimens, reluctance to give up medications), prescriber (*eg*, lack of knowledge, not believing in need for CMR), and system factors (*eg*, lack of institutional support and resources, inadequate time).

Although we found few studies conducted in the context of a specific deprescribing intervention, several recent papers have reported on barriers to and facilitators of deprescribing. To determine patient perspectives on deprescribing, interviews and focus groups were conducted with 27 US Veterans.[136] Few of the participants had discussed discontinuation of medications with their provider. Patients expressed conflicting views of medication. They would like to take fewer medications but were concerned about possible adverse consequences if the medications were discontinued. They also noted the importance of their relationship with their provider. Many commented that they trust their provider and rely on his/her expertise while others expressed a desire for more information about their medications (why they were taking them, possible harms) and more involvement in decision-making.

A 2013 systematic review of 21 studies identified patient barriers and facilitators.[137] Patients who had noted an improvement in their condition when they started a medication (or hoped for an improvement in the future) were reluctant to discontinue the medication. Conversely, if they felt the medication was no longer needed, perceived a lack of effectiveness, were concerned about side effects or addiction, or mistrusted the initial prescriber, they were more accepting of the possibility of deprescribing. Patients expressed concern over insufficient provider time for

discussion and support necessary to discontinue a medication but were more accepting of deprescribing if viewed as a "test" with support from their provider. Some patients felt pressured by family and providers to take the medication initially; others reported prior negative experiences with ceasing medications. The availability of new evidence about medications (particularly potential harms) and support of physicians and family members were facilitators of deprescribing. Patients also reported disliking medications – inconvenient, expensive, unnatural – as a facilitator of deprescribing.

Provider perspectives were identified in interviews with VA physicians, nurse practitioners, and pharmacists.[138] Participants (n=20) identified factors that influence their decisions about discontinuing medications. Responses were categorized as medication factors, patient factors, provider factors, and system factors. Medication factors included issues related to the patient's current medication regimen (*eg,* number of doses, duplicate medications) and uncertainty about indication. Patient factors included complexity of comorbid conditions; age; perception of patient's knowledge, beliefs, and preferences; and uncertainty about adherence. Professional identify was also a factor in decision-making. Providers felt responsible for making prescribing decisions and caring for their patients although their definitions of polypharmacy varied. Included under system factors were concerns about patients receiving care from multiple providers, the work load associated with deprescribing (additional communication, monitoring), and external directives or policies that focus on achieving target goals regardless of patient age or preferences, inaccuracies in medical records, and concern about the number of computer generated reminders and alerts.

A 2014 systematic review[139] focused on provider perspectives from 21 studies (3 of which were also included in the patient-centered review by Reeve et al[137]). Most of the 21 included primary care providers caring for older, community-based patients. Lack of awareness of the appropriateness of their prescribing behavior was an identified barrier along with inertia (*ie,* failure to act despite awareness). Providers noted potential negative outcomes, belief that drugs are effective with few adverse effects, potential increased workload, and concerns about deprescribing of medications prescribed by another provider. Some prescribers believed they lacked the knowledge to address potentially inappropriate medication use or they believed their prescribing was based on guideline recommendations and were hesitant to deviate from those recommendations. Targeted training with more information about potential benefits and harms of deprescribing were identified as factors to overcome those barriers. Some providers cited barriers associated with feasibility including patient resistance to change, limited time, limited availability of treatment options, respect for the prescribing decisions of colleagues, and the need to meet quality metrics.

## RESEARCH GAPS/FUTURE RESEARCH

The most glaring gap is the absence of comparative effectiveness trials. This is particularly important since the literature to date does not conclusively identify 1 deprescribing approach that is clearly superior to others. Since the VA Academic Detailing Service is planning to introduce VIONE, a medication management tool to reduce polypharmacy risk, this might be a good opportunity to acquire comparative effectiveness data. Consultation with implementation and quality improvement evaluation experts within VA Health Services Research & Development to design a robust roll-out plan that varies key conditions across different sites would likely yield important insights into best practices.

Other gaps that could be addressed by future research include:

- Absence of standardized definitions for deprescribing, components of the interventions, and how key outcomes are measured making it difficult to compare studies;

- A paucity of contemporary studies evaluating the role of the electronic medical health record in deprescribing efforts and its effects on patient-centered outcomes (*eg,* quality of life, falls, hospitalizations);

- Few process evaluations accompanying clinical trials; implementation studies would provide guidance on how to incorporate deprescribing interventions into health care settings;

- Few studies were conducted in the US or in VA, and the preponderance of patients enrolled were female; of the 38 trials included, only 10 were conducted in the US, of which only 2 were in VA;

- Little data to support which care team members (*eg*, physician, nurse, pharmacist) can and should be responsible for different aspects of the deprescribing process;

- Insufficient focus on important patient-centered outcomes such as quality of life, falls, major adverse cardiovascular events, and cognitive function, as well as biomarker measures such as glycemic or blood pressure control likely important to patients, providers, and health systems when considering medication deprescribing; and

- Lack of data from RCTs on adverse effects of deprescribing; more information on this topic can be found in reviews that were not limited to clinical trials.[140]

## APPLICABILITY OF FINDINGS TO VA

*Key Question 1:* As noted above, only 2 studies were conducted in VA, most were not conducted in the US, and the preponderance of participants were women. Nevertheless, our findings can, and should, inform efforts in VA to develop deprescribing interventions. Enrolled individuals were community-dwelling older adults with multiple chronic conditions and receiving care in primary care clinics or community settings. Interventions were varied in their components and strategies and typically consistent with, and likely applicable to, VA. As these initiatives are rolled out as pilot projects, concurrent process evaluations should be conducted to determine best practices for implementation within VA.

