Effectiveness of Interventions to Reduce Potentially Inappropriate Medication in Older Patients: A Systematic Review

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Background: Age-related multiple comorbidities cause older adults to be prone to the use of potentially inappropriate medicines (PIM) resulting in an increased risk of adverse events. Several strategies have emerged to support PIM prescription, and a huge number of interventions to reduce PIM have been proposed. This work aims to analyze the effectiveness of PIM interventions directed to older adults.

Methods: A systematic review was performed searching the literature in the MEDLINE PubMed, EMBASE, and Cochrane scientific databases for interventional studies that assessed the PIM interventions in older adults (≥65 years).

Results: Forty-seven articles were included, involving 52 to 124,802 patients. Various types of interventions were analyzed such as medication review, educational strategies, clinical decision support system, and organizational and multifaceted approaches. In the hospital, the most successful intervention was medication review (75.0%), while in primary care, the analysis of all included studies revealed that educational strategies were the most effective. However, the analysis of interventions that have greater evidence by its design was inconclusive.

Conclusion: The results obtained in this work suggested that PIM-setting-directed interventions should be developed to promote the wellbeing of the patients through PIM reduction. Although the data obtained suggested that medication review was the most assertive strategy to decrease the number of PIM in the hospital setting, more studies are necessary.

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Keywords: review, potentially inappropriate medication, interventions, effectiveness, older adults
1 INTRODUCTION

The increase in life expectancy associated with a declined birth rate contributed to rapid population aging (United Nations, 2019). Even though the world population is getting older, aging populations differ by region and level of development (Beard et al., 2016). Globally, it is estimated that in 2050 the number of older adults will reach 1.5 billion and will outnumber adolescents and youth aged 15–24 years (1.3 billion) (United Nations, 2019).

Considering that more than half of older adults have at least two chronic diseases (Barnett et al., 2012), these societal transformations pose a significant challenge in health systems and increase the consumption of health resources, including medicines. In addition, the treatment of chronic diseases is based on single disease-centered guidelines that can lead to an overwhelming of medication, and polypharmacy can easily occur (Barnett et al., 2012). Age-related pharmacokinetic and pharmacodynamic alterations associated with the use of multiple medicines can potentiate the consumption of potentially inappropriate medications (PIM) and facilitate the occurrence of adverse drug reactions (ADR) in frail older adults (Motter et al., 2018; Hefner et al., 2021).

PIM is defined as medicines that should not be prescribed because the risk of adverse events outweighs the clinical benefit, especially when more effective alternatives are available (Renom-Guiñeras et al., 2015). The prescription of PIM has received special attention from the health community, and interventions aim to optimize medication prescribing and increase the benefit/risk ratio associated with the patients (Anderson et al., 1997; Simonson and Feinberg, 2005). In the last decades, several studies have been done to evaluate the effectiveness of PIM interventions in primary care, such as in hospitals and nursing homes. Nevertheless, the studies display widely differing methodology and inconsistent results, and to our knowledge, there are no systematic reviews comparing the effectiveness of different kinds of interventions.

Thus, this study aims to critically review the effectiveness of interventions to reduce PIM prescriptions in older adults.

2 METHODS

This systematic review followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 guidelines (Page et al., 2021) (Supplementary Table S1). The research protocol is registered on PROSPERO (CRD42021233484).

2.1 Search Strategy

A literature search was conducted in January 2021 and updated in February 2021 on the MEDLINE PubMed, EMBASE. A search was also conducted in the Cochrane database in October 2021. The search strategy was designed to identify relevant studies addressing interventions on PIM prescriptions in older adults, using the following broad-based search terms strategy: “(elderly OR “elderly patient” OR “older patient” OR “older adult” OR “geriatric patient””) AND (PIM OR PIP OR “potentially inappropriate medicine” OR “potentially inappropriate medication” OR “potentially inappropriate prescribing” OR “prescribing patterns” OR “Prescription Drug Misuse” OR “Prescription Drug Overuse” OR “deprescribe” OR “potentially inappropriate prescription””) AND (prevention OR reduction OR decrease OR impact) AND (intervention OR trial).”

2.2 Selection Criteria

This systematic review included the following: 1) all studies focused on PIM interventions directed to older adults (≥65 years) that aimed to optimize their pharmacotherapy; 2) controlled intervention studies and case series studies; and 3) all studies published in Portuguese, English, or Spanish between January 1, 2000, and December 31, 2020.

Excluded from this work were reviews, meta-analyses, opinions, letters to the editor that do not provide original data, comments, reports, studies addressing PIM in a specific pathology, and studies targeting a limited and predefined class of PIM.

2.3 Outcomes Measures

Our primary outcome measure was the effectiveness of the PIM interventions through the analysis of the change rate between the mean number of PIM per patient and/or the mean number of patients with PIM before and after an intervention.

2.4 Data Extraction

Two researchers (AP and DR) independently screened all titles and abstracts retrieved from the databases accordingly with the inclusion criteria. To evaluate the eligibility of full-text articles, two researchers (AP and DR) independently screened the full text of the articles. All discrepancies were resolved through discussion with the help of a third researcher (FR).

2.5 Quality Assessment

Two researchers (AP and DR) independently evaluated the quality and susceptibility to the bias of the included studies using the “Quality Assessment of Controlled Intervention Studies” and the “Quality Assessment Tool for Case Series Studies” tools, depending on study design (National Heart Laboratory, 2013). All discrepancies were resolved through discussion with a third (FR) or fourth researcher (MH).

2.6 Data Synthesis and Presentation

Two researchers (AP and DR) independently extracted data from the included studies. The data extracted from each article include authors, publication year, study design, country, sample size, patients’ age, type of intervention applied, PIM screening tool, outcome measures, and main results.

To better analyze the extracted data, studies were grouped according to the intervention used. Within the intervention used, studies were grouped according to the setting where the intervention occurs. Five different interventions were identified in the included studies, and their descriptions were based on the following pre-defined definitions: 1) Medication review: “a structured evaluation of a patient’s medicines to optimize
medicines use and improve health outcomes. This entails detecting drug-related problems and recommending interventions” (Griese-Mammen et al., 2018); 2) educational interventions: “a package of interventions aimed to refresh the basic pharmacology competencies of a healthcare professional to change the prescription. The approaches used in the educational interventions included: interactive teaching, mailed educational material combined with individual feedback, and face-to-face visits to physicians” (Kaur et al., 2009); 3) clinical decision support systems (CDSS): “electronic tools that prompt provider behaviors in various areas of patient care, including medication ordering, chronic disease management, health care screening, and vaccination. CDSS can provide physicians, nurses, pharmacists, and other care providers with patient-specific prompts or warnings, treatment guidelines (e.g., order sets), automatic medication dosing calculators, or reports of overdue tests and medications as appropriate” (Bhugra and Cutter, 2001); 4) multifaceted interventions: “any intervention including two or more components.” In this study we classified as a multifaceted approach studies that used a combination of the interventions described above (Squires et al., 2014); and 4) organizational strategies: a combination of methodologies to improve the quality indicators. This type of intervention can include several methodologies, such as diagnostic activity, team building, intergroup relationship, sensitivity training, etc. In this work, organizational strategies include showing charts with the percentage of patients with PIM, an educational session with practices to identify patients with PIM, and frequent reunions to evaluate PIM indicators (Cady and Kim, 2017).

2.7 Statistical Analysis
A qualitative analysis was done if at least two studies had comparable outcomes. The heterogeneity of the studies was
assessed through the comparison between the interventions. The efficacy of the interventions was presented as a change rate between the mean number of PIM per patient and/or the mean number of patients with PIM before and after an intervention.

3 RESULTS

3.1 Study Selection

The search of the databases yielded 3,406 citations (Figure 1). After screening titles and abstracts, 98 articles potentially met the inclusion criteria. Because seven articles were not retrieved, only 91 articles were fully screened. Among these, 42 were excluded because they did not address interventions (n = 6), did not report PIM specific outcomes (n = 15), addressed PIM in patient-specific diseases (n = 4), addressed a pre-selected and/or a limited number of medicines (n = 14), and did not address older patients (≥65 years old) (n = 5) (Supplementary Table S2).

