9. Reducing Adverse Drug Events in Older Adults

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Introduction

Background

People are living longer than ever. In the United States, the number of Americans age 65 years and older increased from 37.2 million in 2006 to 49.2 million in 2016 (33% increase) and is projected to reach 98 million by 2060.[1] With age comes the likelihood of increasing morbidity. An estimated 98 percent of people age 65 years and older have at least two chronic diseases and take at least five prescription medications.[2]

As the medical field develops clinical therapies, protocols, and treatments to help the elderly population better manage, prevent, and/or enhance quality of life, there are also risks. For instance, polypharmacy—taking multiple medications concurrently—and the use of potentially inappropriate medicines (PIMs) pose the greatest risk of drug-related adverse drug events (ADEs) for older adults, who are more likely than younger people to take multiple medications at the same time.[3,4] Broadly defined as injuries that result from drug-related medical interventions (e.g., medication errors, adverse drug reactions, allergic reactions, or overdoses), ADEs have been associated with thousands of visits to the emergency department (ED) and hospitalizations.[5] However, up to half of identified ADEs are preventable,[6] and ADEs are one of the most common types of preventable adverse events across all healthcare settings.[7]

Importance of Harm Area

Common consequences of ADEs include drug-related morbidity and mortality, heart and/or renal failure, gastrointestinal and internal bleeding, and negative drug-drug interactions.[8,9] Given the prevalence of ADEs, preventing them is an important public health priority. The Joint Commission's 2019 revised National Patient Safety Goals on anticoagulant medicines identifies ADE prevention—in both hospital and ambulatory clinic settings—as a primary objective.[6,10] In addition to potential harm to patients, the estimated cost of treating ADEs in hospital settings was more than $76 billion in 2014 and has likely increased since.[11,12]

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9.1 Reducing ADEs in Older Adults

This chapter summarizes articles published from 2008 to 2018 that describe strategies that effectively reduce ADEs in older adults. Across all studies, the targeted population was adults aged 65 years and older, and the desired outcome was reduced inappropriate medication use or polypharmacy. We describe two approaches that inform how best to identify inappropriate medicines and reduce ADEs. We then describe our literature review strategy and conclude by identifying potential gaps, challenges, and future directions to consider in this field. Resources for future implementation efforts are also included.

9.1.1 Practice Description

Polypharmacy and the use of inappropriate medications present a risk for ADEs. Driven by the need to identify the most precise way to identify ineffective and/or unnecessary medications, several intervention strategies report varied success in implementation and effectiveness. As described in the overview box to the right, this review focuses on two emerging approaches: (1) deprescribing to reduce polypharmacy and (2) the use of the Screening Tool of Older Person's inappropriate Prescriptions (STOPP) criteria to reduce PIMs. Deprescribing involves reducing doses or stopping medications that are not useful or are no longer needed in order to reduce polypharmacy, reduce harm, and improve health. STOPP is a validated, evidence-based list of 80 criteria for potentially inappropriate prescribing in older adults, first published in 2008 and revised in 2014. The box to the right provides an overview.

PSP Overview

Deprescribing

- **Setting(s)**: acute hospital care, ambulatory care (primary care, long-term care, residential aged care facilities, skilled nursing facilities), community pharmacies
- **Patient Population Targets**: older adults, patients at high risk for polypharmacy and comorbidities
- **Provider Targets**: clinical community pharmacists, hospital pharmacists, geriatricians, general practitioners, geriatric nurse practitioners

STOPP Criteria

- **Settings**: acute hospital care, ambulatory care (home care, long-term care, skilled nursing facilities)
- **Patient Population Target**: adults aged 65 or older taking multiple medications
- **Provider Targets**: geriatricians, general practitioners, pharmacists, prescribing physicians

While it is a fairly new tool, evidence suggests that STOPP may be better at predicting PIMs in older adults than other tools, such as the American Geriatrics Society's Beers Criteria®, hereafter referred to as the Beers Criteria.[1] While this patient safety practice (PSP) specifically emphasizes the use of the STOPP criteria, it is often used with a companion screener, the Screening Tool to Alert to Right Treatment (START). START includes a set of 34 evidence-based and validated prescribing indicators for common diseases for the same population. Both have been more commonly used in non-U.S. settings. For the purposes of this review, we focus on STOPP and reference START as appropriate.

9.1.2 Methods

This section describes the literature search and review methods specific to this PSP area. The general methodology used across the project is available in the methods chapter of this report.

We applied search terms in two databases (CINAHL®) and MEDLINE®). Terms used to find deprescribing literature included "deprescribing," "adverse reactions/PC," "adverse drug events," "drug-related side effects," "inappropriate prescribing/PC," "polypharmacy," "polymedication," "cessation," "discontinuation," and "withdrawal." The search terms for STOPP included "STOPP," "potentially inappropriate medication list," "research studies," "prepost," "interventional," "randomized," and "non-

randomized." We further refined each search to focus on the priority population by including "older adult," "aged," "senior," and "elderly."

To make sure we identified all relevant articles, we reviewed the reference lists of systematic literature review articles and read abstracts or full-text of apparently relevant articles to screen them for inclusion.

Methods prescribed by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines guided the review. PRISMA flow diagrams illustrate the process for both the deprescribing and STOPP searches. Overall, 988 publications were identified and 131 articles were considered eligible for further review. Priority was given to intervention studies as opposed to prevalence, incidence, or observational studies. Studies were included if they were published in English; explicitly focused on deprescribing, polypharmacy, PIMs, and/or STOPP; targeted older adults; and effectively (i.e., statistically significantly) reduced medication use as a result of implementing an intervention related to deprescribing and/or using the STOPP criteria. Articles were excluded if the focus was on children/pediatric care. Ultimately, we selected for the evidence summary the 27 studies that are listed in alphabetical order in the evidence tables.

General methods for this report are described in the Methods section of the full report.

For this patient safety practice, a PRISMA flow diagram and evidence table, along with literature-search strategy and search-term details, are included in the report appendixes A through C.

9.1.3 Review of Evidence for Reducing ADEs in Older Adults

This section presents evidence from the 27 studies we reviewed related to the use of deprescribing or using the STOPP criteria to reduce the unnecessary medications that could lead to ADEs in older adults. It is important to note that deprescribing and the STOPP criteria are not actual interventions. Rather, deprescribing is an approach and STOPP is a screening tool. The evidence in this section specifically highlights intervention studies as opposed to prevalence, observational, or incidence studies.

Reference for Section 9.1

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9.2 Patient Safety Practice: Deprescribing To Reduce Polypharmacy in Older Adults

9.2.1 Clinical Outcomes

Key Findings

- Geriatrician and clinical pharmacist reviews can effectively reduce the use of unnecessary medications.
- Educating patients and their families helps them better communicate their medication use to providers in order to discontinue unnecessary medications.
- Deprescribing reduces medication-related costs for patients and healthcare systems.