Importantly, we did not find that deprescribing interventions led to patient-related harms. Furthermore, a strong rationale can be made in future VA work to choose PIMs as an important and patient-centered outcome, based on strong observational data that: 1) exposure to multiple medications is associated with increased risk of negative outcomes, such as falls, cognitive impairment and other geriatric syndromes, hospitalizations, and death; 2) the number of medications a person is taking may be the single most important predictor of adverse drug effects; 3) about 50% of older adults are taking 1 or more potentially inappropriate medications (PIMs), including those without a clear indication, duplicative medications, and medications known to pose risks in the elderly; and 4) costs and burden increase with medication number.

*Evidence Map:* Only 1 study included in the evidence map of studies in settings other than community/primary care, a study of a CMR intervention in hospital setting, was conducted in VA. Only 9 of the 48 studies were from the US and in only 3 of the 48 studies included populations of greater than 50% males.

*Key Question 2:* Our review of barriers to and facilitators of implementation of deprescribing interventions was limited to studies in large health care systems. We included 2 studies within VA – 1 in primary care and 1 in the emergency department. The findings from VA were similar to those in other health care systems, with barriers including time constraints, availability of clinical pharmacists, and concerns about loss of prescriber autonomy and quality of the information provided. Facilitators included perceived ability to improve prescribing safety and the potential for provision of information and training.

## CONCLUSIONS

Several options for deprescribing interventions may reduce the burden of polypharmacy and PIMs in community-dwelling older adults. CMR, the intervention most extensively evaluated, may reduce all-cause mortality, potentially inappropriate medication use, and costs. CMR might be feasible to implement, given the extensive presence of pharmaceutical expertise already embedded in ambulatory care clinics in VA. In designing a program, consideration should be given to incorporating a plan for follow-up contact with patients after the initial CMR. Implementing CMR in a research context or as part of a quality improvement project would increase the evidence base from VA settings.

Educational interventions, which reduced PIMs in most trials, are also worth exploring for implementation. Of particular interest are interventions that can be implemented at a system-level and that include a direct-to-consumer patient engagement component. Provider education with performance feedback may be useful. Provider education-only interventions are not effective.

Computer decision support interventions are a promising area for further research but are not ready to be implemented on a system-wide basis.

Overcoming describing barriers and enhancing facilitators could aide in implementation of optimal deprescribing practices and improve health care quality and value.

# REFERENCES

1.      Linsky A, Gellad WF, Linder JA, Friedberg MW. Advancing the science of deprescribing: a novel comprehensive conceptual framework. *J Am Geriatr Soc.* 2019;67(10):2018-2022.

2.      National Center for Health Statistics (US). United States, 2016: With Chartbook on Long-Term Trends in Health. Hyattsville, MD: National Center for Health Statistics (US); 2017 Report 2017-1232.

3.      Mangin D, Bahat G, Golomb BA, Mallery LH, Moorhouse P, Onder G, et al. International Group for Reducing Inappropriate Medication Use & Polypharmacy (IGRIMUP): position statement and 10 recommendations for action. *Drugs Aging.* 2018;35(7):575-587.

4.      Scott IA, Anderson K, Freeman CR, Stowasser DA. First do no harm: a real need to deprescribe in older patients. *Med J Aust.* 2014;201(7):390-392.

5.      Reeve E, Bell JS, Hilmer SN. Barriers to optimising prescribing and deprescribing in older adults with dementia: a narrative review. *Curr Clin Pharmacol.* 2015;10(3):168-177.

6.      Reeve E, Shakib S, Hendrix I, Roberts MS, Wiese MD. Review of deprescribing processes and development of an evidence-based, patient-centered deprescribing process. *Br J Clin Pharmacol.* 2014;78:738-747.

7.      Thompson W, Farrell B. Deprescribing: what is it and what does the evidence tell us? *Can J Hosp Pharm.* 2013;66:201.

8.      Higgins JP, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration. 2011;Available from http://handbook.cochrane.org. (accessed July 23, 2019)

9.      Higgins JP Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ.* 2003;327:557-560.

10.     Cohen J. Statistical power analysis for the behavioral sciences (2nd ed.). *Hillsdale, NJ: Lawrence Earlbaum Associates.* 1988.

11.     Underwood M, Barnett A, Hajioff S. Cluster randomisation: a trap for the unwary. *Br J Gen Pract.* 1998;48:1089-1090.

12.     GRADEpro GDT: GRADEpro Guideline Development Tool [Software]. Ontario, Canada: McMaster University and Evidence Prime, Inc., 2015.

13.     Schünemann H, Brozek J, Guyatt G, Oxman A, eds. GRADE handbook for grading quality of evidence and strength of recommendations. The GRADE Working Group,

2013. Available from https://gdt.gradepro.org/app/handbook/handbook.html. (accessed September 10, 2019).

14.     Allard J, Hebert R, Rioux M, Asselin J, Voyer L. Efficacy of a clinical medication review on the number of potentially inappropriate prescriptions prescribed for community-dwelling elderly people. *CMAJ.* 2001;164(9):1291-1296.

15.     Avorn J, Soumerai SB, Everitt DE, Ross-Degnan D, Beers MH, Sherman D, et al. A randomized trial of a program to reduce the use of psychoactive drugs in nursing homes. *N Engl J Med.* 1992;327(3):168-173.

16.     Batty GM, Hooper R, Oborne CA, Jackson SHD. Investigating intervention strategies to increase the appropriate use of benzodiazepines in elderly medical in-patients. *Br J Clin Governance.* 2001;6(4):252-258.