Forty-seven articles (Allard et al., 2001; Brown and Earnhart, 2004; Fick et al., 2004; Spinewine et al., 2007; Wessell et al., 2008; Castelino et al., 2010; Lampela et al., 2010; Gallagher et al., 2011; Keith et al., 2013; Rognstad et al., 2013; Dalleur et al., 2014; Franchi et al., 2014, 2016; Frankenthal et al., 2014; Lopatto et al., 2014; Clyne et al., 2015, 2016; Ilić et al., 2015; Tallon et al., 2015; Campins et al., 2016; Moss et al., 2016; Urfer et al., 2016; Frankenthal et al., 2017; Price et al., 2017; Stevens et al., 2017; Van der Linden et al., 2017; Vanderman et al., 2017; Chan et al., 2018; Etxeberria et al., 2018; Fajreldines et al., 2018; Gibert et al., 2018; Hurmuz et al., 2018; Najjar et al., 2018; Sennesael et al., 2018; Vandenberg et al., 2018; Gutiérrez-Valencia et al., 2019; Liu et al., 2019; McDonald et al., 2019; Moss et al., 2019; Regueiro et al., 2019; Vu and Huong, 2019; Akkawi et al., 2020; Winata et al., 2020) and primary care (n = 18) (Allard et al., 2001; Fick et al., 2004; Wessell et al., 2008; Castelino et al., 2010; Lampela et al., 2010; Keith et al., 2013; Rognstad et al., 2013; Lopatto et al., 2014; Clyne et al., 2015; Campins et al., 2016; Price et al., 2017; Etxeberria et al., 2018; Gibert et al., 2018; Hurmuz et al., 2018; Stuckey et al., 2018; Boersma et al., 2019; Khera et al., 2019). The number of participants in the studies ranged from 52 to 124,802. In the included studies, the average age of the participants ranged from 71 to 88.4 years. However, 12 studies did not report an average age of patients, although all of these studies provided an age range: 10 studies included older adults aged ≥65 years (Fick et al., 2004; Wessell et al., 2008; Moss et al., 2016; Frankenthal et al., 2017; Price et al., 2017; Stevens et al., 2017; Najjar et al., 2018; Vandenberg et al., 2018; Moss et al., 2019; Vu and Huong, 2019), one study included patients aged ≥70 years (Rognstad et al., 2013), and one study included patients aged ≥75 years (Lampela et al., 2010).

3.2 Characteristics of Included Studies

A description of the characteristics of the included studies is presented in Table 1. Among the included studies, 24 were conducted in Europe (Spinewine et al., 2007; Lampela et al., 2010; Gallagher et al., 2011; Keith et al., 2013; Rognstad et al., 2013; Dalleur et al., 2014; Franchi et al., 2014; Lopatto et al., 2014; Clyne et al., 2015; Ilić et al., 2015; Tallon et al., 2015; Campins et al., 2016; Clyne et al., 2016; Urfer et al., 2016; Van der Linden et al., 2017; Etxeberria et al., 2018; Gibert et al., 2018; Hurmuz et al., 2018; Sennesael et al., 2018; Van der Linden et al., 2018; Vanderman et al., 2018; Khera et al., 2019) and five in Asia (Frankenthal et al., 2014, 2017; Najjar et al., 2018; Liu et al., 2019; Vu and Huong, 2019; Akkawi et al., 2020), two in Oceania (Castelino et al., 2010; Winata et al., 2020), and one in South America (Fajreldines et al., 2018). The most frequent settings of the included studies were hospital (n = 26) (Brown and Earnhart, 2004; Spinewine et al., 2007; Gallagher et al., 2011; Dalleur et al., 2014; Franchi et al., 2014; Tallon et al., 2015; Franchi et al., 2016; Moss et al., 2016; Urfer et al., 2016; Stevens et al., 2017; Van der Linden et al., 2017; Vanderman et al., 2017; Chan et al., 2018; Fajreldines et al., 2018; Najjar et al., 2018; Sennesael et al., 2018; Van Der Linden et al., 2018; Vandenberg et al., 2018; Gutiérrez-Valencia et al., 2019; Liu et al., 2019; McDonald et al., 2019; Moss et al., 2019; Regueiro et al., 2019; Vu and Huong, 2019; Akkawi et al., 2020; Winata et al., 2020) and primary care (n = 18) (Allard et al., 2001; Fick et al., 2004; Wessell et al., 2008; Castelino et al., 2010; Lampela et al., 2010; Keith et al., 2013; Rognstad et al., 2013; Lopatto et al., 2014; Clyne et al., 2015; Campins et al., 2016; Price et al., 2017; Etxeberria et al., 2018; Gibert et al., 2018; Hurmuz et al., 2018; Stuckey et al., 2018; Boersma et al., 2019; Khera et al., 2019). The number of participants in the studies ranged from 52 to 124,802. In the included studies, the average age of the participants ranged from 71 to 88.4 years. However, 12 studies did not report an average age of patients, although all of these studies provided an age range: 10 studies included older adults aged ≥65 years (Fick et al., 2004; Wessell et al., 2008; Moss et al., 2016; Frankenthal et al., 2017; Price et al., 2017; Stevens et al., 2017; Najjar et al., 2018; Vandenberg et al., 2018; Moss et al., 2019; Vu and Huong, 2019), one study included patients aged ≥70 years (Rognstad et al., 2013), and one study included patients aged ≥75 years (Lampela et al., 2010).

3.3 Quality of Included Studies

The quality assessment tools results of each study are reported in Table 2. Twenty-five articles fulfilled more than 80% of the exploratory questions (Castelino et al., 2010; Gallagher et al., 2011; Rognstad et al., 2013; Frankenthal et al., 2014; Lopatto et al., 2014; Clyne et al., 2015, 2016; Campins et al., 2016; Price et al., 2017; Stevens et al., 2017; Vanderman et al., 2017; Chan et al., 2018; Etxeberria et al., 2018; Fajreldines et al., 2018; Gibert et al., 2018; Hurmuz et al., 2018; Sennesael et al., 2018; Gutiérrez-Valencia et al., 2019; Khera et al., 2019; Liu et al., 2019; Moss et al., 2019; Regueiro et al., 2019; Vu and Huong, 2019; Akkawi et al., 2020; Winata et al., 2020). Eighteen studies pointed out clearly potential sources of bias (Brown and Earnhart, 2004; Fick et al., 2004; Spinewine et al., 2007; Wessell et al., 2008; Lampela et al., 2010; Rognstad et al., 2013; Campins et al., 2016; Franchi et al., 2016; Urfer et al., 2016; Frankenthal et al., 2017; Price et al., 2017; Van der Linden et al., 2017; Etxeberria et al., 2018; Gibert et al., 2018; Boersma et al., 2019; Gutiérrez-Valencia et al., 2019; Khera et al., 2019; Moss et al., 2019). Through analysis of Table 2, the main limitations were related to the low sample size and the lack of blinded intervention. Besides that, most of the studies did not do or report follow-up results, so it is not possible to understand if the interventions were effective in the middle/long-term.

