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 report is based on research conducted by the Evidence Synthesis Program (ESP) Center located at the Minneapolis VA Medical Center, Minneapolis, MN, funded by the Department of Veterans Affairs, Veterans Health Administration, Health Services Research and Development. The findings and conclusions in this document are those of the author(s) who are responsible for its contents; the findings and conclusions do not necessarily represent the views of the Department of Veterans Affairs or the United States government. Therefore, no statement in this article should be construed as an official position of the Department of Veterans Affairs. Dr Linsky was funded by grants from VA Health Services Research and Development (I21HX002406-01 and 5IK2HX001357-05). She is also a Co-Investigator for the Center for Medication Safety in Aging, a VA Patient Safety Center of Inquiry. No other investigators have any affiliations or financial involvement (*eg*, employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties) that conflict with material presented in the report.

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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National Program Director-Psychotropic Drug Safety Initiative

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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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

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:

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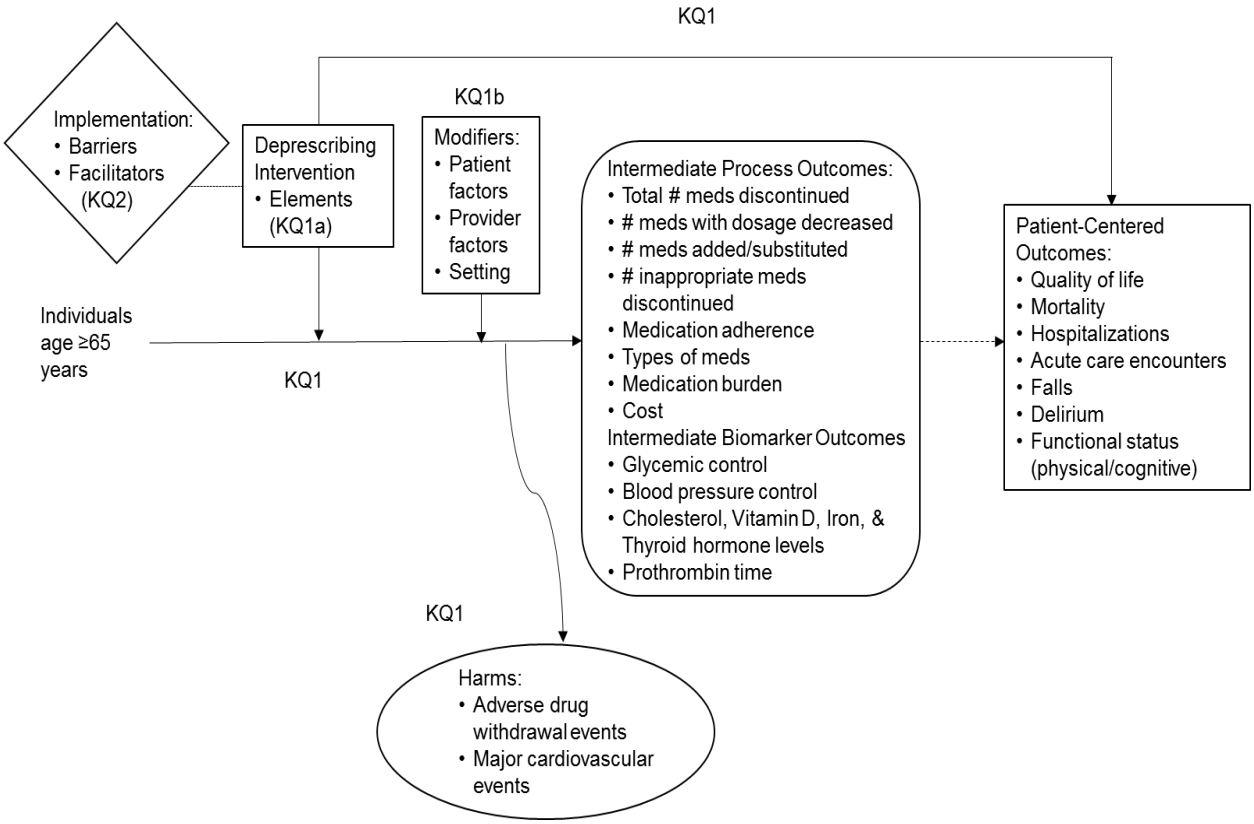
KQ2: What are the identified facilitators and barriers that impact the implementation of deprescribing interventions within large-scale health systems such as VA?

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:
    - 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, or qualitative research
    - 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

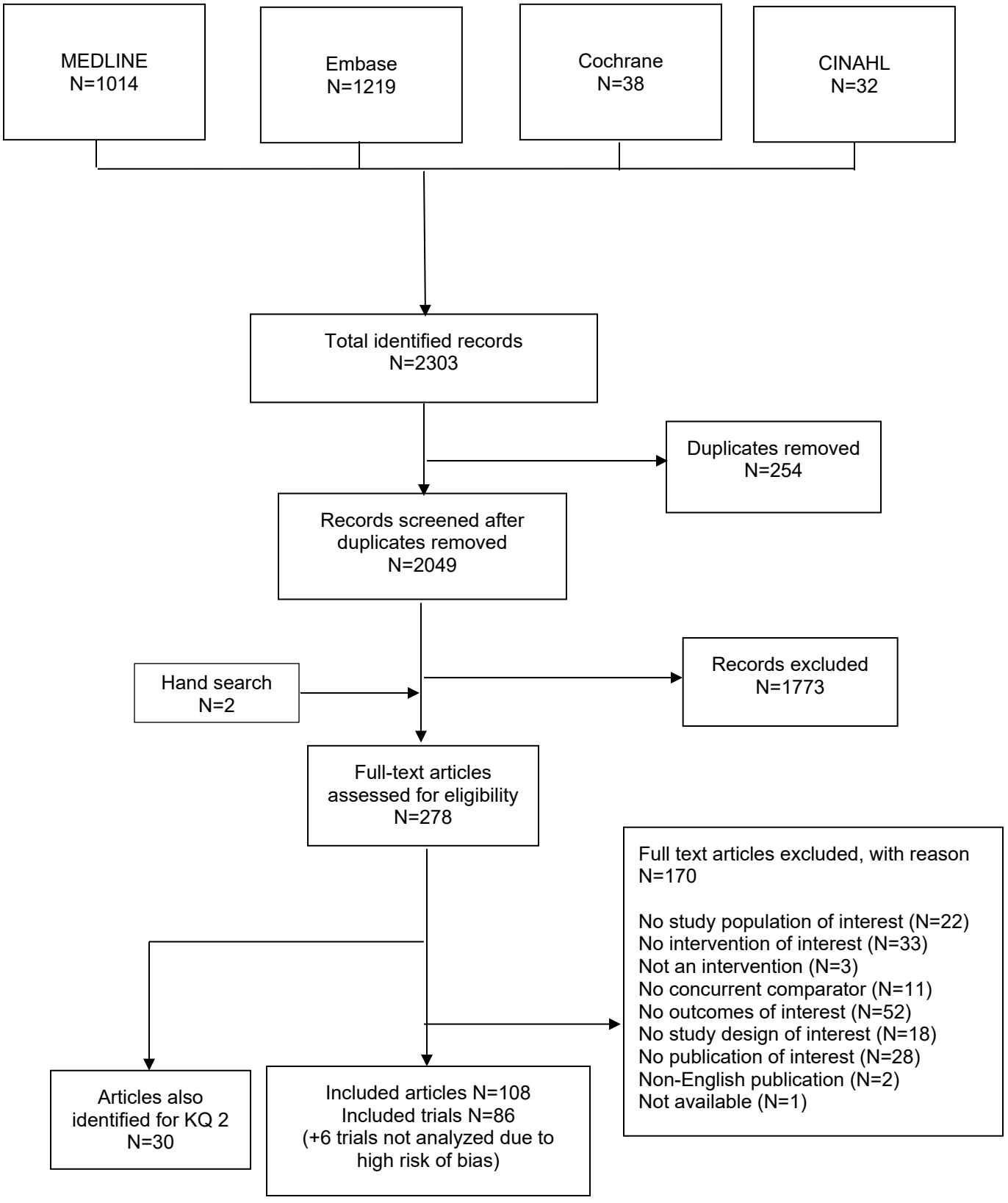
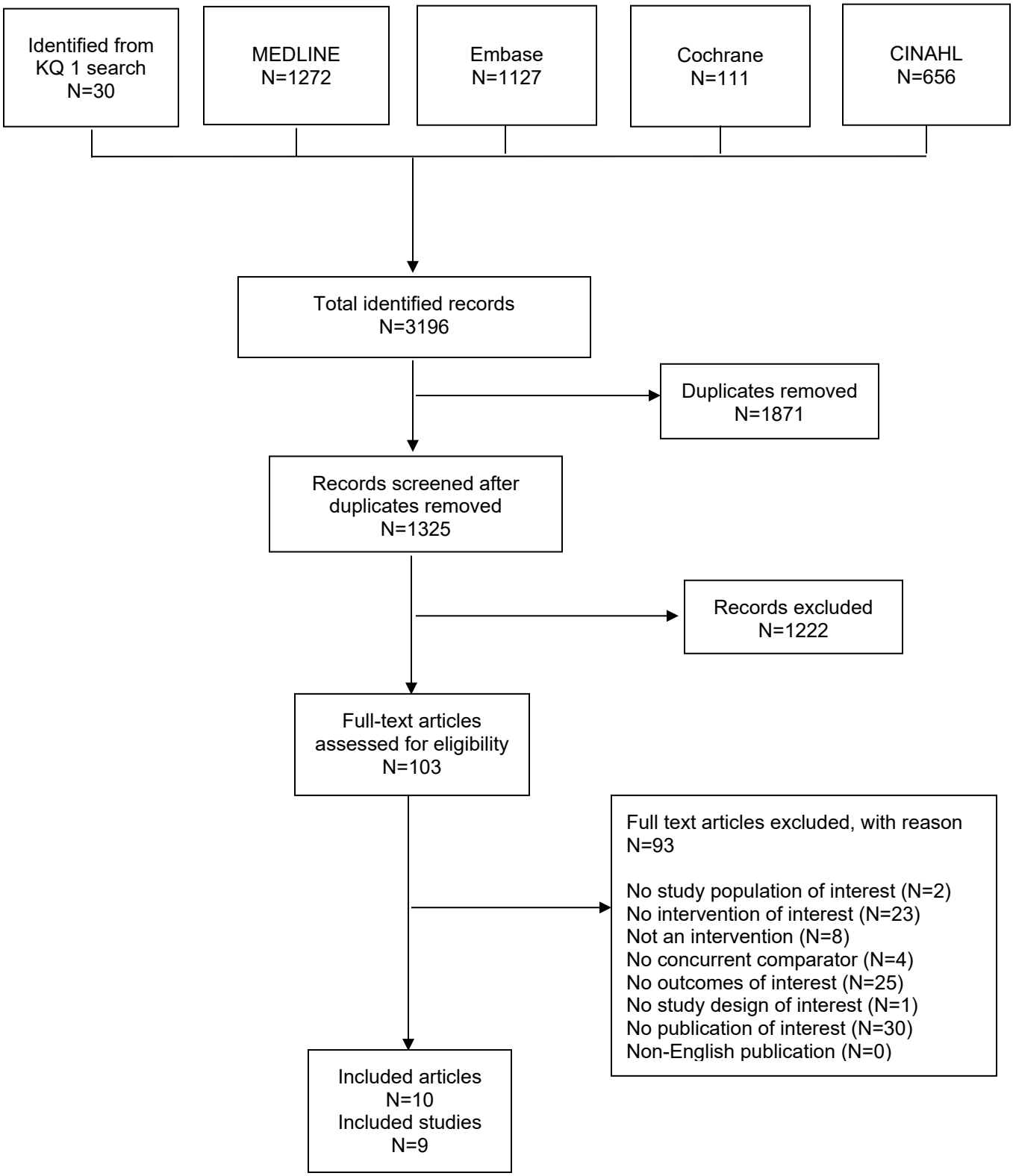


Figure 3: Literature Flow Chart – Key Question 2



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.

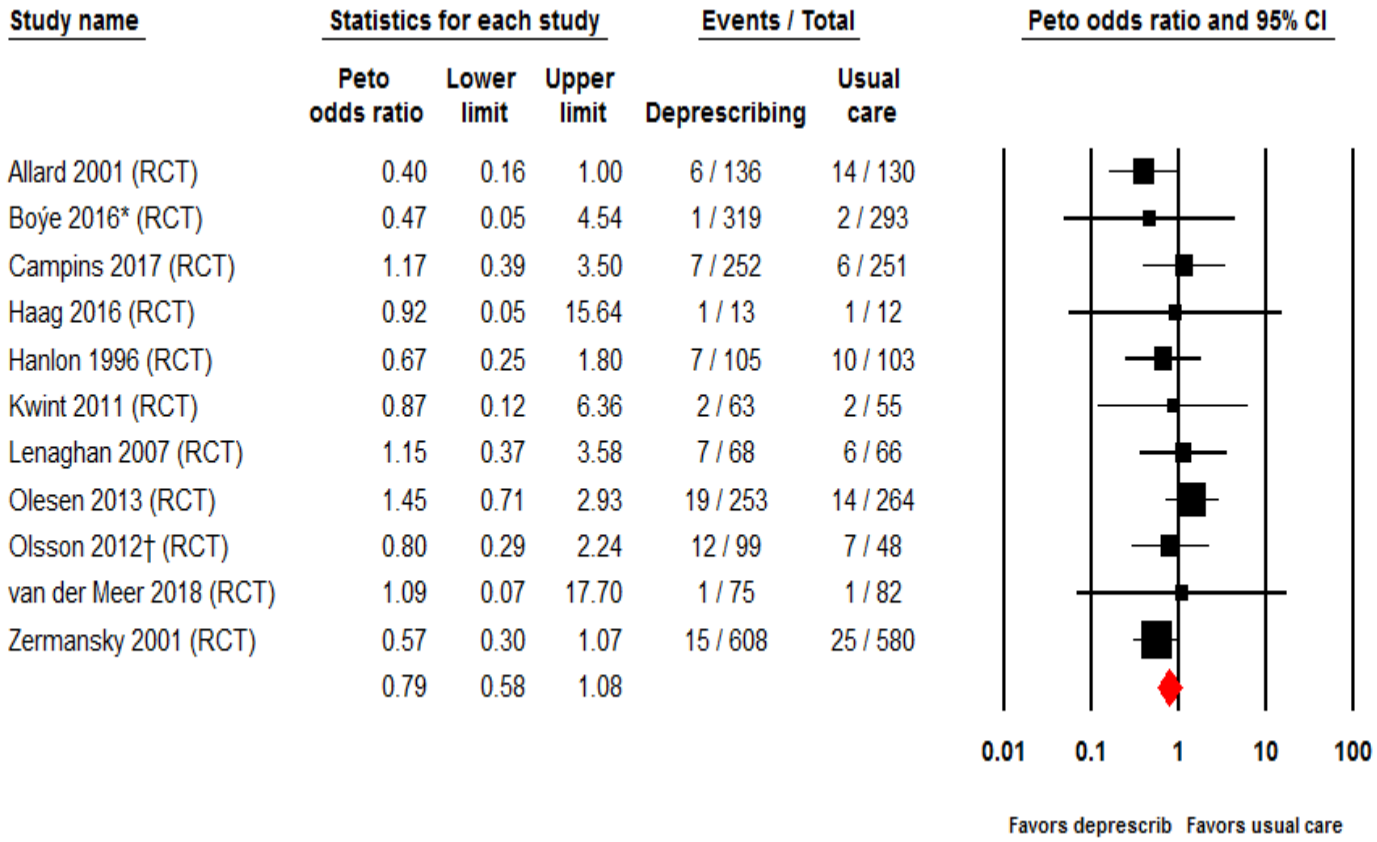
Primary Outcomes

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



$I^2 = 0\%$

* 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]

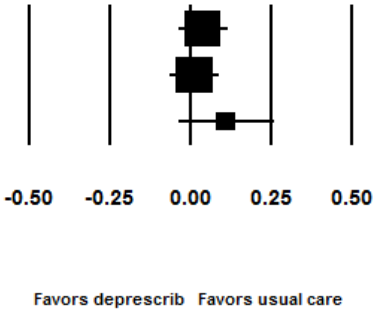
Results from the other 3 trials are summarized in Figure 5. In the IMPROveFALL trial that enrolled 612 older adults who had visited an emergency room because of a fall, there was no difference between intervention and control groups at 12 months in either the number of falls (37% vs 34%; absolute risk 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

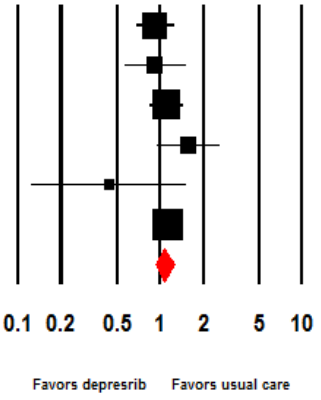
Study name	Risk difference	Lower limit	Upper limit	Events / Total: Deprescrib	Events / Total: Usual Care
Boÿe 2016 (RCT)	0.04	-0.04	0.12	115 / 308	91 / 272
Meredith 2002 (RCT)	0.01	-0.06	0.09	17 / 140	15 / 137
van der Meer 2018 (RCT)	0.11	-0.04	0.26	18 / 59	15 / 77



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	Risk ratio	Lower limit	Upper limit	Events / Total: Deprescrib	Events / Total: 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		



$I^2 = 12\%$

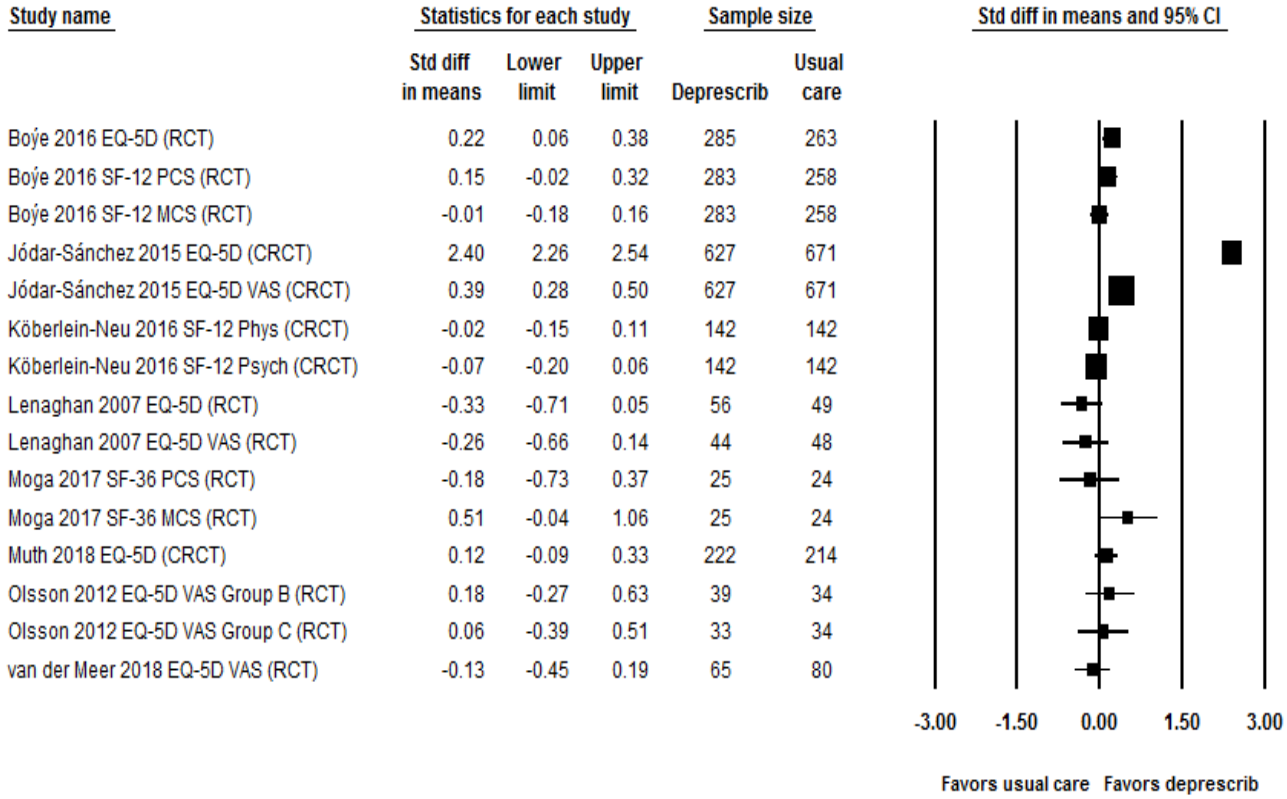
* Data from 3-6 month follow-up with basic and enhanced CMR arms combined

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



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 Number enrolled Length of follow-up	Findings
Allard, 2001[14] n=266 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] n=503 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] n=25 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] n=208 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] Malet-Larrea 2016, 2017[62,63] n=1403 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] n=136 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] n=505 9 months	Adjusted mean difference in number of medications between 2 groups: 1.0 (1.0 to 1.1)
Olsson, 2012[73] n=150 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] n=620 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] n=1188 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

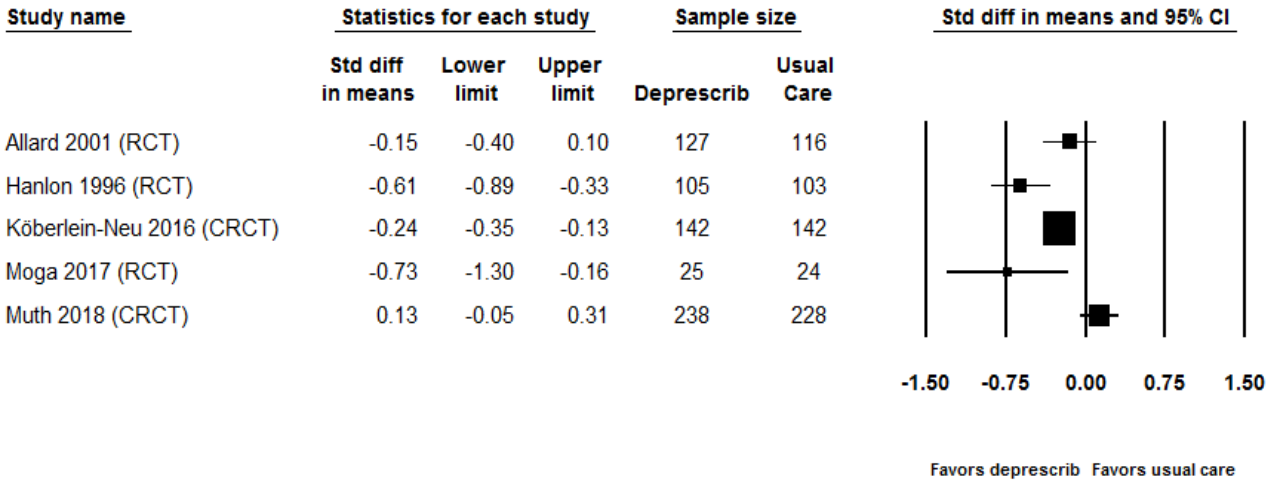
Table 3. Potentially Inappropriate Medications – CMR Studies

Author Number enrolled Length of follow-up	Findings
Allard, 2001[14] n=266 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 n=612 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] n=738 6 months	% of recommendations leading to a medication change: Case conference group: 29.8% vs 17.2% in written feedback group, P=.02; % of maintained medication change at 6 months: 25.5% vs 14.8%, P=.03
Haag, 2016[46] n=25 1 month	No difference between groups in any of multiple measure of PIMs
Hanlon 1996, Schmader 1997[47,92] n=208 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] n=142 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] n=259 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] n=50 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] n=505 9 months	Adjusted mean difference between groups at 6 months: MAI score 0.7 (95% CI: -0.2 to 1.6)
Olsson, 2012[73] n=150 12 months	Change from baseline in % of patients on PIMs was not significant in any of the 3 groups
Shim, 2018[96] n=160 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] n=157 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



* 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

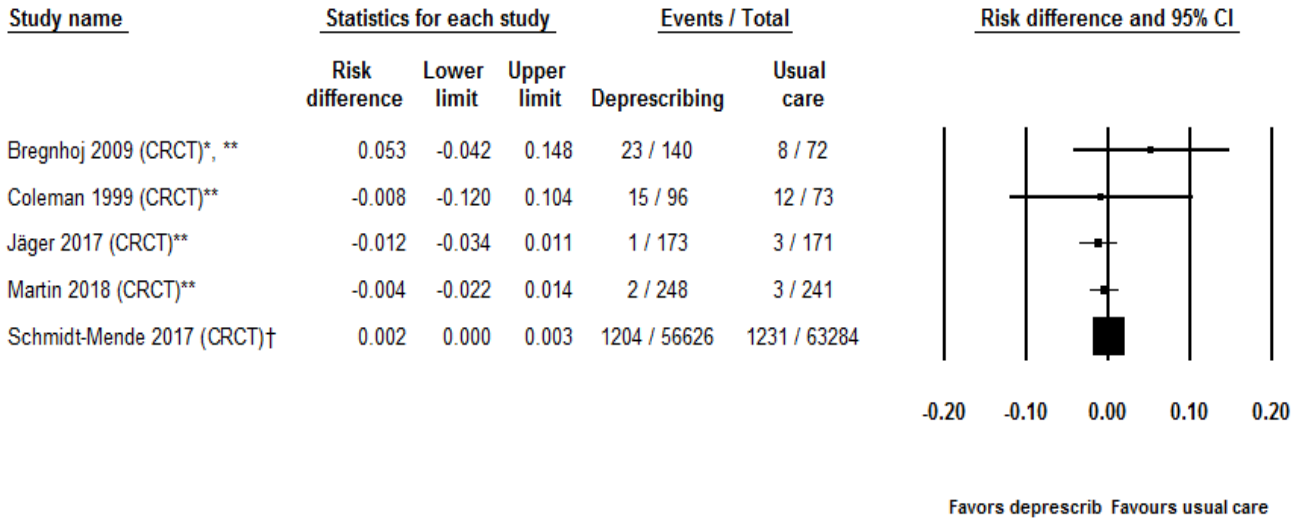
bias to be low in half the trials and medium in the other half (Appendix D, Table 9). Outcomes were reported on a total of 2424 patients in the 7 smaller trials and on 252,684 in the 3 larger trials.

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



* 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 Number enrolled Length of follow-up	Intervention	Risk of Bias	Total Number of Medications at Follow up
Bregnhoj, 2009[21] n=212 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] n=604 12 months	Narrative medicine-based physician-patient dialog sessions	Low	Intervention: 7.3, Control: 6.8, P=.09
Schmidt-Mende, 2017[95] n=119,910 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) Tricyclics: -17.1 (-19.3 to -14.9) Antipsychotics: -24.7 (-27.7 to -21.7) 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
• Treat patients as individuals • Providing education about safer alternatives to current medication regimen • Improve quality of prescribing by addressing costs of medication and difficulties associated with taking medications (*eg*, size, texture, taste)	• Patients did not identify with patient stories presented in education materials they received • Deprescribing not emphasized by providers • Not provided with alternatives to current medication regimen

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

- 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)
    - 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

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.

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APPENDIX A. SEARCH STRATEGIES

MEDLINE SEARCH STRATEGY (OVERALL SEARCH)

1 exp "Aged, 80 and over"/ or exp Aged/

2 exp Frail Elderly/ or frail$.ti,ab.

3 (aged or senior$ or elder$ or geriatric$ or veteran$ or dement$ or Alzheimer$ or ("65" adj year$)).ti,ab.

4 exp Veterans/

5 (old$ adj2 (patient$ or person$ or people or adult$ or inpatient$ or outpatient$ or resident$)).ti,ab.

6 exp Homes for the Aged/ or exp Nursing Homes/ or exp Palliative Care/ or exp Hospice Care/ or ("nursing home" or "residential facility" or "retirement village$" or hospice or palliative).ti,ab.

7 exp Drug Utilization/

8 exp Polypharmacy/ or polypharm$.mp.

9 exp Medication Errors/ or exp Inappropriate Prescribing/

10 ((multi-drug$ or multidrug$) adj3 (prescri$ or regimen$ or therap$ or treatment$)).ti,ab.

11 ((excess$ or inappropriate$ or appropriat$ or multi$ or unnecessary) adj3 (drug$ or prescrip$ or prescrib$ or medication$)).mp.

12 ((incorrect or concurrent or concomitant$ or inadvert$ or suboptim$ or sub-optim$) adj3 (drug$ or prescrip$ or prescrib$ or medication$)).mp.

13 ((over adj1 prescri$) or (over-prescri$ or overprescri$)).ti,ab.

14 or/1-5

15 or/6-13

16 14 and 15

17 exp Deprescriptions/

18 exp Potentially Inappropriate Medication List/

19 (deprescrib$ or de-prescrib$ or deprescipt$ or de-prescript$).ti,ab.

20 (Beer$ adj2 (criter$ or list$)).ti,ab.