As previously discussed, deprescribing addresses polypharmacy by reducing inappropriate prescriptions and can lead to improved clinical outcomes. However, clinical outcomes can vary with the specific approach to deprescribing. Ocampo et al. (2015) found that a pharmacist-led medication review with an 18-month follow-up period in community pharmacies identified 408 negative outcomes related to prescriptions and resolved 393 of these problems, resulting in a significant decrease in hospitalizations (p=0.039) and ED visits (p=0.001). Physical and mental health summary scales increased from 65.8 to 82.7 (p<0.0001) and 66.2 to 81.1 (p<0.0001), respectively, while patients who were nonadherent decreased from 68 to 1 (p<0.0001).[1] Others reported that discontinuing multiple medications simultaneously was significantly associated with reductions in both the number of reported falls and frailty scores for older adults.[2] These researchers also examined collaborative medication reviews with general practitioners of patients age 65 years and older in a residential care facility. Their study noted a significant reduction in drug burden index scores, by 0.34 (p<0.001), reflecting a decrease in the cumulative exposure to medications, and the number of falls and frailty measured using the Edmonton frailty scale dropped by a mean difference of 1.35 (p<0.05). Additionally, the number of adverse drug reactions decreased by 4.24 (p<0.05) after 6 months.[2] However, in a multidisciplinary geriatric specialist medication review panel intervention including registrars in geriatric medicine, hospital pharmacists, and geriatric nurse practitioners, no significant difference was found in mortality (p=0.226) or frequency of hospital transfers (p=0.213) between intervention and regular care groups.[3] A summary of key findings are located in the Key Findings box above.

9.2.1.1 Process Outcomes

Many studies focused on process-related outcomes such as a decrease in the number of medications prescribed, which is expected to lead to clinical outcomes. Findings from the studies are subsequently presented by topical area.

9.2.1.1.1 Protocols, Algorithms, and Clinical Decision Support Systems

Among the studies focusing on the use of protocols, algorithms, and clinical decision support systems to promote deprescribing, patients had a significant decrease in the number of medications prescribed. A patient-centered deprescribing protocol called Shed-MEDS is implemented in four phases: (1) confirm medication history and list, (2) evaluate medication for deprescribing, (3) decide with the patients, (4) synthesize and communicate recommendations. Petersen et al. (2018) found that, among Medicare beneficiaries prescribed five or more medications, the mean number of prescribed medications was significantly reduced, from 11.6 to 9.1 (p=0.032), for those receiving the protocol.[4] Garfinkel et al. (2010) worked with elderly patients in Israel to implement the Good Palliative-Geriatric Practice algorithm, an evidence-based flow chart for drug discontinuation, which recommended discontinuing a total of 311 medications for 64 patients.[5] McKean et al. (2016) worked with patients age 65 or older taking eight or

more medications to implement an intervention consisting of a formal medication review among rounding clinicians, followed by receipt of a paper-based or computerized form listing clinical and medication data linked with a five-step clinical decision support tool to determine drugs eligible for discontinuation. The intervention led to a 34.3-percent decrease in regular medications, a small but nonsignificant decrease in PRN (as needed) medications, and a significant decrease in the number of medications per patient at discharge compared with admission (median change: 7 vs. 10 medications [p<0.001]).[6]

9.2.1.1.2 Interventions

Education-improvement interventions, which directly educate consumers, have also been associated with medication discontinuation to reduce polypharmacy. Tannenbaum et al. (2014) found that a direct-to-consumer education intervention using an 8-page booklet to describe the risks of benzodiazepine use and a step-wise tapering protocol led to a 27 percent discontinuation of benzodiazepines among community pharmacy patients age 65 or older in the intervention group, compared with 5 percent in the control group (95% confidence interval [CI], 14% to 32%), at 6 months after the intervention.[7] Martin et al. (2018) studied a consumer-based education intervention led by pharmacists in community pharmacies providing an educational brochure to patients age 65 and older. The study resulted in 43 percent of the intervention group no longer filling inappropriate medications, compared with 12 percent of the control group (95% CI, 23% to 38%).[8]

9.2.1.1.3 Pharmacist-Led Medication Reviews

Pharmacist-led medication review interventions across a number of settings have also promoted deprescribing. Lenander et al. (2014) found that a pharmacist-led medication review in a primary care setting targeting patients 65 and older with five or more different medications led to a decrease in drug-related problems. Using the Beers Criteria, after 12 months, drug-related problems decreased for the intervention group from 1.73 to 1.31 (p<0.05). There was also a larger reduction in the number of drugs prescribed in the intervention group (p<0.046).[9] Veggeland and Dyb (2008) observed the effect of adding a clinical pharmacist performing medication reviews to a geriatric care hospital team, finding it led to improved medication changes, extensive discontinuation of drugs, dose reductions, or decisions to revise medications at a later stage of hospitalization.[10]

9.2.1.1.4 Clinician-Led Medication Reviews

We found one study of a clinician-led medication review. Tamura and colleagues (2011) worked with geriatric medicine fellows in a nursing facility to implement a medication review using the updated Beers Criteria for patients (average age: 83 years old) with nine or more medications, leading to an average reduction of total medications from 16.64 to 15.53 (p<0.001), average number of scheduled medications from 11.3 to 10.99 (p<0.001), average number of PRN medications from 5.33 to 4.56 (p<0.001), and average number of high-risk medications from 5.33 to 4.56 (p<0.001).[11]

9.2.1.1.5 Pharmacist and Clinician Medication Reviews

Medication reviews involving both pharmacists and clinicians effectively decreased medication use in two studies. Chan and others (2014) determined the effectiveness of a medications safety review clinic for geriatric outpatients age 65 or older who were prescribed eight or more chronic medications or who had visited at least three different physicians at the two participating hospitals within 3 months. Four medication review sessions were performed by two research assistants, one clinical pharmacist, and one

geriatrician, leading to a mean decrease in chronic medications from 9.0 to 8.6 ($p<0.05$).[12] Wouters et al. (2017) sought to improve prescribing in nursing home residents by implementing the Multidisciplinary Multistep Medication Review, also referred to as the 3MR intervention. The randomized controlled trial took place on nursing home wards and consisted of an evaluation of the patient's perspective, medical history, and use of medications; a meeting between the physician and pharmacist; and the execution of medication changes. Results showed that successful discontinuation, without relapse or severe withdrawal symptoms, of at least one inappropriate medication was greater in the intervention group than the control group (39.1% vs. 29.5%; 95% CI, 1.02 to 1.75). In the 4 months after the baseline assessment, there was no deterioration of clinical outcomes, such as neuropsychiatric symptoms, cognitive function, or quality of life, in either group.[13]

9.2.1.2 Economic Outcomes

One study assessed the economic impact of deprescribing. Kojima et al. (2012) evaluated the effect on medication costs of a physician intervention using two tools, the Beers Criteria and the Epocrates online drug-drug interaction program, to reduce polypharmacy among long-term care residents. Findings showed that residents undergoing the intervention had significantly lower health care costs after the intervention. Average monthly medication costs declined from $874 to $843 ($p<0.0001$), scheduled medication costs from $814 to $801 ($p=0.007$), PRN medication costs from $60 to $42 ($p<0.0001$), and nursing medication administration costs from $483 to $461 ($p<0.0001$).[14]

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9.3 Patient Safety Practice: Using the STOPP Criteria To Reduce the Use of PIMs in Older Adults

9.3.1 Clinical Outcomes

The studies evaluating STOPP did not focus on clinical outcomes. There has been more emphasis on assessing the process of implementing or using STOPP criteria to more accurately identify PIMs.