3.4 Evidence of Effectiveness

3.4.1 PIM Screening Tools

Thirty-seven studies used validated and published criteria to identify PIM, including Beers criteria (n = 16) (Brown and
| Author (year) | Country | Study design | Setting | Elderly patients’ sample | Comparator | Quality assessment/ (score obtained/total score) |
|---------------|---------|--------------|---------|--------------------------|-----------|---------------------------------------------|
| Akkawi et al. (2020) | Malaysia | Case series | Hospital | B: 240 A: 240 | Baseline | 8/9a |
| Winata et al. (2020) | Australia | Case series | Hospital (aged care wards) | B: 121 A: 107 | Baseline | 8/9a |
| Boersma et al. (2019) | Netherlands | RCT | Geriatric clinic (outpatients) | C: 59 I: 65 | Usual care | 10/14b |
| Gutiérrez-Valencia et al. (2019) | Spain | Prospective study | Tertiary public hospital (acute geriatric unit) | 234 | Baseline | 8/9a |
| Khera et al. (2019) | Canada | Quasi-experimental pretest-posttest | Primary care (community-dwelling patients) | 54 | Before medication review | 8/9a |
| Liu et al. (2019) | Taiwan | Interventional | Tertiary medical center (emergency department) | B: 243 A: 668 | Before implementation of the intervention | 8/9a |
| McDonald et al. (2019) | Canada | Non-randomized controlled before and after study | Medical clinical teaching units (internal medicine department) | C: 383 I: 417 | Usual care | 8/14b |
| Moss et al. (2019) | United States | Case series | Veteran Affairs Medical Center (emergency department) | C: 2,500 I: 3,162 | Untrained cohort | 8/9a |
| Regueiro et al. (2019) | Spain | Quasi-experimental pre-post | University hospital (internal medicine department) | 174 | Before implementation of the intervention | 8/9a |
| Vu and Huong (2019) | Vietnam | Case series | General hospital (endocrinology, cardiology, and neurology departments) | B: 211 A: 208 | Baseline | 8/9a |
| Chan et al. (2018) | Canada | Retrospective single-center pre-post cohort study | Tertiary hospital (acute care unit) | B: 70 A: 67 | Before implementation of the intervention | 7/9a |
| Etxeberria et al. (2018) | Spain | Case series | Primary health care | 503 | Before implementation of the intervention | 7/9a |
| Fajrelíes et al. (2018) | Argentina | Case series | Hospital | B: 640 A: 622 | Before implementation of the intervention | 8/9a |
| Humuz et al. (2018) | Netherlands | Retrospective longitudinal pretest vs. posttest design | Community pharmacy | 126 | Before implementation of the intervention | 8/9a |
| Najjar et al. (2018) | Saudi Arabia | Prospective pretest vs. posttest design | Hospital | B: 200 A: 200 | Baseline | 6/9a |
| Gibert et al. (2018) | France | — | Primary care | 172 | Before implementation of the intervention | 8/9a |
| Sennesael et al. (2018) | Belgium | Retrospective interrupted time series study | Teaching hospital (geriatric unit) | 120 | Standard geriatric care | 7/9a |
| Stuckey et al. (2018) | United States | Prospective quality improvement project | Family medicine clinic (residency training outpatients) | 34 | Before implementation of the intervention | 5/9a |
| Vandenberg et al. (2018) | United States | Quality improvement program | Veteran Affairs Medical Center (community-based outpatient clinic) | >7,000 | Before implementation of the intervention | 3/14b |
| Van Der Linden et al. (2018) | Belgium | Case series | Teaching hospital | B: 29 A: 30 | Usual care | 8/14b |
| Frankenthal et al. (2017) | Israel | RCT | Chronic care geriatric facility | C: 126 I: 126 | Usual care | 7/14b |
| Price et al. (2017) | Canada | RCT | Primary care | C: 1,086 I: 1,204 | Baseline rate | 11/14b |

(Continued on following page)
| Author (year)         | Country       | Study design                  | Setting                                                   | Elderly patients’ sample | Comparator | Quality assessment/ (score obtained/total score) |
|----------------------|---------------|-------------------------------|-----------------------------------------------------------|--------------------------|------------|-----------------------------------------------|
|                      |               |                               |                                                           |                          |            |                                               |
| Stevens et al. (2017)| United States | —                             | Veteran Affairs Medical Center (emergency department)     | B: 1,539                 | Usual care | 7/9a                                          |
| Vanderman et al. (2017) | United States | Retrospective cohort study    | Veteran Affairs Medical Center (ambulatory clinics)       | A: 1,490                 |             |                                               |
| Van der Linden et al. (2017) | Belgium | Prospective controlled trial | Hospital (acute geriatric ward)                          | C: 81                    | Usual care | 8/14b                                         |
| Campins et al. (2016) | Spain         | RCT                           | Primary Health care center                                | C: 251                   | Routine clinical practice                      | 12/14b                                         |
| Clyne et al. (2016)  | Ireland       | RCT                           | Primary care                                              | C: 97                    | Usual care | 11/14b                                         |
| Franchi et al. (2016) | Italy         | RCT                           | Hospital (internal medicine and geriatric wards)         | C: 350                   | Baseline   | 9/14b                                          |
| Moss et al. (2016)   | United States | —                             | Veteran Affairs Medical Center (emergency department)     | 23,168                   |             |                                               |
| Urfer et al. (2016)  | Switzerland   | Case series                   | Hospital (internal medicine ward)                       | C: 450                   | Patients hospitalized in some division         | 8/14b                                          |
| Clyne et al. (2015)  | Ireland       | RCT                           | Primary care                                              | C: 97                    | Usual care | 13/14b                                         |
| Ilić et al. (2015)   | Serbia        | Case series                   | Nursing homes                                             | 104                      | Before implementation of the intervention     | 7/9b                                           |
| Talon et al. (2015)  | Ireland       | Case series                   | Teaching hospital                                         | B: 60                    | Standard care |                                               |
| Dalleur et al. (2014) | Belgium      | RCT                           | Teaching hospital                                         | C: 72                    |             |                                               |
| Franchi et al. (2014) | Italy         | RCT                           | Hospital (internal medicine ward)                       | Admission C: 41; I: 40   | Only the basic notions of pharmacology        | 9/14b                                          |
|                      |               |                               |                                                           | Admission Discharge C: 33; I: 37 |             |                                               |
|                      |               |                               |                                                           |                          |            |                                               |
| Frankenthal et al. (2014) | Israel     | RCT                           | Chronic care geriatric facility                           | C: 176                   | Usual care | 12/14b                                         |
| Lopatto et al. (2014) | Italy         | —                             | Health authority database                                 |                          |             |                                               |
| Keith et al. (2013)  | Italy         | Multi-phase prospective       | Parma local health authority database                     | C: 81,597                | Region local health authority database        | 6/14b                                          |
| Rognstad et al. (2013) | Norway       | RCT                           | General practice                                          | Control group B: 35,073; After: 35,211 | Baseline data |                                               |
| Gallagher et al. (2011) | Ireland     | RCT                           | Hospital (emergency department)                           | C: 192                   | Usual care | 13/14b                                         |
| Castelino et al. (2010) | Australia   | Retrospective                 | Primary care                                              |                          |             |                                               |
| Lampela et al. (2010) | Finland      | RCT                           | Primary care                                              |                          | Before implementation of the intervention     | 7/9b                                           |
| Wesell et al. (2008) | United States | Prospective                   | Primary care                                              |                          | Standard care |                                               |
| Spinewine et al. (2007) | Belgium     | RCT                           | Teaching hospital                                         |                          |             |                                               |

(Continued on following page)
TABLE 1 | Characteristics of the included studies (n = 47).

| Author (year) | Country     | Study design               | Setting         | Elderly patients' sample | Comparator | Quality assessment/ (score obtained/total score) |
|---------------|-------------|----------------------------|-----------------|--------------------------|------------|-----------------------------------------------|
| Brown and Earnhart (2004) | United States | Retrospective, case series | Teaching hospital | 99 | 77.3 | — | 5/9<sup>a</sup> |
| Fick et al. (2004) | United States | RCT | Primary care | C: 185 | ≥65 | Usual care | 6/14<sup>b</sup> |
| Allard et al. (2001) | Canada | RCT | Primary care | C: 130 | I: 136 | C: 80.7 (4.6) | 10/14<sup>b</sup> |

A, after; B, before; C, control group; I, intervention group; IQR, interquartile range; RCT, randomized controlled trial; SD, standard deviation.

<sup>a</sup>The National Institutes of Health (NIH) quality assessment tool for case series studies.

<sup>b</sup>The National Institutes of Health (NIH) quality assessment tool of controlled intervention study.

TABLE 2 | Quality assessment of included studies through the National Institutes of Health (NIH) quality assessment tools.

| Quality assessment of controlled intervention studies |
|-------------------------------------------------------|
| No | Question | Number of studies (n = 22) |
|----|----------|----------------------------|
| 1  | Was the study described as randomized, a randomized trial, a randomized clinical trial, or an RCT? | 16 | 6 | 0 |
| 2  | Was the method of randomization adequate (i.e., use of randomly generated assignment)? | 11 | 2 | 9 |
| 3  | Was the treatment allocation concealed (so that assignments could not be predicted)? | 10 | 3 | 9 |
| 4  | Were study participants and providers blinded to treatment group assignment? | 6 | 11 | 5 |
| 5  | Were the people assessing the outcomes blinded to the participants’ group assignments? | 8 | 8 | 6 |
| 6  | Were the groups similar at baseline on important characteristics that could affect outcomes (e.g., demographics, risk factors, co-morbid conditions)? | 19 | 2 | 1 |
| 7  | Was the overall drop-out rate from the study at endpoint 20% or lower of the number allocated to treatment? | 13 | 9 | 0 |
| 8  | Was the differential drop-out rate (between treatment groups) at endpoint 15 percentage points or lower? | 19 | 1 | 2 |
| 9  | Were other interventions avoided or similar in the groups (e.g., similar background treatments)? | 22 | 0 | 0 |
| 10 | Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants? | 22 | 0 | 0 |
| 11 | Did the authors report that the sample size was sufficiently large to be able to detect a difference in the main outcome between groups with at least 80% power? | 12 | 4 | 6 |
| 12 | Were outcomes reported or subgroups analyzed prespecified (i.e., identified before analyses were conducted)? | 13 | 2 | 7 |
| 13 | Were all randomized participants analyzed in the group to which they were originally assigned, i.e., did they use an intention-to-treat analysis? | 9 | 0 | 13 |

| Quality assessment tool for case series studies |
|------------------------------------------------|
| No | Question | Number of Studies (n = 25) |
|----|----------|----------------------------|
| 1  | Was the study question or objective clearly stated? | 25 | 0 | 0 |
| 2  | Was the study population clearly and fully described, including a case definition? | 24 | 0 | 1 |
| 3  | Were the cases consecutive? | 4 | 6 | 15 |
| 4  | Were the subjects comparable? | 25 | 0 | 0 |
| 5  | Was the intervention clearly described? | 22 | 3 | 0 |
| 6  | Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants? | 22 | 3 | 0 |
| 7  | Was the length of follow-up adequate? | 4 | 0 | 21 |
| 8  | Were the statistical methods described well? | 21 | 4 | 0 |
| 9  | Were the results described well? | 24 | 1 | 0 |
TABLE 3 | Effects of medication review interventions on inappropriate prescribing in older adults (n = 23).