21 STOPP.ti,ab.

22 (IPET or "Improving Prescribing").ti,ab.

23 (ACOVE or "Assessing Care").ti,ab.

24 (MAI or "Medication Appropriateness").ti,ab.

25 ("GP-GP" or "good palliative").ti,ab.

26 (FORTA or "fit for the aged").ti,ab.

27 PRISCUS.ti,ab.

28 (RASP or "rationali#ation of polypharmacy").ti,ab.

29 (PIM or "potentially inappropriate medication").mp.

30 (Garfinkel adj2 (algorithm or method)).ti,ab.

31 (DBI or "drug burden index").ti,ab.

32 ((improv$ or quality or quantit$) adj3 (drug$ or prescrip$ or prescrib$ or medication$)).mp.

33 Medication therapy management.mp. or exp Medication Therapy Management/

34 exp Medication Reconciliation/ or exp Drug Utilization Review/

35 ("multidisciplinary team" or "case conference" or "patient care team" or care program$).ti,ab.

36 exp "Drug-Related Side Effects and Adverse Reactions"/

37 ((medication$ or drug$) adj2 (review$ or reconciliation)).ti,ab.

38 Decision support systems.mp. or exp Decision Support Systems, Clinical/

39 ((medica$ or clinical or computer$) adj2 decision).ti,ab.

40 exp Geriatric Assessment/

41 exp Electronic Health Records/

42 exp Medication Errors/pc [Prevention & Control]

43 exp Medical Order Entry Systems/

44 (CPOE or ("computeri#ed" adj2 "order entry")).ti,ab.

45 ((medication or prescri$ or drug) adj2 (manage$ or review$ or reconciliation or error$)).ti,ab.

46 ((Electronic or e-) adj2 (prescri$ or medication$)).ti,ab. or exp Electronic Prescribing/

47 exp Communication/ or exp Inservice Training/ or exp Nursing staff/education

48 or/17-47

49 16 and 48

50 limit 49 to english language

51 limit 50 to yr="1990 -Current"

52 randomized controlled trial.pt.

53 controlled clinical trial.pt.

54 exp Randomized Controlled Trial/

55 (random$ adj (enroll$ or assign$ or allocat$)).ti,ab.

56 ((randomi#ed or non-randomi#ed or nonrandom#ed or controlled or placebo or clinical) adj2 trial$).ti,ab.

57 or/52-56

58 51 and 57

MEDLINE SEARCH STRATEGY (BARRIERS AND FACILITATORS SEARCH)

1 exp "Aged, 80 and over"/ or exp Aged/

2 exp Frail Elderly/ or frail$.ti,ab.

3 (aged or senior$ or elder$ or geriatric$ or veteran$ or dement$ or Alzheimer$ or ("65" adj year$)).ti,ab.

4 exp Veterans/

5 (old$ adj3 (patient$ or person$ or people or adult$ or inpatient$ or outpatient$ or resident$)).ti,ab.

6 exp Homes for the Aged/ or exp Nursing Homes/ or ("nursing home" or "residential facilit$" or "retirement village$" or hospice or palliative).ti,ab.

7 exp Drug Utilization/

8 exp Polypharmacy/ or polypharm$.mp.

9 exp Medication Errors/ or exp Inappropriate Prescribing/

10 ((multi-drug$ or multidrug$) adj3 (prescri$ or regimen$ or therap$ or treatment$)).ti,ab.

11 ((excess$ or inappropriate$ or appropriat$ or multi$ or unnecessary) adj3 (drug$ or prescrip$ or prescrib$ or medication$)).mp.

12 ((incorrect or concurrent or concomitant$ or inadvert$ or suboptim$ or sub-optim$) adj3 (drug$ or prescrip$ or prescrib$ or medication$)).mp.

13 ((over adj1 prescri$) or (over-prescri$ or overprescri$)).ti,ab.

14 or/1-5

15 or/6-13

16 14 and 15

17 exp Deprescriptions/

18 exp Potentially Inappropriate Medication List/

19 (deprescrib$ or de-prescrib$ or deprescipt$ or de-prescript$).ti,ab.

20 ((improv$ or quality or quantit$ or discontinue$ or withdraw$ or ceas$ or cessation or reduc$ or optim$) adj3 (drug$ or prescrip$ or prescrib$ or medication$ or medicine$ or polypharmacy)).mp.

21 or/17-20

22 exp "Attitude of Health Personnel"/

23 exp Qualitative Research/

24 exp Implementation Science/

25 exp Quality Improvement/

26 exp Interviews as Topic/

27 exp Focus Groups/

28 exp "Surveys and Questionnaires"/

29 (barrier$ or facilitator$ or enabler$ or belief$ or perception$ or attitude$ or perspective$ or preference$ or insight$ or experience$).ti,ab.

30 (interview$ or discussion$ or questionnaire$ or "focus group$" or qualitativ$ or survey$).ti,ab.

31 or/22-30

32 16 and 21 and 31

33 limit 32 to (address or autobiography or bibliography or biography or case reports or clinical trials, veterinary as topic or comment or congress or consensus development conference or consensus development conference, nih or dataset or dictionary or directory or editorial or "expression of concern" or festschrift or historical article or interactive tutorial or introductory journal article or lecture or legal case or legislation or letter or news or newspaper article or observational study, veterinary or patient education handout or periodical index or personal narrative or portrait or twin study or video-audio media or webcasts)

34 32 not 33

35 limit 34 to (english language and humans and yr="1990 -Current")

APPENDIX B. PEER REVIEW COMMENTS/AUTHOR RESPONSES

Question Text	Comment	Authors' Responses
Are the objectives, scope, and methods for this review clearly described?	Yes	Thank you.
	Yes	
	Yes	
	Yes	
	Yes	
	Yes	
	Yes	
	Yes	
Is there any indication of bias in our synthesis of the evidence?	No	Thank you.
	No	
	No	
	No	
	No	
	No	
	No	
	No	
Are there any published or unpublished studies that we may have overlooked?	Yes - Please see question in the "Additional Suggestions" regarding studies by Amy Linsky et al. on prescriber perceptions.	See response in "Additional Suggestions" section.
	Yes - Polypharmacy and injurious falls in older adults: a nationwide nested case-control study. Morin L, Calderon Larrañaga A, Welmer AK, Rizzuto D, Wastesson JW, Johnell K. Clin Epidemiol. 2019 Jun 24;11:483-493. doi: 10.2147/CLEP.S201614. eCollection 2019. PMID: 31296999	Thank you for the suggestion. The study by Morin et al. is a nested case-control study and therefore not eligible for inclusion in our review (KQ1).
	No	Thank you.
	No	
	No	
	No	
	No	
	No	

Additional suggestions or comments can be provided below. If applicable, please indicate the page and line numbers from the draft report.	This Evidence Synthesis Program is comprehensive and well done. The method of evaluation and analyses used to assess the studies included was well described and excellently conducted. As such, the comments for this review are based on structure versus content, except for a specific question regarding potential studies not included in Key Question 2. All recommended edits follow.	Thank you.
	Page 11 Line 43. The authors should emphasize that the same demographic inclusion criteria were not used for Key Question 2 (i.e. demographics presented in some of the trials are < than mean age of 65 years).	We clarified that the demographic inclusion criteria for the population receiving the intervention were the same for both KQs but most information for KQ2 was collected from providers or others involved in implementing the intervention.
	Page 17 Line 43. Did the authors assess 3 studies by Linsky, Amy et. al. that evaluate prescriber/provider perception in medication discontinuation? Were the studies reviewed and excluded as part of the full text articles identified? If they were not reviewed what was the reason?	The studies by Linsky et al. were reviewed and are included in the Discussion section for KQ2. The studies did not focus on a specific deprescribing intervention.
	Page 23. Line 19 Table 2. The table should be presented in a succinct, descriptive and easy to follow format. Consider breaking findings down into: Intervention, Changes in Medication, Bias. In addition, the studies should be organized into a standard and consistent format either as studies exhibiting a change first vs those without a change, chronological, reverse chronological or alphabetical. The current format of the table takes away from the strength of the information presented.	We re-arranged 2 and 3 (and all of the tables in the Results section) by alphabetical order of the study authors.
	Page 24. Line 7 Table 3. Similar recommendation to Table 2 however the heading under findings will be for PIM vs Changes in Medications.	
	Page 76. Appendix C. Table 1. Comprehensive Medication Review Table 1. Line 32. Inclusion/Exclusion criteria should have the number of medications separated out on its own line and spaced out from the previous inclusion criteria. This should be done for each study so the reader can easily identify the number of medications.	Thank you for the suggestion. We have the actual number of medications in the Demographics/Characteristics column (note: in final report, Appendix C is now Appendix D)
	Table 1. Line 25. Consider changing demographic title to Demographic/Characteristics.	We made the suggested change.
	Page 121. Appendix C. Table 8. Education Interventions Table 8. Line 32. Same recommendation as in Table 1, CMR. Recommend placing number of medications on a separate line in the inclusion criteria.	See comment above
	Table 8. Line 26. Consider changing demographic title to Demographic/Characteristics.	This change was made.

The authors undertook a systematic review of the evidence for interventions focused on deprescribing medications in older adults. Overall this is an excellent effort both in its methods and description. Please see my specific comments below, most of which apply to both the executive summary and full report.	Thank you.
1. Manuscript search and eligibility criteria for KQ2. On page 2 and 11, search and eligibility criteria for both KQ1 and KQ2 are discussed. These questions, the search, and criteria for inclusion are clearly different, but it is unclear from the manuscript, how they are different. For instance, do the exclusion criteria of "no intervention" apply to KQ2 since the KQ2 search criteria used observational studies? These differences should be clarified and include the rationale for in eligibility criteria and the search strategy.	1. As noted above, we clarified that the demographic inclusion criteria for the population receiving the intervention were the same for both KQs but most information for KQ2 was collected from providers or others involved in implementing the intervention. For KQ2, there had to be a deprescribing intervention (*ie,* we did not include studies assessing provider attitudes, in general, about deprescribing).
2. It unclear if the 4 categories of intervention (CMR, etc.) were chosen a priori or as a result of the review. The way the report is written leads me to think it was a priori.	2. Our literature search was broad and not limited to particular intervention types. We organized eligible studies into clinically relevant categories as discussed with our Operational Partners and Technical Expert Panel members.
3. What was the rationale for stratifying the review by in patient vs. outpatient settings.	3. This was done to manage the scope of the review and to report findings for clinically relevant subpopulations.
4. A large proportion of the papers were excluded in the abstract review phase for both questions. Do the authors have an information on why they were excluded?	4. We do not track reasons for exclusion at the abstract level.
5. The effect of the intervention on prescribing is listed as a potential mediator of patient-centered outcomes. The effect on this intervening outcome appears to be pretty low (table 2 on page 23). Could this be a primary mediator of the small effect generally seen in patient-centered outcomes? This issue should be identified and discussed in the discussion.	5. Due to the low number of events and heterogeneity of the studies, there was not enough data to speculate on mediators.
6. Patient perspective on implementation (Page 46). The paragraph at the end of this page is confusing. Perhaps a small table as in the following page would clarify.	6. Thank you for the suggestion. We replaced the text with a table.
7. Prescriber perspective on interventions (Page 47). Some of the barriers/facilitators listed seem to be intervention specific where as other pertain to a provider's opinion on the overall concept of deprescribing. Perspectives on both concept seem to be intermingled in this table. Perhaps a separate table, earlier, which lists provider perspectives on the	7. All of the studies included for KQ2 involved assessment of barriers and facilitators following implementation of a deprescribing intervention. The provider perspectives table represents feedback following implementation of

concept of deprescribing irrespective of the intervention used on them. 8. Page 6. The authors should clarify what “moderate certainty” means in the executive summary. 9. Page 7 line 10-14. The first sentence here is very hard to follow. 10. Page 7 Conclusions. Shouldn’t a main conclusion be the need to increase the evidence (certainty of evidence) on CMR interventions in VA? Additional comments (Page 4 line 46: Heading “Computer Decision Support” is “computer-based” in line 25 Page 4 line 58: Suggest listing categories at end of bullet to clarify Page 5 line 20: Key Messages: What was the evidence synthesis for CMR in these settings – it should be listed or reasons why it’s not Page 5 line 53: Key Messages: “We found few studies” – better to list the number Page 11 line 47: Still unclear if these exclusion criteria applied to both KQ1 and KQ2? If they did, what was the rationale? Search and exclusion criteria for KQ2 is confusing. This appears to be a separate search using separate exclusion criteria but how and if it differs from that of KQ1 is still unclear. Page 46, lines 42-43: Incomplete sentence	comprehensive medication review. We attempted to clarify this in the text and the table title. 8. We added the definitions regarding certainty to the Executive Summary. 9. This sentence was modified. 10. We added this point to the Conclusions. Additional comments Line 46. We made this heading consistent throughout the report. Line 58. We added the categories. Line 30. This Key Message refers to the studies included in the Evidence Map. We do not report (or synthesize) findings from those studies. Line 53. The number of studies has been added. Line 47. The exclusion criteria were similar for KQ1 and KQ2 and the list of criteria has been modified to show any differences. Line 42-43. This sentence was modified with the addition of a table summarizing the patient-reported barriers/facilitators.
This is a very comprehensive and complete systematic review that was conducted in a transparent and rigorous manner. The Summary sections are very helpful. The statements and conclusions were accurately worded, without overstepping the results of the review. The only recommendation is to add a couple sentences in the Research Gaps/Future Research section about what sort of trials (e.g., size, duration, etc) would be needed to address the "most glaring gap" of evidence of effectiveness of deprescribing interventions. There have now been several trials of small/moderate size, and the evidence is not strong for intervention effectiveness. Given that the authors are intimately aware of this literature, it would be helpful to readers to know more about their vision for what an ideal trial might look like.	Thank you. Thank you for the suggestion. The Research Gaps/Future Research section has been revised.
This report synthesizes the evidence regarding effectiveness of deprescribing in community settings on health and health processes in older adults. Strengths of the report are its clinical question, an a priori	Thank you.

	analytic framework, its study inclusion criteria (only including prospective controlled trials without high risk of bias), its examination of interventions of different types and potency (medication review, education, and computerized decision support), a good sample size of studies, reasonable homogeneity of aggregated studies, and rigorous analysis and reporting. The following recommendations are suggestions for improvement that would be considered optional: 1) Consider reporting in each section first the findings related to medication prescribing outcomes (e.g., number of medications, inappropriate medications, etc.) and, following that, reporting patient-centered outcomes (e.g., mortality, falls, hospitalization). This is because a) in many or most studies, the primary outcomes are medication-prescribing outcomes; b) the report's background and logical framework follows this logic; and c) readers may expect this sequence; i.e., examination of evidence of deprescribing effect on medication use before examining whether deprescribing has an impact on patient health. Some clarifications and questions: 2) It would be helpful to know up front when studies are not considered suitable for pooling, and why that is the case; 3) What is the certainty of evidence for the findings related to medication prescribing outcomes? 4) A comparison of the demographics (gender, age, ethnicity) in VA vs. non-VA studies may be appropriate to help VA readers understand the similarities and differences -- it is mentioned that older non-VA populations are predominantly women but many readers would want to know the actual numbers; 5) why were the same exclusion criteria used for KQ2 as for KQ1, since it seems that that question would allow studies without comparators, and would not necessarily require outcomes?	
	I was not clear about the start date and completion date for this review (I might have overlooked). Executive summary and intro were very clear. The charge to ESP was for DePrescribing approaches in the VA settings? There is much reporting on non-VA DePrescribing work...bottomline - not much work is ongoing in the VA with DePrescribing- that message has to be loud and clear. It would be more helpful to review, analyze, report and recommend strategies for CMR - that does not seem to be happening adequately - but is considered helpful as a DePrescribing strategy. It is startling that no studies addressed the comparative effectiveness of the DePrescribing interventions either with or across categories) and	Thank you for your observations.

	could be a recommendation for future, and be projected as a gap). Applicability would be insignificant - given there is not much VA related material and most patients are women, and from non VA, outside America. KQ 1.A : conclusion :: no explicit answers KQ 1 B. only 1 Norwegian study included providers (who are the most engaged, who touch the process regularly and almost solely) - this inclusion is critical and is not available. KQ 2: Again - not much information from within USA. Hard to extrapolate Canadian data to USA VA practice. Patient perspectives: Very true and are universal and applicable to all. Applicability to the VA from this article/submission is minimal - and potential to invest in such studies within USA, within VA is maximal. Agree with the conclusions. Well captured.	

APPENDIX C. EVIDENCE MAP – NURSING HOME, HOSPITAL, EMERGENCY DEPARTMENT, AND PALLIATIVE CARE SETTINGS

We identified 48 studies of deprescribing intervention for individuals age 65 and older in emergency department (k=2), hospital (k=21), nursing home (k=24), and palliative care (k=1) settings. Most studies were from Europe (k=29) with 9 from the US (1 in a VA setting), 8 from Australia/New Zealand, 1 from Canada, and 1 from Israel. Overall, sample sizes ranged from 11 to 5,162 with 6 studies enrolling fewer than 100, 25 enrolling between 100 and 500, and 16 enrolling more than 500; 1 study did not report enrollment. Most enrollees were female, and follow-up periods ranged from 0 (a study in an emergency department setting) to 24 months. Study designs included 27 RCTs, 16 cluster RCTs, and 5 CCTs. Of the 48 studies, 45 reported a measure of medication change (medication change was the primary outcome for 36 studies), 27 reported a measure of resource utilization or cost (resource utilization was the primary outcome for 6 studies), 36 reported a clinical outcome (mortality was the primary outcome for 1 study), and 19 reported a measure of functional status, quality of life, or patient satisfaction. Five studies did not specify a primary outcome. Information about each of the studies is provided in Appendix D, Table 26.

Sixty percent of the studies involved CMR (k=29). Ten studies reported on an educational intervention, 3 on a computer decision support intervention, 1 on comprehensive geriatric assessment, and 5 on multicomponent interventions (typically consisting of medication review and provider and/or patient education).

Key Messages:

An evidence map characterizing key study and participant characteristics and reporting outcome of describing interventions identified the following:

- Most studies were conducted in Nursing Home or Hospital settings; little data exist from Emergency Department or Palliative Care settings
- Most studies were conducted in Europe. Only 1 study was conducted in a VA setting.
- Most enrollees were women
- CMR comprised the majority of studied interventions (60%; 29/48 studies)
- Medication change was the primary outcome for the large majority of studies (36/46: 75%) though patient-centered outcomes including mortality, hospitalizations, patient satisfaction, and functional status, as well as costs and resource use, were widely reported.

Comprehensive Medication Review (CMR)

Appendix C, Table 1 provides an overview of the 29 studies reporting on a CMR intervention. One study was from an emergency department,[22] 13 from nursing

homes,[17,23,31,32,36,38,58,65,69,74,75,82,104,106,111] 14 from hospitals,[18,33,39,42,45,48,61,68,76,81,93,98,102,108,109] and 1 from palliative care.[55]

The emergency department study was an RCT from Australia/New Zealand enrolling over 1,000 patients.[22] The study focused on hospital admissions with a follow-up of 4 months. A medication change outcome was also reported.

The 13 nursing home studies were largely from Australia/New Zealand or Europe and nearly evenly split between RCTs and cluster RCTs. Most enrolled over 100 with fewer than 50% male subjects. More than half had follow-up durations of 6 months or less. Three studies focused on specific medications including psychotropic drugs[74,75,106] and dopaminergic agents.[104] Six focused on appropriateness of medications overall[31,32,36,58,69,111] while 2 addressed the number of medications.[17,82] The remaining 2 studies focused on reducing costs and resources including staff time.[23,38,65] Medication change and clinical outcomes were reported in nearly all studies. Fewer reported on resource utilization/cost or functional status, quality of life, or patient satisfaction.

Of the 14 hospital-based studies, 13 were conducted in Europe. The 1 exception was a VA study.[93] Most studies were RCTS enrolling between 101 and 500 with follow-up durations of 4 months or longer. In several studies, the objective was reducing readmissions[42,45,61,102] or drug-related problems.[76,93,108,109] Others focused on reducing the number of medications,[68,81] particularly inappropriate medications.[18,33,39,48,98] Nearly all hospital-based studies reported on medication change and clinical outcomes. Fewer reported on resource utilization/costs and functional status, quality of life, or patient satisfaction outcomes were infrequently reported.

The 1 palliative care study was an RCT, conducted in the US, and enrolled 381 patients (55% male).[55] Follow-up was 12 months. The focus was on discontinuation of statin medications with the primary outcome of mortality within 60 days of enrollment. The study also reported measures of medication change, resource utilization or cost, and functional status, quality of life, or patient satisfaction.

Appendix C, Table 1. Number of Studies Reporting Characteristics of CMR Interventions for Deprescribing in Nursing Home, Hospital, Emergency Department, and Palliative Care Settings (k=29)

Characteristics	Nursing Home (k=13)	Hospital (k=14)	Emergency Department (k=1)	Palliative Care (k=1)
Country/Region				
USA	2	1 (VA-based)		1
Canada				
Europe	5	13		
Australia/New Zealand	5		1	
Other	1			
Study Design				
RCT	6	12	1	1
Cluster RCT	5			
CCT	2	2		
Number Enrolled[a]				
≤ 10				
11-50	2			
51-100	1	2		
101-500	9[b]	11		1
> 500		1	1	
Percent Male			NR	
≤ 10 %				
11%-30%	5			
31%-50%	7	11		
> 50%	1	1[c]		1
Outcomes Reported				
Medication Changes	12	13	1	1
Resource Utilization/Costs	8	9	1	1
Clinical	11	12		1
Functional Status/Quality of Life/Patient Satisfaction	7	4		1
Follow-up Duration (months)				
< 1		2		
1-3	5	2		
4-6	3	4	1	
> 6	5	6		1

CCT=controlled clinical trial; CMR=comprehensive medication review; RCT=randomized controlled trial; VA=Department of Veterans Affairs

[a]Reported sample size indicates number of participants; in CRCTs, effective sample size is less than if single center study

[b]1 additional study did not report sample size

[c]1 additional studies did not report % male

Education

We provide an overview of the 10 studies reporting on an educational intervention in Appendix C, Table 2. There were 7 studies in nursing homes[15,29,40,51,52,66,79,94,99] and 3 in hospital settings.[16,43,103]

The 7 nursing home studies were conducted in the US or Europe and were predominantly cluster RCTs. Although the number enrolled was moderate-to-large, the effective sample size is less due to the cluster design. Most enrolled predominantly women and included follow-up durations of 1 to greater than 6 months. Five studies focused on specific medications including non-steroidal anti-inflammatory drugs[99] and psychotropic drugs[15,51,52,66,79,94] while 2 focused more broadly on inappropriate prescribing.[29,40] All studies reported a measure of medication change with all but 2[66,94] reporting at least 1 outcome in the other categories of interest.

The 3 hospital-based studies were conducted in Europe or Australia/New Zealand and included 2 cluster RCTs and 1 RCT. One enrolled a small sample size, and in all studies 50% or less of enrollees were male. Follow-up periods were 3 months or less. One of the studies focused on benzodiazepine withdrawal[43] and another on appropriateness of benzodiazepines.[16] The third intervention was directed toward reducing adverse drug events.[103] All studies reported a measure of medication change, 1 reported a measure of functional status, quality of life, or patient satisfaction, and none reported resource utilization, costs, or clinical outcomes.

Appendix C, Table 2. Number of Studies Reporting Characteristics of Education Interventions for Deprescribing in Nursing Home, Hospital, Emergency Department, and Palliative Care Settings (k=10)

Characteristics	Nursing Home (k=7)	Hospital (k=3)	Emergency Department (k=0)	Palliative Care (k=0)
Country/Region				
USA	3			
Canada				
Europe	4	2		
Australia/New Zealand		1		
Other				
Study Design				
RCT		1		
Cluster RCT	6	2		
CCT	1			
Number Enrolled[a]				
≤ 10				
11-50		1		
51-100				
101-500	2			
>500	5	2		
Percent Male				
≤ 10 %				
11%-30%	5			
31%-50%	1[b]	2[a]		
>50%				
Outcomes Reported				
Medication Changes	7	3		
Resource Utilization/Costs	4			
Clinical	5			
Functional Status/Quality of Life/Patient Satisfaction	3	1		
Follow-up Duration (months)				
< 1		1		
1-3	2	2		
4-6	2			
>6	3			

CCT=controlled clinical trial; RCT=randomized controlled trial; VA=Department of Veterans Affairs

[a]Reported sample size indicates number of participants; in CRCTs, effective sample size is less than if single center study

[b]1 additional study did not report % male

Computer Decision Support

Three RCTs evaluated computer support for deprescribing.[30,35,101]

Two studies were from the US with 1 taking place in an emergency department[101] and 1 in nursing homes.[35] The emergency department study included 5,162 patient visits; 35% of the visits were by males. The goal was to examine the effect of decision support on prescribing of potentially inappropriate medications, with the primary outcome being the proportion of emergency department visits by older adults that resulted in at least 1 prescription for an inappropriate medication. No resource utilization, cost, clinical, functional status, quality of life, or patient satisfaction outcomes were reported. Hospital admissions and deaths in the emergency department were excluded.[101] The nursing home study enrolled 813 patients (29% male). The objective of the study was to determine if implementing a decision support system with specific recommendations for dose and choice of psychotropic drugs would increase prescription of recommended treatment and decrease prescription of non-recommended treatment. The primary outcome was the percentage of psychotropic medication orders that were modified in response to an alert. As in the emergency department study, no resource utilization, cost, clinical, functional status, quality of life, or patient satisfaction outcomes were reported.[35]

The third study was from Canada and was conducted in a hospital setting.[30] The study enrolled 231 patients with 254 hospitalizations; 40% of the patients were male. The goal of the study was to assess the medication changes implemented for targeted potentially inappropriate medications, with a primary outcome of the number of discontinued drugs or drugs with dosage decreased. Follow-up was 1 month and reported outcomes included medication changes, resource utilization/costs, and clinical outcomes.[30]

Comprehensive Geriatric Assessment

One RCT from Europe investigated whether medication treatment was more appropriate when hospitalized patients were assigned to a geriatric evaluation and management unit versus general medical wards.[90] The study enrolled 254 with 35% male. The primary outcome was change in medication regimen from enrollment to hospital discharge. At least 1 clinical outcome was also reported. Length of hospital stay was not reported.