9.3.2 Process Outcomes

Four studies demonstrate the effectiveness of STOPP. Campins et al. (2017) reported that the STOPP tool helped pharmacists determine that 27 percent of the intervention population's prescriptions were potentially inappropriate. The majority of these prescriptions were then changed, as follows: 43 percent were discontinued, 33 percent received a dose adjustment, 14 percent were substituted for more appropriate medications, and for 10 percent, the patient received a new prescription.[1] Similarly, Gibert et al. (2018) used STOPP in primary care consultations in France, resulting in a 38-percent reduction in the number of PIMs (n=170 vs. 106) across about 45 percent of patients (n=44) ($p<0.001$).[2] Hannou et al. (2017) introduced a part-time ward-based clinical pharmacist to a psychiatric unit's multidisciplinary team and screened prescriptions for potentially inappropriate drug prescribing (PIDP) using the STOPP/START criteria. The intervention was measured by the acceptance rate of pharmacist interventions (PhIs).The global PhI acceptance rate was 68 percent and the rate based on STOPP/START was 47%. When two STOPP criteria, the prescription of benzodiazepines or of neuroleptic drugs to patients who had fallen in the last 3 months, were removed from analysis, the acceptance rate for STOPP/START-based PhIs increased to 67 percent.[3] In Ilic et al. (2015), an education intervention targeting both physicians and nursing home residents provided information about the START/STOPP and Beers Criteria, as well as adherence, adverse drug reactions, and drug-drug interactions. According to the STOPP criteria, 70 drugs were inappropriately prescribed before the intervention, and 20 drugs after 6 months. The median number of inappropriately prescribed drugs according to the STOPP criteria before education was 3.5 (range 1.0-20.0), and the median number after education was 1.5 (range 0.0-6.0; $Z=2.823$; $p<0.005$).[4]

9.3.3 Economic Outcomes

STOPP has the potential for positive economic outcomes. After implementing a comprehensive geriatric assessment (CGA) that included the STOPP criteria, Unutmaz et al. (2018) suggested that the tool saved patients about $13 per month in medication costs, as well as reducing polypharmacy, PIMs, and potential prescribing omissions (PPOs).[5] O'Connor et al. (2016) reported significant reductions in medication costs. At discharge, median medication cost was significantly lower in the intervention group than in the control group ($p<0.001$).[6] Frankenthal et al. (2017) found that when pharmacists and prescribing physicians discussed medication reviews rather than communicating in writing, the reviews were more effective. Furthermore, the authors reported that the costs of medications were significantly lower in the intervention group than the control group ($p<0.001$) at the 24-month followup.[7] Hill-Taylor et al. reviewed three studies on the direct costs of potentially inappropriate prescribing (PIP). One study, Barry et al., found that the wholesale cost of the PPO instances identified by the START criteria in their study population was €188 per patient per year in 2007. Another, Cahir. et al, reported that the cost associated with the PIP instances identified by condensed STOPP criteria in their study population was

€318 per patient per year. The third study, Byrne et al., determined that the cost associated with PIP instances identified in their study population was €263 per patient per year.[8]

9.3.4 Unintended Consequences

9.3.4.1 Deprescribing: Negative Unintended Consequences

Deprescribing interventions do not always lead to an improvement in cognition scores.[9] One potential unfavorable effect of deprescribing interventions is that, while the interventions have reduced medication costs, they do not always lead to a decrease in healthcare utilization, such as hospital admissions and primary care visits.[10]

9.3.4.2 Using the STOPP Criteria: Negative Unintended Consequences

With the exception of longer lengths of stay found in one study,[6] no other unintended negative consequences were reported in the studies that examined the use of STOPP criteria to reduce ADEs. Although some researchers caution about risks related to cognitive declines when medications are reduced and/or eliminated, such findings were not discussed in the studies noted in this review.

9.3.4.3 Deprescribing: Positive Unintended Consequences

In addition to the clinical and process outcomes reported above, deprescribing also led to more positive quality of life in areas such as health transition, bodily pain, and general health.[11]

9.3.4.4 Using the STOPP Criteria: Positive Unintended Consequences

No unintended positive consequences were reported in our review of the studies that examined the use of STOPP criteria to reduce ADEs.

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9.4 Implementation

9.4.1 Summary of Evidence

We reviewed 27 studies, including 2 systematic reviews and 4 randomized controlled trials. Study interventions were heterogeneous, but most share common features. Interventions were delivered by pharmacists and/or physicians either in step-wise fashion (e.g., pharmacist conducts screening and makes recommendations; physicians review and accept/reject recommendations) or in collaboration (pharmacists and physicians review recommendations together). All studies were restricted to older adults (age 65 and older), but only three explicitly relied on geriatricians in the intervention. All STOPP interventions involved a screening step where STOPP criteria were used and included steps for making and accepting or rejecting recommendations generated from STOPP screening.

9.4.2 Barriers and Facilitators

This section describes barriers and facilitators to implementing interventions that focus on deprescribing or using STOPP criteria to reduce ADEs in older adults.

In the deprescribing literature, notable barriers to implementation included:

- Pharmacists not adhering to study protocols.[1]
- Inadequate documentation of medication history.[2,3]
- Limited communication between pharmacists and physicians.[1,4]
- Patients being discouraged from discontinuing medications by individual providers.[5]
- Patients perceiving deprescribing as contradicting their provider's recommendations.[6]
- Scheduling conflicts, competing demands, and general lack of time, which impacted medication review meetings between pharmacists and physicians.[4,6,7]
- Nonprescription medications (i.e., over-the-counter) that were not documented in medical databases, which prevented providers from seeing the full-range of medication use per patient and therefore not being able to accurately identify and include all patients who were at risk of polypharmacy in the study.[1]
- Lower acceptance rates of pharmacist interventions based on the STOPP criteria due to the lack of discontinuation of benzodiazepines.[3,8,9]

Key facilitators for deprescribing involved communication and collaboration between pharmacists and prescribing physicians during medication reviews,[4,6,10] and educating pharmacists and physicians about the risks of polypharmacy and the use of unnecessary medications in older adult patients.[11]

9.4.3 Resources To Assist With Implementation

The following resources were cited in our review of the evidence and can be used to implement future deprescribing practices:

- Good Palliative Care Algorithm[11]
  - A flow chart developed for use in nursing home settings to inform options for deprescribing.