| Author (year) | Performed by | PIM screening tool | Strategies used | Outcome measures | Significant outcomes |
|--------------|--------------|--------------------|----------------|-----------------|---------------------|
| Gutierrez-Valencia et al. (2019) | Pharm | STOPP criteria version 2 | Pharmacist-led medicine optimization strategy | Difference in the number of patients with STOPP criteria and mean number of STOPP criteria per patient, before and after intervention | Patients with STOPP criteria per patient (total sample) (SD): B: 1.8 (1.4) vs. A: 1.1 (1.2), *p* < 0.001 |
| Khera et al. (2019) | Pharm | 2015 Beers and version 2 of STOPP criteria | Pharmacist-led medication review | Number of medications satisfying explicit criteria of STOPP/Beers for PIM | Mean number of medications from STOPP/Beers criteria per patient (total sample) (SD): B: 1.15 (1.2) vs. A: 0.9 (1.1), *p* = 0.006 |
| Regueiro et al. (2019) | Investigator | Beers 2012 and STOPP 2008 | PIM notification program | Number of PIM that patients were taking at the time of admission and discharge | Not achieved |
| Chan et al. (2018) | Pharm | 2015 Beers criteria | Collaborative medication reviews through a standardized template | Identification of PIM by the pharmacist before (on the admission and discharge) and after (admission and discharge) intervention | Patients with PIM on admission B: 48.9% vs. A: 47.4% (SD = 16.7%) |
| Fajreldines et al. (2018) | Pharm | STOPP criteria (2008) | Lectures and publications on STOPP criteria and suggestions made by clinical pharmacist to the physician on each individual prescription | Number of PIM and appropriateness of prescribed medicines | Average number of PIM was initially 0.6 (SD = 0.8) per patient and decreased to 0.4, after the intervention (SD = 0.6, *p* < 0.05) |
| Humuz et al. (2018) | Pharm, Phys | STOPP criteria (version 2) | Medication reviews were initiated by the pharmacist and further carried out in close cooperation with the corresponding general practitioner | Proportion of patients with ≥1 PIM | Not achieved |
| Sennesael et al. (2018) | Pharm | Short version of STOPP criteria (version 2) | Implementation of a screening tool in routine geriatric practice | Proportion of patients with ≥1 PIM | Not achieved |
| Stuckey et al. (2018) | Pharm, Phys | Beers criteria | Distribution of materials, multidisciplinary discussions, and computerized system | Total high-risk medications based on the Beers list | Total high-risk medications B: 42 vs. A: 28, *p* = 0.0005 |
| Van Der Linden et al. (2018) | Investigators | RASP list | Systematic medication review | Number of RASP identified PIM at discharge; number of discontinued RASP PIM during hospital stay | Average number of RASP PIM at discharge (IQR): B: 2.5 (2.0–3.8) vs. A: 1 (0.0–3.0), *p* = 0.008 |
| Frankenthal et al. (2017) | Study pharm | 2008 STOPP criteria | Review of the medications by the study pharmacist | PIM proportion; number of residents with at least 1 PIM according to the STOPP criteria after 24 months | Mean number of discontinued RASP PIM during hospital stay (SD): B: 0.79 (1.34) vs. A: 2.28 (1.62), *p* < 0.001 |
| Van der Linden et al. (2017) | Pharm | RASP list | Pharmacist-led medication review and recommendations reported to the treating physician daily | Number of RASP PIM, proportion of discontinued or reduced drugs that was identified by the RASP list | Average number of discontinued or reduced drugs identified by the RASP list (IQR): C: 0 (1–2) vs. I: 2 (1–4), *p* = 0.003 |
| Campins et al. (2016) | Pharm | STOPP criteria (version 2) | A pharmacist evaluated all drugs prescribed to each patient and discussed recommendations for each drug with the patient’s physician and then with the pharmacist | Proportion of prescriptions rated as PIM; rate of acceptance by physicians | Not achieved |

(Continued on following page)
| Author (year)          | Performed by | PIM screening tool | Strategies used                                                                 | Outcome measures                                                                 | Significant outcomes                                                                 |
|-----------------------|--------------|--------------------|----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|
| Tallon et al. (2015)  | Pharm        | MAI                | Collaborative PACT model on the medication appropriateness of acute hospitalized older patients | Appropriateness of prescribing at pre-admission, during admission, and at discharge | PACT significantly improved the MAI score from pre-admission to admission (mean difference 2.4, 95% CI 1.0 to 3.9, \( p < 0.005 \)) and from pre-admission to discharge (mean difference 4.0, 95% CI 1.7 to 6.4, \( p < 0.005 \)) | Inappropriate prescribing at discharge (PACT 15.0%, standard 30.5%, \( p < 0.001 \)) |
| Daileur et al. (2014) | Ger          | STOPP criteria (2008) | STOPP criteria recommendations from an inpatient geriatric consultation team (IGCT) | Proportion of PIM discontinued | Discontinuation at discharge of PIM present on admission C: 19.3% vs. I: 39.7%, \( p = 0.013 \) |
| Frankenthal et al. (2014) | Study pham | STOPP criteria (2008) | Medication review for all residents at study opening and 6 and 12 months later based on STOPP criteria | Number of PIM over time | Number of PIM at baseline C: 114 (64.7%) vs. I: 129 (70.5%) \( p = 0.001 \) Number of PIM after 6-month follow-up C: 89 (56%) vs. I: 65 (37.4%), \( p = 0.001 \) Number of PIM after 12-month follow up C: 79 (54.1%) vs. I: 36 (22.5%), \( p < 0.001 \) |
| Lopatto et al. (2014) | Phys         | Maio criteria      | Participatory clinical guidelines development, group educational outreach, and dissemination of educational materials combined with peer-to-peer interactive discussion | PIM incidence rate | Not achieved |
| Keith et al. (2013)   | Phys         | Maio criteria      | Participatory clinical guidelines development, group educational outreach, and dissemination of educational materials combined with peer-to-peer interactive discussion | Quarterly incidence rates of older patients exposed to PIM | Patients exposed to at least 1 PIM 2007 C: 6,315 (7.7%) vs. I: 6,098 (7.7%) 2009 C: 5,111 (6.1%) vs. I: 4,277 (5.3%) \( p < 0.001 \) |
| Gallagher et al. (2011) | Phys       | 2008 STOPP criteria | STOPP screening and recommendations to the attending medical team | Patients with \( \geq 1 \) STOPP criteria at discharge | Patients with \( \geq 1 \) STOPP criteria at discharge C: 93 (48.4%); I: 7 (3.7%), \( p < 0.001 \) |
| Castelino et al. (2010) | Pharm       | 2003 Beers criteria | Home Medicine Review (HMR) service | Rate of PIM | Not achieved |
| Lampela et al. (2010) | Phys, N. physiotherapist, nutritionist | 1997 Beers criteria (US 2000 update) | Adjustment of a patient’s medication when necessary; evaluation of the indications for all drugs in use; clinical examination, including careful evaluation of cognition, mood, orthostatic reactions, and presence of extrapyramidal symptoms; routine blood tests | Numbers of inappropriate drugs or dosages | Not achieved |
| Spinewine et al. (2007) | Pharm       | MAI, Beers (1997), and ACOVE criteria | The appropriateness of treatment was analyzed, and a pharmaceutical care plan was | Appropriateness of prescribing at admission, discharge, and | Intervention patients significantly more likely than control patients to have (Continued on following page) |
(STOPP) criteria ($n = 15$) (Gallagher et al., 2011; Dalleur et al., 2014; Frankenental et al., 2014; Campins et al., 2016; Urfer et al., 2016; Frankenental et al., 2017; Price et al., 2017; Fajredines et al., 2018; Gibert et al., 2018; Hurmuz et al., 2018; Sennesael et al., 2018; Boersma et al., 2019; Gutiérrez-Valencia et al., 2019; Akkawi et al., 2020; Winata et al., 2020), a combination of Beers and STOPP criteria ($n = 5$) (Illic et al., 2015; Etxeberria et al., 2018; Najjar et al., 2018; Khera et al., 2019; Regueiro et al., 2019), and Medication Appropriateness Index (MAI) ($n = 1$) (Tallon et al., 2015). Five studies used self-developed or adapted criteria (Allard et al., 2001; Keith et al., 2013; Lopatto et al., 2014; Van der Linden et al., 2017; Van Der Linden et al., 2018), and the remaining studies used a combination of validated (STOPP and/or Beers) and self-developed or adapted criteria.