Multicomponent

Five studies reported on a multicomponent intervention for deprescribing (Appendix C, Table 3).[19,44,49,59,85,86,88] Three studies were conducted in nursing home settings[44,49,86,88] and 2 in hospital settings.[19,59,85]

The nursing home studies were cluster RCTs conducted in Australia/New Zealand[88] or Europe.[44,49,86] Although the number enrolled was moderate/large, caution in interpretation is needed due to the cluster design. Fewer than one-third of enrollees were male and follow-up periods ranged from 9 to 22 months. One study focused on antipsychotic medications[86] and 1 on antihypertensive medication.[44,49] The third study addressed number of prescribed medications with the goal of changing drug use, mortality, and morbidity.[88] Each of the studies reported on medication change, clinical outcomes, and functional status, quality of life, or patient satisfaction. One study also reported a measure of resource utilization or costs.[88]

Two RCTs, both from Europe, were set in hospitals.[19,59,85] These studies also enrolled moderate-to-large sample size with approximately 45% male. Both studies had a follow-up duration of 6 months. In both studies, the primary outcome was readmissions or emergency department visits within 6 months of the index hospitalization. Both studies also reported a clinical outcome and 1 study reported a medication change outcome.[19,59]

Appendix C, Table 3. Number of Studies Reporting Characteristics of Multicomponent Interventions for Deprescribing in Nursing Home, Hospital, Emergency Department, and Palliative Care Settings (k=5)

Characteristics	Nursing Home (k=3)	Hospital (k=2)	Emergency Department (k=0)	Palliative Care (k=0)
Country/Region				
USA				
Canada				
Europe	2	2		
Australia/New Zealand	1			
Other				
Study Design				
RCT		2		
Cluster RCT	3			
CCT				
Number Enrolled[a]				
≤ 10				
11-50				
51-100				
101-500	1			
>500	2	2		
Percent Male				
≤ 10 %				
11%-30%	2[b]			
31%-50%		2		
>50%				
Outcomes Reported				
Medication Changes	3	1		
Resource Utilization/Costs	1	2		
Clinical	3	2		
Functional Status/Quality of Life/Patient Satisfaction	3			
Follow-up Duration (months)				
< 1				
1-3				
4-6		2		
>6	3			

CCT=controlled clinical trial; RCT=randomized controlled trial; VA=Department of Veterans Affairs

[a]Reported sample size indicates number of participants; in CRCTs, effective sample size is less than if single center study

[b]1 additional study did not report % male

APPENDIX D. EVIDENCE TABLES

Appendix D, Table 1. Study Characteristics – Comprehensive Medication Review

Author, year Trial name Country Funding Study Design Setting Intervention type	Inclusion/Exclusion Criteria	Intervention (n) Control (n) Clusters (if applicable) Follow-up	Demographics/Characteristics
Allard 2001[14] Canada Funding: NR RCT Community Medication review and monthly follow-up	Inclusion: Age >75 years, living in community, at risk of losing their autonomy, taking >3 medications per day Exclusion: <2 risk factors as identified using the Sherbrooke Postal Questionnaire	Intervention: Home visit by a nurse with full medication review followed by comprehensive medication review by 2 physicians, a pharmacist, and a nurse; suggested medication changes mailed to patient's physician; monthly RN phone visits to track med changes (n=127 randomized; n=80 participated in the intervention): Control: Normal social and health care services (n=116): Follow-up: 1 year	N=266 Age (mean): 81 Gender (% male): 32 Race/ethnicity: NR Mean length of stay: NR Comorbidity status: NR Physical status: NR Cognitive status: NR Number of medications (mean (SD)): Experimental (ITT, n=127) 6.1 (1.8) Experimental (per protocol, n=80) 6.3 (2.6) Control (n=116) 6.5 (2.6)

Author, year Trial name Country Funding Study Design Setting Intervention type	Inclusion/Exclusion Criteria	Intervention (n) Control (n) Clusters (if applicable) Follow-up	Demographics/Characteristics
Boyé 2017[20] Polinder 2016[80] IMPROveFALL The Netherlands Funding: Government RCT Community Medication review (FRIDs)	Inclusion: Age ≥65 years, community-dwelling, MMSE score 21/30 or higher; able to walk independently, ED visit because of a fall (defined as coming to rest unintentionally on the ground or a lower level with or without losing consciousness but not induced by acute medical conditions (*eg,* stroke) or exogenous factors (*eg,* traffic accident)), use of 1 or more FRIDs Exclusion: Participant in another trial, fall not meeting definition, likely problems with maintaining follow-up, not willing to complete research protocol	Intervention: Fall-related assessment, FRIDs discontinued or reduced where safely possible in consultation with senior geriatrician and prescribing physician (n=319) Control: Fall-related assessment + usual care (n=293) Follow-up: 12 months	N=612 Age (mean): 76.5 Gender (% male): 38 Race/ethnicity: NR Comorbidity status: Charlson 1.9 Physical status: ADLs 0.80 Cognitive status: MMSE (mean) 27 Number of medications (mean): 6.3
Campins 2017, 2019[24,25] Spain Funding: Government RCT Community Medication review/guide lists	Inclusion: Age ≥70 years, community-dwelling, receiving ≥8 prescribed drugs (excluding topical ointments), resident of 1 of 2 designated municipalities Exclusion: Estimated life expectancy <6 months, active cancer, nursing home resident, participating in another drug evaluation trial or program for the elderly NOTE: randomly selected 10 patients per 54 family physicians (37 did not meet inclusion criteria or did not wish to participate)	Intervention: Pharmacist drug evaluation using GP-GP algorithm and STOPP/START criteria; shared recommendations with physician; final recommendations discussed with patient (n=252) Control: Usual care (n=251) Follow-up: 12 months	N=503 Age (mean): 79 Gender (% male): 41 Race/ethnicity: NR Comorbidity status: No difference in chronic illnesses between groups, except for depression which was more common in the intervention group Physical status: NR Cognitive status: NR Number of medications (mean): 10.8

Author, year Trial name Country Funding Study Design Setting Intervention type	Inclusion/Exclusion Criteria	Intervention (n) Control (n) Clusters (if applicable) Follow-up	Demographics/Characteristics
Denneboom 2007[34] The Netherlands Funding: Professional organization Cluster RCT Community pharmacy Medication review	Inclusion: Pharmacies registered with Service Apotheek Nederland (who supported the research activities) Patients: Age ≥75 years, home dwelling, taking at least 5 medications continuously Exclusion: Patients: terminal illness, deceased, lived in a home for older people, age < 75 years, used fewer than 5 medications	Intervention: Pharmacist review of medications (with help of computerized screening tool) and case conference with GP (n=15 pharmacies, 40 GPs, 387 patients) Control: Pharmacist review of medications (with help of a computerized screening tool) with written feedback to GPs (n=13 pharmacies, 37 GPs, 351 patients Primary endpoint: how many clinically relevant recommendations made by pharmacist, and number medication changes done Follow-up: 9 months	N=28 pharmacies, 77 GPs, 738 patients (analyzed) Age (mean): 81 years (patients) Gender (% male): intervention: 40.6, control: 34.9 Race/ethnicity: NR Comorbidity status: NR Physical status: NR Cognitive status: NR Number of medications (mean): intervention: 7.1, control: 7.3

Author, year **Trial name** **Country** **Funding** **Study Design** **Setting** **Intervention type**	**Inclusion/Exclusion Criteria**	**Intervention (n)** **Control (n)** **Clusters (if applicable)** **Follow-up**	**Demographics/Characteristics**
Haag 2016[46] United States Funding: Government RCT Community Medication review	Inclusion: Age ≥60 years; independently living adults; newly enrolled in local care transitions program (CTP) due to recent hospitalization; eligible for CTP if empaneled in primary care work group (study clinic site), resided within 20 min drive, predicted to be at risk for high healthcare utilization Exclusion: Patients with dementia or a terminal illness (Noted under **results** section)	Intervention: MTM consultation with pharmacist by telephone within 3 to 7 business days after hospital discharge (pharmacist completed review of all medications to identify drug-related adverse event, use of PIMS, and potential prescribing omissions); recommendations sent to CTP provider (n=13) Control: CTP without pharmacist intervention (home visit by NP within 3 business days of discharge, medication review and changes by NP; follow-up calls) (n=12) Follow-up: 30 days (NOTE: study mentions 30 days and 5 weeks for follow-up)	N=25 Age (mean): 83 Gender (% male): 76 Race/ethnicity: 96% white Comorbidity status (*ERA*): 19 Physical status: NR Cognitive status: NR Number of medications (median [IQR]): Intervention: 17 [12-20] Control: 15.5 [13-18.5] P=.96

Author, year Trial name Country Funding Study Design Setting Intervention type	Inclusion/Exclusion Criteria	Intervention (n) Control (n) Clusters (if applicable) Follow-up	Demographics/Characteristics
Hanlon 1996[47] Schmader 1997[92] United States Funding: Government, foundation RCT General medicine clinic Medication review	Inclusion: Age ≥65 years, evidence of polypharmacy (defined as ≥5 regularly scheduled medication by a VA physician), and received primary care in the general medicine clinic; patients with cognitive impairment were eligible if a caregiver was available to be involved in the intervention Exclusion: NR	Intervention: Medication review conducted by clinical pharmacist before visits; drug-related problems discussed with patients and caregivers and medications assessed using MAI; written recommendations presented orally and in writing to patients and primary physician; after physician visit, pharmacist educated patient regarding any drug-related problems detected before visit and medication changes made during visit; pharmacists encouraged medication compliance through enhancing strategies (reminder packages and calendars) and written education materials (n=105) Control: Usual care consisting of patients' medication review conducted by clinic nurse before visits; recommendations filed for review at end of study (n=103) Follow-up: 12 months	N=208 Age (mean): 69.8 Gender (% male): 99.1 Race/ethnicity: White 76.9% Comorbidity status: Number of chronic conditions (mean) 9.1 Physical status: NR Cognitive status: Cognitive impairment 10.1% Number of medications (mean): Intervention 7.6 vs control 8.2, P<.05

Author, year Trial name Country Funding Study Design Setting Intervention type	Inclusion/Exclusion Criteria	Intervention (n) Control (n) Clusters (if applicable) Follow-up	Demographics/Characteristics
Jodar-Sanchez 2015[50] Malet-Larrea 2016, 2017[62,63] ConSIGUE Spain Funding: Government, foundation Cluster RCT Community/ primary care Medication review	Inclusion (pharmacies): Able to recruit up to 10 polypharmacy patients aged ≥65 years and taking ≥5 medication for at least 6 months Exclusion: NR	Intervention: Patient interview followed by a comprehensive medication review, action plan developed with patient and physician if required (88 pharmacies, 688 patients) Control: usual care including dispensing medication and minor ailment advice (n=90 pharmacies, 715 patients) Clusters: community pharmacies and patients Follow-up: 6 months	Patients: N=1403 Age (mean): 75.1 Gender (% male): 40 Race/ethnicity: NR Comorbidity status: Health problems, control 4.9, intervention 4.3, P<.001; Uncontrolled health problems, control 1.5, intervention 0.7, P<.001 Physical status: NR Cognitive status: NR Number of medications (mean): control 7.7, intervention 7.4, P=.009

Author, year Trial name Country Funding Study Design Setting Intervention type	Inclusion/Exclusion Criteria	Intervention (n) Control (n) Clusters (if applicable) Follow-up	Demographics/Characteristics
Köberlein-Neu 2016[53] WestGem Study Germany Funding: Government Cluster RCT Community Medication review	Inclusion: Age ≥65 years, ≥3 chronic disorders affecting 2 different organ systems, ≥1 cardiovascular disease, ≥1 visit to the primary care physician in each of the preceding 3-month intervals, ≥5 long-term drug treatments (>3 months) with systemic effects, ability to complete questionnaires, with assistance if needed Exclusion: Life expectancy <12 months (assessed by the treating primary care physician), participation in another clinical study	Intervention: Interprofessional medication management that involved medication management and care provided by home-care specialists; home-care specialists arranged home visit, assessed patient drug use (drugs taken, adherence, reported problems with medication therapy) and communicated this to pharmacist, along with information provided by primary care physician; pharmacist undertook comprehensive medication review and summarized results in letter of recommendation sent to home-care specialists who in turn added information on patient's home situation and passed information on to primary care physicians (12 physicians, participants n=142). Control: usual care (no intervention) – same patients Follow-up: 15 months	N=142 Age (mean): 77 Gender (% male): 47 Race/ethnicity: NR Comorbidity status: Cumulative Illness Rating Scale-Geriatric (CIRS-G) severity index 1.63 Number of disorders: 12.7 Physical status: NR Cognitive status: NR Number of medications (mean): 9.4 The 12 physicians were allocated randomly to the 3 study cohorts (C) C1: start after the end of the recruitment period, C2: start after 3 months, C3: start after 6 months

Author, year Trial name Country Funding Study Design Setting Intervention type	Inclusion/Exclusion Criteria	Intervention (n) Control (n) Clusters (if applicable) Follow-up	Demographics/Characteristics
Krska 2001[54] United Kingdom Funding: Government (NHS) Cluster RCT Community Pharmacist-led medication review	Inclusion: Age ≥65 years, ≥2 chronic disease states, taking ≥4 prescribed medicines regularly Exclusion: Dementia, or being considered by the GP to be unable to cope with the study	Intervention: Pharmacists reviewed drug therapy of patients using information obtained from practice computer, medical records and patient interviews at their homes; pharmaceutical care plan then drawn up and implemented (n=168 patients) Control: No pharmaceutical care plan implemented (n=164 patients) Follow-up: 3 months	N=332 (381 randomized, 49 withdrew after randomization) Age (mean): 75 Gender (% male): 39 Race/ethnicity: NR Comorbidity status: NR Physical status: NR Cognitive status: NR Chronic diseases (mean): 4 Number of medications “actually being taken” (mean): 7.5
Kwint 2011[56]The Netherlands Funding: Private (but work was done independently) RCT Community Pharmacist-led medication review	Inclusion: Age ≥65 years, used ≥5 medications, and lived at home; >1 of medicines dispensed via an automated system Exclusion: NR	Intervention: Independent pharmacists reviewed data from both community pharmacy and GP collected by community pharmacist and included drug dispensing records, information on co-morbidity, drug intolerance, patient notes, & laboratory data; reviewers used both implicit and explicit criteria to identify potential DRPs (6 pharmacies, n=63 patients); medication reviews sent to community pharmacist to discuss with GP within 4 weeks Control: Wait list (n=55 patients) Follow-up: 6 months	N=118 (125 randomized, 7 excluded after randomization) Age (mean): 79 Gender (% male): 31 Race/ethnicity: NR Comorbidity status: NR Physical status: NR Cognitive status: NR Number of medications (mean): 10 per patient

Author, year Trial name Country Funding Study Design Setting Intervention type	Inclusion/Exclusion Criteria	Intervention (n) Control (n) Clusters (if applicable) Follow-up	Demographics/Characteristics
Lenaghan 2007[60] POLYMED United Kingdom Funding: Government RCT Community Pharmacist medication review	Inclusion; Age >80 years, living at home, on ≥4 daily oral medications AND 1 of these: living alone, record of confusion, vision or hearing impairment, prescribed medications associated with med-related morbidity; or prescribed >7 oral medications Exclusion: residence in nursing home or documented use of an adherence aid	Intervention: Home visits by pharmacist (drug interactions, adverse events, storage issues); pharmacist provided education, removed out-of-date drugs, and assessed need for adherence aids; pharmacist and GP held regular meetings to identify amendments to drug therapy, implemented by GP or practice dispensing team; follow-up visit occurred 6-8 weeks after initial visit (n=69) Control: Standard of care (n=67) Follow-up: 6 months	N=134 analyzed Age (mean): 84.3 Gender (% male): 34 Comorbidity status: NR Physical status: NR Cognitive status: NR Mean number of medications: Intervention (n=68): 9.0 Control (n=66):9.9
Meredith 2002[67] United States Funding: Government/other RCT Community (home healthcare patients) Medication review	Inclusion: Age ≥65 years, Medicare patients admitted to medical and surgical services of participating offices, had 1 of 4 possible study medication problems, met other criteria designed to assure they were candidates for attempting a medication change and could provide study data, identifiable physician who could be contacted to discuss medication changes, projected duration of home health care ≥4 weeks (as estimated by nurse on admission visit), reasonable likelihood of survival through study follow-up Exclusion: NR	Intervention: Medication improvement program that identified patients with potential medication problems and addressed these problems through structured collaboration between a specially trained clinical pharmacist and agency's visiting nurses + usual care (n=160) Control: Usual care (n=157) Follow-up: between 6 and 12 weeks	N=317, 259 for demographics Age (mean): 80 Gender (% male): 25 Race/ethnicity: NR Comorbidity status: NR Physical status: SF-36 physical composite 27 Cognitive status: MMSE 24.5 Number of medications (mean): NR

Author, year Trial name Country Funding Study Design Setting Intervention type	Inclusion/Exclusion Criteria	Intervention (n) Control (n) Clusters (if applicable) Follow-up	Demographics/Characteristics
Moga 2017[70] United States Funding: University, Government RCT University (clinic) Medication review	Inclusion: Age ≥65 years, actively enrolled in Alzheimer's disease clinic; reporting ≥1 drug with anticholinergic properties; willing to participate in study Exclusion: Moderate to severe dementia (measured via a Clinical Dementia Rating global score ≥2); living in a long-term facility	Both groups: Review of patient medication regimen between enrollment and visit 1 (randomization) Intervention: Meet with pharmacist/clinician team for MTM; study pharmacist provided revised medication plan based on drug review (aimed at reducing use of potentially inappropriate medications) (n=25) Control: Participants given opportunity to ask a pharmacist questions about their medications (n=25, 24 completed) Follow-up: 8 weeks	N= 50 Age (mean): 77.7 (6.6) Gender (% male): 30 Race/ethnicity: 90% White, 10% Black Comorbidity status: NR SF-36 Physical component: 63.8 (22.5) Mental component: 75.0 (17.8) Number of medications (mean): NR Number of Anticholinergic drugs: 1 = 50% ≥ 2 = 50%

Author, year Trial name Country Funding Study Design Setting Intervention type	Inclusion/Exclusion Criteria	Intervention (n) Control (n) Clusters (if applicable) Follow-up	Demographics/Characteristics
Muth 2018[71] Prioritising Multi-medication in Multimorbidity (PRIMUM) Germany Funding: Government Cluster RCT Primary Care Medication review with decision support tool	Inclusion: Practices: Healthcare assistant staff ability to access internet in practice Patients: Age >60 years; random sample (7 patients per practice) with ≥3 chronic conditions treated with medications, ≥5 long term systemic drugs, ≥1 visit in past quarter, able to fill in questionnaires and participate in telephone interviews, diseases affecting ≥2 organ systems Exclusion: Practices: Sites specializing in unconventional treatments or in special indications (*ie,* HIV) Patients: Diseases of eyes, ears and thyroid gland without hypothyroidism; dementia and cognitive impairments (MMSE <26); life expectancy ≤12 months; alcohol and drug abuse (clinician's assessment); participation in another clinical trial in past 30 days; nutraceuticals not rated per MAI	Intervention: Healthcare assistant conducted brown bag review; checklist-based interview with patient; CDSS-assisted medication review by GP; and GP-patient consultation to optimize and prioritize medications (n=252) Control: Usual care (n=253) Follow-up: 9 months	72 practice sites enrolled N=505 Age (mean): 72.1 Gender (% male): 47 Race/ethnicity: NR Comorbidity status: Charlson (mean): 3.1 Physical status: NR Cognitive status: NR but "intact cognition inclusion criteria" Number of prescriptions (mean): 8.0
Olesen 2013[72] Denmark Funding: Government and Association of Danish Pharmacies RCT Community Medication review and phone follow-up	Inclusion: Age ≥65 years; taking ≥5 prescriptions without assistance Exclusion: Nursing home resident, terminal illness, cognitive disorders, medication supervised by healthcare providers, immigration to Denmark after January 2005, and severe motor impairment	Intervention: Home visit by a pharmacist with a comprehensive medication review using a pharmaceutical care approach (explanation, education, attempt to decrease complexity of regimen); subsequent phone follow-ups at 3, 6, and 9 months (n=253) Control: Usual care (n=264) Follow-up: 24 months	N=517 Age (median): 74 Gender (% male): 48 Race/ethnicity: NR Comorbidity status: NR Physical status: NR Cognitive status: NR Number of medications (median): 7

Author, year Trial name Country Funding Study Design Setting Intervention type	Inclusion/Exclusion Criteria	Intervention (n) Control (n) Clusters (if applicable) Follow-up	Demographics/Characteristics
Olsson 2012[73] Sweden Funding; Government RCT (3 arm) community Medication review with home visits by nurse	Inclusion: Age ≥75 years, ready for discharge from a university hospital, on ≥5 drugs, living at home Exclusion: Dementia, abuse or malignant disease diagnoses, moving to a nursing home during the study period	Intervention A: Home visit by study nurse for medication review and adherence assessment, within a month of discharge (n=48) Intervention B: Same as A, plus letter with assessment of medications by physician, sent to patient's provider (n=49) Intervention C: Same as B, plus current medication record sent to patient with drug regimen and indications (n=50) Follow-up: 1 year	N=150 randomized (data for 147) Age, mean (SD) A: 82.5 (4.9); B: 83.4 (5.1); C: 83.9 (5.1) Gender (% male) A: 44%; B: 37%; C. 36% Comorbidity status: NR Physical status: NR Cognitive status: NR Number of drugs per patient (median) A: 8.0; B: 10.0; C: 10.0
Shim 2018[96] Malaysia Funding: University RCT Community Medication review	Inclusion: Age ≥65 years; on 5 types of medications; spoke English, Bahasa Malaysia, or Mandarin Exclusion: Medical conditions that could prevent patient from effective communication (deaf, mute, dementia, psychiatric problems); medications supervised by caregivers; participating in other studies or services	Intervention: Pharmaceutical care (medication review and reconciliation with counseling on indications for medications and how to use them); medication adherence emphasized and reason(s) for non-adherence documented and resolved; pharmacists could also consult/discuss with providers (n=73) Control: Usual care, with dispensing of medications by pharmacists (n=79) Follow-up: 6 months	N=160 (152 analyzed) Age (mean): 71.5 Gender (% male): 57.2 Race/ethnicity (% Chinese [vs other]): 63.8 Comorbidity status: Median number of comorbidities: 4.5 Physical status: NR Cognitive status: NR Number of medications: NR Med Adherent (MALMAS score ≥6): 34.2%

Author, year Trial name Country Funding Study Design Setting Intervention type	Inclusion/Exclusion Criteria	Intervention (n) Control (n) Clusters (if applicable) Follow-up	Demographics/Characteristics
Touchette 2012[114] United States Funding: Government RCT Community/ primary care Comprehensive Medication Review	Inclusion: Age ≥65 years, primary use of English for written/oral communication; access to a telephone for study duration, presence of ≥3 comorbid chronic conditions associated with increased health care use, ≥2 visits to clinic provider in past year, ≥6 chronic prescription medications during 6 months before enrollment, ≥1 recent situation placing patient at higher risk of DRPs Exclusion: terminal condition with life expectancy ≤6 months, prior enrollment in an MTM program in past 12 months	Intervention: 2 arms a) Basic MTM: MTM pharmacist performed CMR and DRP assessment; DRPs resolved through patient education and/or physician notification; pharmacist had no access to clinical information other than information ascertained in patient interview (n=211) b) Enhanced MTM: CMR and DRP assessment plus 2-page clinical synopsis with basic data on patient's medical history, laboratory values, current medications, and 2 most recent blood pressures and heart rates (n=218) Control: Usual care (medication counseling per their pharmacy's normal routine) (n=208) Follow-up: 6 months (CMR and DRP assessment at 0 and 3 months)	N=637 Age (mean): 74.6 Gender (% male): 33.8 Race/ethnicity: Black 51%, White 48%, Asian or American Indian <1% each Comorbidity status (mean (SD) number of comorbidities): 4.9 (1.6) Physical status: NR Cognitive status: NR (cognitive impairment was reported for 14% at baseline) Number of chronic medications (mean (SD)): 7.98 (2.4)

Author, year Trial name Country Funding Study Design Setting Intervention type	Inclusion/Exclusion Criteria	Intervention (n) Control (n) Clusters (if applicable) Follow-up	Demographics/Characteristics
Van der Meer 2018[105] Netherlands Funding: Dutch Pharmacy Society RCT Community Medication review	Inclusion: Age ≥65 years, living independently, ≥5 medications for ≥3 months (including ≥1 psycholeptic or psychoanaleptic medication [ATC code N05 or N06]), and DBI≥1 Exclusion: Limited life expectancy (<3 months), non-Dutch language speaker, advanced dementia, receipt of medication review within past 9 months, in need of urgent medication review	Intervention: Medication review by community pharmacist involving patients' GP and other medical specialists, if needed; included 1) face-to-face consultation; 2) medication review, 3) meeting with GP, 4) discuss draft action plan with patient and/or GP, 5) follow-up (n=75 in primary analyses, 65 in secondary analyses) Control: Receipt of medication review after study period (n=82 in primary analyses, 80 in secondary analyses) Follow-up: 3 months	N=157 for primary analyses Age (mean): 76.2 Gender (% male): 29.3 Race/ethnicity: NR Comorbidity score: NR Physical status: Groningen Activity Restriction Scale (% with "best scoring"): intervention 46/64 (72%); control 54/78 (69%) Cognitive status: several cognitive measures reported; groups did not differ significantly at baseline Number of medications (mean): intervention 8.5; control, 9.3; no p-value given
Weber 2008[107] United States Funding: Government Cluster RCT Community/ primary care Medication review	Inclusion: Clinics: >20 eligible patients Patients: Age ≥70 years, ≥4 active prescription medications, ≥1 psychoactive medication prescribed within last year, and Geisinger Health Plan Medicare+Choice coverage Exclusion: NR	Intervention: Medication review via electronic medical records by clinical pharmacists or trained geriatrician; primary care physicians sent patient tailored recommendations and evidence-based guideline for fall prevention via EHR (n=15 clinics, 413 patients) Control: Usual care (n=3 clinics, 207 patients) Follow-up: 15 months	N=620 Age (mean): 76.9 Gender (% male): 20 Race/ethnicity: NR Comorbidity status: Depression 0.2% Physical status: Falls 3.8%, lower extremity weakness 1% Cognitive status: Dementia 1.7% Number of medications (mean): 7.6; psychoactive medications 1.8

Author, year Trial name Country Funding Study Design Setting Intervention type	Inclusion/Exclusion Criteria	Intervention (n) Control (n) Clusters (if applicable) Follow-up	Demographics/Characteristics
Zermansky 2001[110] United Kingdom Funding: Government RCT Community Medication review	Inclusion: Age ≥65; on ≥1 repeat prescription Exclusion: Resident of nursing or residential home; terminally ill; involved in another clinical trial; exclusion requested by GP	Intervention: Pharmacist consultation with patient (medication review, interview); medication interventions (pharmacist with or without GP involvement) (n=608) Control: Usual care (GP) (n=580) Follow-up: 12 months	N=1188 Age (mean): 73.5 Gender (% male): 44 Race/ethnicity: NR Comorbidity status: NR Physical status: NR Cognitive status: NR Number of medications (median): 4 (repeat prescriptions)

ADL=activities of daily living; BMI=body mass index; CDSS=computer decision support system; CMR=comprehensive medication review; CTP=care transitions program; DRP=drug-related problem; ED=emergency department; EHR=electronic health record; ERA=Elders Risk Assessment; FRIDs=fall risk increasing drugs; GeMS=Geriatric Multidisciplinary Strategy for Good Care of the Elderly; GP=general practitioner or general practice; GP-BP=Good Palliative-Geriatric Practice; IQR=Interquartile Range; ITT=intent-to-treat; MAI=Medication Appropriateness Index; MALMAS=Malaysian Medication Adherence Scale; MMSE=Mini Mental State Examination; MTM=medication therapy management; NR=not reported; RCT=randomized controlled trial; SD=standard deviation; SF-36=short form 36 item; START=Screening Tool to Alert Doctors to Right Treatment; STOPP=Screening Tool of Older Persons' Prescriptions

Appendix D, Table 2. Risk of Bias – Comprehensive Medication Review Studies

Author, Year Randomization	Sequence Generation	Allocation Concealment	Recruitment Bias	Baseline Imbalance	Blinded Outcome Assessment	Incomplete Cluster Data	Incomplete Outcome Data	Selective Outcome Reporting	Overall Risk of Bias
Allard 2001[14] Patients randomized	Unclear (not reported)	Unclear (not reported)	N/A	Low	Low (nurse blinded to study group and not involved in program)	N/A	Low (9% did not complete trial)	Low	Medium

Author, Year Randomization	Sequence Generation	Allocation Concealment	Recruitment Bias	Baseline Imbalance	Blinded Outcome Assessment	Incomplete Cluster Data	Incomplete Outcome Data	Selective Outcome Reporting	Overall Risk of Bias
Bernsten, 2001[121] Sites randomized	Unclear (not reported)	Unclear (not reported)	High (pharmacists recruited patients)	Low	Medium (some blinding)	Medium (2 of 7 countries did not complete 18 months)	High (45% of patients did not complete 18 months; incomplete hospitalization data)	Low	High
Boyé 2017[20] Patients randomized	Low (web-based)	High (not blinded)	N/A	Low	Unclear (not reported)	N/A	Low (5% lost in ITT analysis)	Low/ Medium	Medium
Bryant 2011[116] (GPPC) Practices randomized	Unclear (generation not reported)	Low (central computer)	High (patients invited by practitioner after randomized)	Low (higher % males in control group)	Medium (pharmacists blinded to study group; other outcomes unclear)	Low	High (39% of intervention and 51% of control lost to excluded from analysis at 6 months – end of RCT period)	Low	High
Campins 2017, 2019[24,25] Patients randomized	Low (statistical program for random numbers)	Low ("blindly randomized" – sealed, opaque envelopes)	N/A	Low	Medium (not blinded but many outcomes were from medical records)	N/A	Low (3% lost to follow-up)	Low	Medium
Dennenboom 2007[34] Pharmacies randomized	Unclear	Unclear	Medium/High (patient identified after randomization of pharmacies)	Medium	Unclear	Low (3%)	Low (7%)	Low	Medium
Haag 2016[46] Patients randomized	Low (random number generator)	Low (study coordinator)	N/A	Low/Medium (age higher in usual care group)	Low (blinded outcomes assessment)	N/A	Medium (12% lost at follow-up)	Low	Low

Author, Year Randomization	Sequence Generation	Allocation Concealment	Recruitment Bias	Baseline Imbalance	Blinded Outcome Assessment	Incomplete Cluster Data	Incomplete Outcome Data	Selective Outcome Reporting	Overall Risk of Bias
Hanlon 1996[47] Schmader 1997[92] (VA) Patients randomized	Low (computer generated)	Unclear (not reported)	N/A	Medium (baseline imbalance for marital status, and medication variables)	Low	N/A	Medium (17% lost at 12 month follow-up)	Low	Medium
Jodar Sanchez 2015[50] Malet-Larrea 2016, 2017[62,63] (conSIGUE) Pharmacies randomized	Low (computer generated)	Low (independent researcher)	High (patients recruited after pharmacies randomized)	Medium (more health problems in intervention group; gender and partner status variables differed but not significantly)	High (no blinding)	Medium (14% (28/206) of pharmacies withdrew after allocation)	Low (5% patient loss to follow-up in main study)	Low	Medium
Köberlein Neu 2016[53] (WestGem) Practices randomized	Low (independent biometrician)	Medium (allocation disclosed at time of change-over)	Low	Medium (gender differences between groups)	Low/Medium (blinded pharmacists calculated medication outcome)	Low	Medium (87% in intent-to-treat analysis)	Low	Medium
Krska 2001[54] Patients randomized	Unclear (not reported)	Unclear (not reported)	N/A	Low	High (no blinding reported)	N/A	Medium (13% did not complete study)	Low	Medium
Kwint 2011[56] Polymed study Patients randomized	Low (computer-generated random numbers)	Unclear (not reported)	N/A	Low	Unclear (control was wait list so all initial reviews were intervention group)	N/A	Medium (14% overall loss to follow-up)	Low	Medium

