
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.

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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:

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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.

EXECUTIVE SUMMARY

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. 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. The number of medications a person is taking may be the single most important predictor of adverse drug effects. 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.

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 when they cause harm or no longer provide benefit”.

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?

METHODS

Data Sources and Searches

We searched MEDLINE, Embase, the Cumulative Index of Nursing and Allied Health (CINAHL), and the Cochrane Library 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. 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.

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, intermediate biomarker outcomes, and harms.

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 2 only);
- No outcomes of interest;
- Not a study design of interest:
 - KQ1: study design other than randomized controlled trial (RCT), cluster randomized controlled trial (CRCT), or controlled clinical trial (CCT)
 - KQ2: study design other than trials, observational studies, and qualitative research
 - Narrative reviews, case report/case series, editorials, letters (other than “Research Letters”), theses/dissertations are excluded; and
- Full text of article not available in English.

Data Abstraction and Risk of Bias Assessment

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, demographic, and outcomes data. 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.

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.

Risk of bias was determined for community or primary care setting studies included for Key Question 1. Risk of bias for 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.

Data Synthesis and Analysis

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 reported comparable outcomes measures and study designs. Categorical outcomes data were pooled using the Peto odds ratio (Peto OR) method or risk ratios (RR) with corresponding 95% confidence intervals (CI). Standardized mean differences (SMDs) between intervention and control groups, with corresponding 95% CIs, were calculated for continuous efficacy outcomes. 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 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.

We also 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). 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).

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

RESULTS

Results of Literature Search

From the overall literature search (Key Questions 1 and 2), we identified 2,049 records after removing duplicates. Of those, 1,773 were excluded at the abstract level. Two articles included in a recent systematic review were identified as potentially eligible leaving 278 articles for full-text review. We included 102 articles representing 86 trials. An additional 6 trials met eligibility criteria but were rated high risk of bias and not included in analyses.

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. We did a full-text review of 103 articles and included 9 studies reported in 10 papers.

Summary of Results

Key Question 1. What are the effectiveness, comparative effectiveness, and harms of deprescribing interventions among adults age 65 and older?

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

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

We identified 38 trials (12 RCTs, 26 cluster RCTs) from community and primary care settings that met our inclusion criteria and were rated as low or medium risk of bias. We also identified 48 studies from nursing home, hospital, emergency department, or palliative care settings. We focus our analysis on the community/primary care studies; the remaining studies are included in an evidence map (Appendix).

We divided the community and primary care trials into 4 intervention categories: comprehensive medication review (CMR) (k=21), education (k=10), computer decision support (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 (PIMs), and costs compared to usual care.
- Education (Provider and 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 (*ie*, CMR, Education, Computer Decision Support).
- 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.

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 or 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 (k=6), education (k=2), and computer decision support (k=1). 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:

- We found 9 studies of 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 the 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).

DISCUSSION

Certainty of Evidence

We assessed certainty of evidence for critical outcomes in Key Question 1. For studies comparing CMR to usual care, we found moderate certainty of evidence that CMR interventions likely result in little to no difference in hospitalizations and low certainty of evidence that CMR interventions may result in a slight reduction 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, we found moderate certainty of evidence that the education interventions likely 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.

Applicability

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, 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.

Key Question 2: Our review of barriers 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 concurred with 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.

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.

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. Provider education with performance feedback may be useful. Provider education-only interventions are not effective. Of particular interest are interventions that can be implemented at the system level and that include a direct-to-consumer patient engagement component.

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.

ABBREVIATIONS TABLE

Abbreviation	Definition
ADWE	Adverse drug withdrawal events
CCT	Controlled clinical trial
CDS	Computer decision support
CMR	Comprehensive Medication Review
CRCT	Cluster randomized controlled trial
FRIDs	Fall risk-increasing drugs
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation
KQ	Key question
MAI	Medication Appropriateness Index
PIMs	Potentially inappropriate medications
QoL	Quality of life
RCT	Randomized controlled trial
START	Screening Tool to Alert Doctors to Right Treatment
STOPP	Screening Tool of Older Persons' Prescriptions
TRIM	Tool to Reduce Inappropriate Medications (TRIM)
VHA	Veterans Health Administration
VA	Veterans Affairs