### 3.4.2 Interventions Used

After thorough analysis of the studies, five different types of interventions have emerged: medication review, educational interventions, CDSS, multifaceted approaches, and organizational strategies (Tables 3–7, respectively). Twenty-three studies used a medication review approach (Allard et al., 2001; Brown and Earnhart, 2004; Spinewine et al., 2007; Castelino et al., 2010; Lampela et al., 2010; Gallagher et al., 2011; Keith et al., 2013; Dalleur et al., 2014; Frankenental et al., 2014; Lopatto et al., 2014; Tallon et al., 2015; Campins et al., 2016; Frankenental et al., 2017; Van Der Linden et al., 2017; Chan et al., 2018; Fajredines et al., 2018; Hurmuz et al., 2018; Sennesael et al., 2018; Stuckey et al., 2018; Van Der Linden et al., 2018; Gutiérrez-Valencia et al., 2019; Khera et al., 2019; Regueiro et al., 2019), an educational intervention was the strategy used in eight studies (Fick et al., 2004; Rognstad et al., 2013; Franchi et al., 2014, 2016; Illic et al., 2015; Clyne et al., 2016; Etxeberria et al., 2018; Moss et al., 2019), multifaceted approach was present in nine (Clyne et al., 2016; Moss et al., 2016; Gibert et al., 2018; Najjar et al., 2018; Vandenberg et al., 2018; Boersma et al., 2019; Liu et al., 2019; Vu and Huong, 2019; Akkawi et al., 2020) (i.e., a combination of different interventions), five studies used a CDSS (Urfer et al., 2016; Price et al., 2017; Vanderman et al., 2017; McDonald et al., 2019; Winata et al., 2020), and two used organizational strategies (Wessell et al., 2008; Stevens et al., 2017) (i.e., regulatory policies developed to decrease the number of PIM).

### 3.4.3 Impact of Medication Review Interventions

Medication review was conducted by different healthcare professionals: physicians (Gallagher et al., 2011; Keith et al., 2013; Lopatto et al., 2014), pharmacists (Brown and Earnhart, 2004; Spinewine et al., 2007; Castelino et al., 2010; Frankenental et al., 2014; Tallon et al., 2015; Campins et al., 2016; Van der Linden et al., 2017; Chan et al., 2018; Fajredines et al., 2018; Sennesael et al., 2018; Gutiérrez-Valencia et al., 2019; Khera et al., 2019), pharmacists and physicians (Hurmuz et al., 2018; Stuckey et al., 2018), gerontologists (Dalleur et al., 2014), investigators (Van Der Linden et al., 2018; Regueiro et al., 2019), pharmacist students (Frankenthal et al., 2017), and multidisciplinary teams (Allard et al., 2001; Lampela et al., 2010). Although medication review intervention varies in the included studies, this intervention involved the analysis of the patient’s pharmacotherapeutic needs and prescribed drugs, followed by a recommendation to optimize medication.

Six (Brown and Earnhart, 2004; Spinewine et al., 2007; Tallon et al., 2015; Van der Linden et al., 2017; Fajredines et al., 2018; Gutiérrez-Valencia et al., 2019) of eight medication review interventions conducted by pharmacists at the hospital (Brown and Earnhart, 2004; Spinewine et al., 2007; Tallon et al., 2015; Van der Linden et al., 2017; Chan et al., 2018; Fajredines et al., 2018; Sennesael et al., 2018; Gutiérrez-Valencia et al., 2019) demonstrate a positive impact on PIM reduction. Among these, in two studies the intervention improved the PIM

### Table 3 (Continued) Effects of medication review interventions on inappropriate prescribing in older adults ($n = 23$).

| Author (year) | Performed by | PIM screening tool | Strategies used | Outcome measures | Significant outcomes |
|---------------|--------------|--------------------|-----------------|------------------|----------------------|
| Brown and Earnhart (2004) | Pharm | Beers criteria (1997) | prepared. Whenever an opportunity for optimization was identified, the pharmacist discussed that opportunity with the prescriber, who could accept or reject the intervention | 3 months after discharge using Beers’ criteria | Improvements in Beers’ criteria (OR 0.6 [95% CI 0.3, 1.1]) |
| Allard et al. (2001) | Pharm, N, Phys | List of PIM developed by the Quebec Committee on Drug Use in the Elderly | Acute Care for Elders (ACE) team improvement on the medication regime of geriatric inpatients | Prevalence of PIM | Rate of PIM at admission 10.1%, and discharge 2.02%, $p < 0.02$ Not achieved |

A, after group; B, before group; C, control group; CI, confidence interval; Ger, geriatrician; I, intervention group; IQR, interquartile range; MAI, Medication Appropriateness Index; N, nurse; Pharm, pharmacist; Phys, physician; PACT, pharmaceutical care at Tallaght Hospital; PIM, potentially inappropriate medication; RASP, Rationalization of Home Medication by an Adjusted STOPP list in Older Patient; SD, standard deviation; STOPP, Screening Tool of Older People’s potentially inappropriate Prescriptions; US, United States.

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screening tool score (Spinewine et al., 2007; Tallon et al., 2015). Fajreldines et al. (2018) and Gutiérrez-Valencia et al. (2019) reported that the number of patients with PIM significantly decreased after medication review (19.2% and 30.7%, respectively). Van der Linden et al. (2017) observed a decrease in the average number of PIM after an intervention. Finally, Brown and Earnhart (2004) conclude that their intervention led to an 8.08% absolute risk reduction. Among the studies performed by physicians in hospitals, one was conducted at an emergency department of a hospital (Gallagher

| TABLE 4 | Effects of educational interventions on inappropriate prescribing in older adults (n = 8). |
|---|---|---|---|---|---|---|
| Author (year) | Performed by | Receivers | PIM screening tool | Strategies used | Outcome measures | Significant outcomes |
| Moss et al. (2016) | Pharm, Phys | Medical residents | Table 2 of 2012 Beers criteria | Enhancing Quality of Prescribing Practices for Veterans Discharged from the Emergency Department (EQUIPPED) provider education through academic detailing, clinical decision support, and provider feedback on prescribing practices | Prescription rate ratio before and after the intervention | The group after the intervention were less likely to prescribe a PIM when compared to the group before the intervention (rate ratio = 0.73, 95% CI = 0.632–0.850; p < 0.0001) |
| Etxeberria et al. (2018) | Research team | Phys | STOPP and Beers criteria | Electronic identification of PIM, training for physicians and structured review of medication Academic detailing, review of medicines with web-based pharmaceutical treatment algorithms that provide recommended alternative-treatment options, and tailored patient information leaflets | Change in the number of PIM per patient | Number of PIM/patients (SD) B: 0.70 (0.91) vs. A: 0.51 (0.77), p < 0.0001 |
| Clyne et al. (2016) | Pharm | Phys (C: 10, l: 11) | Beers, STOPP, McLeod, IPET, ACOVE, and the Prescription Peer Academic Detailing (RxPAD) study—MRC framework | | | |
| Franchi et al. (2016) | Research team | Phys | 2012 Beers criteria | E-learning educational program | Reduction in the PIM prescriptions at hospital discharge (at least 1 PIM) | Not achieved |
| Ilić et al. (2015) | Investigator (Phys) | 27 Phys | 2012 Beers criteria and 2008 STOPP criteria | Lectures and brochures | Inappropriately prescribed drugs | Average number of PIM (Beers) (IQR) B: 11.0 (1.0–43.0) vs. A: 1.0 (1.0–2.0), p < 0.001 Average number of PIM (STOPP) (IQR) B: 3.5 (1.0–20.0) vs. A: 1.5 (0.0–6.0), p < 0.005 |
| Franchi et al. (2014) | Research Team | Phys (C: 22, l: 54) | 2012 Beers criteria | E-learning educational program Multifaceted educational intervention with feedback and audit | Reduction of prescription of PIM | Not achieved |
| Rognstad et al. (2013) | Research team | Phys (C: 209, l: 256) | 13 explicit PIM criteria, assumed to be relevant for the Norwegian general practice setting (based on Beers criteria and The Swedish National Board of Health and Welfare) | | | |
| Fick et al. (2004) | Research team | Phys (C: 185, l: 170) | 1997 Beers criteria for medications to avoid in older adults | Integrated decision support service: 1) a detailed educational brochure listing PIM, 2) a list of suggested PIM alternative medications, and 3) a personally addressed letter that described in detail all the physician's patients who were determined to be in receipt of 1 or more PIM | Rate of providers that prescribed at least 1 PIM | Number of continuously enrolled members with at least 1 PIM declined significantly ($\chi^2$ = 13.20, p < 0.001) to 17.9% (3,007/16,818), from a baseline of 19.4% (3,364/17,330) |