17.     Beer C, Loh PK, Peng YG, Potter K, Millar A. A pilot randomized controlled trial of deprescribing. *Ther Adv Drug Saf.* 2011;2(2):37-43.

18.     Bladh L, Ottosson E, Karlsson J, Klintberg L, Wallerstedt SM. Effects of a clinical pharmacist service on health-related quality of life and prescribing of drugs: a randomised controlled trial. *BMJ Qual Saf.* 2011;20(9):738-746.

19.     Bonnet-Zamponi D, d'Arailh L, Konrat C, Delpierre S, Lieberherr D, Lemaire A, et al. Drug-related readmissions to medical units of older adults discharged from acute geriatric units: Results of the optimization of medication in AGEd multicenter randomized controlled trial. *J Am Ger Soc.* 2013;61(1):113-121.

20.     Boyé NDA, Van der Velde N, De Vries OJ, Van Leshout EMM, Harthold KA, Mattace-Raso FUS, et al. Effectiveness of medication withdrawal in older fallers: results from the Improving Medication Prescribing to reduce Risk Of FALLs (IMPROveFALL) trial. *Age Ageing.* 2017;46(1):142-146.

21.     Bregnhoj L, Thirstrup S, Kristensen MB, Bjerrum L, Sonne J. Combined intervention programme reduces inappropriate prescribing in elderly patients exposed to polypharmacy in primary care. *Eur J Clin Pharmacol.* 2009;65(2):199-207.

22.     Briggs S, Pearce R, Dilworth S, Higgins I, Hullick C, Attia J. Clinical pharmacist review: A randomised controlled trial. *Emerg Med Australas.* 2015;27(5):419-426.

23.     Burns A, Furniss L, Cooke J, Lloyd Craig SK, Scobie S. Pharmacist medication review in nursing homes: a cost analysis. *Int J Geriatr Psychopharmacol.* 2000;2(3):137-141.

24.     Campins L, Serra-Prat M, Gozalo I, Lopez D, Palomero E, Agusti C, et al. Randomized controlled trial of an intervention to improve drug appropriateness in community-dwelling polymedicated elderly people. *Fam Pract.* 2017;34(1):36-42.

25.     Campins L, Serra-Prat M, Palomera E, Bolibar I, Martinez MA, Gallo P. Reduction of pharmaceutical expenditure by a drug appropriateness intervention in polymedicated elderly subjects in Catalonia (Spain). *Gac Sanit.* 2019;33(2):106-111.

26.   Clyne B, Smith SM, Hughes CM, Boland F, Bradley MC, Cooper JA, et al. Effectiveness of a multifaceted intervention for potentially inappropriate prescribing in older patients in primary care: a cluster-randomized controlled trial (OPTI-SCRIPT Study). *Ann Fam Med.* 2015;13(6):545-553.

27.   Clyne B, Smith SM, Hughes CM, Boland F, Cooper JA, Fahey T. Sustained effectiveness of a multifaceted intervention to reduce potentially inappropriate prescribing in older patients in primary care (OPTI-SCRIPT study). *Implement Sci.* 2016;11(1):79.

28.   Coleman EA, Grothaus LC, Sandhu N, Wagner EH. Chronic care clinics: a randomized controlled trial of a new model of primary care for frail older adults. *J Am Geriatr Soc.* 1999;47(7):775-783.

29.   Cool C, Cestac P, McCambridge C, de Souto Barreto P, Rolland Y, et al. Reducing potentially inappropriate drug prescribing in nursing home residents: effectiveness of a geriatric intervention. *Br J Clin Pharmacol.* 2018;84(7):1598-1610.

30.   Cossette B, Ethier JF, Joly-Mischlich T, Bergeron J, Ricard G, Brazeau S, et al. Reduction in targeted potentially inappropriate medication use in elderly inpatients: a pragmatic randomized controlled trial. *Eur J Clin Pharmacol.* 2017;73(10):1237-1245.

31.   Crotty M, Halbert J, Rowett D, Giles L, Birks R, Williams H, et al. An outreach geriatric medication advisory service in residential aged care: a randomised controlled trial of case conferencing. *Age Ageing.* 2004;33(6):612-617.

32.   Crotty M, Rowett D, Spurling L, Giles LC, Phillips PA. Does the addition of a pharmacist transition coordinator improve evidence-based medication management and health outcomes in older adults moving from the hospital to a long-term care facility? Results of a randomized, controlled trial. *Am J Geriatr Pharmacother.* 2004;2(4):257-264.

33.   Dalleur O, Boland B, Losseau C, Henrard S, Wouters D, Speybroeck N, et al. Reduction of potentially inappropriate medications using the STOPP criteria in frail older inpatients: a randomised controlled study. *Drugs Aging.* 2014;31(4):291-298.

34.   Denneboom W, Dautzenberg MG, Grol R, De Smet PA. Treatment reviews of older people on polypharmacy in primary care: cluster controlled trial comparing two approaches. *Br J Gen Pract.* 2007;57(542):723-731.

35.   Donovan JL, Kanaan AO, Thomson MS, Rochon P, Lee M, Gavendo L, et al. Effect of clinical decision support on psychotropic medication prescribing in the long-term care setting. *J Am Geriatr Soc.* 2010;58(5):1005-1007.

36.   Frankenthal D, Kalendaryev E, Lerman Y. Intervention with the screening tool of older persons potentially inappropriate prescriptions/screening tool to alert doctors to right treatment criteria in elderly residents of a chronic geriatric facility: a randomized clinical trial. *J Am Geriatr Soc.* 2014;62(9):1658-1665.