Author, Year Randomization	Sequence Generation	Allocation Concealment	Recruitment Bias	Baseline Imbalance	Blinded Outcome Assessment	Incomplete Cluster Data	Incomplete Outcome Data	Selective Outcome Reporting	Overall Risk of Bias
Lenaghan 2007[60] Patients randomized	Unclear (not reported)	Low (third party)	N/A	Low	Unclear (control was wait list so all initial reviews were intervention group)	N/A	Medium (<2% excluded from primary analysis; 23% for secondary outcomes)	Low	Medium
Lenander 2014[118] Patients randomized	Unclear (not reported)	Unclear (not reported)	N/A	High (control group lower numbers of drugs and diagnoses per patient)	Low (for drug-related problems)	N/A	High (33% without 12 month follow-up)	Low	High
Meredith 2002[67] Patients randomized	Low (computer generated)	Low (centralized)	N/A	Low	Low ("masked reviewer")	N/A	Medium (large number of participants lost to follow-up)	Low	Medium
Moga 2017[70] Patients randomized	Low (computer generated)	Low (opaque envelopes)	N/A	Low	Medium (unable to blind intervention; blinded initial medication review and data analysis)	N/A	Low (2% lost to follow-up)	Low	Low
Muth 2018[71] Practices randomized	Low (external researcher with random number generator)	Low (study center, concealed until after baseline completed)	Low	Low	Low (blinded pharmacist rating medication appropriate-ness and statistician)	Low (1 practice lost)	Low (no patients lost from analysis)	Low	Low

Author, Year Randomization	Sequence Generation	Allocation Concealment	Recruitment Bias	Baseline Imbalance	Blinded Outcome Assessment	Incomplete Cluster Data	Incomplete Outcome Data	Selective Outcome Reporting	Overall Risk of Bias
Olesen 2014[72] (MICMI) Patients randomized	Unclear ("patients were asked to select 1 envelope")	Unclear (not reported if envelopes were sequentially numbered and opaque)	N/A	Low	High (drug-related problems identified by pharmacists during home visits)	N/A	High (large overall attrition; 82% were analyzed)	Low	Medium
Olsson 2012[73] Patients randomized	Unclear (not reported)	Low (research assistant unconnected to study)	N/A	Low	Medium (home visits completed by study nurse blinded to groups)	N/A	High (29% with no 12-month nurse visit)	Low	Medium
Richmond 2010[119] (Respect trial) Order of implementing randomized ("clusters")	Unclear (not reported)	Low (centralized)	Medium (participants recruited after sites but pharmacists and physicians were blinded until start of intervention)	Low	Medium (appropriate-ness outcome blinded, unclear for others)	Medium (some practices lost because of medical record system)	High (27% did not complete study)	Low	High
Shim 2018[96] Patients randomized	Low (computer generated)	Low (assigned by researcher)	N/A	Low	Medium (single-blind; outcomes assessed by blinded research assistant)	N/A	Low (5% lost from analysis)	Low	Low

Author, Year Randomization	Sequence Generation	Allocation Concealment	Recruitment Bias	Baseline Imbalance	Blinded Outcome Assessment	Incomplete Cluster Data	Incomplete Outcome Data	Selective Outcome Reporting	Overall Risk of Bias
Touchette 2012[114] Patients randomized	Low - computer-based	Unclear	N/A	Low	Medium-telephone interviews were blinded	N//A	Medium (12-13% attrition)	High – several outcomes from protocol not reported	Medium
Van der Meer 2018[105] Patients randomized	Unclear (not reported)	Low (investigator not involved in recruitment or data collection)	N/A	Low	Medium (single-blind; outcomes assessed by blinded researchers)	N/A	Low (4% lost for "first analysis" – all patients with baseline measures)	Low	Medium
Weber 2008[107] Clinic sites randomized	Unclear (not reported)	Unclear (not reported)	Low (patients identified before randomization)	High (no clinic information)	Unclear (not reported)	Unclear (not reported)	Unclear (not reported)	Low	Medium
Zermansky 2001[110] Patients randomized	Low (computer generated)	Unclear (not reported)	N/A	Low	Unclear (not reported)	N/A	Low (approx. 5% lost to follow-up)	Low	Medium

GP=general practitioner; ITT=intention-to-treat; MICMI=Methods for Improving Compliance with Medicine Intake; N/A=not applicable

Appendix D, Table 3. Patient-centered Outcomes, Part 1 – Comprehensive Medication Review

Author Year Study Design Setting Intervention Type Follow-up	Hospitalizations % (n/N)		Acute Care Encounters % (n/N)		Delirium % (n/N)	
	Intervention	Control	Intervention	Control	Intervention	Control
Boyé 2017[20] Polinder 2016[80] RCT Community Medication review (FRIDs) Follow-up: 12 months	NR	NR	Fall-related 5% (16/308) P=.22	Fall-related 8% (21/272)	NR	NR
Campins 2017, 2019[24,25] RCT Community Medication review/guide lists Follow-up: 12 months	Hospitalized patients 0-12 months 23.3% (57/252) P=.62	Hospitalized patients 0-12 months 25.2% (63/251)	Visits per patient 0-12 months mean (SD) 0.9 (1.5) P=.06	Visits per patient 0-12 months mean (SD) 1.1 (1.5)	NR	NR
Haag 2016[46] RCT Community Medication review Follow-up: 30 days	30 day readmission* 18% (2/11) P=.53 *Population was community-dwelling but enrolled at time of hospitalization	30 day readmission 9% (1/11)	30 day emergency department visits 9% (1/11) P>.99	30 day emergency department visits 9% (1/11)	NR	NR

Author Year Study Design Setting Intervention Type Follow-up	Hospitalizations % (n/N)		Acute Care Encounters % (n/N)		Delirium % (n/N)	
	Intervention	Control	Intervention	Control	Intervention	Control
Hanlon 1996[47] Schmader 1997[92] RCT Setting: Community/ primary care Intervention: Medication review Follow-up: 12 months	Overall 38% (78/208) admitted to the hospital		NR	NR	NR	NR
Jodar-Sanchez 2015[50] Malet-Larrea 2016, 2017[62,63] ConSIGUE Cluster RCT Community/ primary care Medication review Follow-up: 6 months	Drug-related hospital admissions* 11 P=.042 Adj OR 3.7 (95%CI 1.2, 11.3) *Number of patients not reported	Drug-related hospital admissions 31	Emergency department visits* 30 P<.001 *Number of patients not reported Mean number of visits per patient 6 months prior to study: 0.43 (0.83) 6 months of study: 0.19 (0.51) Difference 0.24 (P<.001)	Emergency department visits 59 Mean number of visits per patient 6 months prior to study: 0.55 (1.55) 6 months of study: 0.42 (1.21) Difference 0.13 (P<.001)	NR	NR
Krska 2001[54] Cluster RCT Community Intervention: Pharmacist-led medication review 3 months	Emergency admissions* 6 *Number of patients not reported	Emergency admissions 8	NR	NR	NR	NR

Author Year Study Design Setting Intervention Type Follow-up	Hospitalizations % (n/N)		Acute Care Encounters % (n/N)		Delirium % (n/N)	
	Intervention	Control	Intervention	Control	Intervention	Control
Kwint 2011[56] RCT Community Pharmacist-led medication review Follow-up: 6 months	1 hospitalization overall		NR	NR	NR	NR
Lenaghan 2007[60] POLYMED RCT Community Pharmacist medication review Follow-up: 6 months	Non-elective* 29% (20/68) RR:0.92 (95%CI 0.5, 1.7, P=.8)	Non-elective 32% (21/66)	NR	NR	NR	NR
Meredith 2002[67] RCT Community Medication review Follow-up: 12 weeks	Composite of died or hospitalized or entered nursing home 6% (10/160)	Composite of died or hospitalized or entered nursing home 5% (8/157)	NR	NR	NR	NR
Muth 2018[71] Cluster RCT Community primary care Medication review Follow-up: 9 months	Mean Number of Hospital Stays Baseline 1.7 (1.0) n=42 Follow-up 1.3 (0.6) n=28 P=.95 RR 1.0 (95%CI 0.3, 3.1)	Mean Number of Hospital Stays Baseline 1.4 (0.7) n=40 Follow-up 1.2 (0.4) n=25	NR	NR	NR	NR

Author Year Study Design Setting Intervention Type Follow-up	Hospitalizations % (n/N)		Acute Care Encounters % (n/N)		Delirium % (n/N)	
	Intervention	Control	Intervention	Control	Intervention	Control
Olesen 2013[72] RCT Setting: Patients' Homes Intervention Type: Medication review and phone follow-up Follow-up: 2 years	One or More Hospitalization 30% (77/253) OR 1.14 (95%CI 0.78-1.67)	One or More Hospitalization 28% (73/264)	NR	NR	NR	NR

Author Year Study Design Setting Intervention Type Follow-up	Hospitalizations % (n/N)		Acute Care Encounters % (n/N)		Delirium % (n/N)	
	Intervention	Control	Intervention	Control	Intervention	Control
Touchette 2012[114] RCT Community/ primary care Comprehensive Medication Review Follow-up: 6 months	≥1 visit Basic MTM: 0 – 3 months 13.9% (25/180) 3 – 6 months 17.5% (32/183) Enhanced MTM: 0 – 3 months 7.9% (15/190) 3 – 6 months 12.1% (23/190) All comparisons between groups P NS Visits per patient 0 – 3 months Basic MTM: 0.17 (0.46) Enhanced MTM: 0.11 (0.44) 3 – 6 months Basic MTM: 0.20 (0.48) Enhanced MTM: 0.15 (0.44) All comparisons between groups P NS	≥1 visit 0 – 3 months 10.4% (20/193) 3 – 6 months 9.3% (17/183) Visits per patient 0 – 3 months 0.12 (0.37) 3 – 6 months 0.11 (0.36)	Visits per patient 0 – 3 months Basic MTM: 0.26 (0.57) Enhanced MTM: 0.24 (0.56) 3 – 6 months Basic MTM: 0.25 (0.51) Enhanced MTM: 0.25 (0.64) All comparisons between groups P NS	Visits per patient 0 – 3 months 0.23 (0.48) 3 – 6 months 0.35 (0.81)	NR	NR

Author Year Study Design Setting Intervention Type Follow-up	Hospitalizations % (n/N)		Acute Care Encounters % (n/N)		Delirium % (n/N)	
	Intervention	Control	Intervention	Control	Intervention	Control
Van der Meer 2018[105] RCT Community Medication review Follow-up: 3 months	5.1% (3/59)* P=.15 *Hospitalization data from 136 patients	11.7% (9/77)*	NR	NR	NR	NR
Zermansky 2001[110] RCT Community Medication review Follow-up: 12 months	Number of patients with 1 admission 13% (78/579) Number with >1 admission 6% (32/579) P=NS	Number of patients with 1 admission 10% (55/550) Number with >1 admission 7% (37/550)	NR	NR	NR	NR

CI=confidence interval; FRIDs=fall risk increasing drugs; MTM=medication therapy management; NR=not reported; NS=not statistically significant; OR=odds ratio; RCT= randomized controlled trial; RR=relative risk; VA=Veterans Affairs

Appendix D, Table 4. Patient-centered Outcomes, Part 2 – Comprehensive Medication Review

Author Year Study Design Setting Intervention Type Follow-up	Functional Status (mean, SD) – describe measure		Quality of Life (mean, SD) – describe measure		Patient Satisfaction (mean, SD) – describe measure	
	Intervention	Control	Intervention	Control	Intervention	Control
Boyé 2017[20] Polinder 2016[80] RCT Community Medication review (FRIDs) Follow-up: 12 months	NR	NR	EQ-5D Baseline 0.74 (0.26) Follow-up 0.75 (0.26) n=285 Change from baseline: 0.01 (0.24) P=.02 SF-12 PCS Score Change from baseline -2.6 (8.5) n=283 P=.08 SF-12 MCS Score Change from baseline -0.8 (9.7) n=283 P=.90	EQ-5D Baseline 0.78 (0.22) Follow-up 0.74 (0.25) n=263 Change from baseline: -0.04 (0.22) SF-12 PCS Score Change from baseline -3.9 (8.5) n=258 SF-12 MCS Score Change from baseline -0.7 (9.7) n=258	NR	NR
Campins 2017, 2019[24,25] Community Medication review/guide lists Follow-up: 12 months	NR	NR	EQ-5D (0-100 scale) Change from baseline -2.09 n=252 P=.32	EQ-5D (0-100 scale) Change from baseline 0.67 n=251	NR	NR

Author Year Study Design Setting Intervention Type Follow-up	Functional Status (mean, SD) – describe measure		Quality of Life (mean, SD) – describe measure		Patient Satisfaction (mean, SD) – describe measure	
	Intervention	Control	Intervention	Control	Intervention	Control
Hanlon 1996[47] Schmader 1997[92] RCT Community/ primary care Medication review Follow-up: 12 months	SF-36-Physical Function Baseline 48.0 (2.7) n=104 Follow-up 44.1 (2.0) n=86	SF-36-Physical Function Baseline 45.3 (2.7) n=103 Follow-up 42.2 (2.0) n=83	No between-group differences in SF-36 change scores at 12 months P=.99 (adjusted for number of baseline medications, hospitalizations during study period, marital status, number of medications for which clinical pharmacist developed recommendations prior to randomization)		General health satisfaction 1.5 (0.7) P=.70 Pharmacy-related health care satisfaction 5.2 (1.5) P=.52	General health satisfaction 1.6 (0.8) Pharmacy-related health care satisfaction 5.4 (1.7)

Author Year Study Design Setting Intervention Type Follow-up	Functional Status (mean, SD) – describe measure		Quality of Life (mean, SD) – describe measure		Patient Satisfaction (mean, SD) – describe measure	
	Intervention	Control	Intervention	Control	Intervention	Control
Jodar-Sanchez 2015[50] Malet-Larrea 2016, 2017[62,63] ConSIGUE Cluster RCT Community/ primary care Medication review Follow-up: 6 months	NR	NR	EQ-5D Utility score (0=death, 1=best state of health) Baseline 0.71 (0.28) Follow-up 0.77 (0.27) Mean change 0.05 (0.20) n=627 Between groups 0.55 (0.01) (95%CI 0.03, 0.08) Health State VAS (0=worst, 100=best) Baseline 65.44 (18.07) Follow-up 70.46 (17.06) Mean change 4.97 (15.29) Between groups 5.87 (95%CI 4.20, 7.54)	EQ-5D Utility score Baseline 0.70 (0.31) Follow-up 0.69 (0.32) Mean change -0.002 (0.24) n=671 Health State VAS (0=worst, 100=best) Baseline 63.22 (19.42) Follow-up 62.29 (19.20) Mean change -0.90 (15.19)	NR	NR

Author Year Study Design Setting Intervention Type Follow-up	Functional Status (mean, SD) – describe measure		Quality of Life (mean, SD) – describe measure		Patient Satisfaction (mean, SD) – describe measure	
	Intervention	Control	Intervention	Control	Intervention	Control
Köberlein-Neu 2016[53] Cluster RCT Community Medication review Follow-up: 15 weeks	Barthel Index Intervention phase 1 95.0 (95%CI 93.8, 96.1) Mean difference 0.5 (95%CI -0.9, 1.8) Effect size 0.04 (95%CI -0.08, 0.16) MobilityTest Intervention phase 1 21.7 (95%CI 20.6, 22.8) Mean difference -0.4 (95%CI -1.1, 0.4) Effect size -0.06 (95%CI – 0.18, 0.06)	Barthel Index Control phase 94.8 (95%CI 93.8, 95.9) Mobility Test Control phase 22.2 (95%CI 21.1, 23.3)	SF-12 (physical sum scale) Intervention phase 1 38.3 (95%CI 37.2, 39.3) Mean difference -0.3 (95%CI -1.7, 1.2) Effect size -0.02 (95%CI -0.16, 0.11) SF-12 (psychological sum scale) 46.1 (95%CI 44.8, 47.4) Mean difference in contrast -0.96 (95%CI -2.74, 0.82) Effect size -0.07 (95%CI -0.20, 0.06)	SF-12 (physical sum scale) Control phase 38.5 (95%CI 37.5, 39.5) SF-12 (psychological sum scale) 46.3 (95%CI 45.0, 47.6)	NR	NR
Krska 2001[54] Cluster RCT Community Pharmacist-led medication review Follow-up: 3 months	NR	NR	No significant changes from baseline were observed in any domain of the SF-36 between groups (scores not reported).		NR	NR

Author Year Study Design Setting Intervention Type Follow-up	Functional Status (mean, SD) – describe measure		Quality of Life (mean, SD) – describe measure		Patient Satisfaction (mean, SD) – describe measure	
	Intervention	Control	Intervention	Control	Intervention	Control
Lenaghan 2007[60] POLYMED RCT Community Pharmacist medication review Follow-up: 6 months	NR	NR	EQ-5D utility (1=perfect health) Baseline 0.62 n=68 Follow-up 0.57 n=56 Difference in change over 6 months: 0.09 (95%CI -0.19 to 0.02, P=.10 EQ-5D VAS (100=best health state) Baseline 63.7 n=67 Follow-up 63.8 n=44 Difference in change over 6 months: 4.8 (95%CI -12.5 to 2.8, P=.21	EQ-5D Baseline 0.57 n=66 Follow-up 0.56 n=49 EQ-5D VAS (100=best health state) Baseline 65.2 n=64 Follow-up 68.3 n=48	NR	NR

Author Year Study Design Setting Intervention Type Follow-up	Functional Status (mean, SD) – describe measure		Quality of Life (mean, SD) – describe measure		Patient Satisfaction (mean, SD) – describe measure	
	Intervention	Control	Intervention	Control	Intervention	Control
Moga 2017[70] RCT University clinic Pharmacist medication review Follow up: 8 weeks	SF-36 Physical Functioning Baseline 74.2 (23.9) n=25 Change at follow-up -5.2 (15.6) n=25 P=.06	SF-36 Physical Functioning Baseline 60.4 (25.9) n=25 Change at follow-up 3.6 (16.0) n=24	SF-36 PCS Baseline 66.8 (25.3) n=25 Change at follow-up -1.2 (13.2) n=25 P=.53 SF-36 MCS Baseline 72.7 (21.0) n=25 Change at follow-up 2.1 (12.9) n=25 P=.09	SF-36 PCS Baseline 60.7 (19.1) n=25 Change at follow-up 1.5 (16.5) n=24 SF-36 MCS Baseline 77.5 (13.6) n=25 Change at follow-up -4.7 (14.0) n=24	NR	NR
Muth 2018[71] Cluster RCT Community primary care Medication review Follow-up: 9 months	VES-13 Baseline 2.6 (2.7) n=223 Follow-up 2.8 (2.8) n=204 P=.68	VES-13 Baseline 3.0 (2.9) n=228 Follow-up 2.7 (2.8) n=199	EQ-5D Baseline 73.9 (24.4) n=241 Follow-up 74.8 (23.4) n=222 P=.25	EQ-5D Baseline 74.9 (23.0) n=240 Follow-up 72.8 (25.1) n=214	NR	NR

Author Year Study Design Setting Intervention Type Follow-up	Functional Status (mean, SD) – describe measure		Quality of Life (mean, SD) – describe measure		Patient Satisfaction (mean, SD) – describe measure	
	Intervention	Control	Intervention	Control	Intervention	Control
Olsson 2012[73] RCT 3 arm Setting community Intervention type Medication review with home visits by nurse Follow-up: 12 months	NR	NR	EQ-5D (graph) Group B Baseline: 0.66 12 months: 0.62 Group C Baseline: 0.61 12 months: 0.41 EQ-5D-VAS Group B Baseline: 51 (17) 12 months: 54 (14) Group C Baseline: 51 (16) 12 months: 56 (17) *Group B* *Baseline n=49* *12 months n=39* *Group C* *Baseline n=48* *12 months n=33* No significant differences between any of 3 intervention groups for EQ-5D or EQ-VAS over time	EQ-5D (graph) Group A Baseline: 0.62 12 months: 0.72 EQ-5D-VAS Group A Baseline: 50 (19) 12 months: 56 (17) *Group A* *Baseline n=47* *12 months n=34*	NR	NR

Author Year Study Design Setting Intervention Type Follow-up	Functional Status (mean, SD) – describe measure		Quality of Life (mean, SD) – describe measure		Patient Satisfaction (mean, SD) – describe measure	
	Intervention	Control	Intervention	Control	Intervention	Control
Van der Meer 2018[105] RCT Community Medication review Follow-up: 3 months	Groningen Activity Restriction Scale (“best scoring”) Baseline: 72% n=46 Change with follow-up: 2% n=45 OR 1.73 (95%CI 0.62, 4.84)	Groningen Activity Restriction Scale (“best scoring”) Baseline: 69% n=54 Change with follow-up: 0 n=54	EQ-5D-3L (“best scoring”) Baseline 74% n=48 Change with follow-up 9; n=42 OR 1.43 (95%CI 0.51, 4.03) EQ-5D VAS Baseline 6.6 (1.6) Change with follow-up -0.2 (0.0) Unstandardized b: -0.09 (95%CI -0.50, 0.32)	EQ-5D-3L (“best scoring”) Baseline 76% n=61 Change with follow-up 4; n=58 EQ-5D VAS Baseline 6.8 (1.4) Change with follow-up -0.1 (0.1)	NR	NR

CI=confidence interval; DQI=Dementia Quality-of-Life Instrument; EQ-5D=EuroQoL-5 dimensions; EQ-5D-3L=EuroQol-5D (3 level version); FRIDs=fall risk increasing drugs; MCS=mental component summary; MMSE=Mini-Mental State Examination; NR=not reported; OR=odds ratio; PCS=physical component summary; RCT=randomized controlled trial; SD=standard deviation; SF-12 (or SF-36): Short Form 12 item (or 36 item); SIB-S=Severe Impairment Battery (short form); VAS=visual analog scale; VES-13=Vulnerable Elderly Survey-13 items

Appendix D, Table 5. Patient-centered Outcomes, Part 3 – Comprehensive Medication Review

Author Year Study Design Setting Intervention Type	Falls % (n/N)		Major Adverse Cardiovascular Events[a] % (n/N)		Adverse Drug Withdrawal Events % (n/N)		All-cause Mortality % (n/N)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Allard 2001[14] Design: RCT Community Medication review and monthly follow-up Follow-up: 1 year	NR	NR	NR	NR	NR	NR	4% (6/136) P=.049	11% (14/130)

Author Year Study Design Setting Intervention Type	Falls % (n/N)		Major Adverse Cardiovascular Events[a] % (n/N)		Adverse Drug Withdrawal Events % (n/N)		All-cause Mortality % (n/N)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Boyé 2017[20] Polinder 2016[80] RCT Community Medication review (FRIDs) Follow-up: 12 months	37% (115/308) P=.33	34% (91/272)	NR	NR	NR	NR	<1% (1/319) Deaths not included in study analyses (Note: Other deaths during study [number not reported]; those participants included in analyses)	<1% (2/293) Deaths not included in study analyses
Campins 2017, 2019[24,25] Community Medication review/guide lists Follow-up: 12 months	NR	NR	NR	NR	NR	NR	0-12 months 2.8% (7/252) P=.78	0-12 months 2.4% (6/251)
Haag 2016[46] RCT Community Medication review Follow-up: 30 days	NR	NR	NR	NR	NR	NR	8% (1/13)	8% (1/12)
Hanlon 1996[47] Schmader 1997[92] RCT Community/ primary care (VA) Medication review Follow-up: 12 months	NR	NR	NR	NR	NR	NR	6% (7/105)	10% (10/103)

Author Year Study Design Setting Intervention Type	Falls % (n/N)		Major Adverse Cardiovascular Events[a] % (n/N)		Adverse Drug Withdrawal Events % (n/N)		All-cause Mortality % (n/N)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Jodar-Sanchez 2015[50] Malet-Larrea 2016, 2017[62,63] ConSIGUE Cluster RCT Community/ primary care Medication review Follow-up: 6 months	NR	NR	NR	NR	NR	NR	0% (0/688)	0% (0/715)
Kwint 2011[56] RCT Community Pharmacist-led medication review Follow-up: 6 months	NR	NR	NR	NR	NR	NR	3.2% (2/63)	3.6% (2/55)
Lenaghan 2007[60] POLYMED RCT Community Pharmacist medication review Follow-up: 6 months	NR	NR	NR	NR	NR	NR	10.3% (7/68) 1.3% difference in proportions (95%CI -12.1, 14.7) P=.81	9.1% (6/66)
Meredith 2002[67] RCT Community Medication review Follow-up: 12 weeks	New fall 12% (17/140)	New fall 11% (15/137)	NR	NR	NR	NR	Composite of died, hospitalized, or entered nursing home 6% (10/160)	Composite of died, hospitalized, or entered nursing home 5% (8/157)

Author Year Study Design Setting Intervention Type	Falls % (n/N)		Major Adverse Cardiovascular Events[a] % (n/N)		Adverse Drug Withdrawal Events % (n/N)		All-cause Mortality % (n/N)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Olesen 2013[72] RCT Community Intervention Type: Medication review and phone follow-up Follow-up: 2 years	NR	NR	NR	NR	NR	NR	7.5% (19/253) OR 1.41 (95%CI 0.71-2.82)	5% (14/264)
Olsson 2012[73] RCT 3 arm Community Intervention type Medication review with home visits by nurse Follow-up 12 months	NR	NR	NR	NR	NR	NR	B: 10% (5/49) C: 14% (7/50) “No significant differences between the groups”	A: 15% (7/48)
Van der Meer 2018[105] Design: RCT Community Medication review Follow-up: 3 months	30.5% (18/59) P=.10 (Note: falls data from 136 patients)	19.5% (15/77)	NR	NR	NR	NR	1.3% (1/75) P=.73	1.2% (1/80)

Author Year Study Design Setting Intervention Type	Falls % (n/N)		Major Adverse Cardiovascular Events[a] % (n/N)		Adverse Drug Withdrawal Events % (n/N)		All-cause Mortality % (n/N)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Weber 2008[107] Cluster RCT Community Medication review Follow-up: 15 months	≥1 Fall (15 months) 14.13% Epicare data OR 0.38 P<.01 Epicare + self report data OR 0.86 P NS	≥1 Fall (15 months) 15.44%	NR	NR	NR	NR	4.1% (17/413)	6.8% (14/207)
Zermansky 2001[110] RCT Community Medication review Follow-up: 12 months	NR	NR	NR	NR	NR	NR	2.5% (15/608) OR 0.56 (95%CI 0.29, 1.10)	4.3% (25/580)

CI=confidence interval; FRIDs=fall risk increasing drugs; NR=not reported; NS=not statistically significant; OR=odds ratio; RCT=randomized controlled trial;
[a]Includes cardiovascular death, nonfatal myocardial infarction, acute coronary syndrome, nonfatal stroke, revascularization, or heart failure exacerbation

Appendix D, Table 6. Intermediate Process Outcomes, Part 1 – Comprehensive Medication Review

Author Year Study Design Setting Intervention Type Follow-up	Total Number of Medications Discontinued, mean (SD)		Number of Medications with Dosage Decreased, mean (SD)		Number of Medications Added or Substituted, mean (SD)		Number of Inappropriate Medications Discontinued, mean (SD)	
	Intervention	**Control**	**Intervention**	**Control**	**Intervention**	**Control**	**Intervention**	**Control**
Allard 2001[14] Design: RCT Community Medication review and monthly follow-up Follow-up: 1 year	**Reduction in Number of Drugs Prescribed** Experimental Group (ITT) 0.24 (2.15) n=127 P=.46 Experimental with Case Conference (per protocol) 0.31 (2.29) n=80 P=.44	**Reduction in Number of Drugs Prescribed** 0.13 (1.67)	NR	NR	NR	NR	**Reduction in PIPs Per Patient** Experimental Group (ITT) 0.24 (0.69) n=127 P=.13 Experimental with Case Conference (per protocol) 0.31 (0.77) n=80 P=.08	**Reduction in PIPs Per Patient** 0.15 (0.52) n=116
Boyé 2017[20] Polinder 2016[80] RCT Community Medication review (FRIDs) Follow-up: 12 months	NR	**NR**	NR	NR	Number of patients with increased FRIDs 22% (66/308)	Number of patients with increased FRIDs 25% (68/272)	Number of patients with decreased FRIDs 37% (115/308)	Number of patients with decreased FRIDs 19% (53/272)