- Epocrates Online Drug-Drug Interaction Tool[12]
  - Free web-based drug interaction tool that assists in identifying combinations of medications that could be harmful. Visit https://online.epocrates.com/interaction-check for more information.
- Canadian Deprescribing Network Patient and Pharmacist-Physician Materials[1]
  - A compilation of materials to inform and educate patients and prescribing physicians about ways to reduce the use of inappropriate medications, including alternative treatment options and evidence-based pharmaceutical opinions. Visit https://www.deprescribingnetwork.ca/patient-handouts for patient materials and https://www.deprescribingnetwork.ca/pharmaceutical-opinions for physician information.

The following resources were cited in our review of the evidence related to using the STOPP criteria:

- STOPP/START Toolkit Supporting Medication Review[13]
  - Designed to be used by healthcare professionals as a reference tool to support medication review for older adults. Developed by a consortium of professionals at the National Health Service North of England Commissioning Support Unit in the United Kingdom, the tool was validated for adults 65 years of age and older and can be downloaded at: https://www.herefordshireccg.nhs.uk/your-services/medicines-optimisation/prescribing-guidelines/deprescribing/748-stopp-start-herefordshire-october-2016/file.
- Comprehensive Geriatric Assessment (CGA) Toolkit Plus[14]
  - A series of rules/suggestions related to high-yield problems in prescribing for older people in terms of both reducing medication burden (STOPP) and adding in potentially beneficial therapy (START). Visit https://www.cgakit.com/m-2-stopp-start for more information.

9.4.4 Gaps and Future Directions

9.4.4.1 Gaps

9.4.4.1.1 Deprescribing

There are notable gaps in the research of implementation efforts related to deprescribing. While many interventions have applied the use of specific criteria, algorithms, and protocols, only a few studies have considered other patient-related factors, including cost, patient preference, compliance and convenience, life expectancy, and other health outcomes associated with deprescribing. Furthermore, most interventions take place in either the acute care setting or ambulatory care setting. Finally, few interventions focus on the transition from acute care to ambulatory care and primary care settings.

9.4.4.1.2 STOPP Criteria

Research in STOPP is advancing rapidly, and increasing numbers of well-designed randomized or prospective studies are being published. Little if any progress has been made, however, in examining the impact of these interventions on short- and long-term clinical,[15] utilization, and economic outcomes. Additionally, consensus is lacking on the most appropriate structure, format, and staffing, leading to heterogeneity of interventions.

9.4.4.2 Future Directions

9.4.4.2.1 Deprescribing

Recommendations for future deprescribing efforts include: factoring in perspectives and preferences of patients during the deprescribing process;[7] developing protocols that target multiple rather than specific medications and/or diseases;[7] and, with the expanding role of pharmacists, focusing on involving community pharmacists.[16] More rigorous, long-term examination is necessary to further support the promise of this approach on reducing polypharmacy and ADEs.[7,17,18]

9.4.4.2.2 STOPP Criteria

Based on the emergent evidence, STOPP appears to be most effective in reducing PIMs in older adults when used in concert with other approaches. Recommendations for future investigations call for the integration of the STOPP criteria with clinical decision support procedures as part of electronic health records as a means to improve efficiency during the screening process.[19] Combining STOPP—especially the 2014 revised version—with, or comparing it with, other screening tools such as the As Beers Criteria or the Medication Appropriateness Index could improve clinical appropriateness.[20] Researchers also recommend that future research examine the long-term clinical effects of using the STOPP criteria to reduce inappropriate medications and reduce ADEs.[21]

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Conclusion and Comment

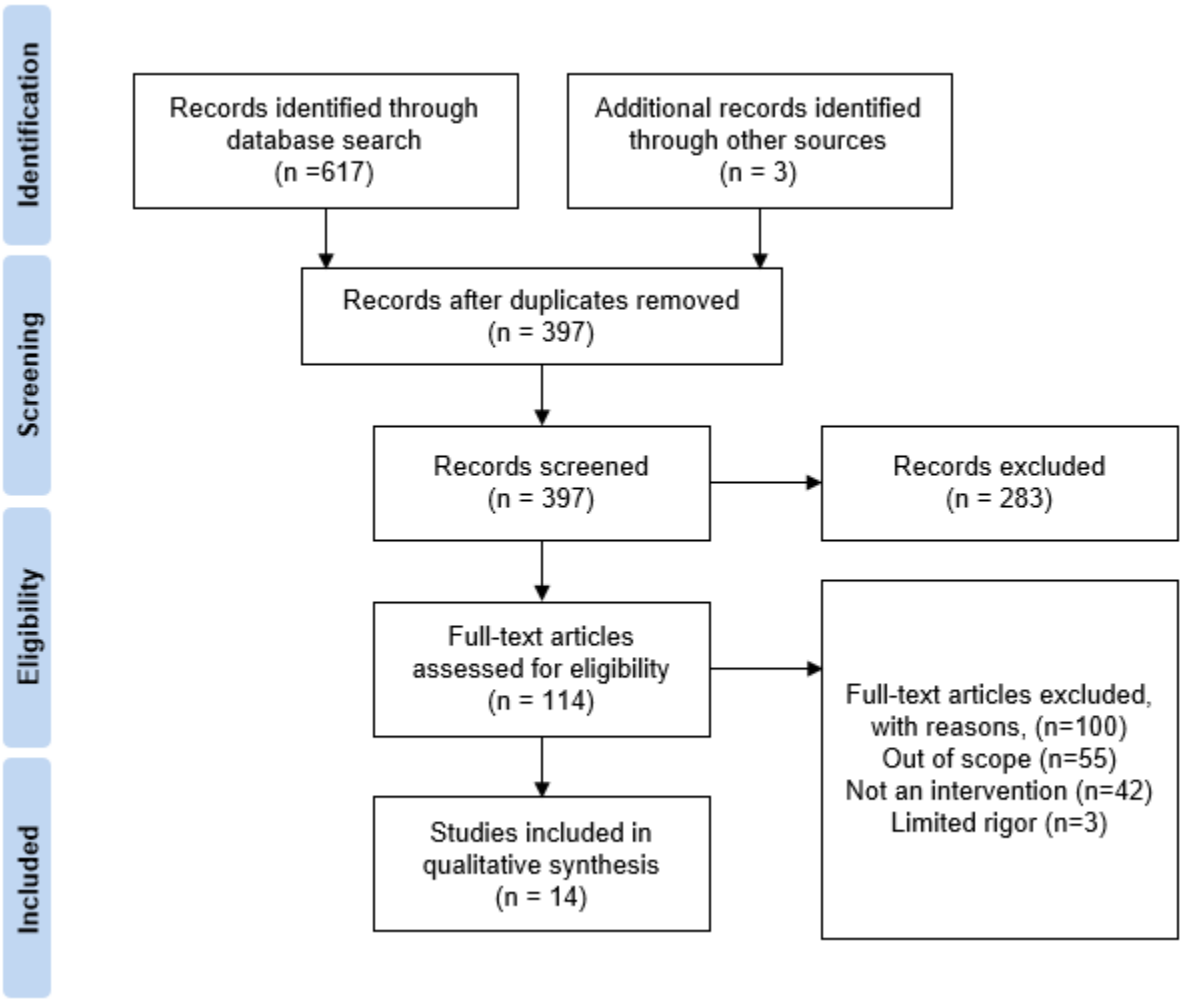
Being able to prevent unnecessary ADEs that are associated with the use of inappropriate medication use or polypharmacy is especially important for older adults who are affected by multiple ailments and who inevitably traverse multiple healthcare settings and providers for treatment. As the evidence reviewed in this chapter suggests, deprescribing to reduce polypharmacy and use of the STOPP criteria to reduce PIMS are two approaches to consider. Albeit still emerging, studies on deprescribing highlight its potential in helping providers adjust down and/or eliminate medications based on the condition/need of patients. However, more research is needed to assess deprescribing in relation to patient adherence, compliance, and preference, as patients play a key role in a provider's ability to effectively monitor and adjust medication and treatment plans.