37.    Fried TR, Niehoff KM, Street RL, Charpentier PA, Rajeevan N, Miller PL, et al. Effect of the Tool to Reduce Inappropriate Medications on medication communication and deprescribing. *J Am Geriatr Soc.* 2017;65(10):2265-2271.

38.    Furniss L, Burns A, Craig SKL, Scobie S, Cooke J, Faragher B. Effects of a pharmacist's medication review in nursing homes. Randomised controlled trial. *Br J Psychiatry.* 2000;176:563-567.

39.    Gallagher M. Evaluating a protocol to train hospice staff in administering individualized music. *Int J Palliat Nurs.* 2011;17(4):195-201.

40.    Garcia-Gollarte F, Baleriola-Julvez J, Ferrero-Lopez I, Cuenllas-Diaz A, Cruz-Jentoft AJ. An educational intervention on drug use in nursing homes improves health outcomes resource utilization and reduces inappropriate drug prescription. *J Am Med Dir Assoc.* 2014;15(12):885-891.

41.    Gillespie P, Clyne B, Raymakers A, Fahey T, Hughes CM, Smith SM. Reducing potentially inappropriate prescribing for older people in primary care: cost-effectiveness of the OPTI-SCRIPT intervention. *Int J Technol Assess Health Care.* 2017;33(4):494-503.

42.    Gillespie U, Alassaad A, Hammarlund-Udenaes M, Morlin C, Henrohn D, Bertilsson M, et al. Effects of pharmacists' interventions on appropriateness of prescribing and evaluation of the instruments' (MAI, STOPP and STARTs') ability to predict hospitalization--analyses from a randomized controlled trial. *PLoS One.* 2013;8(5):e62401.

43.    Gnjidic D, Ong HMM, Leung C, Jansen J, Reeve E. The impact of in hospital patient-education intervention on older people's attitudes and intention to have their benzodiazepines deprescribed: a feasibility study. *TherAdv Drug Saf.* 2019;10:1-11.

44.    Gulla C, Flo E, Kjome RLS, Husebo BS. Deprescribing antihypertensive treatment in nursing home patients and the effect on blood pressure. *J Geriatr Cardiol.* 2018;15(4):275-283.

45.    Gustafsson M, Sjolander M, Pfister B, Schneede J, Lovheim H. Effects of pharmacists' interventions on inappropriate drug use and drug-related readmissions in people with dementia-a secondary analysis of a randomized controlled trial. *Pharmacy.* 2018;6(1) pii: E7. doi: 10.3390/pharmacy6010007

46.    Haag JD, Davis AZ, Hoel RW, Armon JJ, Odell LJ, Dierkhising RA, et al. Impact of pharmacist-provided medication therapy management on healthcare quality and utilization in recently discharged elderly patients. *Am Health Drug Benefits.* 2016;9(5):259-267.

47.    Hanlon JT, Weinberger M, Samsa GP, Schmader KE, Uttech KM, Lewis IK, et al. A randomized, controlled trial of a clinical pharmacist intervention to improve

inappropriate prescribing in elderly outpatients with polypharmacy. *Am J Med.* 1996;100(4):428-437.

48.     Hellstrom LM, Bondesson A, Hoglund P, Midlov P, Holmdahl L, Rickhag E, et al. Impact of the Lund Integrated Medicines Management (LIMM) model on medication appropriateness and drug-related hospital revisits. *Eur J Clin Pharmacol.* 2011;67(7):741-752.

49.     Husebo BS, Ballard C, Aarsland D, Selbaek G, Slettebo DD, Gulla C,et al. The effect of a multicomponent intervention on quality of life in residents of nursing homes: a randomized controlled trial (COSMOS). *J Am Med Dir Assoc.* 2019;20:330-339.

50.     Jodar-Sanchez F, Malet-Larrea A, Martin JJ, Garcia-Mochón L, López del Amo MP, Martinez-Martinez F, et al. Cost-utility analysis of a medication review with follow-up service for older adults with polypharmacy in community pharmacies in Spain: the conSIGUE program. *PharmacoEconomics.* 2015;33(6):599-610.

51.     Juola AL, Bjorkman MP, Pylkkanen S, Finne-Soveri H, Soini H, Kautiainen H, et al. Feasibility and baseline findings of an educational intervention in a randomized trial to optimize drug treatment among residents in assisted living facilities. *Eur Geriatr Med.* 2014;5(3):195-199.

52.     Juola AL, Bjorkman MP, Pylkkanen S, Finne-Soveri H, Soini H, Kautiainen H, et al. Nurse education to reduce harmful medication use in assisted living facilities: effects of a randomized controlled trial on falls and cognition. *Drugs Aging.* 2015;32(11):947-955.

53.     Köberlein-Neu J, Mennemann H, Hamacher S, Waltering I, Jaehde U, Schaffert C, et al. Interprofessional medication management in patients with multiple morbidities. *Dtsch Arztebl Int.* 2016;113(44):741-748.

54.     Krska J, Cromarty JA, Arris F, Jamieson D, Hansford D, Duffus PRS, et al. Pharmacist-led medication review in patients over 65: a randomized, controlled trial in primary care. *Age Ageing.* 2001;30(3):205-211.

55.     Kutner JS, Blatchford PJ, Taylor DH, Ritchie CS, Bull JH, Fairclough DL, et al. Safety and benefit of discontinuing statin therapy in the setting of advanced, life-limiting illness a randomized clinical trial. *JAMA Int Med.* 2015;175(5):691-700.