A, after group; B, before group; C, control group; I, intervention group; Pharm, pharmacist; Phys, physician; PIM, potentially inappropriate medication; SD, standard deviation; STOPP, Screening Tool of Older People’s potentially inappropriate Prescriptions.
et al., 2011), and the remaining two studies used the local health authority databases (Keith et al., 2013; Lopatto et al., 2014). Gallagher et al. (2011) observed a significant reduction in the proportion of patients with at least one PIM in the intervention group (from 43.2% in admission to 3.7%, at discharge). This trend remains stable during the 6 months of follow-up. One study performed a quality improvement program across an Italian region with more than 80,000 older adults and observed that the PIM exposure incidence rate significantly declined 31.4% (from the baseline to the post-intervention period) (Keith et al., 2013).

The intervention performed by a gerontologist in hospitalized patients results in a significant decrease in the number of PIM in patients discharged (PIM discontinuation of 39.7%) (Dalleur et al., 2014). Similar outcomes were achieved in the intervention performed by investigators in hospitalized patients (Van Der Linden et al., 2018).

In primary care, the medication review performed by both physicians and pharmacists results in a significant reduction in the mean number of PIM per patient [from 0.6 to 0.4 (Hurmuz et al., 2018) and from 1.24 to 0.82 (Stucyek et al., 2018)]. In this setting, a multidisciplinary team failed to achieve a significant reduction in the number of PIM, and only one (Khera et al., 2019) of the three pharmacists’ interventions (Castelino et al., 2010; Campins et al., 2016; Khera et al., 2019) results in a significant impact in PIM reduction.

Finally, in a chronic care geriatric facility, pharmacy students observed a decline in PIM prescriptions after a follow-up of 12 and 24 months (Frankenthal et al., 2014; Frankenthal et al., 2017).

### 3.4.4 Impact of Educational Interventions

In the eight included studies (Fick et al., 2004; Rognstad et al., 2013; Franchi et al., 2014, 2016; Ilić et al., 2015; Clyne et al., 2016; Etxeberria et al., 2018; Moss et al., 2019) that used educational approaches to reduce PIM, the interventions were performed by the following: a researcher and/or a research team (Fick et al., 2004; Franchi et al., 2014, 2016; Ilić et al., 2015; Etxeberria et al., 2018), a multifaceted team containing a pharmacist and a physician (Moss et al., 2019) or physicians (peer academic detailers) (Rognstad et al., 2013), or a pharmacist (Clyne et al., 2016). In all studies the target of the educational interventions were physicians. The outcomes of the interventions were measured through the reduction of PIM use or PIM prescriptions. In one of the studies, the included population was polymedicated older adults (Etxeberria et al., 2018); in the three studies that have a positive impact on PIM, the average number of PIM per patient ranged from 0.7–11 before intervention to 0.51–1.5 after the intervention (Ilić et al., 2015; Clyne et al., 2016; Etxeberria et al., 2018). One study reported that the number of physicians that prescribed at least one PIM declined 17.9% (Fick et al., 2004). Finally, one study reported that after the educational intervention the PIM rate ratio before and after the intervention is 0.73 (Moss et al., 2019).

### 3.4.5 Impact of Clinical Decision Support System Interventions

Five studies used CDSS to reduce PIM (Urfer et al., 2016; Price et al., 2017; Vanderman et al., 2017; McDonald et al., 2019; Winata et al., 2020). Two of four studies performed in hospitalized patients reported that the implementation of CDSS has a positive impact on PIM deprescription (Urfer et al., 2016; Vanderman et al., 2017). In one study, the introduction of a PIM checklist, in an internal medicine ward, leads to a significant reduction (22.0%) of the risk of

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**TABLE 5 | Effects of clinical decision support system (CDSS) interventions on inappropriate prescribing in older adults (n = 5).**

| Author (year) | PIM screening tool | Strategies used | Outcome measures | Significant outcomes |
|---------------|-------------------|-----------------|-----------------|---------------------|
| Winata et al. (2020) | STOPP version 2 | Introduction of an electronic medication management system (EMMS) | Number of PIM on admission and discharge per patient; number of patients with ≥1 PIM on admission and discharge | Not achieved |
| McDonald et al. (2019) | Beers and STOPP criteria (version 2), and Choosing Wisely lists | Electronic decision support tool that generates deprescribing opportunities | Proportion of patients with ≥1 or more home medications identified as a PIM and deprescribed at hospital discharge | Not achieved |
| Price et al. (2017) | STOPP criteria | Electronic medical record with automated STOPP rules | Change in measured PIM rates between the intervention and control groups before the intervention as compared with the difference after the intervention period | Not achieved |
| Vanderman et al. (2017) | Beers criteria | Medication alert message | Overall PIM, top 10 PIM, and flagged PIM | New top 10 PIM/new total medications |
| Urfer et al. (2016) | STOPP criteria | Easy-to-use 5-point checklist: 1) ascertain all current medications used; 2) identify patients at high risk of adverse drug reactions; 3) estimate life expectancy; 4) identify medications which are not indicated and/or are potentially dangerous; and 5) monitor the patient if drugs were stopped or new drugs were added | Proportion of patients prescribed PIM at discharge | Patients with >1 PIM at discharge |

**A, after group; B, before group; PIM, potentially inappropriate medication; STOPP, Screening Tool of Older People’s potentially inappropriate Prescriptions.**
### TABLE 6 | Effects of multifaceted interventions on inappropriate prescribing in older adults (n = 9).

| Author (year) | Educational CDSS | Medication review | PIM screening tool | Strategies used | Outcome measures | Significant outcomes |
|---------------|------------------|------------------|-------------------|----------------|----------------|---------------------|
| Akkawi et al. (2020) | Not reported | Phys, Pharm | X | STOPP version 2 | PIM prevalence | Not achieved |
| Boersma et al. (2019) | X | Phys | STOPP version 1 | The intervention consisted of written prescribing recommendations prepared by an independent, clinically experienced research physician using the STRIP Assistant | PIM changes implementation | C: 15.3% vs. I: 46.2% (p < 0.001) |
| Liu et al. (2019) | X | Pharm, Phys | Modified and updated 2015 Beers criteria according to common practice and culture in Taiwan | Creation of a multidisciplinary Chi-Mei Integrated Geriatric Emergency Team; creation of a PIM list; computer-based medication reconciliation and integration system to obtain information about medications prescribed | Number of PIM at hospital admission and discharge | Number of PIM on admission B: 173 vs. A: 480, and at discharge B: 88 vs. A: 156, p < 0.001 |
| Vu and Huong (2019) | Pharm | Phys | Pharm | 2015 Beers criteria | Prevalence of PIM | Prevalence of PIM B: 34.1% vs. A: 23.1%, (odds ratio (OR) = 0.337, 95% CI = 0.207–0.551, p < 0.001) |
| Najjar et al. (2018) | Head of geriatric medicine, 2 Pharm | Pharm | Pharm, Phys | STOPP (version 2) and Beers (2015) criteria | Change in the incidence rate of PIM | Incidence rate of PIM B: 61% vs. A: 29.5%, p < 0.001 |

(Continued on following page)
being prescribed one or more PIM (Urfer et al., 2016). Finally, one study observed that although the total number of newly prescribed PIM did not decrease, the top 10 most common new PIM significantly decreased from 9.0% to 8.3% (Vanderman et al., 2017).