With regard to using the STOPP criteria to reduce PIMS, evidence suggests it is the most effective approach, but also note that it often does not—and should not—stand alone. In order to ensure that older adults are given the best possible care, in addition to screening their prescriptions for PIMS (i.e., using STOPP), it is equally important to identify more appropriate treatment options, thus also including the START criteria. More appropriate medication selection is also achieved through the use of the Beers Criteria or the Medical Appropriateness Index (MAI), which are other interventions that often accompany the use of STOPP.

While the literature in this review expands the existing knowledge of practices to reduce harm and preventable ADEs for elderly patients, in particular, the field will undoubtedly benefit from more studies that examine the short- and long-term clinical effects of reducing polypharmacy and PIMS through deprescribing and using the STOPP criteria.

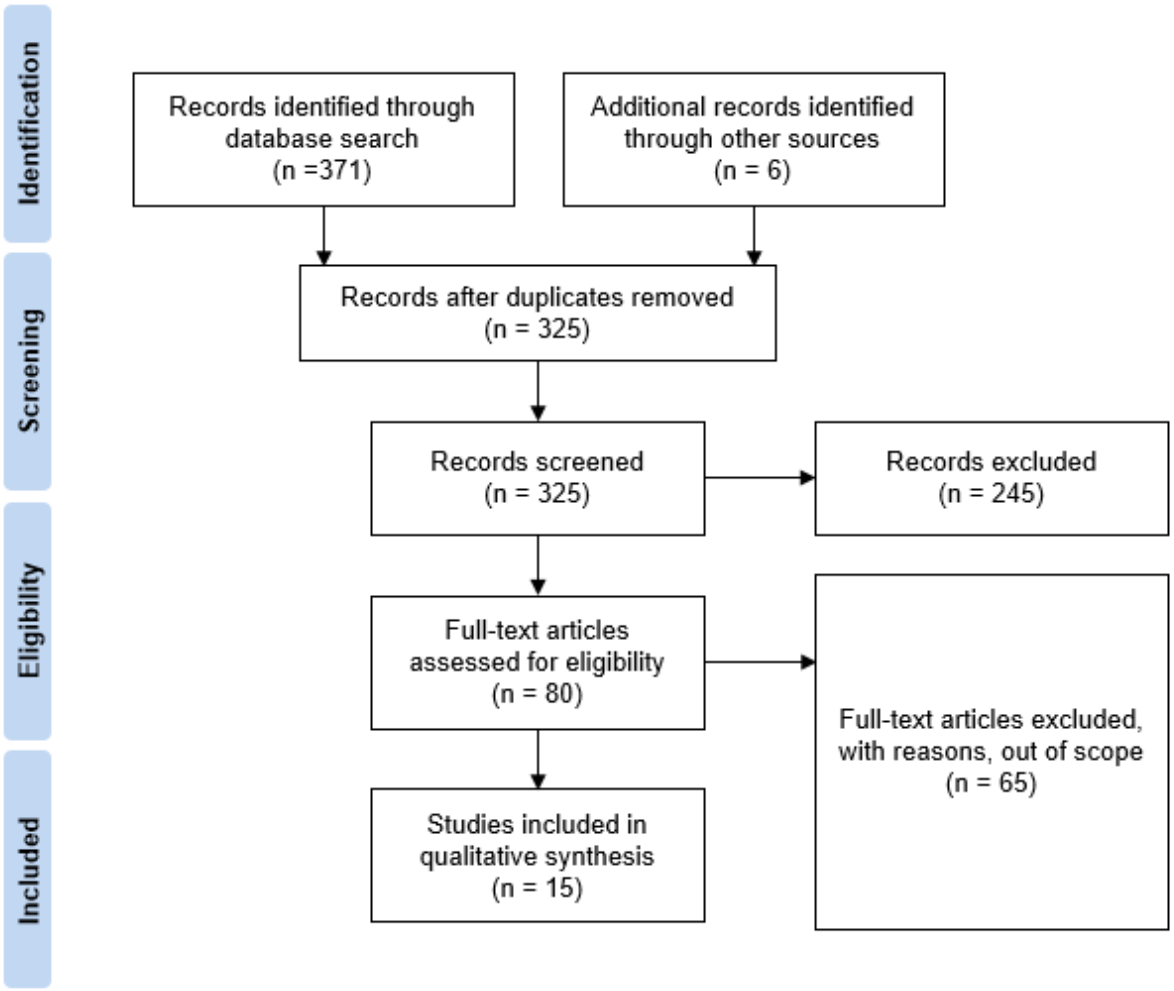
Appendix A. Reducing Adverse Drug Events in Older Adults PRISMA Diagrams

Figure A.1: Reducing Adverse Drug Events in Older Adults, Deprescribing To Reduce Polypharmacy—Study Selection for Review



PRISMA criteria described in Moher D, Liberati A, Tetzlaff J, et al. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med. 2009 Jul 21;6(7): e1000097. doi:10.1371/journal.pmed1000097.

Figure A.2: Reducing Adverse Drug Events in Older Adults, Using the STOPP (Screening Tool of Older Person's inappropriate Prescriptions) Criteria—Study Selection for Review



PRISMA criteria described in Moher D, Liberati A, Tetzlaff J, et al. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med. 2009 Jul 21;6(7): e1000097. doi:10.1371/journal.pmed1000097.

Appendix B. Reducing Adverse Drug Events in Older Adults Evidence Tables

Table B.1: Reducing Adverse Drug Events in Older Adults, Deprescribing to Reduce Polypharmacy-Single Studies

Note: Full references are available in the Section 9.2 reference list.