Author Year Study Design Setting Intervention Type Follow-up	Total Number of Medications Discontinued, mean (SD)		Number of Medications with Dosage Decreased, mean (SD)		Number of Medications Added or Substituted, mean (SD)		Number of Inappropriate Medications Discontinued, mean (SD)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Campins 2017, 2019[24,25] Community Medication review/guide lists Follow-up: 12 months	3 months 1.27 (1.29) 6 months 1.95 (1.67) 12 months 2.69 (1.98) P<.001 at all time points At least 1 drug discontinued at 12 months 85% (215/252) OR 1.85 (95%CI 1.17, 2.90)	3 months 0.42 (0.90) 6 months 0.85 (1.27)) 12 months 2.05 (1.91) At least 1 drug discontinued at 12 months 75% (189/251)	Dose Adjustments 3 months 0.96 (1.15) 6 months 1.08 (1.22) 12 months 1.14 (1.25) P<.001 at all time points At least 1 dose adjustment at 12 months 61% (152/252) OR 3.94 (95%CI 2.70, 5.74)	Dose Adjustments 3 months 0.18 (0.43) 6 months 0.31 (0.58) 12 months 0.37 (0.65) At least 1 dose adjustment at 12 months 28% (69/251)	Drug Substitutions 3 months 0.49 (0.80) 6 months 0.67 (0.97) 12 months 0.95 (1.16) P<.001 (3 and 6 months); P=.005 (12 months) New Prescriptions 3 months: 135 6 months: 62 12 months: 209 P NS at all time points	Drug Substitutions 3 months 0.19 (0.46) 6 months 0.31 (0.59) 12 months 0.64 (0.85) New Prescriptions 3 months: 120 6 months: 78 12 months: 208	NR	NR
Denneboom 2007[34] Cluster RCT Community pharmacy Medication review feedback vs case conferences Follow up: 9 months	NR	NR	Case Conference Medication “changes” initiated 0-6 months 42 total n=141 P=.016 Sustained change at 6 months 36 P=.022	Written Feedback Medication “changes” initiated 0-6 months 22 total n=128 Sustained change at 6 months 19	NR	NR	NR	NR

Author Year Study Design Setting Intervention Type Follow-up	Total Number of Medications Discontinued, mean (SD)		Number of Medications with Dosage Decreased, mean (SD)		Number of Medications Added or Substituted, mean (SD)		Number of Inappropriate Medications Discontinued, mean (SD)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Haag 2016[46] RCT Community Medication review Follow-up: 30 days	Total Medications, median (IQR) Baseline 17 (12-20) P=.96 30 days 18 (12-20) P=.95	Total Medications, median (IQR) Baseline 15.5 (13-18.5) 30 days 17 (13-18)	NR	NR	NR	NR	No significant differences between groups at baseline or 30-day follow-up for: a) STOPP medications on patient's medication lists b) START medications missing from lists c) any MAI criterion (no indication, medication not effective for condition, or unnecessary duplication)	
Hanlon 1996[47] Schmader 1997[92] RCT Community/ primary care Medication review Follow-up: 12 months	VA prescribed medications at 12 months 6.9 (2.6) n=86 P=.83	VA prescribed medications at 12 months 7.9 (3.3) n=83	NR	NR	NR	NR	MAI Baseline 17.7 (0.6) n=105 12 months 12.8 (0.7) n=86 Mean change -4.9 (28% improvement) P=.0002	MAI Baseline 17.6 (0.6) n=103 12 months 16.7 (0.7) n=83 Mean change -0.9 (5% improvement)
Jodar-Sanchez 2015[50] Malet-Larrea 2016, 2017[62,63] ConSIGUE Cluster RCT Community/ primary care Medication review Follow-up: 6 months	Reduction of prescribed medications at 6 months (n=627) -0.28 (1.25) P=.001 Mean difference 0.21 (95%CI 0.09, 0.34)	Reduction of prescribed medications at 6 months (n=671) -0.27 (0.95)	NR	NR	NR	NR	NR	NR

Author Year Study Design Setting Intervention Type Follow-up	Total Number of Medications Discontinued, mean (SD)		Number of Medications with Dosage Decreased, mean (SD)		Number of Medications Added or Substituted, mean (SD)		Number of Inappropriate Medications Discontinued, mean (SD)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Köberlein-Neu 2016[53] Cluster RCT Community Medication review Follow-up: 15 weeks	Number of prescribed medications per patient 9.83 (95%CI 9.54, 10.12) P=NS	Number of prescribed medications per patient 9.77 (95%CI 9.51, 10.04),	NR	NR	NR	NR	**Number of PIMs Prescribed** Control phase: 0.39 (95%CI 0.34, 0.44) Intervention phase 1: 0.32 (95%CI 0.26, 0.38) Mean difference: -0.04 (95%CI -0.09, 0.01) Effect size (Cohen's d): -0.08 (95%CI -0.19, 0.03) **MAI** Control phase: 29.21 (95%CI 26.09, 32.33) Intervention phase 1: 22.27 (95%CI 19.00, 25.54) Mean difference: -4.51 (95%CI -6.66, -2.36) Effect size (Cohen's d): -0.24 (95%CI -0.36, -0.13) Intervention phase 1: see above Intervention phase 2: 19.08 (95%CI 15.47, 22.69) Mean difference: -0.99 (95%CI -3.99, 1.97) Effect size: -0.04 (95%CI -0.17, 0.08) **Drug-related problems (DRPs)** Baseline: 7.3 (3.4) per patient Control phase: 6.98 (95%CI 6.27, 7.66) Intervention phase 1: 5.87 (95%CI 5.23, 6.54) Mean difference: -0.45 (95%CI -0.81, -0.09) Effect size (Cohen's d) -0.13 (95%CI, -0.23, -0.03)	

Author Year Study Design Setting Intervention Type Follow-up	Total Number of Medications Discontinued, mean (SD)		Number of Medications with Dosage Decreased, mean (SD)		Number of Medications Added or Substituted, mean (SD)		Number of Inappropriate Medications Discontinued, mean (SD)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Krska 2001[54] Cluster RCT Community Intervention: Pharmacist-led medication review Follow-up: 3 months	NR	NR	PCI-Inappropriate dosage resolved 78% (54/69) P<.0001	PCI-Inappropriate dosage resolved 18% (17/95)	NR	NR	PCI-potential ineffective therapy resolved 57% (80/140) P<.0001 PCI-repeat prescription or no longer required resolved 96% (53/55) P<.0001	PCI-potential ineffective therapy resolved 24% (41/169) PCI-repeat prescription or no longer required resolved 6% (4/66)
Kwint 2011[56] RCT Community Pharmacist-led medication review Follow-up: 6 months	Cessations related to recommend-ation 82% (32/39) P=.01	Cessations related to recommend-ation 44% (5/9)	Dose change related to recommend-ation 53% (16/30)	Dose change related to recommend-ation 15% (2/13)	Addition of drug related to recommend-ation 44% (15/34) Replacement 60% (9/15)	Addition of drug related to recommend-ation 9% (2/23) Replacement 17% (1/16)	DRPs (mean) Baseline: 4.5 Follow-up: 3.2 (29% reduction) P<.01	DRPs (mean) Baseline: 4.4 Follow-up: 4.2 (5% reduction)
Lenaghan 2007[60] POLYMED RCT Community Pharmacist medication review Follow-up: 6 months	Mean total medications Baseline 9.01 n=68 Follow-up: 8.68 n=59 Change: -0.31 Difference in change: -0.87 (95%CI -1.66, -0.08), P=.03	Mean total medications Baseline 9.85 n=66 Follow-up: 10.33 n=55 Change: 0.56	NR	NR	NR	NR	NR	NR

Author Year Study Design Setting Intervention Type Follow-up	Total Number of Medications Discontinued, mean (SD)		Number of Medications with Dosage Decreased, mean (SD)		Number of Medications Added or Substituted, mean (SD)		Number of Inappropriate Medications Discontinued, mean (SD)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Meredith 2002[67] RCT Community Medication review Follow-up: 12 weeks	NR	NR	Improvement in medication use[a] 50% (65/130) P=.05	Improvement in medication use[a] 38% (49/129)	NR	NR	≥1 duplicative drugs stopped 71% (17/24) P=.003	≥1 duplicative drugs stopped 24% (4/17)
Moga 2017[70] RCT University clinic Pharmacist medication review Follow up: 8 weeks	NR	NR	NR	NR	NR	NR	MAI for anticholinergic medications Baseline 12.2 (7.9) n=25 Unadjusted change from baseline -4.2 (5.1) n=25 P=.02	MAI for anticholinergic medications Baseline 13.0 (4.4) n=25 Unadjusted change from baseline -1.1 (3.1) n=24
Muth 2018[71] Cluster RCT Community primary care Medication review Follow-up: 9 months	Number of prescriptions Baseline 8.1 (2.8) n=252 Follow-up 8.4 (3.2) n=235 P=.31 RR 1.0 (95%CI 1.0, 1.1)	Number of prescriptions Baseline 8.0 (2.4) n=253 Follow-up 7.8 (2.2) n=227	NR	NR	NR	NR	MAI Baseline 4.8 (5.4) n=252 Follow-up 4.8 (5.2) n=238 P=.27 Mean Difference 0.6 (95%CI -0.5, 1.7)	MAI Baseline 4.6 (5.8) n=253 Follow-up 3.9 (4.9) n=228

Author Year Study Design Setting Intervention Type Follow-up	Total Number of Medications Discontinued, mean (SD)		Number of Medications with Dosage Decreased, mean (SD)		Number of Medications Added or Substituted, mean (SD)		Number of Inappropriate Medications Discontinued, mean (SD)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Olsson 2012[73] RCT 3 arm Community Medication review with home visits by nurse Follow-up: 12 months	Median number of medications per patient Group B Baseline 10 Follow-up: 11 P=.66 Group C Baseline 10 Follow-up: 10 P=.45 OVERALL comparing all 3 groups P=.38	Median number of medications per patient Group A Baseline 8 Follow-up: 9 P=.03	NR	NR	NR	NR	Number of Drug-risk Indicators per Patent (median) Group B Baseline 2 Follow-up: 2 P=.81 Group C Baseline 2 Follow-up: 2 P=.40 OVERALL comparing all 3 groups P=.44	Number of Drug-risk Indicators per Patent (median) Group A Baseline 2 Follow-up: 2 P=.18
Shim 2018[96] RCT Community Medication review Follow-up: 6 months	NR	NR	NR	NR	NR	NR	MAI score Median (IQR) Baseline 15.0 (13.5) Follow-up: 8.0 (9.0) P<.001	MAI score Median (IQR) Baseline 18.0 (15.0) Follow-up: 20.0 (16.0)

Author Year Study Design Setting Intervention Type Follow-up	Total Number of Medications Discontinued, mean (SD)		Number of Medications with Dosage Decreased, mean (SD)		Number of Medications Added or Substituted, mean (SD)		Number of Inappropriate Medications Discontinued, mean (SD)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Touchette 2012[114] RCT Community/ primary care Comprehensive Medication Review Follow-up: 6 months	NR	NR	NR	NR	NR	NR	DRPs (mean) Baseline (0 months) Basic MTM: 2.13 Enhanced MTM: 2.44 3-month visit Basic MTM: 0.96 Enhanced MTM: 0.96	NR
Weber 2008[107] Cluster RCT Community Medication review Follow-up: 15 months	No statistically significant trends were seen in the total number of medications over the 12-month period of study when comparing medication numbers during each month of study		NR	NR	NR	NR	NR	NR
Zermansky 2001[110] RCT Community Medication review Follow-up: 12 months	Number of patients with medications stopped 41% (239/581)	Number of patients with medications stopped 33% (180/550)	Number of patients with dosage changed 17% (98/581)	Number of patients with dosage changed 11% (61/550)	Number of patients with new drug started 46% (265/581)	Number of patients with new drug started 49% (270/550)	NR	NR

CI=confidence interval; DRP=drug related problem; FRID=fall risk increasing drug; IQR=interquartile range; ITT=intent to treat; MAI=Medication Appropriateness Index; MTM=medication therapy management; NR=not reported; NS=not statistically significant; OR=odds ratio; PCIs=pharmaceutical care issues; PIMs=potentially inappropriate medications; PIPs=potentially inappropriate prescriptions; RCT=randomized controlled trial; RRadj=adjusted relative risk; START=Screening Tool to Alert Doctors to Right Treatment; STOPP=Screening Tool of Older Persons' Prescriptions; VA=Department of Veterans Affairs

[a]defined by predetermined objective criteria that varied by drug class (all but cardiovascular medications) or by a masked reviewer (for cardiovascular medications)

Appendix D, Table 7. Intermediate Process Outcomes, Part 2 – Comprehensive Medication Review

Author Year Study Design Setting Intervention Type Follow-up	Adherence to Medications		Types of Medications		Medication Burden		Costs	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Boyé 2017[20] Polinder 2016[80] RCT Community Medication review Follow-up: 12 months	NR	NR	**Cardio-vascular FRIDs** Withdrawal not possible or necessary: 62% (164/265) Successful withdrawal: 24% (64/265) Failed withdrawal: 14% (37/265) **Psycho-tropic FRIDs** Withdrawal not possible or necessary: 32% (37/114) Successful withdrawal: 35% (40/114) Failed withdrawal: 33% (37/114)	NR	NR	NR	Total Health Care Costs (including intervention) per patient during 12 month follow-up 2324 € P not reported Change in Medication Costs -38 € P<.05 Mean cost of the Intervention 120 €	Total Health Care Costs per patient during 12 month follow-up 2285 € Change in Medication Costs -3 €

Author Year Study Design Setting Intervention Type Follow-up	Adherence to Medications		Types of Medications		Medication Burden		Costs	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Campins 2017, 2019[24,25] Community Medication review/guide lists Follow-up: 12 months	Morisky-Green Baseline: 61.8% n=251 P=.71 vs control 6 months: 76.4% P=.005 vs control (NOTE: adherence not measured at 12 months)	Morisky-Green Baseline: 60.2% n=252 6 months: 64.1%	NR	NR	NR	NR	Total annual drug expenditure n=245* Pre-intervention 317,520.00 € Post-intervention 260,263.00 € Savings per patient 233.75 € (95%CI 169.83, 297.67) *Slightly different cohort analyzed for costs	Total annual drug expenditure n=245* Pre-intervention 338,271.00 € Post-intervention 296,768.00 € Savings per patient 169.40 € (95%CI 103.37, 235.43)

Author Year Study Design Setting Intervention Type Follow-up	Adherence to Medications		Types of Medications		Medication Burden		Costs	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Denneboom 2007[34] Cluster RCT Community pharmacy Medication review Follow up: 9 months	NR	NR	NR	NR	NR	NR	Cost of intervention (pharmacist time) per patient 8.68 € n=163 Difference 5.27 (95%CI 2.21, 8.34) Medication cost savings per patient at 9 months -7.78 € n=365 Difference 3.44 (95%CI -3.89, 10.77) Net expenses per patient at 9 months (pharmacy costs plus medication savings) 7.23 n=365 Difference 1.72 (95%CI -5.80, 9.23)	Cost of intervention (pharmacist time) per patient 6.22 € n=97 Medication cost savings per patient at 9 months: -4.33 € n=320 Net expenses per patient at 9 months (pharmacy costs plus medication savings) 5.52 n=319

Author Year Study Design Setting Intervention Type Follow-up	Adherence to Medications		Types of Medications		Medication Burden		Costs	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Haag 2016[46] RCT Community Medication review Follow-up: 30 days	"Do you sometimes forget to take any of your medications?" Baseline (Yes) 31% (4/13) P=.16 30 day follow-up (Yes) 9% (1/11) P=.53 Adapted MMAS No significant difference between groups at baseline (P=.14) or 30 day follow-up (P=.65)	"Do you sometimes forget to take any of your medications?" Baseline (Yes) 8% (1/12) 30 day follow-up (Yes) 18% (2/11)	NR	NR	NR	NR	NR	NR
Hanlon 1996[47] Schmader 1997[92] RCT Community/ primary care Medication review Follow-up: 12 months	Compliance 12 months n=86 77.4% P=.88	Compliance 12 months n=83 76.1%	NR	NR	NR	NR	NR	NR

Author Year Study Design Setting Intervention Type Follow-up	Adherence to Medications		Types of Medications		Medication Burden		Costs	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Jodar-Sanchez 2015[50] Malet-Larrea 2016, 2017[62,63] ConSIGUE Cluster RCT Community/ primary care Medication review Follow-up: 6 months	NR	NR	NR	NR	NR	NR	Medication 655.91 € (818.53 €) Mean difference 0.19 €/day P=.079 Healthcare costs related to NOMs/ person 207.04 € (1,207.20 €) Mean difference 308.73 € P=.037 Total cost/ person 977.57 € (1,455.88 €) Mean difference -195.88 € Mean cost of intervention per person 16.27 €	Medication 657.67 € (666.09 €) Healthcare costs related to NOMs/ person 570.97 € (3,621.15 €) Total cost/ person 1,173.44 € (3,671.65 €)

Author Year Study Design Setting Intervention Type Follow-up	Adherence to Medications		Types of Medications		Medication Burden		Costs	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Krska 2001[54] Cluster RCT Community Pharmacist-led medication review Follow-up: 3 months	PCI - potential/ actual compliance issues resolved 69% (51/74) P<.0001*	PCI - potential/ actual compliance issues resolved 30% (21/69)	NR	NR	NR	NR	Medicine costs (monthly, per patient) Baseline 39.29 £ (29.07 £) Follow-up 38.83 £ (29.60 £) No significant differences between group at baseline or follow-up	Medicine costs (monthly, per patient) Baseline 42.80 £ (33.50 £) Follow-up 42.61 £ (31.84 £)
Meredith 2002[67] RCT Community Medication review Follow-up: 12 weeks	NR	NR	More appropriate medication regimen **Cardio-vascular** 55% (11/20) P=.02 **Psycho-tropic** 40% (19/47) P>.2 **NSAIDS** 42% (19/45) P>.2	More appropriate medication regimen **Cardio-vascular** 18% (3/17) **Psycho-tropic** 32% (18/57) **NSAIDS** 52% (24/46)	NR	NR	NR	NR

Author Year Study Design Setting Intervention Type Follow-up	Adherence to Medications		Types of Medications		Medication Burden		Costs	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Moga 2017[70] RCT University clinic Pharmacist medication review Follow up: 8 weeks	NR	NR	NR	NR	ADS Baseline 2.8 (1.9) n=25 Unadjusted Change from Baseline -1.2 (1.6) n=25 P=.01	ADS Baseline 2.9 (1.3) n=25 Unadjusted Change from Baseline -0.2 (0.9) n=24	NR	NR
Muth 2018[71] Cluster RCT Community primary care Medication review Follow-up: 9 months	Morisky Baseline 3.7 (0.6) n=250 Follow-up 3.7 (0.7) n=231 P=.63 Mean Difference 0.0 (95%CI -0.2, 0.1)	Morisky Baseline 3.7 (0.8) n=252 Follow-up 3.7 (0.6) n=225	NR	NR	NR	NR	NR	NR

Author Year Study Design Setting Intervention Type Follow-up	Adherence to Medications		Types of Medications		Medication Burden		Costs	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Olesen 2013[72] RCT Community Medication review and phone follow-up Follow-up: 2 years	Non-adherent to All Drugs 11% (28/253) Risk Difference 1 (95%CI -4, 7) Non-adherent 0-6 months 14% (35/253) OR 0.93 (95%CI 0.57, 1.52) Non-adherent 6-12 months 19% (48/253) OR 1.24 (95%CI 0.78, 1.95)	Non-adherent to All Drugs 10% (26/264) Non-adherent 0-6 months: 15% (39/264) Non-adherent 6-12 months: 16% (42/264)	NR	NR	NR	NR	NR	NR
Shim 2018[96] RCT Community Medication review Follow-up: 6 months	MALMAS Score ≥6 (adherent) Baseline 35.6% (26/73) Follow-up: 69.9% (51/73) P<.001	MALMAS Score ≥6 (adherent) Baseline 32.9% (26/79) Follow-up: 31.6% (25/79)	NR	NR	NR	NR	NR	NR

Author Year Study Design Setting Intervention Type Follow-up	Adherence to Medications		Types of Medications		Medication Burden		Costs	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Van der Meer 2018[105] RCT Community Medication review Follow-up: 3 months	NR	NR	NR	NR	Proportion of Patients with Decrease in DBI≥0.5 ITT (all with baseline measure) 17.3% (13/75) P=.93 Per-protocol analysis 18.5% (12/65) P=.86	Proportion of Patients with Decrease in DBI≥0.5 15.9% (13/82) Per-protocol analysis 16.3% (13/80)	NR	NR
Weber 2008[107] Cluster RCT Community Medication review Follow-up: 15 months	NR	NR	By month 3, psychoactive medication was lower for the intervention group; this persisted to the end of study P=.10		NR	NR	Baseline $443.69 per quarter No significant trends in medical costs were seen over the period of the study	Baseline $418.66 per quarter
Zermansky 2001[110] RCT Community Medication review Follow-up: 12 months	NR	NR	NR	NR	NR	NR	Change in cost 1.80 £ (17.55) Group difference: -4.72 £ (95%CI -7.04, -2.41), P=.0001	Change in cost 6.53 £ (21.99)

ADS=anticholinergic drug scale (higher score indicated higher burden); CI=confidence interval; DBI=Drug Burden Index; FRID=fall risk increasing drug; ITT=intent-to-treat; MALMAS=Malaysian Medication Adherence Scale; MMAS=Morisky Medication Adherence Scale; NOMS=negative outcomes associated with medications; OR=odds ratio; PCIs=pharmaceutical care issues; RCT=randomized controlled trial

Appendix D, Table 8. Study Characteristics – Education Interventions

Author, year Trial name Country Funding Study Design Setting Intervention type	Inclusion/Exclusion Criteria	Intervention (n) Control (n) Clusters (if applicable) Follow-up	Demographics/Characteristics
Bregnhoj 2009[21] Denmark Funding: Foundation, Government Cluster RCT Community Education plus feedback	Inclusion: GPs: Single-handed practice in a specific county Patients: Age ≥ 65 years, on ≥ 5 medications, capable of consenting Exclusion: NR	Intervention – education + feedback: Interactive meeting on polypharmacy in the elderly + feedback provided on participating patients' medications (n=15 GPs, 79 patients) Intervention – education only: (n=12 GPs, 61 patients) Control: Usual care (n=14 GPs, 72 patients) Follow-up: Approximately 1 year	N=212 (patients) Age (mean): 77 Gender (% male): 34 Race/ethnicity: NR Comorbidity status: NR Physical status: NR Cognitive status: NR Number of medications (mean): 7.7
Coleman 1999[28] United States Funding: Foundation Cluster RCT Community Education	Inclusion: Age ≥65 years; at highest risk for hospitalization and functional decline based on a previously validated computer-based predictive index Exclusion: Moderate to severe dementia, too ill to participate, terminal illness, in a nursing home, no longer in the health care system	Intervention: Chronic Care Clinic (½ day visit including development of shared treatment plan, education session with pharmacist, patient self-management group session, health status assessment information given to practice team) and training sessions for physicians and nurses (96 subjects in 5 practices) Control: Usual care (73 subjects in 4 practices) Follow-up: 24 months	N=169 (patients) Age (mean): 77 Gender (% male): 52% Race/ethnicity: 3% non-white Comorbidity status (Chronic Disease Score): Intervention: 7.3 Control: 7.7; P=.06 Physical status: SF-36 did not differ between groups Cognitive status: NR High risk medications (mean): Intervention: 1.99 Control: 3.92; P=.04

Author, year Trial name Country Funding Study Design Setting Intervention type	Inclusion/Exclusion Criteria	Intervention (n) Control (n) Clusters (if applicable) Follow-up	Demographics/Characteristics
Jager 2017[112] PomP Germany Funding: Government Cluster RCT Community Education	Inclusion: *Practices/GPs:* Quality Circles (QCs) of GP-Centered care contracts, Primary Care Practices (PCPs) within QCs, GPs within PCPs *Patients of GPs:* Age >50 years, prescriptions for >4 different drugs in ≥2 quarters of preceding year, diagnosis of at least 3 chronic conditions Exclusion: *Practices/GPs:* Participation in another study focusing on multimorbidity or polypharmacy in previous year *Patients:* Cognitive or clinical status which hindered active participation in the study	Intervention: Training and resources for GPs and Medical Assistants (4 hour workshop, training in brown bag reviews, online resources); educational materials for patients; implementation action plans (Allocated: n=5 QCs, 7 PCPs, 11 GPs, 173 patients; Analyzed n=5 QCs, n=6 PCPs, n=10 GPs, n=143 patients) Control: Informed of best practices only (Allocated: n=6 QCs, 11 PCPs, 11 GPs, 171 patients; Analyzed n=6 QCs, n=11 PCPs, n=11 GPs, n=130 patients) Follow-up: 9 months	N=273 (patients analyzed) Age (mean): 72.2 total; intervention 70.8, control 73.8; P=.006 Gender (% male): 44.3 total; intervention 44.1, control 44.6; P=.93 Race/ethnicity: NR Comorbidity status: Mean number of diagnosed chronic diseases: 5.7 total; intervention 5.5, control 6.0; P=.08 Physical status: NR Cognitive status: NR Number of medications (mean): Highest number of prescribed drugs in 1 quarter of the year: 7.3 total; intervention 7.0, control 7.7; P=.03

Author, year Trial name Country Funding Study Design Setting Intervention type	Inclusion/Exclusion Criteria	Intervention (n) Control (n) Clusters (if applicable) Follow-up	Demographics/Characteristics
Martin 2018[64] D-PRESCRIBE Canada Funding: Government Cluster RCT Community Education (patient and physician)	Inclusion: *Pharmacies:* Part of 3 pharmacy chains within 100-km radius of research center; clientele of ≥20% adults ≥65 years *Patients:* Age ≥65 years, had filled prescription for a targeted medication for ≥3 consecutive months before screening (if prescriptions for >1 targeted medication, only received 1 intervention for duration of trial based on first medication on list given to pharmacist Exclusion: *Patients:* Diagnosis of severe mental illness or dementia (based on prescribed medications), significant cognitive impairment (MMSE<24), inability to communicate in English or French, assisted-living resident	Intervention: Patient educational brochures and evidence-based pharmaceutical opinion (distributed to patients and their prescribers) (n=34 pharmacies, 248 patients) Control: Usual care (n=35 pharmacies, 241 patients) Follow-up: 6 months Targeted medications: 1) all benzodiazepines and zopiclone/zolpidem (sedative-hypnotic Z-drugs); 2) 1st generation antihistamines; 3) glyburide; 4) selective NSAIDS NOTE: pharmacies randomized after eligible patients identified and consented	N=489 patients Age (mean): 74.7 Gender (% male): 34 Comorbidity status: 83% good to excellent health; 17% fair to poor health (self-rated) Physical status: 27% Frail Cognitive status (MMSE, mean): 29 Number of Medications at Baseline: 8.7

Author, year Trial name Country Funding Study Design Setting Intervention type	**Inclusion/Exclusion Criteria**	**Intervention (n) Control (n) Clusters (if applicable) Follow-up**	**Demographics/Characteristics**
Pimlott 2003[77] Canada Funding: Foundation RCT Community/ primary care: Education on targeted drug (benzodiazepines)	Inclusion: *Providers:* Primary care physicians linked to Ontario Drug Benefit Database and wrote ≥10 prescriptions for target drugs in a 2-month period *Patients:* Age ≥65 years Exclusion: NR	Intervention: Mailed packages of feedback about participants' prescribing and evidence-based education materials, sent every 2 months for 6 months, feedback presented as bar graphs comparing prescriber with peers and hypothetical "best practice" (n=168 physicians) Control: Educational material and feedback on antihypertensive prescribing for elderly patients (n=206 physicians) Follow-up: 6 months	Physicians N=374 physicians Age (mean): 50.7 Gender (% male): 84 Race/ethnicity: NR Patients N=NR Age (mean of patients prescribed benzodiazepines): 76 Gender (% male prescribed benzodiazepines): 35 Comorbidity status: Depression NR Physical status: NR Cognitive status: NR Number of medications (mean): NR

Author, year Trial name Country Funding Study Design Setting Intervention type	Inclusion/Exclusion Criteria	Intervention (n) Control (n) Clusters (if applicable) Follow-up	Demographics/Characteristics
Rognstad 2013, 2018[89,113] Norway Funding: Government Cluster RCT Community Education	Inclusion: Peer CME groups in Southeastern Norway Exclusion: NR	Intervention: Educational package (delivered by peer academic detailers, who were trained GPs) on safer prescribing practice for older patients (n=41 CME groups, 250 GPs, 46,737 patients) Control: Educational intervention targeting antibiotic prescribing practice for respiratory tract infections (n=39 CME groups, 199 GPs, 35,073 patients) Clusters: Medical education groups (CMEs) Follow-up: 12 months	N=81 CME groups, 449 GPs, 81,810 patients) Age (mean): (Note: prescription criteria were developed for patients ≥70) GPs: 50 Patients: NR Gender (% male): GPs: 69 Patients: NR Race/ethnicity: NR Comorbidity status: NR Physical status: NR Cognitive status: NR Number of medications (mean): NR