### 3.4.6 Impact of Multifaceted Interventions

Nine studies used a multifaceted approach as a strategy to decrease the number of PIM (Clyne et al., 2016; Moss et al., 2016; Gibert et al., 2018; Najjar et al., 2018; Vandenberg et al., 2018; Boersma et al., 2019; Liu et al., 2019; Vu and Huong, 2019; Rodrigues et al. Effectiveness of PIM Interventions in Older Adults

#### TABLE 6 | (Continued) Effects of multifaceted interventions on inappropriate prescribing in older adults (n = 9).

| Author (year) | Educational CDSS Medication screening Strategies used Outcome measures Significant outcomes |
|---------------|-----------------------------------------------|---------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------|
| Gibert et al. (2018) | Research team | 20 Phys | STOPP criteria | Proportion of patients with a reduction of PIM after the intervention |
| Vandenberg et al. (2018) | Geriatrician, Pharm, Gerontologist | 20 primary care providers, 4 Pharm | 2012 Beers criteria | This intervention reduced PIM for 44.9% of the patients (n = 44), p < 0.001 during the intervention, reaching significance (p = 0.009) during the postintervention period. PIM prevalence declined at baseline, 22.6% encounters per month were with older veterans taking at least 1 PIM. After the intervention, this proportion had dropped to 16.7% (p < 0.001), a 26% relative reduction. Encounters with veterans taking 2 or more PIM showed steady and significant decline, from a baseline of 6.2–4.1% after the intervention (p < 0.001), representing a 33.9% relative reduction in multiple PIM prevalence |
| Moss et al. (2016) | Phys, Geriatricians, Gerontologists, Pharm, N, Clinical application coordinators | 73 ED providers (10 physicians, 60 medical residents), 3 advanced practice providers | X 2012 Beers criteria | Rate of PIM prescribing over the observation period |
| Clyne et al. (2015) | Pharm | Phys (C: 11, I: 10) | 2012 Beers criteria | Mean number of PIM (SD) at baseline C: 1.39 (0.6) vs. I: 1.31 (0.8) |

A, after group; B, before group; C, control group; CDSS, clinical decision support system; CI, confidence interval; ED, emergency department; GP, general practitioner; I, intervention group; N, nurse; Pharm, pharmacist; Phys, physician; PIM, potentially inappropriate medication; SD, standard deviation; STRIP, systematic tool to reduce inappropriate prescribing; STOPP, Screening Tool of Older People’s potentially inappropriate Prescriptions.

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TABLE 7 | Effects of organizational interventions1 on inappropriate prescribing in older adults (n = 2).

| Author (year) | PIM screening tool | Strategies used | Outcome measures | Significant outcomes |
|---|---|---|---|---|
| Stevens et al. (2017) | 2012 Beers criteria | Education, informatics-based clinical decision support designed for improved workflow, and individual provider feedback | Average percentage of PIM | Average percentage of PIM per month (SD): Site 1 – B: 11.9% (1.8) vs A: 5.1% (1.5), p < 0.0001 Site 2 – B: 8.2% (0.8) vs A: 4.5% (1.0), p < 0.0001 Site 3 – B: 8.9% (1.9) vs A: 6.1% (1.7), p = 0.0007 Site 4 – B: 7.4% (1.7) vs A: 5.7% (0.8), p = 0.04 |
| Wessell et al. (2008) | 1997 Beers criteria (US 2003 update) | A quarterly PIM performance report; biannual on-site visits | Change in the prescription rate | Absolute annual decline of 0.018% for always inappropriate medications (p = 0.03) |

A, After group; B, Before group; PIM, Potentially inappropriate medication; SD, Standard deviation; US, United States.

1Organizational intervention- a combination of strategies to improve the quality indicators of institutions/organizations and involved in the approach all stakeholders, health professionals, and non-health professionals. This intervention uses several approaches, including diagnostic activity (including medication review), Team Building, Intergroup relationship, sensitivity training (including educational sessions).

Akkawi et al., 2020) In two studies, the multifaceted approach consisted in the application of a CDSS followed by a medication review (Boersma et al., 2019; Liu et al., 2019). One study used a combination of educational and CDSS approaches (Akkawi et al., 2020). The remaining studies used, as an approach to decrease the number of PIM, a combination of an educational approach followed by a medication review (Clyne et al., 2016; Moss et al., 2016; Gibert et al., 2018; Najjar et al., 2018; Vandenberg et al., 2018; Vu and Huong, 2019).

Clinical Decision Support System and Medication Review
The combined use of CDSS and medication review strategies led to a significant reduction of the mean number of PIM per patient from 0.7 to 0.23 (Boersma et al., 2019) and an increasing number of PIM changes implementation (intervention: 46.2% vs. control: 15.3%) (Liu et al., 2019).

Educational Intervention and Medication Review
Five of the six studies that used a combination of educational and medication review strategies observed a significant impact on the PIM reduction (Clyne et al., 2016; Gibert et al., 2018; Najjar et al., 2018; Vandenberg et al., 2018; Vu and Huong, 2019). Among these, two studies reported a significant decrease in the mean number of PIM per patient from 0.99–1.18 before intervention to 0.66 to 0.7, after intervention (Clyne et al., 2015; Gibert et al., 2018). Vandenberg et al. (2018) and Vu and Huong (2019) reported that the prevalence of PIM decreased 5.9% and 10.9%, respectively. According to Najjar et al. (2018), the multifaceted approach led to a decrease in the PIM incidence of 31.5%.

Educational Intervention and Clinical Decision Support System
In one study (Akkawi et al., 2020), the multifaceted intervention consists of three educational sessions about PIM and discussion of STOPP criteria, coupled with an introduction of a CDSS. This approach did not achieve significant outcomes.

3.4.7 Impact of Organizational Interventions
One study performed an organizational intervention in four different hospitals and observed a significant decrease in the average percentage of prescribed PIM per month (1.7–6.8) after intervention (Stevens et al., 2017). Another study performed in 99 primary care practices observed that the organizational intervention that includes PIM performance reports, on-site visits, and network meetings was responsible for an absolute annual decline of 0.018% for always inappropriate medication (Wessell et al., 2008).

3.4.8 Impact of Interventions That Have Greater Evidence by Its Design
The analysis of the studies that included a concurrent control and low risk of bias revealed that in the hospital, all the five medication review interventions were effective (Spinewine et al., 2007; Gallagher et al., 2011; Dalleur et al., 2014; Van der Linden et al., 2017; Van Der Linden et al., 2018), two CDSS interventions were effective (Urfier et al., 2016; McDonald et al., 2019), one multifaceted intervention achieved significant impact (Vandenberg et al., 2018), and none of the educational interventions achieved a successful reduction of PIM. In primary care it was observed that all the two multifaceted interventions achieved a significant reduction of PIM (Clyne et al., 2015; Boersma et al., 2019), one (Clyne et al., 2016) of two educational strategies was effective, and none of the medication review and CDSS strategies was well successful.

4 DISCUSSION
Despite the extensive number of studies in the literature on PIM in older patients, only 31 of the included studies reported effective intervention. Among these, 21 presented methodological intervention limitations and could not ensure that the intervention used can be replicated and identical outcomes achieved (Brown and Earnhart, 2004; Fick et al., 2004; Spinewine et al., 2007; Wessell et al., 2008; Gallagher et al.,
2011; Dalleur et al., 2014; Frankenthal et al., 2014; Clyne et al., 2015; Tallon et al., 2015; Urfer et al., 2016; Frankenthal et al., 2017; Van der Linden et al., 2017; Etxeberria et al., 2018; Gibert et al., 2018; Hurmuz et al., 2018; Van Der Linden et al., 2018; Boersma et al., 2019; Gutiérrez-Valencia et al., 2019; Khera et al., 2019; Liu et al., 2019; Vu and Huong, 2019). Although a meta-analysis was not done, our findings suggested that in the hospital, the most adequate strategy to decrease the number of PIM and/or the patients with at least one PIM was medication review. Concerning primary care setting, the analysis of all the included studies indicated that educational interventions were the most successful. However, when only randomized controlled trial (RCT) studies were analyzed, it did not find greater effectiveness of some interventions over others.

The data of this study also suggested that the inclusion of pharmacists can upgrade the quality of the PIM intervention and effectively promote the well-being of the patients.

Regarding the influence of the number of prescribed medicines per patient in PIM interventions, our data suggested that the success of an intervention is not medicines number-dependent, since the analysis of the successful intervention rate in polymedicated and non-polymedicated patients was similar (~67%).