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings
Ailabouni et al., 2019[2]	Pharmacist medication review with physician consult	Study Design: Feasibility study Sample: n=46 Patient Population: Adults 65 years and older living in residential care facilities and prescribed at least one anticholinergic or sedative medication	Residential care facilities in New Zealand	Primary Outcomes: Pharmacist-led intervention model led to implementation of 72% of deprescribing recommendations and a significant reduction in adverse drug reactions.	No change in cognition scores or reported quality of life	Reduction in drug burden index scores, numbers of falls, and adverse drug reactions 6 months post intervention.
Ocampo et al., 2015[1]	Pharmacist medication review with an 18-month followup	Study Design: Effectiveness-implementation hybrid design Sample: n=132 Patient Population: Community pharmacy patients, prescribed at least one medication, were offered the service when they sought advice, when a drug administration aid was required or when the provision of service was requested during the 18 month follow up period.	Community pharmacy in Spain	Primary Outcomes: Pharmacist-conducted medication review decreased the number of medications prescribed from 6.1 to 3.3, decreased observed hospitalizations, and decreased emergency department (ED) visits.	Not provided	Intervention led to a reduction in the number of medicines used, reduction in hospitalizations, reduction in ED visits, and improvement in physical and mental health.

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings
Chan et al., 2014[12]	Use of medication safety review clinics, including a team of research assistants, pharmacist, and geriatric clinician for solving drug-related problems	Study Design: Intervention Sample: n=139 Patient Population: Outpatients age 65 or older who had been prescribed eight or more chronic medications (28 days or longer) or had visited more than three physicians at two participating hospitals	University hospital in Taiwan	Implementation of medication safety review clinics led to a reduction in chronic medication prescribed and led to the improvement of good health status from 22% to 38% in 24 weeks.	Not provided	Intervention led to a reduction in chronic medication and improvement of good health status rating.
Garfinkel and Mangin, 2010[5]	Good-Palliative-Geriatric Practice algorithm was used to recommend drug discontinuations	Study Design: Feasibility trial Sample: 70 intervention Patient Population: Community-dwelling adults referred by family physician or family for comprehensive geriatric assessments.	Day center for senior citizens and/or home care in Israel	Primary Outcome: Algorithm led to discontinuation recommendations for 58% of drugs.	Not provided	Protocol indicated that discontinuation was recommended for 311 medications in 64 patients.
Kojima et al., 2012[14]	Physician-led intervention using the Beers Criteria® and the Epocrates online drug-drug interaction program to reduce polypharmacy in long-term care residents	Design: Quality improvement cost study Sample: n=70 Patient Population: Patients age 65 years or older with polypharmacy	Skilled nursing facility and intermediate care facility in Hawaii	Primary Outcome: Physician-led, tool-assisted medication review led to a decrease in monthly medication costs by $22 per resident and a decrease in nursing medication administration costs.	Not provided	Intervention led to a decrease in monthly medication costs and nursing medication administration costs.

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings
Lenander et al., 2014[9]	Pharmacist-led structured medication review involving a patient questionnaire and pharmacist consultation in primary care setting	Design: Randomized controlled trial (RCT) Sample: 209 total patients: 107 intervention group; 102 control group Patient Population: Patients age 65 or older with five or more prescribed medications	Primary care center in Sweden	Primary Outcome: Drug-related problems and number of drugs Secondary Outcome: Healthcare utilization and self-rated health during 12-month follow-up.	Not provided	1. Pharmacist-led medication review led to a decrease in the number of drug-related problems from 1.63 to 1.31 at followup and a decrease in the number of drugs prescribed. 2. No significant difference in healthcare utilization, but a significant change in self-rated health.
McKean et al., 2016[6]	Physician-led education intervention supported by listing clinical and medication data linked with clinical decision support tool	Design: Prospective pilot study Sample: n=50 Patient Population: General medicine patients 65 years or older receiving eight or more medications	Tertiary teaching hospital in Australia	Primary Outcome: Physician-led education intervention led to a decrease in the number of medications prescribed at discharge from 10 to 7.	Not provided	Intervention led to decrease in the number of medications per patient.
Martin et al., 2018[8]	Consumer based, pharmacist-led education intervention using an educational deprescribing brochure in parallel to sending the physicians an evidence-based pharmaceutical opinion	Design: Cluster RCT Sample: 489 patients: 219 intervention group; 218 control group Patient Population: Patients age 65 or older, prescribed at least one of four prescribed peer criteria medications (sedative-hypnotics, first-generation antihistamines, glyburide, or nonsteroidal anti-inflammatory drugs)	Community pharmacies in Canada	Primary Outcome: Pharmacist-led education intervention led to a reduction in the number of inappropriate medications prescribed by 43% in the intervention group.	Not provided	Intervention led to a decrease in number of inappropriate medications filled.

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings
Petersen et al., 2018[4]	Use of a deprescribing intervention (Shed-Meds) to identify deprescribing targets and priorities, decide on appropriate deprescribing through patient interview, synthetize and communicate deprescribing recommendations to providers	Design: Single site feasibility study Sample: 40 total patients: 20 intervention group; 20 control group Patient Population: Medicare beneficiaries 65 years of age or older receiving five or more prescribed medications and admitted to hospital with intended discharge to a skilled nursing facility	Tertiary care hospital in Tennessee	Primary Outcome: Deprescribing protocol led to a reduction in medications at discharge from 11.6 to 9.1.	Not provided	Intervention decreased the mean number of medications prescribed at discharge and reduced medication burden in older adults.
Pope et al., 2011[3]	Intervention included medical assessment by a geriatrician and medication review by a multidisciplinary expert panel	Design: Prospective RCT Sample: 225 permanent patients: 110 intervention group; 115 control group Patient Population: Permanent patients on continuing care wards	Two residential continuing care hospitals in Ireland	Primary Outcome: Geriatric specialist medication review led to a reduction in the number of medications from 11.65 to 11.09 in the intervention group.	Intervention did not lead to a significant difference in mortality or acute hospitalization outcomes	Intervention led to a decrease in the total amount of medications in the intervention group.
Tamura et al., 2011[11]	Geriatric fellow and faculty medication review using the Beers Criteria® and Epocrates online drug interaction program	Design: Intervention study Sample: n=74 Patient Population: Residents with nine or more medications	Kuakini Geriatric Care, long-term care facility in Hawaii	Primary Outcome: Geriatrician-led medication review led to a decrease in the number of prescribed regular medications.	Not provided	Intervention led to a decrease in the number of regular prescribed medications, as-needed medications, and high-risk medications per patient.

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings
Tannenbaum et al., 2014[7]	Direct-to-consumer education intervention using an 8-page booklet based on self-efficacy and a self-assessment of benzodiazepine use in community pharmacies	Design: Cluster RCT Sample: 303 total patients: 148 intervention; 155 control group Patient Population: Community pharmacy patients age 65 or older with a minimum of five active prescriptions, one being an active benzodiazepine prescription, dispensed for at least 3 consecutive months	Community pharmacies in Canada	Primary Outcome: Direct-to-consumer pharmacist-led intervention led to a significant decrease in benzodiazepine use in the intervention group.	Not provided	Intervention led to a significant decrease in benzodiazepine use in the intervention group.
Wouters et al., 2017[13]	Multidisciplinary Multistep Medication Review	Design: Pragmatic cluster RCT Sample: Total 426: 233 intervention group; 193 control group Patient Population: Nursing home residents	Nursing home wards for long-term care in the Netherlands	Primary Outcome: Pharmacist and clinician-led medication review led to a 39.1% reduction of inappropriate medications in the intervention group.	Intervention did not lead to a change in clinical outcomes between groups	Intervention led to a decrease in the number of inappropriate medications.