Author, year Trial name Country Funding Study Design Setting Intervention type	Inclusion/Exclusion Criteria	Intervention (n) Control (n) Clusters (if applicable) Follow-up	Demographics/Characteristics
Schafer 2018[91] MultiCare AGENDA Germany Funding: Government Cluster RCT Community Education	Inclusion: *Practices:* Willing to participate in study regardless of randomization, established GP practice for ≥2 years and, if used, practice software able to create list of all patients based on age *Patients:* Age 65 to 84 years; consulted their GP in the past 3 months; ≥3 chronic conditions from list of 42; up to 25 patients per practice site were randomly selected Exclusion: *Practices*: Participated in feasibility study or in the Multi-Care Cohort Study; in group practices, only 1 GP allowed to participate in study *Patients*: Hardly known by GP (*ie,* ad hoc consultation, patient for <12 months), not able to consent (*eg,* dementia) or not able to participate in interviews according to the GP (*eg,* severe psychiatric illness, deafness, insufficient German language skills); life expectancy ≤3 months according to their GP, nursing home residence, and participation in other scientific trials at the time of recruitment.	Intervention: GPs received 12 hrs training on narrative-based medicine; during 12-month intervention, GPs had three 30-minute talks with their patients based on narrative medicine training (brown-bag medication review and subsequent de-prescribing based on patient and provider's conversation) (n=299 patients, 28 practice sites, 28 GPs) Control: Usual care (n=305 patients, 27 practice sites; 27 GPs) Follow-up Intervention: 441 days	Providers (N=55) Age (mean): 49.5 Gender (% male): 52.7 Race: NR Patients (N=604) Age (mean): 73.4 Gender (%male): 45.4 Race: NR Comorbidity status: 8.6 chronic diseases (based on list of 46 diseases) Physical status: NR Cognitive status: NR Number of medications (mean): 7.05

Author, year Trial name Country Funding Study Design Setting Intervention type	Inclusion/Exclusion Criteria	Intervention (n) Control (n) Clusters (if applicable) Follow-up	Demographics/Characteristics
Schmidt-Mende 2017[95] Sweden Funding: Government Cluster RCT Community/primary care Education	Inclusion: Clinics: Located in Stockholm's county with list size ≥3000, authorized for clinical service prior to July 1, 2009 Patients: Age ≥65 years, representing ≥5% of list size, and ≥10 home care patients Exclusion: Researchers working at practice and other education on PIMs at practice after January 2012	Intervention: Educational PowerPoint presentation including theoretical knowledge on PIMs based on national indicators; feedback on prescribing of PIMs; training conducted by pharmacists with special training (n=34 clinics, median 1,597 patients; one clinic did not receive intervention) Control: Usual care (n=35 clinics, median 1,433 patients) Follow-up: 9 months	N=119,910 Age (mean): NR (all ≥65 yrs) Gender (% male): 44.8 Race/ethnicity: NR Comorbidity status: 2-3 chronic diseases 22%, ≥3 chronic diseases 35.8% Physical status: NR Cognitive status: NR Number of medications (mean): NR

Author, year Trial name Country Funding Study Design Setting Intervention type	Inclusion/Exclusion Criteria	Intervention (n) Control (n) Clusters (if applicable) Follow-up	Demographics/Characteristics
Simon 2006[97] United States Funding: Government, Foundation Cluster RCT and interrupted time series Community Education	Inclusion: All primary care clinicians at 15 enrolled clinics and elderly patients receiving primary care at those sites Medication Dispensing analysis was included for patients age ≥65 and older at the time of dispensing Exclusion: None	Intervention: 1-hour group academic detailing session focusing on evidence for age-specific prescribing alerts for high risk medications (*ie,* amitriptyline, doxepin, imipramine, chlordiazepoxide, diazepam, flurazepam, indomethacin, piroxicam, propoxyphene, carisoprodol, cyclobenzaprine, and methocarbamol); detailing occurred shortly after new alerts were implemented in EHR; alerts were for patients ≥65 years for a new high-risk medication not dispensed in past 6 months; providers were also mailed a reminder letter 4-7 months after detailing session (n=24,119 patients, 113 primary care clinicians, 7 clinics) Control: Age-specific prescribing alerts only (as above) (n=26,805 patients, 126 primary care clinicians, 8 clinics) Follow-up: 1.5 years after implementing age-specific alerts and group detailing. ***Quasi-experimental design**	Patients N=50,924 Age (mean): 74 Gender (% male): 36 Race/ethnicity: NR Comorbidity status (Clark chronic disease score): Intervention: 4,891.6 Control: 4,641.2 P=.04 Physical status: NR Cognitive status: NR Number of medications (mean): NR Providers N=239 (Physician=178, Nurse Practitioner=28, Physician Assistant=34) Age (mean): 45.3 Gender (% male): 55.9

Author, year Trial name Country Funding Study Design Setting Intervention type	Inclusion/Exclusion Criteria	Intervention (n) Control (n) Clusters (if applicable) Follow-up	Demographics/Characteristics
Tannenbaum 2014[115] Canada Funding: Government Cluster RCT Community pharmacies Patient education	Inclusion: Age ≥65 or older, willing to consent, at least 5 active prescriptions, use of ≥1 benzodiazepine for ≥3 consecutive months prior to screening Exclusion: Severe mental illness or dementia (active prescription for antipsychotic and/or medication for dementia in preceding 3 months), unable to communicate in French/English, significant cognitive impairment (MoCA score <21)	Intervention: 7-page letter-size paper brochure developed for trial, mailed to participants (15 pharmacies and n=148 participants enrolled) Control: Usual care, monitored for 6 months (15 pharmacies and n=155 participants enrolled) Clusters: Community pharmacies Follow-up: 6 months	N=303 randomized, 261 completed 6-month follow up (85%) Age (mean): 75 Gender (% male): 31% male Race/ethnicity: NR Comorbidity status: NR Physical status: NR Cognitive status: Mean MoCA score: 25.4 (range 21-30) Number of medications (mean): 9.9/day

BMI=body mass index; CME=Continuing Medical Education; EHR=electronic health record; eGeMS=Geriatric Multidisciplinary Strategy for Good Care of the Elderly; GP=general practitioner; MMSE=Mini-Mental State Examination; MoCA=Montrial Cognitive Assessment; NR=not reported; NSAIDS=non-steroidal anti-inflammatory medications; PIMs=potentially inappropriate medications; RCT=randomized controlled trial

Appendix D, Table 9. Risk of Bias – Education Intervention Studies

Author, Year Randomization	Sequence Generation	Allocation Concealment	Recruitment Bias	Baseline Imbalance	Blinded Outcome Assessment	Incomplete Cluster Data	Incomplete Outcome Data	Selective Outcome Reporting	Overall Risk of Bias
Bregnhoj 2009[21] Physicians randomized	Low	Unclear (did consultant assign GPs?)	N/A	Low (patients)	MAI blinded; unclear if treatment level was blinded	N/A	High (22% of patients without data)	Low	Medium

Author, Year Randomization	Sequence Generation	Allocation Concealment	Recruitment Bias	Baseline Imbalance	Blinded Outcome Assessment	Incomplete Cluster Data	Incomplete Outcome Data	Selective Outcome Reporting	Overall Risk of Bias
Coleman 1998[28] Practices randomized	Unclear ("simple" randomization)	Unclear (not reported)	Low	Unclear (clinic data not reported; participant demographics balanced)	Unclear (chart abstraction was blinded; unclear if survey review was blinded)	Unclear (staff transitions)	High (19% of intervention and 33% of control group lost at 24 months)	Low	Medium
Jager 2017[112] "Quality Circles" randomized	Low	Low	Low	Unclear (data for GPs not clusters)	Low	Low (all quality circles analyzed; 1 provider lost)	High (21% of patients lost)	Low	Low
Martin 2018[64] D-Prescribe Community pharmacies randomized	Low	Low	Low	Low	Low	Low (no pharmacies lost)	Low (ITT and per-protocol [11% lost] analyses)	Unclear (not all protocol outcomes reported)	Low
Pimlott 2003[77] Physicians randomized (NOTE: low response rate for participation)	Unclear (not reported)	Unclear (not reported)	N/A	Low	Unclear (not reported)	N/A	Unclear (not reported)	Low	Medium
Rognstad 2013, 2018[89,113] CME groups randomized	Unclear (not reported)	Low	Low	Low	Unclear	Low (2 groups merged into 1 group in the control arm)	Low	Low	Low

Author, Year Randomization	Sequence Generation	Allocation Concealment	Recruitment Bias	Baseline Imbalance	Blinded Outcome Assessment	Incomplete Cluster Data	Incomplete Outcome Data	Selective Outcome Reporting	Overall Risk of Bias
Schafer 2018[91] Primary care practices randomized	Unclear for GPs	Low	Low	Low	Medium (outcomes assessors independent of practices)	Low (all practices completed study)	Low (<10%)	Low	Low
Schmidt-Mende 2017[95] Primary care practices randomized	Low	High (not blinded)	Unclear (all patients from practices included)	Medium (patient-level differences between groups)	Unclear (outcomes from Data Warehouse)	Low (1 cluster [1%] did not receive intervention)	Low (ITT)	Medium (unable to report all outcomes due to data linkage issue)	Medium
Simon 2006[97] Clinics randomized	Unclear (blocks of 2)	Unclear (not reported)	Low	Unclear (not reported)	Low (claims data and blinded analyst)	Low	Low	Low	Medium
Tannenbaum 2014[115] EMPOWER Community pharmacies randomized	Low	Low	Low	Unclear (data not reported for clusters; patient groups were similar)	Low	Low (no pharmacies lost)	Medium (14% of patients lost)	Low	Low

CME=continuing medical education; GP=general practitioner; ITT=intention-to-treat; N/A=not applicable

Appendix D, Table 10. Patient-centered Outcomes, Part 1 – Education Interventions

Author Year Study Design Setting Intervention Type Follow-up	Hospitalizations % (n/N)		Acute Care Encounters % (n/N)		Delirium % (n/N)	
	Intervention	Control	Intervention	Control	Intervention	Control
Coleman 1999[28] Cluster RCT Community Education Follow-up: 24 months	Mean Number of Hospital Admissions per Year (at 24 months) 0.58, P=.94 Percentage with >1 Hospitalization 36.5%, P=.77	Mean Number of Hospital Admissions per Year (at 24 months) 0.59 Percentage with >1 Hospitalization 34.3%	Mean Number of Emergency Visits per Year (at 24 months) 0.23 P=.67	Mean Number of Emergency Visits per Year (at 24 months) 0.27	NR	NR
Martin 2018[64] Cluster RCT Community Education Follow-up: 6 months	Due to Adverse Events 0% (0/248)	Due to Adverse Events 0% (0/241)	NR	NR	NR	NR
Schafer 2018[91] Cluster RCT Primary Care Clinic Education (physician and patient) Follow-up: 441 ± 66 days	Days in Hospital Baseline 2.6 (8.7) n=299 Follow-Up 2.6 (8.3) n=298 P=.26 vs control Intervention Effect Model 1 (adjusted - age, gender, time from baseline to follow-up) β=-3.07 (95%CI -5.25, -0.89), P=.006	Days in Hospital Baseline 2.0 (6.9) n=305 Follow-up 3.5 (12.1) n=305	NR	NR	NR	NR

Author Year Study Design Setting Intervention Type Follow-up	Hospitalizations % (n/N)		Acute Care Encounters % (n/N)		Delirium % (n/N)	
	Intervention	Control	Intervention	Control	Intervention	Control
Schmidt-Mende 2017[95] Cluster RCT Community/ primary care Education Follow-up: 4 months	≥1 Unplanned Admission Baseline 13.3% Post-intervention 12.8% Risk Difference 0.2 (95%CI -0.8, 1.2) Difference-in-Difference Analysis -0.5 (95%CI -0.96, 0.03)	≥1 Unplanned Admission Baseline 12.6% Post-intervention 12.6%	≥1 Emergency Department Visit Baseline 22.5% Post-intervention 22.1% Risk Difference 0.9 (95%CI -0.6, 2.5) Difference-in-Difference Analysis -0.2 (95%CI -0.7, 0.4)	≥1 Emergency Department Visit Baseline 21.4% Post-intervention 21.2%	NR	NR
Tannenbaum 2014[115] Cluster RCT Community pharmacy Education Follow-up: 6 months	No major adverse events requiring hospitalization	NR	NR	NR	NR	NR

CI=confidence interval; GP=general practitioner; NR=not reported; RCT=randomized controlled trial

Appendix D, Table 11. Patient-centered Outcomes, Part 2 – Education Interventions

Author Year Study Design Setting Intervention Type Follow-up	Functional Status (mean, SD) – describe measure		Quality of Life (mean, SD) – describe measure		Patient Satisfaction (mean, SD) – describe measure	
	Intervention	Control	Intervention	Control	Intervention	Control
Coleman 1999[28] Cluster RCT Community Education Follow-up:24 months	SF-36 Physical Function Baseline 47.7 P=.72 12 months 43.9 P=.73 24 months 37.5 P=.99	SF-36 Physical Function Baseline 43.8 12 months 44.5 24 months 37.5	NR	NR	Overall Medical Care Rating* (% Excellent) Baseline: 50% P=.03 12 months: 35% P=.66 24 months: 40% P=.13 *using questions based on standardized instruments	Overall Medical Care Rating* (% Excellent) Baseline: 33% 12 months: 37% 24 months: 25%

Author Year Study Design Setting Intervention Type Follow-up	Functional Status (mean, SD) – describe measure		Quality of Life (mean, SD) – describe measure		Patient Satisfaction (mean, SD) – describe measure	
	Intervention	**Control**	**Intervention**	**Control**	**Intervention**	**Control**
Schafer 2018[91] Cluster RCT Primary Care Clinic Education (physician and patient) Follow-up:(intervention): 441 ± 66 days	NR	NR	EQ-5D Baseline 0.67 (0.30) n=299 Follow-up 0.68 (0.32) n=298 P=.47 *Intervention Effect Model 1** Intention to treat: β =0.34 (95%CI -0.05, 0.74 P=.09 *adjusted - age, gender, time from baseline to follow-up	EQ-5D Baseline 0.69 (0.28) n=302 Follow-up 0.70 (0.28) n=303	**Patient Satisfaction with Provider** Europep-Clinical Performance Baseline 3.1 (0.69) n=277 Follow-up: 3.0 (0.71) n=260 P=.47 Europep-Organisation of Care Baseline: 3.2 (0.56) n=244 Follow-up 3.1 (0.55) n=240 P=.483 *Intervention Effects Model 1** Europep-Clinical Performance β=0.01 (95%CI -0.11, 0.13), P=.916 Europep-Organisation of Care β=-0.05 (95%CI -0.18, 0.08) P=.416	**Patient Satisfaction with Provider** Europep-Clinical Performance Baseline: 3.1 (0.72) n=284 Follow-up: 2.9 (0.72) n=268 Europep-Organisation of Care Baseline: 3.0 (0.71) n=267 Follow-up: 3.0 (0.63) n=263

Author Year Study Design Setting Intervention Type Follow-up	Functional Status (mean, SD) – describe measure		Quality of Life (mean, SD) – describe measure		Patient Satisfaction (mean, SD) – describe measure	
	Intervention	Control	Intervention	Control	Intervention	Control
Tannenbaum 2014[115] Cluster RCT Community pharmacy Education Follow-up: 6 months	NR	NR	NR	NR	98% (120/123) acknowledged satisfaction with receiving medication risk information (telephone interview at 6 months	NR

DQI=Dementia Quality-of-Life Instrument; EQ-5D-3L=EuroQol-5D (3 level version); MMSE=Mini-Mental State Examination; RCT=randomized controlled trial; SD=standard deviation; SIB-S=Severe Impairment Battery (short form); SF-36=Short Form 36 item

Appendix D, Table 12. Patient-centered Outcomes, Part 3 – Education Interventions

Author Year Study Design Setting Intervention Type	Falls % (n/N)		Major Adverse Cardiovascular Events[a] % (n/N)		Adverse Drug Withdrawal Events % (n/N)		All-cause Mortality % (n/N)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Bregnhoj 2009[21] Cluster RCT Community GP education + feedback Follow-up: approx. 1 year	NR	NR	NR	NR	NR	NR	Education + Feedback 22% (17/79) Education Only 10% (6/61)	11% (8/72)

Author Year Study Design Setting Intervention Type	Falls % (n/N)		Major Adverse Cardiovascular Events[a] % (n/N)		Adverse Drug Withdrawal Events % (n/N)		All-cause Mortality % (n/N)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Coleman 1999[28] Cluster RCT Community Education Follow-up: 24 months	Falls in Past 12 Months Baseline: 44% P=.56 12 months: 44% P=.37 24 months: 44% P=.35	Falls in Past 12 Months Baseline: 49% 12 months: 38% 24 months: 36%	NR	NR	NR	NR	At 24 Months 16% (15/96)	At 24 Months 16% (12/73)
Jager 2017[112] Cluster RCT Community Education Follow-up: 9 months	NR	NR	NR	NR	NR	NR	0.6% (1/173)	1.8% (3/171)
Martin 2018[64] Cluster RCT Community Education Follow-up: 6 months	NR	NR	NR	NR	38% (29/77) attempting to taper sedative hypnotics reported withdrawal symptoms	NR	0.8% (2/248)	1.2% (3/241)
Schafer 2018[91] Cluster RCT Primary Care Clinic Education (physician and patient) Follow-up: (intervention): 441 ± 66 days	NR	NR	NR	NR	GPs reported no adverse events of the intervention		NR	NR

Author Year Study Design Setting Intervention Type	Falls % (n/N)		Major Adverse Cardiovascular Events[a] % (n/N)		Adverse Drug Withdrawal Events % (n/N)		All-cause Mortality % (n/N)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Schmidt-Mende 2017[95] Cluster RCT Community/ primary care Education Follow-up: 4 months	NR	NR	NR	NR	NR	NR	2.1% (1,204/ 56,626) Risk Difference 0.1 (95%CI -0.1, 0.6) Difference-in-Difference -0.08 (95%CI -0.28, 0.12)	2.0% (1,231/ 63,284)
Tannenbaum 2014[115] Cluster RCT Community pharmacy Education Follow-up: 6 months	NR	NR	NR	NR	Rebound insomnia or anxiety reported by 42% of those attempting to taper	NR	NR	NR

CI=confidence interval; GP=general practitioner; RCT=randomized controlled trial; RD=risk difference

[a]Includes cardiovascular death, nonfatal myocardial infarction, acute coronary syndrome, nonfatal stroke, revascularization, or heart failure exacerbation

Appendix D, Table 13. Intermediate Process Outcomes, Part 1 – Education Interventions

Author Year Study Design Setting Intervention Type Follow-up	Total Number of Medications Discontinued, mean (SD)		Number of Medications with Dosage Decreased, mean (SD)		Number of Medications Added or Substituted, mean (SD)		Number of Inappropriate Medications Discontinued, mean (SD)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Bregnhoj 2009[21] Cluster RCT Community GP education + feedback Follow-up: approx. 1 year	Number of Medications Baseline Education + Feedback 7.9 Education 6.8 Post-intervention Education + Feedback 7.0 Education 7.3 Change Education + Feedback 0.9 Education -0.5.	Number of Medications Baseline: 7.5 Post-intervention 7.7 Change -0.2	NR	NR	NR	NR	MAI Baseline Education + Feedback 11.2 Education 7.5 Post-intervention Education + Feedback 6.0 (mean change -5.1) Education 8.2 (mean change 0.7) Mean change for combined groups -5.0 (95%CI -7.3, -2.6)	MAI Baseline: 9.3 Post-intervention 10.1 Change 0.8
Coleman 1999[28] Cluster RCT Community Education Follow-up: 24 months	NR	NR	NR	NR	NR	NR	Mean Number of High Risk Medication Fills* in Prior 12 Months Baseline: 1.99, P=.04 12 months 2.94, P=.67 24 months 1.86, P=.17 *8 classes of medications	Mean Number of High Risk Medication Fills in Prior 12 Months Baseline: 3.92 12 months 3.26 24 months 2.54

Author Year Study Design Setting Intervention Type Follow-up	Total Number of Medications Discontinued, mean (SD)		Number of Medications with Dosage Decreased, mean (SD)		Number of Medications Added or Substituted, mean (SD)		Number of Inappropriate Medications Discontinued, mean (SD)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Jager 2017[112] Cluster RCT Community Education Follow-up: 9 months	NR	NR	NR	NR	NR	NR	Number of PIM Prescriptions per Year Baseline: 0.8 (1.8) n=39 Follow-up: 0.8 (1.8) n=37 P=.37 Patients with ≥1 PIM Baseline: 27.7% n=39 Follow-up: 26.2% (37/141) P=.81	Number of PIM Prescriptions per Year Baseline: 0.9 (1.8) n=42 Follow-up: 1.0 (1.9) n=39 Patients with ≥1 PIM Baseline: 32.3% n=42 Follow-up: 30.0% (39/3130)
Martin 2018[64] Cluster RCT Community Education Follow-up: 6 months	NR	NR	NR	NR	NR	NR	All Medication Classes 42.7% (106/248) RR 3.55 (95%CI 2.45, 5.15) Medication class interaction: P=.09 No significant interactions with age, sex, health status, or number of medications	All Medication Classes 12.0% (29/241)

Author Year Study Design Setting Intervention Type Follow-up	Total Number of Medications Discontinued, mean (SD)		Number of Medications with Dosage Decreased, mean (SD)		Number of Medications Added or Substituted, mean (SD)		Number of Inappropriate Medications Discontinued, mean (SD)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Pimlott 2003[77] RCT Community/ primary care Education on targeted drug (benzodiazepines) Follow-up: 6 months	Number of Benzo-diazepine Prescriptions Baseline: 148.8 12 months 147.2 n=168 P NS Number of Long-acting Benzo-diazepine Prescriptions Baseline: 29.5 12 months 27.7 n=168 P=.04 vs baseline P NS vs control	Number of Benzo-diazepine Prescriptions Baseline: 136.4 12 months 142.2 n=206 Number of Long-acting Benzo-diazepine Prescriptions Baseline: 26.4 12 months 27.7 n=206	NR	NR	NR	NR	NR	NR

Author Year Study Design Setting Intervention Type Follow-up	Total Number of Medications Discontinued, mean (SD)		Number of Medications with Dosage Decreased, mean (SD)		Number of Medications Added or Substituted, mean (SD)		Number of Inappropriate Medications Discontinued, mean (SD)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Rognstad 2013, 2018[89,113] Cluster RCT Community (GPs) Education (CME) Follow-up: 12 months	NR	NR	NR	NR	NR	NR	PIPs per 100 patients Baseline: 27.3 Follow-up: 22.4 Absolute change due to Intervention -3.3 (-4.6 to -1.9) Relative change due to Intervention -12.1% (95%CI -16.8, -6.9) Patients Exposed to ≥1 PIP Baseline 19.9% (9,278/46,737) Follow-up: 16.9% (7,655/45,310) Relative Change due to Intervention -8.1%	PIPs per 100 patients Baseline: 25.8 Follow-up: 24.2 Patients Exposed to ≥1 PIP Baseline 18.6% (6,427/35,073)Follow-up 17.2% (5,977/35,211)

Author Year Study Design Setting Intervention Type Follow-up	Total Number of Medications Discontinued, mean (SD)		Number of Medications with Dosage Decreased, mean (SD)		Number of Medications Added or Substituted, mean (SD)		Number of Inappropriate Medications Discontinued, mean (SD)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Schafer 2018[91] Cluster RCT Primary Care Clinic Education (physician and patient) Follow-up:(intervention): 441 ± 66 days	Medications Taken by Patient Baseline 7.1 (3.5) n=299 Follow-up 7.3 (3.4) n=299 P=.086 Intervention Effect Model 3 Intention to Treat β=0.43 (95%CI -0.07, 0.93) P=.095	Medications Taken by Patient Baseline 7.0 (3.5) n=304 Follow-up 6.8 (3.5) n=304	NR	NR	NR	NR	NR	NR

Author Year Study Design Setting Intervention Type Follow-up	Total Number of Medications Discontinued, mean (SD)		Number of Medications with Dosage Decreased, mean (SD)		Number of Medications Added or Substituted, mean (SD)		Number of Inappropriate Medications Discontinued, mean (SD)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Schmidt-Mende 2017[95] Cluster RCT Community/ primary care Education Follow-up: 4 months	*Minor polypharmacy* (5-9 drugs) Baseline 31.1% (17,611/ 56,720) 4 months 31.3% (17,740/ 56,626) RD 0.5 (95%CI -0.5, 1.6) *Major polypharmacy* (≥10 drugs) Baseline 11.1% (6,274/ 56,720) 4 months 10.8% (6,852/ 56,626) RD 0.5 (95%CI -0.4, 1.4)	*Minor polypharmacy* (5-9 drugs) Baseline 31.2% (19,182/ 61,579) 4 months 30.8% (19,505/ 63,284) *Major polypharmacy* (≥10 drugs) Baseline 10.5% (6,457/61.579) 4 months 11.3% (6,297/63,284)	NR	NR	NR	NR	*≥1 Drug to Avoid/Anti-cholinergic* Baseline 13.6% (7,685/ 56,720) 4 months 14.3% (8,095/ 56,626) RD 0.7 (95%CI -0.4, 1.5) *≥1 Drug-Drug Interaction* Baseline 12.3% (6,990/ 56,720) 4 months 12.1% (6,823/ 56,626) RD 0.5 (95%CI -0.4, 1.2) *≥1 Drug-Disease Interaction* Baseline: 4.9% (2,776/ 56,720) 4 months 4.8% (2,743/ 56,626) RD 0.2 (95%CI -0.2, 0.8)	*≥1 Drug to Avoid/Anti-cholinergic* Baseline 13.4% (8,236/ 61,579) 4 months 13.7% (8,687/ 63,284) *≥1 Drug-Drug Interaction* Baseline 11.8% (7,242/ 61,579) 4 months 11.6% (7,355/ 63,284) *≥1 Drug-Disease Interaction* Baseline 4.8% (2,937/ 61,579) 4 months 4.6% (2,883/ 63,284

Author Year Study Design Setting Intervention Type Follow-up	Total Number of Medications Discontinued, mean (SD)		Number of Medications with Dosage Decreased, mean (SD)		Number of Medications Added or Substituted, mean (SD)		Number of Inappropriate Medications Discontinued, mean (SD)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Simon 2006[97] Cluster-RCT Ambulatory care clinics Education Follow-up: 1.5 years	NR	NR	NR	NR	NR	NR	Use of Targeted Medications Pre-intervention (academic detailing + alerts) 146.3/10,000 members Post 126.6/10,000 members Decrease of 19.7/10,000 members *No significant difference between control/ intervention groups noted. Level change: (P=.52) Slope change: (P=.27)	Use of Targeted Medications Pre-intervention (alerts only) 150.2/10,000 members Post 137.2/10,000 members Decrease of 13/10,000 members

Author Year Study Design Setting Intervention Type Follow-up	Total Number of Medications Discontinued, mean (SD)		Number of Medications with Dosage Decreased, mean (SD)		Number of Medications Added or Substituted, mean (SD)		Number of Inappropriate Medications Discontinued, mean (SD)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Tannenbaum 2014[115] Cluster RCT Community pharmacy Education Follow-up: 6 months	Discontinued Benzo-diazepine use ITT analysis 27% (40/148) RD 0.23 (95%CI 0.14, 0.32) 32% (39/122) with CI 38% (53/139) with normal cognition OR 0.79 (95%CI 0.45, 1.38)	Discontinued Benzo-diazepine use 4.5% (7/155)	Discontinued Benzo-diazepine use Plus Dose Reduction ITT analysis 37.8% (56/148) RD 0.27 (95%CI 0.18, 0.37)	Discontinued Benzo-diazepine use plus Dose Reduction 11.0% (17/155)	13% (5/40) who discontinued benzo-diazepine use had substitutions of non-benzo-diazepine medications	NR	NR	NR

CD=cognitive impairment; CI=confidence interval; ITT=intent-to-treat; NR=not reported; OR=odds ratio; PIM=potentially inappropriate medication; PIP=potentially inappropriate prescription; RCT=randomized controlled trial; RD=risk difference; RRadj=adjusted relative risk

Appendix D, Table 14. Intermediate Process Outcomes, Part 2 – Education Interventions

Author Year Study Design Setting Intervention Type Follow-up	Adherence to Medications		Types of Medications		Medication Burden		Costs	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Bregnhoj 2009[21] Cluster RCT Community GP education + feedback Follow-up: approx. 1 year	NR	NR	Improvements were seen for all therapeutic groups		NR	NR	NR	NR