56.     Kwint HF, Faber A, Gussekloo J, Bouvy ML. Effects of medication review on drug-related problems in patients using automated drug-dispensing systems: A pragmatic randomized controlled study. *Drugs Aging.* 2011;28(4):305-314.

57.     Lampela P, Hartikainen S, Lavikainen P, Sulkava R, Huupponen R. Effects of medication assessment as part of a comprehensive geriatric assessment on drug use over a 1-year period: a population-based intervention study. *Drugs Aging.* 2010;27(6):507-521.

58.     Lapane KL, Hughes CM, Christian JB, Daiello LA, Cameron KA, Feinberg J. Evaluation of the Fleetwood Model of long-term care pharmacy. *J Am Med Dir Assoc.* 2011;12(5):355-363.

59.     Legrain S, Tubach F, Bonnet-Zamponi D, Lemaire A, Aquini JP, Paillaud E, et al. A new multimodal geriatric discharge-planning intervention to prevent emergency visits and rehospitalizations of older adults: the optimization of medication in AGEd multicenter randomized controlled trial. *J Am Geriatr Soc.* 2011;59(11):2017-2028.

60.     Lenaghan E, Holland R, Brooks A. Home-based medication review in a high risk elderly population in primary care--the POLYMED randomised controlled trial. *Age Ageing.* 2007;36(3):292-297.

61.     Lenssen R, Schmitz K, Griesel C, Heidenreich A, Schulz JP, Trautwein C, et al. Comprehensive pharmaceutical care to prevent drug-related readmissions of dependent-living elderly patients: a randomized controlled trial. *BMC Geriatr.* 2018;18(1):135.

62.     Malet-Larrea A, Goyenechea E, Garcia-Cardenas V, Calvo B, Arteche JM, Aranegui P, et al. The impact of a medication review with follow-up service on hospital admissions in aged polypharmacy patients. *Br J Clin Pharmacol.* 2016:82:831-838.

63.     Malet-Larrea A, Goyenechea E, Gastelurrutia MA, Calvo B, Garcia-Cardenas V, Cabases JM, et al. Cost analysis and cost-benefit analysis of a medication review with follow-up service in aged polypharmacy patients. *Eur J Health Econ.* 2017;18(9):1069-1078.

64.     Martin P, Tamblyn R, Benedetti A, Ahmed S, Tannenbaum C. Effect of a pharmacist-led educational intervention on inappropriate medication prescriptions in older adults: the D-PRESCRIBE randomized clinical trial. *JAMA.* 2018;320(18):1889-1898.

65.     McDerby N, Kosari SB, Bail K, Shield A. Peterson G, Naunton M. The effect of a residential care pharmacist on medication administration practices in aged care: A controlled trial. *J Clin Pharm Ther.* 2019:1-8.

66.     Meador KG, Taylor JA, Thapa PB, Fought RL, Ray WA. Predictors of antipsychotic withdrawal or dose reduction in a randomized controlled trial of provider education. *J Am Geriatr Soc.* 1997;45(2):207-210.

67.     Meredith S, Feldman P, Frey D, Giammarco L, Hall K, Arnold K, et al. Improving medication use in newly admitted home healthcare patients: A randomized controlled trial. *J Am Geriatr Soc.* 2002;50(9):1484-1491.

68.     Michalek C, Wehling M, Schlitzer J, Frohnhofen H. Effects of "Fit fOR The Aged" (FORTA) on pharmacotherapy and clinical endpoints--a pilot randomized controlled study. *Eur J Clin Pharmacol.* 2014;70(10):1261-1267.

69.     Milos V, Rekman E, Bondesson A, Eriksson T, Jakobsson U, Westerlund T, et al. Improving the quality of pharmacotherapy in elderly primary care patients through medication reviews: a randomised controlled study. *Drugs Aging.* 2013;30(4):235-246.

70.     Moga DC, Abner EL, Rigsby DN, Eckmann L, Huffmyer M, Murphy RR, et al. Optimizing medication appropriateness in older adults: a randomized clinical interventional trial to decrease anticholinergic burden. *Alzheimers Res Ther.* 2017;9(1):36.

71.    Muth C, Uhlmann L, Haefeli WE, Rochon J, Van Den Akker M, Perera R, et al. Effectiveness of a complex intervention on Prioritising Multimedication in Multimorbidity (PRIMUM) in primary care: results of a pragmatic cluster randomised controlled trial. *BMJ Open.* 2018;8(2):e017740.

72.    Olesen C, Harbig P, Buus KM, Barat I, Damsgaard EM. Impact of pharmaceutical care on adherence, hospitalisations and mortality in elderly patients. *Int J Clin Pharm.* 2014;36(1):163-171.

73.    Olsson IN, Runnamo R, Engfeldt P. Drug treatment in the elderly: an intervention in primary care to enhance prescription quality and quality of life. *Scand J Prim Health Care.* 2012;30(1):3-9.

74.    Patterson SM, Hughes CM, Cardwell C, Lapane KL, Murray AM, Crealey GE. A cluster randomized controlled trial of an adapted U.S. model of pharmaceutical care for nursing home residents in Northern Ireland (fleetwood Northern Ireland study): A cost-effectiveness analysis. *J Am Geriatr Soc.* 2011;59(4):586-593.

75.    Patterson SM, Hughes CM, Crealey G, Cardwell C, Lapane KL. An evaluation of an adapted U.S. model of pharmaceutical care to improve psychoactive prescribing for nursing home residents in Northern Ireland (Fleetwood Northern Ireland Study). *J Am Geriatr Soc.* 2010;58(1):44-53.