This work also suggested that most of the studies presented important design limitations, something that limits the grade of their evidence.

Medication review was the most frequent strategy used to improve pharmacotherapy and reduce the number of PIM in hospitalized patients. A reduction in the number of PIM per patient or/and in the number of patients with at least a PIM was achieved for 75% of the medication review interventions (Brown and Earnhart 2004; Spinewine et al., 2007; Gallagher et al., 2011; Keith et al., 2013; Dalleur et al., 2014; Ilić et al., 2015; Tallon et al., 2015; Van der Linden et al., 2017; Chan et al., 2018; Fajredines et al., 2018; Van Der Linden et al., 2018; Gutiérrez-Valencia et al., 2019). Among the three studies that do not have efficacy in hospitalized patients, the main reasons pointed were as follows: 1) the difficulty to engage physicians to actively participate in the study—they preferred to receive the documentation about drug therapy issues by paper instead of discussing face-to-face the patients’ pharmacotherapy (Chan et al., 2018); and 2) the low acceptance of the recommendation by the physicians (Regueiro et al., 2019).

In primary care, 42.9% of the interventional studies (Keith et al., 2013; Hurmuz et al., 2018; Stuckey et al., 2018; Khera et al., 2019) used medication review to improve the pharmacotherapy through the reduction of PIM. The lack of efficacy can be related to 1) the low acceptance rate of recommendations by the physicians (Allard et al., 2001); 2) the PIM list used—for example, Castelino et al. reported that in Australia the medicines listed in Beers criteria were rarely used; 3) the physicians did not use routinely any checklist and do not access computer programs to evaluate hypothetical interactions, and they do not record short-term drug alterations (Lampela et al., 2010); 4) in some cases the patients did not receive the full intervention (Allard et al., 2001); and 6) contamination between control and intervention groups (Campins et al., 2016).

The analysis of all educational interventions performed in primary care revealed that this type of intervention has been successfully implemented in 75%. However, only one of the two studies that have greater evidence by its design effectively decreased the number of PIM. The success of educational interventions in primary care can be related to the promotion of a specific web training on PIM tools used by physicians in clinical practice, updating the knowledge of physicians in PIM detection (Fick et al., 2004; Clyne et al., 2016; Etxeberria et al., 2018). The lack of efficacy of educational intervention observed in one study can be related to a change in the participants’ behavior due to the knowledge that they are taking part in an experiment (Hawthorne effect) (Rognstad et al., 2013).

In hospitalized patients, the poor outcomes achieved by educational interventions can be related to the low interactivity during the education intervention, the lack of knowledge of the clinicians, and the characteristics of the ward included that sometimes make difficult the collection of the data (Franchi et al., 2016).

The implementation of a CDSS in hospitals had a positive impact on 50% of the studies (Urfer et al., 2016; Vanderman et al., 2017). The lack of efficacy of the intervention in the remaining studies can be related to the study design and the fact that the applied criteria are not setting-directed originating a high number of alerts that tend to be ignored by a healthcare professional (McDonald et al., 2019; Winata et al., 2020).

Multifaceted interventions were described as mixed interventions that can reduce the number of PIM (Rahme et al., 2005). In the hospital setting, it was observed that in the two studies that used a combination of educational and medication review strategies, the intervention was well successful (Najjar et al., 2018; Vu and Huong, 2019). In primary care, a combination of educational and medication review strategies results in increased efficacy of the intervention (Clyne et al., 2015; Gibert et al., 2018; Vandenbergh et al., 2018).

The results of the included studies suggested that medication review is the most indicated intervention to promote the well-being of the hospitalized patients through the reduction of PIM. The success of medication review strategies at hospital discharge could be related to the fact that the inpatient setting may predispose older adults to new prescriptions and probably unnecessary drugs (Page et al., 2010). Moreover, during the hospitalization physicians tend to resist the change or discontinuation of chronic medication, particularly if the medication is not related to the reason for hospitalization (Page et al., 2010). This high number of prescribed PIM during the hospitalization can be the result of the lack of implemented PIM programs directed to each hospital ward and/or specific condition (Motter et al., 2018).

To improve the well-being of older adults, besides strategies to reduce PIM, strategies to promote appropriate prescription have also been developed. Medication review is a widely used strategy and with better outcomes to reduce potentially inappropriate prescribing (PIP) in hospitalized older adults. However, in a recent review, Dautzenberg et al. (2021) reported that the heterogeneity between studies does not allow reaching significant conclusion. According to dos Santos et al. (2019), the choice of outcome measures, study design, and
methodological quality of medication review studies make it difficult to analyze the effectiveness of this strategy. The failure of medication review strategies in primary care can be attributed to the lack of time of physicians to perform the medication review (Plácido et al., 2020); also, as a result of this lack of time, even when the medication review was performed, patients’ follow-up did not occur (Campins et al., 2016). On the other hand, educational strategies allow the empowerment of primary care physicians who already had enough handling in managing older adults but not the right confidence and knowledge to manage PIM prescription (Maio et al., 2011). Moreover, educational strategies had more impact on prescribing patterns than presenting a physician only with a decision algorithm (Rahme et al., 2005). A previous work observed similar results regarding the effectiveness of educational strategies to reduce PIP in primary care. According to Kunstler et al. (2019), educational strategies are well successful in changing health professional prescribing behavior.

A recent systematic review focused on non-clinical programs to reduce the inappropriate or unnecessary use of medicines observed that interventions consisting of education messages and recommended behavior alternatives were more likely to be successful in reducing the inappropriate use of medicines or medical procedures (Lin et al., 2020). Educational strategies are essential to improve prescription, as observed by Amorim et al. (2021) since physician-related characteristics can influence the number of PIM prescriptions.

Regarding the multifaceted strategies, the scarcity of studies using this approach did not allow clarifying their benefits in PIM reduction.

In the hospital setting, CDSS interventions significantly reduced the PIM number in older adults. Similar results were found in another systematic review (Dalton et al., 2018). The lack of CDSS in primary care can be related to the outdated user interface model (Price et al., 2017).

Regarding the organizational strategies, the studies achieved a significant impact on pharmacotherapy independently of the setting (Wessell et al., 2008; Stevens et al., 2017).

In 47.8% of the included studies, the intervention was performed by a pharmacist or by a multifaceted team that includes at least one pharmacist. Among these studies, the rate that interventions succeeded well was 72.7%. In the remaining studies, the rate of success observed was 62.5%, suggesting that the inclusion of a pharmacist in the PIM interventions team can be beneficial. Previously it was demonstrated that pharmacists are actively engaged in several care-delivery models such as direct care and collaborative team-based care, improving pharmacotherapy and ameliorating the patients-related health outcomes (Lee et al., 2015). It was also reported that pharmacists could play an important role in patients’ medication review in practice settings such as community pharmacies long-term care facilities, outpatient clinic home care, and hospitals. Moreover, pharmacists-led deprescribing interventions can reduce the number of unnecessary and potentially harmful medications (Silva et al., 2019; Hernández-Prats et al., 2021).

Although this study was performed with scientific rigors, some limitations are present. The search strategy was limited to the three main health research databases and articles written in English, Portuguese, and Spanish. The included studies were heterogeneous in practice settings, population, size of the samples, and PIM definition that can be variable depending on the screening tool used, which can influence PIM number detected (Thomas and Thomas, 2019; Perpétuo et al., 2021).

Because this review includes studies independently of the quality assessment analysis, an outcomes bias can be aroused. The bias can be attributed to a lack of randomization and blinded interventions and absences/inadequate follow-up period in some studies, compromising a possible scaling up of the interventions.

This study provided valuable data regarding PIM-reduction strategies; however, most of the included studies presented limitations that restrain the extrapolation of the results and a lack of an economic evaluation. Only one study reported that in the intervention group, a significantly lower medication cost was achieved (Frankenthal et al., 2014).

A recent systematic review only found seven articles reporting the economic impact of PIM interventions and suggested that although limited, interventions to optimize medication may outweigh their implementation costs (Laberge et al., 2021).

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

All authors meet all four ICMJE criteria for authorship. Conceptualization: FR and MH; Data curation: DR, AP, FR, MH, and AF; Formal analysis: DR and AP; Funding acquisition: FR and MH; Investigation: AP and DR; Methodology: FR and MH; Project administration: FR; Resources: FR; Supervision: FR, MH, RM-C, and AF; Validation: FR, AF, and MT-H; Roles/ Writing—original draft: AP and DR; Writing—review and editing: FR, MH, RM-C, and AF.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2021.777655/full#supplementary-material
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