Author Year Study Design Setting Intervention Type Follow-up	Adherence to Medications		Types of Medications		Medication Burden		Costs	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Coleman 1999[28] Cluster RCT Community Education Follow-up: 24 months	NR	NR	Meds for urinary incontinence at 12 months: 3% Meds for Depression At 12 months 39%	Meds for urinary incontinence: 18% P=.04 Meds for Depression 44% P=.74	NR	NR	Total cost/year at 24 month follow/up No differences between the 2 study groups (table 4)	NR
Jager 2017[112] Cluster RCT Community Education Follow-up: 9 months	MARS score Baseline 23.3 (3.7) Follow-up 22.3 (3.3) P=.11	MARS score Baseline 23.3 (2.3) Follow-up 23.3 (2.6)	NR	NR	NR	NR	NR	NR
Martin 2018[64] Cluster RCT Community Education Follow-up: 6 months	NR	NR	*Discontinued* Sedative-hypnotics 43% (63/146) Absolute RD 34% (95%CI 25%, 43%) NSAIDs 57.6% (19/33) Absolute RD 35% (95%CI 10%, 55%) Glyburide 30.6% (19/62) Absolute RD 17% (2%, 31%)	*Discontinued* Sedative-hypnotics 0% (14/155) NSAIDs 21.7% (5/23) Glyburide 13.8% (8/58)	NR	NR	NR	NR

Author Year Study Design Setting Intervention Type Follow-up	Adherence to Medications		Types of Medications		Medication Burden		Costs	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Rognstad 2013, 2018[89,113] Cluster RCT Community GPs Education Follow up: 12 months	NR	NR	Adjusted Relative Change due to Intervention Tricyclic antidepressants -16.7% (95%CI -32.8, 0.0) Antihistamines -15.3% (95%CI -34.5, 3.8) Antipsychotics -24.1% (95%CI -41.3, -10.3) Long Acting Benzodiazepines -8.5% (95%CI -23.4, 4.3) NSAID + diuretic -12.8% (95%CI -28.2, 2.6)		NR	NR	NR	NR
Schafer 2018[91] Cluster RCT Primary Care Clinic Education (physician and patient) Follow-up: 441 ± 66 days	NR	NR	*Statistically significant increase in Antiphlogisitics/anti-inflammatory, Analgesics, Calcium Antagonists, and Psychoanaleptics classes (data not reported)		NR	NR	NR	NR

CI=confidence interval; MARS=Medication Adherence Report Scale; NSAID=non-steroidal anti-inflammatory drug; RCT=randomized controlled trial; RD=risk difference

Appendix D, Table 15. Study Characteristics – Computer Decision Support Interventions

Author, year Trial name Country Funding Study Design Setting Intervention type	Inclusion/Exclusion Criteria	Intervention (n) Control (n) Clusters (if applicable) Follow-up	Demographics/Characteristics
Fried 2017[37] United States (VA study) Funding: Foundation, Government, University Design: RCT Community Computer Decision Support	Inclusion: Age ≥65 years; community dwelling Veterans; ≥7 medications including at least 1 each for hypertension and diabetes mellitus; upcoming primary care appointment Exclusion: Severe hearing loss, prescriptions by non-VA provider, medication management by someone other than patient, severe acute illness	Intervention: TRIM (algorithm linking CDS to VA EHR and evaluating appropriateness of medication regimen) with clinician and patient feedback report (n=81) Control: Usual care (n=36) Control + TRIM assessment (no feedback reports): (n=36) Follow-up: 90 days	N=128 (completed study) Age: <70: 40.7% 70-79: 44.5% ≥80: 14.9% Gender (% male): 98.4 Race/ethnicity: white 76% Comorbidity status: NR Physical status: Self-rated Good or Excellent/Very Good: Intervention: 72% Control: 69% Cognitive status: NR Number of medications (mean):13.6
Price 2017[83] Canada Funding: Government Design: Cluster RCT Community Computer Decision Support	Inclusion: Primary care physicians in British Columbia providing office-based care to patients ≥65 years and using the open-source OSCAR EHR for ≥12 months Exclusion: Providers who did not provide longitudinal care (*eg,* walk in clinics) or only hospital care, did not use OSCAR for writing prescriptions, or provide care to younger populations (*eg,* a maternity clinic)	Intervention: STOPP guidelines content in EHR providing suggestions to providers when specific criteria were met (n=4 clinics, 16 physicians, 37,615 patients) Control: No STOPP content (n=4 clinics, 12 physicians, 44,290 patients) Follow-up: 16 weeks	N=81,905 Age (mean): NR Gender (% male): NR Race/ethnicity: NR Comorbidity status: NR Physical status: NR Cognitive status: NR Number of medications (mean): NR

Author, year Trial name Country Funding Study Design Setting Intervention type	Inclusion/Exclusion Criteria	Intervention (n) Control (n) Clusters (if applicable) Follow-up	Demographics/Characteristics
Raebel 2007[84] United States Funding: Foundation, Government RCT Community Computer Decision Support	Inclusion: Age ≥65 years; all health plan members Exclusion: NR	Intervention: Pharmacist notified via a medication alert generated from pharmacy information management system when patient was newly prescribed a potentially inappropriate medication (n=29,840) Control: Usual care (no alerts) (n=29,840) Follow-up: 12 months	N=59,680 Age (median): 74 Gender (% male): 43 Race/ethnicity: NR Comorbidity status: NR Physical status: NR Cognitive status: NR Number of medications (mean): NR
Tamblyn 2003[100] Canada Funding: Government, Industry (software) Design: Cluster RCT Community Computer Decision Support	Inclusion *Physicians*: General practitioners ≥30 years old who practiced in Montreal, spent ≥70% of week in private fee-for-service practice, minimum of 100 elderly patients. *Participants*: Age ≥66 years, had been seen on ≥2 occasions by study physician in past year, living in the community at start of study Exclusion: NR	Intervention: CDS; physicians received information on current and past prescriptions through a dedicated computer link to provincial seniors' drug-insurance program; relevant prescribing problems identified by CDS software; alerts to physicians that identified nature of problem, possible consequences and alternative therapy (n=54 physicians) Control: Usual care; physician given computer, printer, health record software and dialup access to internet; software documented health problems and medications supplied (n=53 physicians)	N=12,560 (patients) Age (mean): 75 Gender (% male): 37 Race/ethnicity: NR Comorbidity status: NR Physical status: NR Cognitive status: NR Number of medications (mean): From primary care physician in 18 months before study period Intervention: 30.3 Control: 32.4 At least 1 potentially inappropriate prescription 2 months before the study Intervention: 31.8% Control: 33.3%

Author, year Trial name Country Funding Study Design Setting Intervention type	Inclusion/Exclusion Criteria	Intervention (n) Control (n) Clusters (if applicable) Follow-up	Demographics/Characteristics
		Clusters: Primary care physicians in private practices Follow-up: 13 months	

CDS=computer decision support; EHR=electronic health record; NR=not reported; RCT=randomized controlled trial; STOPP=Screening Tool of Older People's Prescriptions; TRIM=Tool to Reduce Inappropriate Medications; VA=Veterans Affairs

Appendix D, Table 16. Risk of Bias – Computer Decision Support Interventions

Author, Year Random-ization	Sequence Generation	Allocation Concealment	Recruitment Bias	Baseline Imbalance	Blinded Outcome Assessment	Incomplete Cluster Data	Incomplete Outcome Data	Selective Outcome Reporting	Overall Risk of Bias
Fried 2017[37] Patients randomized	Unclear (not reported)	Unclear (not reported)	N/A	Low	Unclear (audio files coded by blinded rater; blinding not reported for other outcomes)	N/A	High (21% intervention group, 15% control group)	Low	Medium
Price 2017[83] Clinics randomized	Low	Unclear	Low (clinics randomized at same time)	High (some baseline imbalance, unclear if adjustments made)	High (unblinded)	Low	Low	Low	Medium
Raebel 2007[84] Patients randomized	Unclear (not reported)	Unclear (physicians, patients, and pharmacists were blinded to study group assignment)	N/A	Low	Unclear (outcomes data derived from automated databases)	N/A	Unclear	Low	Medium
Tamblyn 2003[100] Practices randomized	Unclear (not reported)	High (physicians were aware of which group they'd been assigned to)	Low	Low	Unclear (outcomes obtained from claims data)	Unclear	Unclear	Low	Medium

N/A=not applicable

Appendix D, Table 17. Intermediate Process Outcomes, Part 1 – Computer Decision Support Interventions

Author Year Study Design Setting Intervention Type Follow-up	Total Number of Medications Discontinued, mean (SD)		Number of Medications with Dosage Decreased, mean (SD)		Number of Medications Added or Substituted, mean (SD)		Number of Inappropriate Medications Discontinued, mean (SD)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Fried 2017[37] RCT Community Computer decision support Follow-up: 90 days	Number of medications Baseline: 13.4 (5.2) 90 days 13.1 (SD not reported) n=64 P=.65	Number of medications Baseline: 13.8 (4.9) 90 days 13.8 (SD not reported) n=64	NR	NR	At least 1 TRIM recommendation implemented 29.7% P=.42	At least 1 TRIM recommendation implemented 21.9%	Proportion of medication reconciliation errors corrected 48.4% P<.001	Proportion of medication reconciliation errors corrected 14.3%
Price 2017[83] RCT Community/ primary care Computer decision support Follow-up: 16 weeks	NR	NR	NR	NR	NR	NR	PIPs Baseline: 4% During Treatment 4.1% Change 0.1% P=.80	PIPs Baseline: 2.6% During Treatment 2.7% Change 0.1%
Raebel 2007[84] RCT Community Computer decision support Follow-up: 12 months	NR	NR	NR	NR	Newly dispensed ≥1 medication considered potentially inappropriate 1.8% (543/29,840) P=.002	Newly dispensed ≥1 medication considered potentially inappropriate 2.2% (644/29,840)	NR	NR

Author Year Study Design Setting Intervention Type Follow-up	Total Number of Medications Discontinued, mean (SD)		Number of Medications with Dosage Decreased, mean (SD)		Number of Medications Added or Substituted, mean (SD)		Number of Inappropriate Medications Discontinued, mean (SD)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Tamblyn 2003[100] Cluster RCT Community Computer decision support Follow-up: 13 months	NR	NR	NR	NR	Percentage of patients given inappropriate prescription during study period 16% (755/4767 patients at risk) Relative rate 0.82 (95%CI 0.69, 0.98)	Percentage of patients given inappropriate prescription during study period 20% (909/4603 patients at risk)	Patients who had all inappropriate prescriptions discontinued 47.5% or 35.5 per 1000 visits; Relative rate 1.14 (95%CI 0.98, 1.33)	Patients who had all inappropriate prescriptions discontinued 44.5% or 32.1 per 1000 visits

CI=confidence interval; NR=not reported; PIPs=potentially inappropriate prescriptions; RCT=randomized controlled trial; RRadj=adjusted relative risk; TRIM=Tool to Reduce Inappropriate Medications

Appendix D, Table 18. Intermediate Process Outcomes, Part 2 – Computer Decision Support Interventions

Author Year Study Design Setting Intervention Type Follow-up	Adherence to Medications		Types of Medications		Medication Burden		Costs	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Raebel 2007[84] RCT Community Computer decision support Follow-up: 12 months	NR	NR	Dispensings of targeted potentially inappropriate medications - for medication use indications in which an intervention should occur: significantly lower in the intervention group overall and for amitriptyline and diazepam		NR	NR	NR	NR

NR=not reported; RCT=randomized controlled trial

Appendix D, Table 19. Study Characteristics – Hybrid/Other Interventions

Author, year Trial name Country Funding Study Design Setting Intervention type	Inclusion/Exclusion Criteria	Intervention (n) Control (n) Clusters (if applicable) Follow-up	Demographics/Characteristics
Gillespie 2017[41] Clyne 2015, 2016[26,27] OPTI-SCRIPT Ireland Funding: Government Cluster RCT Community/ primary care Intervention: Multicomponent	Inclusion: *Clinics*: ≥80 patients aged 70 years or older and based in greater Dublin *Patients*: Age ≥70 years Exclusion: NR	Intervention: Academic detailing with pharmacist including discussion of potentially inappropriate prescribing (PIP), medicine review, and web-based pharmaceutical treatment algorithms; medication review with web-based treatment algorithms and alternative treatment options; and patient information leaflets describing PIPs and alternative therapies (n=11 clinics, 99 patients) Control: Usual care and list of patient-level PIP feedback summarizing medications by class (n=10 clinics, 97 patients) Follow-up: 6 and 12 months	N=196 Age (mean): 76.8 Gender (% male): 54 Race/ethnicity: NR Comorbidity status: NR Physical status: NR Cognitive status: NR Number of medications (mean): 9.9
Lampela 2010[57] Rikala 2011[87] Subpopulation of GeMS Finland Funding: Government, University Design: RCT Community Multicomponent	Inclusion: Age ≥75 years; random sample of 1000 residents of Kuopio city (Finland) on November 1, 2003 Exclusion: NR	*Lampela:* Intervention: Comprehensive Geriatric Assessment (CGA) at baseline by members of study team; included adjustment of medications, evaluation of indications for all drugs (and withdrawal if no indication), clinical exam, routine blood tests (n=500; analysis limited to 331 home dwelling)	*Lampela:* N=644 (analyzed) Age: 75-79: 52% 80-84: 30% ≥85: 18% Gender (% male): 30% Race/ethnicity: NR Comorbidity status: NR Physical status: NR

Author, year Trial name Country Funding Study Design Setting Intervention type	Inclusion/Exclusion Criteria	Intervention (n) Control (n) Clusters (if applicable) Follow-up	Demographics/Characteristics
		Control: standard care (included visits to clinic/hospital when needed) (n=500; analysis limited to 313 home dwelling) Follow-up: 1 year *Rikala:* Intervention: CGA at baseline (see Lampela), 1 year, and 2 years by members of study team; included review of psychotropic drugs (n=500; analysis limited to 361 community dwelling) Control: Usual care (n=500; analysis limited to 339 community dwelling) Follow-up: 3 years	Cognitive status: MMSE (mean)=26 Number of regular* medications (mean): 4.7 (intervention), 4.8 (control) *medications taken at regular intervals or daily *Rikala 2011* N=700 Age (mean): 81 years Gender (% male): 31% Race/ethnicity: NR Comorbidity status: NR Physical status: IADL ≤6: 25%; unable to walk 400 m independently: 38% Cognitive status: MMSE ≤24: 24%; dementia diagnosis: 15% Number of medications (mean): 5.6 (non-psychotropic drugs)
Pit 2007[78] Australia Funding: Government Cluster RCT Community Multicomponent	Inclusion *Physicians*: based at current practice site for at least 12 months and practiced 10 or more hours/week *Patients:* ≥65 years, community dwelling, seen at the practice during the study period Exclusion: NR	Intervention: Education, facilitated medication review; financial incentives (13 GPs from 10 practices allocated, 11 GPs from 9 practices included; 452 patients from 9 practices) Control: Medication risk assessment only (9 GPs from 7	N=849 Age (mean): NR Gender (% male): Intervention: 33% Control: 49% Race/ethnicity: NR Comorbidity status: NR Physical status: NR Cognitive status: NR

Author, year Trial name Country Funding Study Design Setting Intervention type	Inclusion/Exclusion Criteria	Intervention (n) Control (n) Clusters (if applicable) Follow-up	Demographics/Characteristics
		practices; 397 patients from 7 practices) Follow-up: 12 months	Number of medications at baseline (mean): NR

BMI=body mass index; GeMS=Geriatric Multidisciplinary Strategy for Good Care of the Elderly; iADLs=instrumental activities of daily living; MMSE=mini mental state examination; NR=not reported; RCT=randomized controlled trial

Appendix D, Table 20. Risk of Bias – Hybrid/Other Intervention Studies

Author, Year	Sequence Generation	Allocation Concealment	Recruitment Bias	Baseline Imbalance	Blinded Outcome Assessment	Incomplete Cluster Data	Incomplete Outcome Data	Selective Outcome Reporting	Overall Risk of Bias
Gillespie 2017[41] Clyne 2015, 2016[26,27] (OPTI-SCRIPT) GP practices randomized	Low (minimization method)	Low (independent researcher)	Low	Low but noted that control practices were situated in more socioeconomically deprived areas	Low (outcome assessor blinded)	Low	Low (~3% per group at 4-6 months, <6% at 1 year)	Low	Low
Gnjidic 2010[117] Self-care villages randomized	Unclear (not reported)	Unclear (not reported)	High ("attendees were then approached individually and asked to participate" after sites allocated)	High (significantly younger participants in intervention group and higher DBI in control group (53% vs 33%))	High (single investigator performed all assessments, unblinded)	Unclear (no information about drop-outs)	Unclear (no information about drop-outs)	Low	High
Lampela 2010[57] Rikala 2011[87] Patients randomized	Low (computer-generated)	Unclear	N/A	Medium (imbalance reported for several variables)	Unclear (not reported)	N/A	High (19% randomized to intervention did not receive intervention; 34% not analyzed at follow-up; 34% of control group not analyzed at follow-up)	Low	Medium

Author, Year	Sequence Generation	Allocation Concealment	Recruitment Bias	Baseline Imbalance	Blinded Outcome Assessment	Incomplete Cluster Data	Incomplete Outcome Data	Selective Outcome Reporting	Overall Risk of Bias
Pit 2007[78] Practices randomized	Low (computer generated)	Low (independent statistician)	High (patients recruited after GP randomization)	Medium ("generally" or "reasonably" similar)	Low (blinded for medication outcomes; self-report for others)	Low	High (23% of participants lost at 12 months)	Low	Medium
Steinman 2018[120] (CC-MAP) Primary care clinics selected as intervention or control sites	High (not random)	High (nurses trained in CC-MAP model were imbedded in intervention clinics)	N/A.	High (differences in age, number of chronic conditions, and number of medications at baseline)	Unclear (not reported)	N/A	Low (1% lost to follow-up in each group)	High (primary outcome [hospital admissions] not reported; selected 2 new outcomes of interest related to medications)	High

CC-MAP=Comprehensive Care for Multimorbid Adults Project; DBI=Drug Burden Index; GP=general practitioners; N/A=not applicable

Appendix D, Table 21. Patient-centered Outcomes, Part 1 – Hybrid/Other Interventions

Author Year Study Design Setting Intervention Type Follow-up	Hospitalizations % (n/N)		Acute Care Encounters % (n/N)		Delirium % (n/N)	
	Intervention	Control	Intervention	Control	Intervention	Control
Gillespie 2017[41] Clyne 2015, 2016[26,27] Cluster RCT Community Multicomponent Follow-up: 6 and 12 months	Inpatient admissions Baseline 0.9 (3.5) n=99 Follow-up 1.9 (5.7) n=99	Inpatient admissions Baseline 0.9 (3.2) n=97 Follow-up 1.6 (5.2) n=97	Accident and emergency department visits Baseline 0.1 (0.4) n=99 Follow-up 0.2 (0.4) n=99	Accident and emergency department visits Baseline 0.1 (0.3) n=97 Follow-up 0.1 (0.4) n=97	NR	NR
Pit 2007[78] Cluster RCT Community Multicomponent Follow-up: 12 months	NR	NR	Medical attention (doctor, hospital) for Injury from a fall, trip or accident in past 12 months Baseline 11% (43/396 At 12 months 6% (22/350) Adjusted OR 0.46 (95%CI 0.30, 0.70) P=.0014	Medical attention (doctor, hospital) for Injury from a fall, trip or accident in past 12 months Baseline 15% (54/351) At 12 months 13% (40/308)	NR	NR

CI=confidence interval; NR=not reported; OR=odds ratio; RCT=randomized controlled trial

Appendix D, Table 22. Patient-centered Outcomes, Part 2 – Hybrid/Other Interventions

Author Year Study Design Setting Intervention Type Follow-up	Functional Status (mean, SD) – describe measure		Quality of Life (mean, SD) – describe measure		Patient Satisfaction (mean, SD) – describe measure	
	Intervention	Control	Intervention	Control	Intervention	Control
Gillespie 2017[41] Clyne 2015, 2016[26,27] Cluster RCT Community Multicomponent Follow-up: 6 and 12 months	NR	NR	WBQ-12 Baseline: 24.3 6 months 23.6 n=99 OR -0.41 (95%CI -0.80, 1.07) P=.99 EQ5D-3L Baseline 0.63 (0.30) n=45 Follow-up: (12 months) 0.67 (0.27) n=41	WBQ-12 Baseline: 24.4 6 months 24.0 n=97 EQ5D-3L Baseline 0.69 (0.24) n=63 Follow-up: (12 months) 0.65 (0.25) n=63	NR	NR

Author Year Study Design Setting Intervention Type Follow-up	Functional Status (mean, SD) – describe measure		Quality of Life (mean, SD) – describe measure		Patient Satisfaction (mean, SD) – describe measure	
	Intervention	Control	Intervention	Control	Intervention	Control
Pit 2007[78] Cluster RCT Community Multicomponent Follow-up: 12 months	NR	NR	SF-12 PCS Mean (SE) Baseline 44.1 (0.7) n=389 Follow-up: 47.0 (0.6) n=350 P=.61 (adjusted) SF-12 MCS Mean (SE) Baseline 54.1 (0.4) n=389 55.0 (0.3) n=350 P=.71 (adjusted) EQ-5D index score Mean (SE) Baseline 0.83 (0.02) n=395 Follow-up 0.89 (0.01) n=350 P=.70 (adjusted) EQ-5D VAS Mean (SE) Baseline 77.0 (0.8) n=389 Follow-up 80.4 (0.8) n=346 P=.54 (adjusted)	SF-12 PCS Mean (SE) Baseline 42.4 (0.5) n=339 Follow-up 45.3 (0.4) n=309 SF-12 MCS Mean (SE) Baseline 53.1 (0.8) n=339 54.3 (0.4) n=309 EQ-5D index score Mean (SE) Baseline 0.78 (0.02) n=348 Follow--up 0.87 (0.01) n309 EQ-5D VAS Mean (SE) Baseline 73.5 (0.8) n=348 Follow-up 77.9 (0.5) n=302	NR	NR

EQ-5D=EuroQol; MCS=mental component score; NR=not reported; PCS=physical component score; RCT=randomized controlled trial; SE=standard error; SF-12=Short Form 12 item; VAS=visual analog scale; WBQ-12=12-item Well-Being Questionnaire

Appendix D, Table 23. Patient-centered Outcomes, Part 3 – Hybrid/Other Interventions

Author Year Study Design Setting Intervention Type	Falls % (n/N)		Major Adverse Cardiovascular Events[a] % (n/N)		Adverse Drug Withdrawal Events % (n/N)		All-cause Mortality % (n/N)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Gillespie 2017[41] Clyne 2015, 2016[26,27] Cluster RCT Community Multicomponent Follow-up: 6 and 12 months	NR	NR	NR	NR	NR	NR	3% (3/99) At 1 year	5% (5/97)
Lampela 2010[57] Rikala 2011[87] RCT Community Multicomponent Follow-up: 1 to 3 years	NR	NR	NR	NR	NR	NR	12.5% (45/361) At 3 years 5.3% (19/361) At 1 year	13.9% (47/339) At 3 years 3.8% (13/339) At 1 year
Pit 2007[78] Cluster RCT Community Multicomponent Follow-up: 12 months	In last 12 months Baseline: 22% (86/396) At 12 months 20% (70/350) Adjusted OR 0.61 (95%CI 0.41, 0.91) P=.02	In last 12 months Baseline: 29% (100/351) At 12 months 30% (94/309)	NR	NR	NR	NR	NR	NR

CI=confidence interval; OR=odds ratio; RCT=randomized controlled trial

[a]Includes cardiovascular death, nonfatal myocardial infarction, acute coronary syndrome, nonfatal stroke, revascularization, or heart failure exacerbation

Appendix D, Table 24. Intermediate Process Outcomes, Part 1 – Hybrid/Other Interventions

Author Year Study Design Setting Intervention Type Follow-up	Total Number of Medications Discontinued, mean (SD)		Number of Medications with Dosage Decreased, mean (SD)		Number of Medications Added or Substituted, mean (SD)		Number of Inappropriate Medications Discontinued, mean (SD)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Gillespie 2017[41] Clyne 2015, 2016[26,27] Cluster RCT Community Multicomponent Follow-up: 6 and 12 months	NR	NR	NR	NR	New instance of PIP at 12 months 13% (12/92) P=.38	New instance of PIP at 12 months 20% (12/90)	Proportion of Patients with PIP Baseline: 100% (99/99) Follow-up 51% (51/99) OR 0.28 (95%CI 0.11, 0.76) P=.01 PIPs Baseline 1.31 (0.6) n=99 Follow-up 0.70 (0.1) n=99 Mean difference -0.48 (95%CI -0.80, -0.17), P=.02	Proportion of Patients with PIP Baseline: 100% (97/97) Follow-up 76% (76/97) PIPs Baseline 1.39 (0.6) n=97 Follow-up 1.18 (0.1) n=97

Author Year Study Design Setting Intervention Type Follow-up	Total Number of Medications Discontinued, mean (SD)		Number of Medications with Dosage Decreased, mean (SD)		Number of Medications Added or Substituted, mean (SD)		Number of Inappropriate Medications Discontinued, mean (SD)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Lampela 2010[57] Rikala 2011[87] RCT Community Multicomponent Follow-up: 1 to 3 years	Total number of regularly used drugs Baseline: 1563 1 year: 1737	Total number of regularly used drugs Baseline: 1520 1 year: 1644	At 1 year (vs controls) Alimentary tract: OR 1.2 (95%CI 0.5, 2.9) Blood related: OR 2.4 (95%CI 0.8, 7.7) Cardiovascular: OR 1.6 (95%CI 1.0, 2.7) Musculoskeletal: OR 0.7 (95%CI 0.1, 4.1) Nervous system: OR 7.8 (95%CI 1.7, 35.0)		# patients with alterations in regularly used drugs over 1 year 84% (227/331) OR 1.9 (95%CI 1.3, 2.8) *New Prescriptions at 1 year* Alimentary tract: OR 2.0 (95%CI 1.3, 3.0) Blood related: OR 1.8 (95%CI 1.2, 2.6) Cardiovascular: OR 1.1 (95%CI 0.8, 1.5) Musculoskeletal: OR 1.6 (95%CI 0.8, 3.4) Nervous system: OR 0.9 (95%CI 0.6, 1.4) ***Rikala*** Psychotropic drug use Baseline: 40% (144/361) 1 year: 41% (135/331) 3 years: 38% (106/281)	#f patients with alterations in regularly used drugs over 1 year 73% (228/313) ***Rikala*** Psychotropic drug use Baseline: 37% (125/339) 1 year: 35% (109/313) 3 years: 36% (93/257)	***Lampela*** Inappropriate drugs or dosages (Beers criteria) Baseline 97 drugs 21% (71/331) 1 year 81 drugs 18% (60/331)	***Lampela*** Inappropriate drugs or dosages (Beers criteria) Baseline 80 drugs 19% (61/313) 1 year 80 drugs 24% (75/313)

Author Year Study Design Setting Intervention Type Follow-up	Total Number of Medications Discontinued, mean (SD)		Number of Medications with Dosage Decreased, mean (SD)		Number of Medications Added or Substituted, mean (SD)		Number of Inappropriate Medications Discontinued, mean (SD)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Pit 2007[78] Cluster RCT Community Multicomponent Follow-up: 12 months	NR	NR	NR	NR	NR	NR	Intervention group had increased odds of having an improved medication use composite score at 4 months (OR 1.84 [95%CI 1.21, 2.85]) but not 12 months (OR 1.33 [95%CI 0.83, 2.14]) (composite score reflected use of benzodiazepines, NSAIDs, and thiazide diuretics)	

NR=not reported; NSAIDs=non-steroidal anti-inflammatory drugs; OR=odds ratio; PIP=potentially inappropriate prescription; RCT=randomized controlled trial; RRadj=adjusted relative risk

Appendix D, Table 25. Intermediate Process Outcomes, Part 2 – Hybrid/Other Interventions

Author Year Study Design Setting Intervention Type Follow-up	Adherence to Medications		Types of Medications		Medication Burden		Costs	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Gillespie 2017[41] Clyne 2015, 2016[26,27] Cluster RCT Community Multicomponent Follow-up: 6 and 12 months	NR	NR	Benzodiazepines Baseline: 14.1% Follow-up (6 months): 9.1% OR 1.31 (95%CI 0.47, 3.68) Proton pump inhibitor (6 months, n=99) 23 (23.2) OR 0.30 (95%CI 0.14, 0.68) P=.04 Proton pump inhibitor at 12 months 26% adjOR 0.40 (95%CI 0.17, 0.94) P=.04)	Benzodiazepines Baseline: 8.1% Follow-up (6 months): 9.1% Proton pump inhibitor (6 months, n=97) 46 (47.4) Proton pump inhibitor at 12 months 43%	NR	NR	Total Cost at 12 Month Follow-up 3075 € (95%CI 2704, 3446) Mean difference 407 € (95%CI -357, 1170)	Total Cost at 12 Month Follow-up €2668 (2297, 3040)

Author Year Study Design Setting Intervention Type Follow-up	Adherence to Medications		Types of Medications		Medication Burden		Costs	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Lampela 2010[57] Rikala 2011[87] RCT Community Multicomponent Follow-up: 1 to 3 years	NR	NR	Discontinued at 1 year (vs control) Cardiovascular: OR 1.1 (95%CI 0.7, 1.6) Musculoskeletal: OR 1.3 (95%CI 0.6, 2.7) Nervous system: OR 1.2 (95%CI 0.7, 2.1) ***Rikala*** Anti-psychotics Baseline: 6% (22/361) 1 year: 5% (15/331) 3 years: 5% (14/281) Anxiolytics/ Hypnotics Baseline: 33% (120/361) 1 year: 35% (115/331) 3 years: 31% (87/281) Anti-depressants Baseline: 13% (46/361) 1 year: 12% (40/331) 3 years: 13% (35/281)	***Rikala*** Anti-psychotics Baseline: 5% (18/339) 1 year: 6% (20/313) 3 years: 5% (14/257) Anxiolytics/ Hypnotics Baseline: 29% (99/339) 1 year: 29% (90/313) 3 years: 27% (70/257) Anti-depressants 11% (37/339) 1 year: 11% (35/313) 3 years: 15% (39/257)	NR	NR	NR	NR