76.    Pazan F, Burkhardt H, Frohnhofen H, Weiss C, Throm C, Kuhn-Thiel A, et al. Changes in prescription patterns in older hospitalized patients: the impact of FORTA on disease-related over- and under-treatments. *EurJ Clin Pharmacol.* 2018;74(3):339-347.

77.    Pimlott NJG, Hux JE, Wilson LM, Kahan M, Li C, Rosser WW. Educating physicians to reduce benzodiazepine use by elderly patients: a randomized controlled trial. *CMAJ.* 2003;168(7):835-839.

78.    Pit SW, Byles JE, Henry DA, Holt L, Hansen V, Bowman DA. A quality use of medicines program for general practitioners and older people: a cluster randomised controlled trial. *Med J Aust.* 2007;187(1):23-30.

79.    Pitkala KH, Juola AL, Kautiainen H, Soini H, Finne-Soveri UH, Bell JS, et al. Education to reduce potentially harmful medication use among residents of assisted living facilities: a randomized controlled trial. *J Am Med Dir Assoc.* 2014;15(12):892-898.

80.    Polinder S, Boyé NDA, Mattace-Raso FUS, Van der Velde N, Hartholt KA, De Vries, OJ, et al. Cost-utility of medication withdrawal in older fallers: results from the improving medication prescribing to reduce risk of FALLs (IMPROveFALL) trial. *BMC Geriatr.* 2016;16(179).

81.    Pope G, Wall N, Peters CM, O'Connor M, Saunders J, O'Sullivan C, et al. Specialist medication review does not benefit short-term outcomes and net costs in continuing-care patients. *Age Ageing.* 2011;40(3):307-312.

82.   Potter K, Flicker L, Page A, Etherton-Beer C. Deprescribing in frail older people: a randomised controlled trial. *PLoS One.* 2016;11(3):e0149984.

83.   Price M, Davies I, Rusk R, Lesperance M, Weber J. Applying STOPP guidelines in primary care through electronic medical record decision support: randomized control trial highlighting the importance of data quality. *JMIR Med Inform.* 2017;5(2):e15.

84.   Raebel MA, Charles J, Dugan J, Carroll NM, Korner EJ, Brand DW, et al. Randomized trial to improve prescribing safety in ambulatory elderly patients. *J Am Geriatr Soc.* 2007;55(7):977-985.

85.   Ravn-Nielsen LV, Duckert ML, Lund ML, Henriksen JP, Nielsen ML, Eriksen CS, et al. Effect of an in-hospital multifaceted clinical pharmacist intervention on the risk of readmission a randomized clinical trial. *JAMA Int Med.* 2018;178(3):375-382.

86.   Richter CB, Berg A, Langner H, Meyer G, Köpke S, Balzer K, et al. Effect of person-centred care on antipsychotic drug use in nursing homes (EPCentCare): a cluster-randomised controlled trial. *Age Ageing.* 2019;0:1-7.

87.   Rikala M, Korhonen MJ, Sulkava R, Hartikainen S. The effects of medication assessment on psychotropic drug use in the community-dwelling elderly. *Int Psychogeriatr.* 2011;23(3):473-484.

88.   Roberts MS, Stokes JA, King MA, Lynne TA, Purdie DM, Glasziou PP, et al. Outcomes of a randomized controlled trial of a clinical pharmacy intervention in 52 nursing homes. *Br J Clin Pharmacol.* 2001;51(3):257-265.

89.   Rognstad S, Brekke M, Fetveit A, Dalen I, Straand J. Prescription peer academic detailing to reduce inappropriate prescribing for older patients: a cluster randomised controlled trial. *Br J Gen Pract.* 2013;63(613):e554-562.

90.   Saltvedt I, Spigset O, Ruths S, Fayers P, Kaasa S, Sletvold O. Patterns of drug prescription in a geriatric evaluation and management unit as compared with the general medical wards: a randomised study. *Eur J Clin Pharmacol.* 2005;61(12):921-928.

91.   Schafer I, Kaduszkiewicz H, Mellert C, Loffler C, Mortsiefer A, Ernst A, et al. Narrative medicine-based intervention in primary care to reduce polypharmacy: results from the cluster-randomised controlled trial MultiCare AGENDA. *BMJ Open.* 2018;8(1):e017653.

92.   Schmader KE, Hanlon JT, Landsman PB, Samsa GP, Lewis IK, Weinberger M. Inappropriate prescribing and health outcomes in elderly veteran outpatients. *Ann Pharmacother.* 1997;31(5):529-533.

93.   Schmader KE, Hanlon JT, Pieper CF, Sloan R, Ruby CM, Twersky J, et al. Effects of geriatric evaluation and management on adverse drug reactions and suboptimal prescribing in the frail elderly. *Am J Med.* 2004;116(6):394-401.

94.     Schmidt I, Claesson CB, Westerholm B, Nilsson LG, Svarstad BL. The impact of regular multidisciplinary team interventions on psychotropic prescribing in swedish nursing homes. *J Am Geriatr Soc.* 1998;46(1):77-82.

95.     Schmidt-Mende K, Andersen M, Wettermark B, Hasselstrom J. Educational intervention on medication reviews aiming to reduce acute healthcare consumption in elderly patients with potentially inappropriate medicines-a pragmatic open-label cluster-randomized controlled trial in primary care. *Pharmacoepidemiol Drug Saf.* 2017;26(11):1347-1356.

96.     Shim YW, Chua SS, Wong HC, Alwi S. Collaborative intervention between pharmacists and physicians on elderly patients: a randomized controlled trial. *Ther Clin Risk Manag.* 2018;14:1115-1125.