Table B.2: Reducing Adverse Events in Older Adults, Using STOPP (Screening Tool of Older Peron's Inappropriate Prescriptions)

Note: Full references are available in the Section 9.3 reference list.

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Risk of Bias (High, Moderate, Low)
Campins et al., 2017[1]	Clinical pharmacist-led review based on algorithm and STOPP/START criteria (Screening Tool of Older People's Prescriptions/Screening Tool to Alert to Right Treatment)	Design: Randomized controlled trial (RCT) Sample: 251 control group; 252 intervention group Patient Population: Community-dwelling older adults, aged 70 years and older, receiving six or more drugs and resident in municipalities of Martaro and Argentona, Spain.	Primary Health Care Centers in Spain	Primary Outcomes: About 26.5% of prescriptions were rated as potentially inappropriate and 21.5% were changed (9.1% discontinuation, 6.9% dose adjustment, 3.2% substitution, and 2.2% new prescription). The mean number of prescriptions per patient was significantly lower in the intervention group at 3- and 6-month followup.	Not provided	Not provided	Moderate

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Risk of Bias (High, Moderate, Low)
Cossette et al., 2017[15]	Use of a computer alert system-based pharmacist-physician intervention model to compare change in the use of potentially inappropriate medications (PIMs) with usual clinical care. A panel of experts used STOPP criteria to develop the model	Design: RCT with block randomization. Patients were randomly assigned to control and intervention groups with a 1:1 ratio using block sizes of 2, 4, and 6, and stratification by hospital site. Sample: 139 intervention (126 analyzed); 133 control group (128 analyzed). Patient Population: Older adults, 65 years and older. with at least one geriatric-explicit criterion for PIMs	University hospital in Canada	Primary outcome: Drug cessation or dosage decrease implemented in targeted PIMs. Secondary outcome: Length of stay, in-hospital death, ED visits, and readmissions within 30 days of discharge.	Not provided	1. Clinical relevance of the computer alert system alerts: 50% in control group and 30% in intervention group. 2. Significant drug cessation and dosage decreases in intervention compared with control group at 48 hours post alert: (30%) and hospital discharge (20.8%). Average time (means) to analyze a patient file and complete the interventions was about 44.25 minutes in intervention group. 3. No significant decrease in readmissions or inpatient death rates for intervention vs. control group.	Moderate

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Risk of Bias (High, Moderate, Low)
De Bock et al., 2018[16]	Medication review process that used STOPP to assess appropriateness of medication	Design: RCT Sample: 52 patients who were taking a median of 10 medications at the time of the study. Patient Population: Older adults, 70 years of age or older, with an unplanned admission to the geriatric ward; took at least five drugs chronically; not hospitalized in the preceding 3 months; and no documented cognitive impairments	University Hospital in Belgium (235 beds)	Primary Outcome: Reduction in number of drug discrepancies and potentially inappropriate prescriptions (PIPs). Secondary Outcome: Positive reports of satisfaction with services and opinions on interprofessional communication.	Medication reconciliation was time consuming and did not involve an integrated electronic patient file to record diagnoses, lab results, and medications	1. Time needed to review and make recommendations was considered reasonable. 2. Successes for medication review: full access to patient file; relatively fast screening; identification of significant amount of PIMs; improvement in prescribing appropriateness; 20% of recommendations accepted. 3. Barriers for medication review: scattered information; inefficient communication; lack of continuity of care. There were no service level agreements in place prior to intervention implementation.	Moderate
Frankenthal et al., 2017[7]	Review by study pharmacist using STOPP/START criteria at beginning of study and 6 months later	Design: Retrospective cohort study Sample: 160 intervention; 146 control group Patient Population: Older adults, 65 years and older	Chronic care geriatric facility in Israel	Primary Outcome: The prevalence of PIPs was significantly lower in the intervention group (33.3%) than the control group (48.4%) at 24-month followup (p=0.02).	Not provided	Between baseline and 24 months, there was a significant reduction in costs of medications in the intervention group (113 Israeli shekels [$29]] per patient per month, p<0.001) but not in the control group.	Low

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Risk of Bias (High, Moderate, Low)
Gibert et al., 2018[2]	STOPP used during primary care general practitioner consultations on PIMs	Design: Intervention study Sample: 170 patients Patient Population: Older adults, 75 years and older	Primary care in Isere County, France	Primary Outcome: The number of PIMs decreased by 37.6% (n=170 vs. 106) with the application of STOPP criteria by general practitioners. This intervention reduced PIMs for 44.9% of patients (n=44, p<0.001).	Not provided	Not provided	High
Hannou et al., 2017[3]	Clinical pharmacist medication reviews to reduce potentially inappropriate drug prescriptions	Design: Prospective interventional study Sample: 102 intervention; no control group Patient Population: Older adults, 65 years and older, being admitted to an acute psychiatric geriatric facility	Geriatric psychiatry admission unit of a university hospital in Switzerland (16 beds)	Primary Outcome: Global pharmacist intervention acceptance rate was 68% (78% for standard pharmacist recommendations [recs], and 47% for STOPP/START recs). Of 186 STOPP recs, 82 were accepted (44%).	Not provided	Not provided	High

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Risk of Bias (High, Moderate, Low)
Hill-Taylor et al., 2013[8]	Assessment of effectiveness of STOPP/START criteria on prescribing quality and clinical, humanistic, and economic outcomes in adults aged 65 and older (updating a 2013 review).	Design: Systematic review with meta-analysis of PIM rates, and narrative summary of other outcomes. Four studies were included in analysis. Sample: 1,925 adults. Patient Population: Adults age 65 years and older; one study restricted participants to 75 years and older	Acute care admission, long-term care	Primary Outcomes: All followup rates showed improvement in PIM rates in both the intervention and control groups. At every time point in every study, the intervention demonstrated some success, with the intervention PIM rates being lower than control rates. Three studies reported a significant and sustained drop in potential prescribing omissions (PPOs) in the intervention group. There was also a reduction in PPOs in all control groups on followup.	Not provided	Two studies reported cost outcomes and found cost efficiencies in medication choices in the intervention group compared with the control group.	Moderate