Author Year Study Design Setting Intervention Type Follow-up	Adherence to Medications		Types of Medications		Medication Burden		Costs	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Pit 2007[78] Cluster RCT Community Multicomponent Follow-up: 12 months	NR	NR	NSAIDS Baseline 24% (94/397) At 12 months 22% (76/350) Adjusted OR: 0.77 (95%CI 0.51,1.16) P=.19 Thiazides Baseline: 19% (75/397) At 12 months 19% (66/350) Adjusted OR: 0.85 (95%CI 0.53, 1.38) P=.50 Benzodiazepines Baseline: 8% (30/397) At 12 months 7% (26/350) Adjusted OR: 0.65 (95%CI 0.27,1.57) P=.31	NSAIDS Baseline 28% (99/352) At 12 months 25% (78/309) Thiazides Baseline: 20% (70/352) At 12 months 21% (66/309) Benzodiazepines Baseline: 12% (42/352) At 12 months 12% (36/309)	NR	NR	NR	NR

CI=confidence interval; OR=odds ratio; NSAIDS=non-steroidal anti-inflammatory drugs; NR=not reported

Appendix D, Table 26. Studies Included in Evidence Map

Study, year	Country/ Region	Setting	Study design	Number enrolled	Intervention category[a]	Follow-up (months)	Primary outcome (as specified by trial author)	Outcomes Reported[b]			
								Medication changes	Resource utilization/ costs	Clinical	Functional status, QoL, patient satisfaction
Saltvedt 2005[90]	Europe	Hospital	RCT	254	CGA	NR	Changes in medication regiment from inclusion to discharge	X		X	
Terrell 2009[101]	USA	ED	RCT	5162	CPOE/CDS	0	Proportion of ED visits by seniors that resulted in 1 or more prescriptions for an inappropriate medication	X			
Cossette 2017[30]	Canada	Hospital	RCT	231	CPOE/CDS	1	Changes in medication defined as the number of discontinued drugs or drugs with a dosage decrease	X	X	X	
Donovan 2010[35]	USA	Nursing home	RCT	813	CPOE/CDS	12	Percentages of psychotropic medication orders modified in response to an alert	X			
Gnjidic 2019[43]	Australia/ NZ	Hospital	RCT	43	Educ	1	Initiated discussion of benzodiazepine withdrawal and outcome of discussion	X			X
Batty 2001[16]	Europe	Hospital	Cluster RCT	1391	Educ	1-1.5	Change in the rate of appropriate	X			

Study, year	Country/ Region	Setting	Study design	Number enrolled	Intervention category[a]	Follow-up (months)	Primary outcome (as specified by trial author)	Outcomes Reported[b]			
								Medication changes	Resource utilization/ costs	Clinical	Functional status, QoL, patient satisfaction
							prescribing of benzodiazepines				
Trivalle 2010[103]	Europe	Hospital	Cluster RCT	576	Educ	0.46	Change in the proportion of ADEs in elderly patients in the intervention units compared to the control group	X			
Cool 2018[29]	Europe	Nursing home	CCT	974	Educ	18	Potentially inappropriate drug prescribing defined by unfavorable benefit-to-risk ratio, questionable efficacy, absolute contraindication, significant drug-drug interaction	X	X	X	
Garcia-Gollarte 2014[40]	Europe	Nursing home	Cluster RCT	1018	Educ	3	Appropriateness and quality of drug use; incidence of selected geriatric syndromes; health resource utilization	X	X	X	
Juola 2014, 2015[51,52] Pitkala 2014[79]	Europe	Nursing home	Cluster RCT	227	Educ	12	Proportion of persons using inappropriate, anticholinergic, or more than 2 psychotropic drugs, and the change in the mean number of	X	X	X	X

Study, year	Country/ Region	Setting	Study design	Number enrolled	Intervention category[a]	Follow-up (months)	Primary outcome (as specified by trial author)	Outcomes Reported[b]			
								Medication changes	Resource utilization/ costs	Clinical	Functional status, QoL, patient satisfaction
							inappropriate, anticholinergic and psychotropic drugs among residents				
Schmidt 1998[94]	Europe	Nursing home	Cluster RCT	1854	Educ	12	Quantity and quality of psychotropic drug prescribing	X			
Avorn 1992[15]	USA	Nursing home	Cluster RCT	823	Educ	5	Drug use and clinical status	X	X	X	X
Meador 1997[66]	USA	Nursing home	Cluster RCT	1152	Educ	6	Proportion of days of nursing home residence with anti-psychotic drug administered (RCT analysis)	X			
Stein 2001[99]	USA	Nursing home	Cluster RCT	147	Educ	3	NSAID and acetaminophen use, and pain, function, and disability scores	X		X	X
Briggs 2015[22]	Australia/ NZ	ED	RCT	1021	Med Rev	4	Hospital admissions	X	X		
Spinewine 2007[98]	Europe	Hospital	RCT	186	Med Rev	12	Appropriateness of prescribing based on MAI, Beers criteria for drugs that should be avoided, and ACOVE criteria related to underuse	X	X	X	
Michalek 2014[68]	Europe	Hospital	RCT	114	Med Rev	0.66	Impact of application of the FORTA list on number and quality	X		X	X

Study, year	Country/ Region	Setting	Study design	Number enrolled	Intervention category[a]	Follow-up (months)	Primary outcome (as specified by trial author)	Outcomes Reported[b]			
								Medication changes	Resource utilization/ costs	Clinical	Functional status, QoL, patient satisfaction
							of drugs, including number of over- and under-prescriptions				
Wehling 2016[108] Pazan 2018[76]	Europe	Hospital	RCT	409	Med Rev	0.57	Difference of the FORTA score (sum of medication errors) between admission and discharge	X			X
Pope 2011[81]	Europe	Hospital	RCT	225	Med Rev	6	Difference in number of drugs prescribed and medication cost	X	X	X	X
Bladh 2011[18]	Europe	Hospital	RCT	400	Med Rev	6	Primary not defined	X		X	X
Gustafsson 2018[45]	Europe	Hospital	RCT	429	Med Rev	6	Risk of drug-related readmissions	X	X	X	
Lenssen 2018[61]	Europe	Hospital	RCT	60	Med Rev	12	Occurrence of drug-related readmissions (DRRs), measured over 1 year at 4 pre-defined contact times after discharge	X	X	X	
Hellstrom 2011[48]	Europe	Hospital	CCT	210	Med Rev	3	Change in number of drugs with ≥1 inappropriate score between admission and discharge, according to the MAI	X	X	X	

Study, year	Country/ Region	Setting	Study design	Number enrolled	Intervention category[a]	Follow-up (months)	Primary outcome (as specified by trial author)	Outcomes Reported[b]			
								Medication changes	Resource utilization/ costs	Clinical	Functional status, QoL, patient satisfaction
Dalleur 2014[33]	Europe	Hospital	RCT	158	Med Rev	12	Proportion of PIMs discontinued or corrected between hospital admission and discharge	X		X	
Gallagher 2011[39]	Europe	Hospital	RCT	400	Med Rev	6	Appropriateness of prescribing at time of discharge and at 2-month intervals during 6-month period after discharge	X	X	X	
Gillespie 2013[42]	Europe	Hospital	RCT	368	Med Rev	12	Scores for appropriateness of prescribing on admission and at discharge and extent of utilization of hospital-based care during 12 months after index admission	X	X		
Torisson 2013[102]	Europe	Hospital	CCT	200	Med Rev	12	Readmission and hospital nights		X	X	
Willoch 2012[109]	Europe	Hospital	RCT	77	Med Rev	3	Types and frequencies of drug-related problems	X	X	X	
Schmader 2004[93]	USA	Hospital	RCT	834	Med Rev	12	Number of adverse drug reactions	X		X	
McDerby 2019[65]	Australia/ NZ	Nursing home	CCT	117	Med Rev	6	Rates of inappropriate	X	X		

Study, year	Country/ Region	Setting	Study design	Number enrolled	Intervention category[a]	Follow-up (months)	Primary outcome (as specified by trial author)	Outcomes Reported[b]			
								Medication changes	Resource utilization/ costs	Clinical	Functional status, QoL, patient satisfaction
							dosage form modification				
Beer 2011[17]	Australia/ NZ	Nursing home	RCT	35	Med Rev	2	Number of intervention participants in whom medication withdrawal could be achieved	X			X
Crotty 2004[31]	Australia/ NZ	Nursing home	Cluster RCT	154	Med Rev	3	Medication Appropriateness Index (MAI)	X	X	X	
Crotty 2004[32]	Australia/ NZ	Nursing home	RCT	110	Med Rev	2	Quality of prescribing (appropriateness of patients' medication plans)	X	X	X	X
Potter 2016[82]	Australia/ NZ	Nursing home	RCT	95	Med Rev	12	Change in the mean number of unique regular medicines	X	X	X	X
Furniss 2000[38] Burns 2000[23]	Europe	Nursing home	Cluster RCT	330	Med Rev	4	Primary not specified	X	X	X	X
Milos 2013[69]	Europe	Nursing home	RCT	374	Med Rev	2	Proportion of patients taking potentially inappropriate medications (PIMs)	X		X	
Wouters 2017[111]	Europe	Nursing home	Cluster RCT	426	Med Rev	4	Proportion of residents who successfully	X	X	X	X

Study, year	Country/ Region	Setting	Study design	Number enrolled	Intervention category[a]	Follow-up (months)	Primary outcome (as specified by trial author)	Outcomes Reported[b]			
								Medication changes	Resource utilization/ costs	Clinical	Functional status, QoL, patient satisfaction
							discontinued use of ≥1 inappropriate medication				
Patterson 2010[75] Patterson 2011[74]	Europe	Nursing home	Cluster RCT	334	Med Rev	12	Proportion of residents prescribed ≥1 inappropriate; psycho-active medicine	X		X	
van der Spek 2018[106]	Europe	Nursing home	Cluster RCT	380	Med Rev	18	Level of appropriateness of psychotropic drug use	X		X	
Frankenthal 2014[36]	Other	Nursing home	RCT	359	Med Rev	12	Primary not specified	X	X	X	
Lapane 2011[58]	USA	Nursing home	CCT	NR	Med Rev	24	Primary not specified	X	X	X	X
Tse 2008[104]	USA	Nursing home	RCT	11	Med Rev	1	Primary not specified			X	X
Kutner 2015[55]	USA	Pallia-tive care	RCT	381	Med Rev	12	Mortality within 60 days of enrollment	X	X	X	X
Legrain 2011[59] Bonnet-Zamponi 2013[19]	Europe	Hospital	RCT	639	Multi	6	Primary not specified	X	X	X	
Ravn-Nielsen 2018[85]	Europe	Hospital	RCT	1499	Multi	6	Readmissions (including drug-related) within 30 or 180 days and ED		X	X	

Study, year	Country/ Region	Setting	Study design	Number enrolled	Intervention category[a]	Follow-up (months)	Primary outcome (as specified by trial author)	Outcomes Reported[b]			
								Medication changes	Resource utilization/ costs	Clinical	Functional status, QoL, patient satisfaction
							visits within 180 days				
Roberts 2001[88]	Australia/ NZ	Nursing home	Cluster RCT	3230	Multi	22	Changes in number of prescribed medications	X	X	X	X
Gulla 2018[44] Husebo 2019[49] COSMOS	Europe	Nursing home	Cluster RCT	295	Multi	9	Primary not specified	X		X	X
Richter 2019[86]	Europe	Nursing home	Cluster RCT	1042	Multi	12	Proportion of residents with ≥1 anti-psychotic prescription after 12 months	X		X	X

CCT=controlled clinical trial; CDS=computerized decision support; CPOE=computerized physician order entry; ED=emergency department; NZ=New Zealand; QoL=quality of life; RCT=randomized controlled trial

[a]**Intervention Types**

Comprehensive Geriatric Assessment (CGA)
Education (Educ)
Multi-component (Multi)
Computer Decision Support (CDS) or Order Entry (CPOE)
Medication Review/Case Conference/Academic Detailing (Med Rev)

[b]**Outcomes**

Medication Changes

Total Number of Medications Discontinued
Number of Medications Added or Substituted
Adherence to Medications
Medication Burden
Number of Medications with Dosages Decreased
Number of Inappropriate Medications Discontinued
Types of Medications

Resource Utilization and Costs

Hospitalizations
Costs
Acute Care Encounters

Clinical Outcomes

Falls
Major Adverse Cardiovascular Events
All-cause Mortality

Functional Status, Quality of Life, & Patient Satisfaction

Delirium
Adverse Drug Withdrawal Events
Biomarkers (Glycemic Control; Blood Pressure Control; Cholesterol, Vitamin D, Iron, Thyroid Hormone Levels; Prothrombin Time; Other)

Appendix D, Table 27. Barriers and Facilitators – Study Characteristics

Author, year Country Intervention Category	Setting and Participant Inclusion	Data Collection Instrument/Methods	Response Rate	Participant Characteristics
Community/Primary Care				
Vandenberg 2018[129] US/VA study Medication Review	Setting: VA community-based outpatient clinics (CBOCs) serving rural Veterans; located within 3 hours of Atlanta VA; filled pharmacist positions Participants: Primary care physicians and pharmacists who implemented the Integrated Management and Polypharmacy Review of Vulnerable Elders (IMPROVE) model (academic detailing with audit and feedback)	Telephone interview with physicians, pharmacists, and individuals seen by pharmacists	Physicians: 65% (13/20) were interviewed	N=20 (physicians who participated in at least some aspects of the intervention) Demographics NR
Jager 2017[130] Germany Medication Review	Setting: Primary care practices in 1 area of Germany in a special care contract with a large health insurer; practices also participated in “quality circles” in local area Participants: General practitioners from intervention and control groups of intervention study; medical assistants from intervention group	Survey: physicians from intervention and control groups Interviews: physicians and medical assistants from intervention group Also evaluated action plans and documentation forms for medication reviews	Survey: 100% (21/21) Interviews: NR (12 interviews conducted)	Physicians: N=21 Age (mean, yrs): 55 Male (%): 82 (n=18) Medical Assistants: NR

Author, year Country Intervention Category	Setting and Participant Inclusion	Data Collection Instrument/Methods	Response Rate	Participant Characteristics
Kempen, 2018[125] Sweden Medication Review	Setting: Region Uppsala (regional health authority responsible for quality of and access to healthcare for all inhabitants in Uppsala County); all clinical pharmacists conducting medication reviews are employed by Region Uppsala (effective in 2012) (NOTE: study also includes data from prior to 2012) Participants: Key informants who had been influential in implementation of mediation reviews by clinical pharmacists and authors of or mentioned in documents identified in literature search	Interviews: semi-structured; included questions on rationale for introduction of medication reviews, implementation strategies, integration into daily practice, evaluation, and plans for future development Focus group: to confirm interview findings; same eligibility; received summary report from interviews prior to focus group session; additional follow-up with 2 members of focus group and an added key informant	100% (all who were invited to participate did so)	Total N=10 (6 physicians, 3 pharmacists, 1 nurse)
Kuntz 2018[126] US Medication Review with Education	Setting: Primary care at Kaiser Permanente Northwest (KPNW); patients 64 and older with multiple dispensings of Z-drugs in previous year received an intervention to encourage deprescribing of Z-drugs Participants: a) Randomly selected group of intervention recipients (patients) and b) Primary care clinicians who prescribed Z-drugs for patients who received an intervention	Telephone interviews using interview guides created for either patients or providers; patient interviews (45-60 min) explored past and current used of Z-drugs, prior education/educational needs, and reaction to intervention materials; provider interviews (25-35 min) explored approaches to care of older adults with insomnia, sedative medication prescribing, reaction to intervention materials, and factors that hinder or support deprescribing of sedatives	Patients: 67% (10/15 able to be contacted; unable to contact additional 10 patients who were recruited) Physicians: 17% (6/36 contacted)	Patients: N=10 Age: NR Gender (% male): 10% Providers: N=6 Age: NR Gender (% male): 50%

Author, year Country Intervention Category	Setting and Participant Inclusion	Data Collection Instrument/Methods	Response Rate	Participant Characteristics
Ranson 2018[128] United Kingdom Medication Review	Setting: Safer Prescribing for Frailty project; general practices from Harrogate and Rural District Clinical Commissioning Group (CCG) medicines management team partnering with an Academic Health Science Network Improvement Academy Participants: Prescribers from 12 general practice teams	NR	NR	NR
Nursing Homes				
Brooker 2016[122] Latham 2017[127] United Kingdom Education	Setting: Care homes receiving Focused Intervention Training and Support (FITS) program; aim was patient-centered care for people with dementia including reducing inappropriate prescription and use of anti-psychotic medications Participants: Dementia Care Coaches (DCCs) (staff members including care assistants, registered nurses, or activity coordinators; 1 per home)	Case-study approach; semi-structured interviews with DCCs, care home manager, other care home staff	14 care homes recruited; 10 DCCs from 9 care homes completed data collection	N=9 DCCs (4 managers, 1 deputy manager, 1 trainee manager, 2 senior carers*, 1 registered nurse*, 1 care assistant) *1 senior carer and 1 registered nurse shared the DCC role at 1 site

Author, year Country Intervention Category	Setting and Participant Inclusion	Data Collection Instrument/Methods	Response Rate	Participant Characteristics
Cheek 2004[123] Australia Medication Review	Setting: Residential aged-care facilities (RACFs) in Australia implementing best practice guidelines for quality use of medicines (QUM) including medication review Participants: consumers and staff of 12 representative RACFs; all received honorarium; excluded sites with <20 beds	3 methods of data collection 1) Critical Incident Technique (CIT) interviews 2) Focus groups 3) Nominal groups	NR	**CIT Interviews (N=33)*** Nurse: 36%; General Practiti1r: 18%; Pharmacist: 18%; Allied Health or Other Care: 15%; Owner/Manager: 12%; Resident/Family: 0% **Focus Groups (N=82)*** Nurse: 28%; General Practitioner: 17%; Pharmacist: 12%; Allied Health or Other Care: 16%; Owner/Manager: 11%; Resident/Family: 16% **Nominal Groups (N=47)*** Nurse: 19%; General Practitioner: 11%; Pharmacist: 13%; Allied Health or Other Care: 15%; Owner/Manager: 30%; Resident/Family: 13% **Many participated in more than 1 of the activities*

Author, year Country Intervention Category	Setting and Participant Inclusion	Data Collection Instrument/Methods	Response Rate	Participant Characteristics
Desveaux 2017[124] Canada Education (Academic Detailing)	Setting: Nursing homes randomized to either active intervention or standard quality improvement support; partnership of Ontario government and medical association; focus on prescribing of anti-psychotic medication and management of behavioral and psychological symptoms of dementia Participants: Nursing home administrators, medical directors, nurses, social workers, personal support workers, academic detailers	Interviews at participant's place of work using interview guide; 15-75 min duration	NR	N=23 (18 staff across 5 nursing homes, 4 academic detailers) Age: Gender (% male): 5
Emergency Department				
Vandenberg 2017[131] US/VA study Computer Decision Support	Setting: Emergency Departments (EDs) of 2 VAMCs; 1 site received geriatric order sets implemented as part of multicomponent EQUiPPED quality improvement initiative; 2nd site had access to order sets via an option on the ED order menu within patient's medical record Participants: ED staff providers (EQUiPPED site) and "moonlighting' physicians or resident trainees (comparison site)	Structured interview guide for telephone interviews with 10 EQUiPPED site providers (5 each site) and 10 comparison site providers (5 each site); assessed 'use', 'usefulness', and 'usability' (ease of use – for those who reported using system)	NR	N=20; majority were physicians with emergency medicine certification Demographics: NR 11 reported being "users" of order sets including 7/10 EQUiPPED site providers and 4/10 comparison site providers

EQUiPPED=Enhancing Quality of Prescribing Practices for Older Veterans Discharged from the Emergency Department; NR=not reported; VA-Veterans Affairs; VAMC=Veterans Affairs Medical Center; Z-drugs=nonbenzodiazepine sedative-hypnotic medications

Appendix D, Table 28. Barriers and Facilitators Findings

Author, year Country Intervention Category	Study Overview	Facilitators	Barriers
Community/Primary Care			
Vandenberg 2018[129] United States/VA study Medication Review	Interviews with 13 physicians who participated in a quality improvement intervention at 4 rural VA outpatient clinics	-Individualized feedback forms were helpful in prescribing practice -Education on geriatric prescribing (refresh annually)	-Lack of availability of clinical pharmacists -Inadequate time for medication reconciliation -Inadequate time to access online resources (preferred paper tools)
Jager 2017[130] Germany Medication Review	Survey and interviews with physicians and medical assistants involved in a medication review intervention	-Development of work routines for implementing intervention recommendations -Templates for standardized medication lists -Provision of patient materials designed to improve patient self-management abilities and to address language barriers and difficulties of comprehension	-Lack of knowledge -Effort to attend educational workshop -Patients not carrying medication lists -Changes in trade names of medications -Software errors/limitations -List of patients meeting inclusion criteria for intervention didn't include all patients perceived to need medication review -Checklists and guidelines: too many, for issues which were not feasible, too time consuming, 'question' provider competence and experience, impede individual care for patient -Tools for medication review not integrated into practice software -Lack of standards for information to be included on medication lists; different ideas about what information to include -Providers concerned about 'unsettling' patients by giving too much information about medications and side effects

Author, year Country Intervention Category	Study Overview	Facilitators	Barriers
Kempen, 2018[125] Sweden Medication Review	Interviews and focus group with key informants associated with implementation of medication review by clinical pharmacists	-*Creating a sense of urgency* – share evidence on inappropriate polypharmacy; national focus on quality of care for the elderly	
		-*Building a guiding coalition and cognitive participation* – multi-professional collaboration, key individuals to drive change, support from stakeholders	-*Building a guiding coalition and cognitive participation* – lack of team setting in primary care, skepticism towards physician/pharmacist collaboration
		-*Develop a vision, communicate the vision, coherence* – national, regional, and local levels; public involvement	-*Develop a vision, communicate the vision, coherence* – lack of a national plan for implementation; unclear allocation of tasks and responsibilities, lack of belief in the need for medication reviews
		-*Enable action by removing barriers and collective action* – education for healthcare professionals, financial support and pay-for-performance, national legislation and guidance on medication reviews; shared electronic medical records and prescribing tools	-*Enable action by removing barriers and collective action* – lack of time and continuity in healthcare
		-*Generate short-term wins and reflexive monitoring* – periodic reports on quality indicators; local evidence on effects of medication reviews	-*Generate short-term wins and reflexive monitoring* – lack of national monitoring and evaluation
		-*Sustain acceleration and institute change* – from project funding to permanent positions; continual monitoring and development plans	-*Sustain acceleration and institute change* – focus (political) shifting away from care for the elderly, deregulation of state's pharmacy monopoly making collaboration more complex

Author, year Country Intervention Category	Study Overview	Facilitators	Barriers
Kuntz 2018[126] United States Medication Review with Education	Interviews with a) patients receiving an intervention about Z-drugs and b) primary care providers prescribing Z-drugs to patients who received intervention	*Patient Perspective* -Education about possible safer alternatives *Provider Perspective* -Health care system could prioritize deprescribing -Education about medications and alternatives; focus on patient safety	*Patient Perspective* -Possible effect on quality of life (restful sleep is key component) -Perceived lack of alternatives -Wish to be treated as an individual; didn't identify with patient stories in educational materials -Deprescribing not emphasized by providers *Provider Perspective* -Lack of institutional support and resources (tapering and deprescribing viewed as time-intensive and requiring follow-up) -Deprescribing is counter to health care system values (*eg,* patient satisfaction) -Patients reluctant to give up Z-drugs (dependence) -Lack of effective alternatives -Long-term users don't experience the reported side effects and don't identify with the safety concerns
Ranson 2018[128] United Kingdom Medication Review	Feedback from prescribers participating in the Safer Prescribing for Frailty project; aim of project was to improve medication review and reduce inappropriate prescribing for frail older people	The intervention was tailored to specific barriers within a practice but commonalities included -Use of template to record medication reviews -Better use of skills available to the practice (*eg,* optimal use of practice pharmacists) -Protected time for polypharmacy medication review consultations -Home visits for medication review consultations -Shared learning with wider team within practice	-Lack of knowledge -Environment (time available, processes) -Social influences -Fear of consequences

Author, year Country Intervention Category	Study Overview	Facilitators	Barriers
Nursing Homes			
Brooker 2016[122] Latham 2017[127] United Kingdom Education	Interviews with Dementia Care Coaches (DCCs) responsible for implementing a training and support program for care home staff aimed at reducing inappropriate anti-psychotic prescribing for people with dementia	-Skills and attributes of DCCs (listening, confidence, team work, relationships with colleagues, communication skills, ability to influence other staff) -Nature of the training and support sessions (specific tools, supportive relationships with Dementia Practice Development Coach and peers to facilitate exchange of successes and failures)	-Insufficient time allocated to the DCCs to implement their learning -Resource pressures -Complexities associated with multiple levels of management especially in large provider organizations (communication, unclear expectations, awareness of role); possibility of contradictory requirements -Confusion regarding organizational aims -Program being implemented 'challenges' other organizational forces -External relationships with residents' families and prescribers
Cheek 2004[123] Australia Medication Review	Critical Incident Technique (CIT) interviews, focus groups, and nominal groups to identify factors that influence best practice related to quality use of medicines; CIT used to inform questioning plan for other groups	-Teamwork -Communication and effective information exchange -Use of information technology and information systems -Recognition of each other's roles; mutual respect and trust -Appropriately qualified and educated staff -Workplace literacy (access to and use of information resources) -Continuing education/current practices	-Inflexible work practices and legislative requirements -'Plethora' of documentation -Lack of standardized procedures -Untrained or lack of qualified staff -Time pressures -Complexity – changing case-mix of facility residents and available medications *Residents/Families* -Costs of medications -Difficulties taking medication

Author, year Country Intervention Category	Study Overview	Facilitators	Barriers
Desveaux 2017[124] Canada Education (Academic Detailing)	Interviews with nursing home staff and academic detailers following implementation of academic detailing intervention focused on prescribing of anti-psychotic medications and management of behavioral and psychological symptoms of dementia (BPSD)	*Facility Level* -Engaged leaders committed to improving quality -Availability of education and guidelines for staff on site -Involvement of administrators, physician, pharmacists, and front-line staff (unified the home and strengthened quality improvement efforts) -Easier to engage homes when detailers had direct access to staff -Ability to vary amount of resources provided to each home depending on needs *Intervention* -Credibility (knowledge, understanding of context, confidence) of academic detailers; "third-party" perspective -Adaptability of academic detailers (approachable, flexible) -Evidence-based intervention	*System Level* -Competing priorities (mandatory initiatives and directives from governing bodies that often conflicted with routine ways of managing BPSD in nursing homes) -External peer pressures following public reporting of variation in home-level rates of anti-psychotic prescribing; focus shifted from individual residents to home-level prescribing rates -Public and media attention adopted a negative perspective focusing on adverse consequences without acknowledging proper management *Facility Level* -Fragmented communication and documentation processes -Time constraints

Author, year Country Intervention Category	Study Overview	Facilitators	Barriers
Emergency Department			
Vandenberg 2017[131] United States/VA study Computer Decision Support	Interviews with a) providers participating in an initiative to improve quality of prescribing that included geriatric order sets and b) providers who had access to the order sets without other initiative components	-Safety (reported by 7/11 users of order sets and 1/9 non-users); reducing risk of adverse events -Efficiency (7/11 users, 0/9 non-users); saving time -Information (2/11 users, 1/9 non-users); a resource -Training (2/11 users, 6/9 non-users); value for providers other than themselves *Among 'users' only:* -Location of order sets under ED orders (reported by 6/7 EQUiPPED providers and 1/5 comparison providers) -Categorical organization (7/7 EQUiPPED; 1/5 comparison) -Prepopulated fields (2/7 EQUipPPED, 0/6 comparison)	-Autonomy (reported by 5/11 users of order sets and 3/9 non-users); desire to make their own prescribing judgements based on medical experience -Comfort level (1/11 users, 5/9 non-users); comfortable with existing order sets; enough information in posted reminders *Among 'users' only:* -Learning curve (reported by 2/7 EQUiPPED providers and 2/5 comparison providers); non-intuitive navigation and change in prescribing behavior

ED=Emergency Department; EQUiPPED=Enhancing Quality of Prescribing Practices for Older Veterans Discharged from the Emergency Department; VA-Veterans Affairs; Z-drugs=nonbenzodiazepine sedative-hypnotic medications