97.     Simon SR, Smith DH, Feldstein AC, Perrin N, Yang X, Zhou Y, et al. Computerized prescribing alerts and group academic detailing to reduce the use of potentially inappropriate medications in older people. *J Am Geriatr Soc.* 2006;54(6):963-968.

98.     Spinewine A, Swine C, Dhillon S, Lambert P, Nachega JB, Wilmott L, et al. Effect of a collaborative approach on the quality of prescribing for geriatric inpatients: A randomized, controlled trial. *J Am Geriatr Soc.* 2007;55(5):658-665.

99.     Stein CM, Griffin MR, Taylor JA, Pichert JW, Brandt KD, Ray WA. Educational program for nursing home physicians and staff to reduce use of non-steroidal anti-inflammatory drugs among nursing home residents: a randomized controlled trial. *Med Care.* 2001;39(5):436-445.

100.    Tamblyn R, Huang A, Perreault R, Jacques A, Roy D, Hanley J, et al. The medical office of the 21st century (MOXXI): effectiveness of computerized decision-making support in reducing inappropriate prescribing in primary care. *CMAJ.* 2003;169(6):549-556.

101.    Terrell KM, Perkins AJ, Dexter PR, Hui SL, Callahan CM, Miller DK. Computerized decision support to reduce potentially inappropriate prescribing to older emergency department patients: a randomized, controlled trial. *J Am Geriatr Soc.* 2009;57(8):1388-1394.

102.    Torisson G, Minthon L, Stavenow L, Londos E. Multidisciplinary intervention reducing readmissions in medical inpatients: A prospective, non-randomized study. *Clin Interv Aging.* 2013;8:1295-1304.

103.    Trivalle C, Cartier T, Verny C, Mathieu AM, Davrinche P, Agonstini H, et al. Identifying and preventing adverse drug events in elderly hospitalised patients: A randomised trial of a program to reduce adverse drug effects. *J Nutr Health Aging.* 2010;14(1):57-61.

104.    Tse W, Frisina PG, Halbig TD, Gracies JM, Liang L, Tarshish C, et al. The effects of withdrawal of dopaminergic medication in nursing home patients with advanced Parkinsonism. *J Am Med Dir Assoc.* 2008;9(9):670-675.

105.    Van Der Meer HG, Wouters H, Pont LG, Taxis K. Reducing the anticholinergic and sedative load in older patients on polypharmacy by pharmacist-led medication review: A randomised controlled trial. *BMJ Open.* 2018;8(7):e019042.

106.    Van Der Spek K, Koopmans RT, Smalbrugge M, Nelissen-Vrancken MH, Wetzels RB, Smeets CH, et al. The effect of biannual medication reviews on the appropriateness of psychotropic drug use for neuropsychiatric symptoms in patients with dementia: a randomised controlled trial. *Age Ageing.* 2018;47(3):430-437.

107.    Weber V, White A, McIlvried R. An electronic medical record (EMR)-based intervention to reduce polypharmacy and falls in an ambulatory rural elderly population. *J Gen Int Med.* 2008;23(4):399-404.

108.    Wehling M, Burkhardt H, Kuhn-Thiel A, Pazan F, Throm C, Weiss C, et al. VALFORTA: a randomised trial to validate the FORTA (Fit fOR The Aged) classification. *Age Ageing.* 2016;45(2):262-267.

109.    Willoch K, Blix HS, Pedersen-Bjergaard AM, Eek AK, Reikvam A. Handling drug-related problems in rehabilitation patients: a randomized study. *Int J Clin Pharm.* 2012;34(2):382-388.

110.    Zermansky AG, Petty DR, Raynor DK, Freemantle N, Vail A, Lowe CJ. Randomised controlled trial of clinical medication review by a pharmacist of elderly patients receiving repeat prescriptions in general practice. *BMJ.* 2001;323(7325):1340-1343.

111.    Wouters H, Scheper J, Koning H, Brouwer C, Twisk JW, Van Der Meer H, et al. Discontinuing inappropriate medication use in nursing home residents :a cluster randomized controlled trial. *Ann Int Med.* 2017;167(9):609-617.

112.    Jager C, Freund T, Steinhauser J, Stock C, Krisam J, Kaufmann-Kolle P, et al. Impact of a tailored program on the implementation of evidence-based recommendations for multimorbid patients with polypharmacy in primary care practices-results of a cluster-randomized controlled trial. *Implement Sci.* 2017;12(1):8.

113.    Rognstad S, Brekke M, Mdala I, Fetveit A, Gjelstad S, Straand J. Characteristics of GPs responding to an educational intervention to minimise inappropriate prescriptions: subgroup analyses of the Rx-PAD study. *BJGP Open.* 2018;2(1).

114.    Touchette DR, Masica AL, Dolor RJ, Schumock GT, Choi YK, Kim Y, et al. Safety-focused medication therapy management: a randomized controlled trial. *J Am Pharm Assoc.* 2012;52(5):603-612.

115.    Tannenbaum C, Martin P, Tamblyn R, Benedetti A, Ahmed S. Reduction of inappropriate benzodiazepine prescriptions among older adults through direct patient education: the EMPOWER cluster randomized trial. *JAMA Int Med.* 2014;174(6):890-898.

116.    Bryant LJM, Coster G, Gamble GD, McCormick RN. The General Practitioner-Pharmacist Collaboration (GPPC) study: a randomised controlled trial of clinical medication reviews in community pharmacy. *Int J Pharm Practice.* 2011;19(2):94-105.