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Risk of Bias (High, Moderate, Low)
Ilic et al., 2015[4]	Using START/STOPP criteria to assess the appropriateness of prescribing before and 6 months after the intervention implementation	Design: Pre- and post-observation trial that included a 3-month pre-phase; a 1-month intervention phase; a 6-month post-intervention phase; and a 3-month period of repeated recording and analysis of prescribing practices. Sample: 104 nursing home residents and 27 nursing home physicians; no control group. Patient Population: Older adults, 65 years and older, who resided in the nursing home. Average age was 83 years,	Twenty nursing home facilities in Serbia	Primary Outcome: Seventy PIPs prescribed pre intervention and 20 PIPs 6 months post intervention (median 3.5, range 1–20 pre intervention, and median 1.5, range 0–6 post). The decrease in PIPs was significant ($z=2.823$; $p<0.005$).	Not provided	Not provided	Moderate
Kiel and Phillips, 2017[12]	Clinical pharmacist comprehensive medication reviews using START/STOPP criteria	Design: Prospective cohort with post-hoc analysis Sample: 26 intervention and 26 control group participants Patient Population: Older adults, 65 years and older, taking at least five prescription medications	Primary care clinic in Michigan	Primary Outcome: Difference in number of medication-related problems, as defined by the START and STOPP criteria. The acceptance rate for recommendations on STOPP/START med problems was 35% (n=17).	Not provided	Not provided	High

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Risk of Bias (High, Moderate, Low)
Kimura et al., 2017[14]	Clinical pharmacist medication reviews using STOPP-2 criteria to reduce PIMs	Design: Prospective observational study Sample: 822 in intervention group; no control group Patient Population: Older adults, 65 years and older, who were newly admitted into inpatient care and prescribed more than one prescription medication	University hospital in Japan	Primary outcomes: Number of PIMs was 651; of these, it was recommended to doctors that 310 (47.6%) be changed, and 292 (44.9%) were discontinued/ changed after the pharmacist's assessment. Acceptance rate of pharmacists' recommendations was 94.2%.	Not provided	The mean time for pharmacist's assessment was 6.2 +/- 3.1 minutes per patient.	High
O' Connor et al., 2016[6]	Using START/STOPP criteria to help attending physicians identify PIMs	Design: Single-blinded, clustered RCT Sample: 732 in intervention group; no control group Patient Population: Consecutively admitted adults aged 65 and older	Tertiary referral hospital in Ireland	Primary Outcome: When STOPP/START was applied, 451 recommendations were made on 233 participants (64.7%). Of these, 292 were STOPP recommendations; attending doctors accepted and implemented 237 STOPP recs (81.2%).	Not provided	Application of STOPP/START criteria resulted in significant reductions in adverse drug reaction incidence and medication costs in acutely ill older adults but did not affect median length of stay.	Low

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Risk of Bias (High, Moderate, Low)
Price et al., 2017[14]	Using STOPP guidelines as part of an electronic medical records clinical decision support system to identify PIPs for older adults	Design: Mixed-method, pragmatic, cluster RCT Sample: 44,290 in intervention group; 37,615 in control group Patient Population: Consecutively admitted adults aged 65 and older	Primary care offices	Primary Outcome: Regression analysis showed no significant difference in change of recorded PIPs in control versus intervention group (p=0.80).	Not provided	Barriers to implementation: The STOPP rules were presented in a different location from simple drug alerts; the guideline tool did not have a clear way to support users in prioritizing suggestions and alerts as recommended.	Low
Unutmaz et al., 2018[5]	Comprehensive geriatric assessment (CGA) complemented by STOPP/START criteria	Design: Retrospective assessment of before and after intervention Sample: 1,579 patients Patient Population: Older adults, age 65 and older	Geriatrics outpatient clinic of tertiary hospital in Turkey	Primary Outcome: Mean number of drugs decreased from 5.3±3.4 before CGA to 4.6 ±2.5 (p<0.05).	Not provided	After CGA, monthly saved total per capita cost of PIMs was $12.8 and monthly increased total per capita cost of PPOs was $5.6.	Moderate

Appendix C. Reducing Adverse Drug Events in Older Adults Search Terms

Method	Search	Search String for: CINAHL	Search String for: MEDLINE
Search 2008-Present, English Only MedLine Publication Types: • Clinical Trial • Clinical Trial, Phase I • Clinical Trial, Phase II • Clinical Trial, Phase III • Clinical Trial, Phase IV • Comparative Study • Controlled Clinical Trial • Corrected and Republished Article • Evaluation Studies • Guideline • Journal Article • Meta-Analysis • Multicenter Study • Practice Guideline • Published Erratum • Randomized Controlled Trial • Review	Deprescribing	(((MH "Inappropriate Prescribing/PC") OR (MH "Adverse Drug Event/PC") OR (AB “Deprescription*” OR “Deprescribing” OR “Cessation” OR “Discontinuation” OR “Withdrawal”)) AND ((MH "Polypharmacy" OR AB (Polymedication OR Polypharmacy)) AND ((MH Aged OR AB ("Older Adult*" OR Elder* OR Aged OR "Elder Adult" OR Senior)))	(((MH "Deprescriptions") OR (MH "Drug-Related Side Effects and Adverse Reactions/PC") OR (MH "Inappropriate Prescribing/PC") OR AB (“Deprescription*” OR “Deprescribing” OR “Cessation” OR “Discontinuation” OR “Withdrawal”)) AND ((MH "Polypharmacy" OR AB (polymedication OR Polypharmacy)) AND ((MH Aged OR AB ("Older Adult*" OR Elder* OR Aged OR "Elder Adult" OR Senior)))

Method	Search	Search String for: CINAHL	Search String for: MEDLINE
• Scientific Integrity Review • Technical Report • Twin Study • Validation Studies CINAHL Publication Types: • Clinical Trial • Corrected Article • Journal Article • Meta-Analysis • Meta Synthesis • Practice Guidelines • Randomized Controlled Trial • Research Review • Systematic Review			
Search 2008-Present, English Only MedLine Publication Types: • Clinical Trial • Clinical Trial, Phase I • Clinical Trial, Phase II	Use of STOPP Criteria	((AB "Potentially Inappropriate Medication List") AND ((MH Aged OR AB ("Older Adult*" OR Elder* OR Aged OR "Elder Adult" OR Senior)))	(((MH "Potentially Inappropriate Medication List") OR (AB "Potentially Inappropriate Medication List")) AND ((MH Aged OR AB ("Older Adult*" OR Elder* OR Aged OR "Elder Adult" OR Senior)))

Method	Search	Search String for: CINAHL	Search String for: MEDLINE
• Clinical Trial, Phase III • Clinical Trial, Phase IV • Comparative Study • Controlled Clinical Trial • Corrected and Republished Article • Evaluation Studies • Guideline • Journal Article • Meta-Analysis • Multicenter Study • Practice Guideline • Published Erratum • Randomized Controlled Trial • Review • Scientific Integrity Review • Technical Report • Twin Study • Validation Studies CINAHL Publication Types: • Clinical Trial • Corrected Article • Journal Article			

Method	Search	Search String for: CINAHL	Search String for: MEDLINE
• Meta-Analysis • Meta Synthesis • Practice Guidelines • Randomized Controlled Trial • Research Review • Systematic Review			

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