117.    Gnjidic D, Le Couteur DG, Abernethy DR, Hilmer SN. A pilot randomized clinical trial utilizing the drug burden index to reduce exposure to anticholinergic and sedative medications in older people. *Ann Pharmacother.* 2010;44(11):1725-1732.

118.    Lenander C, Elfsson B, Danielsson B, Midlov P, Hasselstrom J. Effects of a pharmacist-led structured medication review in primary care on drug-related problems and hospital admission rates: a randomized controlled trial. *Scand J Prim Health Care.* 2014;32(4):180-186.

119.    Richmond S, Morton V, Cross B, Chi Kei Wong I, Russell I, Philips Z, et al. Effectiveness of shared pharmaceutical care for older patients: RESPECT trial findings. *Br J Gen Pract.* 2010;60(570):14-20.

120.    Steinman MA, Low M, Balicer RD, Shadmi E. Impact of a nurse-based intervention on medication outcomes in vulnerable older adults. *BMC Geriatr.* 2018;18(1):207.

121.    Bernsten C, Bjorkman I, Caramona M, Crealey G, Frokjaer B, Grundberger E, et al. Improving the well-being of elderly patients via community pharmacy-based provision of pharmaceutical care. A multicentre study in seven European countries. *Drugs Aging.* 2001;18(1):63-67.

122.    Brooker DJ, Latham I, Evans SC, Jacobson N, Perry W, Bray J, et al. FITS into practice: translating research into practice in reducing the use of anti-psychotic medication for people with dementia living in care homes. *Aging Ment Health.* 2016;20(7):709-718.

123.    Cheek J, Gilbert A, Ballantyne A, Penhall R. Factors influencing the implementation of quality use of medicines in residential aged care. *Drugs Aging.* 2004;21(12):813-824.

124.    Desveaux L, Saragosa, M., Rogers, J., Bevan, L. Improving the appropriateness of antipsychotic prescribing in nursing homes: a mixed-methods process evaluation of an academic detailing intervention. *Implement Sci.* 2017;12:71.

125.    Kempen TGH, Gillespie U, Fardborg M, McIntosh J, Mair A, Stewart D. A case study of the implementation and sustainability of medication reviews in older patients by clinical pharmacists. *Res Social Adm Pharm.* 2018;19:19.

126.    Kuntz J, Kouch L, Christian D, Peterson PL, Gruss I. Barriers and facilitators to the deprescribing of nonbenzodiazepine sedative medications among Older Adults. *Perm J.* 2018;22:17-157.

127.    Latham I, Brooker D. Reducing anti-psychotic prescribing for care home residents with dementia. *Nurse Prescr.* 2017;15(10):504-511.

128. Ranson C, Jamieson T, Humphreys M, De Biase S, Dyson J, McGeorge M,. Understanding cognitive barriers to safer prescribing for frail patients. *Clin Pharm.* 2018;10(5).

129. Vandenberg AE, Echt KV, Kemp L, McGwin G, Perkins MM, Mirk AK. Academic detailing with provider audit and feedback improve prescribing quality for older Veterans. *J Am Geriatr Soc.* 2018;66(3):621-627.

130. Jager C, Steinhauser J, Freund T, Kuse S, Szecsenyi J, Wensing M. A tailored programme to implement recommendations for multimorbid patients with polypharmacy in primary care practices-process evaluation of a cluster randomized trial. *Implement Sci.* 2017;12(1):31.

131. Vandenberg A, Vaughan C, Stevens M, Hastings SN, Powers J, Markland A, et al. Improving geriatric prescribing in the ED: a qualitative study of facilitators and barriers to clinical decision support tool use. *Int J Qual Health Care.* 2017;29(1):117-123.

132. 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. *BrJ Clin Pharmacol.* 2016:82:583-623.

133. Johansson T, Abuzahra ME, Keller S, Mann E, Faller B, Sommerauer C, et al. Impact of strategies to reduce polypharmacy on clinically relevant endpoints: a systematic review and meta-analysis. *Br J Clin Pharmacol.* 2016;82:532-548.

134. Rankin A, Cadogan CA, Patterson SM, Kerse N, Cardwell CR, Bradley MC, et al. Interventions to improve the appropriate use of polypharmacy for older people. *Cochrane Database of Systematic Reviews. 2018(9) No.: CD008165.*

135. Tasai S, Kumpat N, Dilokthornsakul P, Chaiyakunapruk N, Saini B, Dhippayom T. Impact of medication reviews delivered by community pharmacist to elderly patients on polypharmacy: a meta-analysis of randomized controlled trials. *J Patient Saf.* 2019;00(00):1-9.

136. Linsky A, Simon SR, Bokhour B. Patient perceptions of proactive medication discontinuation. *Patient Educ Couns.* 2015;98(2):220-225.

137. Reeve E, To J, Hendrix I, Shakib S, Roberts MS, Wiese MD. Patient barriers to and enablers of deprescribing: a systematic review. *Drugs Aging.* 2013;30(10):793-807.

138. Linsky A, Simon SR, Marcello TB, Bokhour B. Clinical provider perceptions of proactive medication discontinuation. *Am J Manag Care.* 2015;21(4):277-283.

139. Anderson K, Stowasser D, Freeman C, Scott I. Prescriber barriers and enablers to minimising potentially inappropriate medications in adults: a systematic review and thematic synthesis. *BMJ Open.* 2014;4(12):e006544.

140.    Reeve E, Moriarty F, Nahas R, Turner JP, Kouladjian O'Donnel L, Hilmer SN. A narrative review of the safety concerns of deprescribing in older adults and strategies to mitigate potential harms. *Expert Opin Drug Saf.* 2018;17(1):39-49.