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SYSTEMATIC REVIEW

Deprescribing Interventions among Community-Dwelling Older Adults: A Systematic Review of Economic Evaluations

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Abstract

Background Deprescribing can reduce the use of inappropriate or unnecessary medication; however, the economic value of such interventions is uncertain.

Objective This study seeks to identify and synthetise the economic evidence of deprescribing interventions among community-dwelling older adults.

Methods Full economic evaluation studies of deprescribing interventions, conducted in the community or primary care settings, in community-dwelling adults aged ≥ 65 years were systematically reviewed. MEDLINE, EconLit, Scopus, Web of Science, CEA-TUFTS, CRD York and Google Scholar databases were searched from inception to February 2021. Two researchers independently screened all retrieved articles according to inclusion and exclusion criteria. The main outcome was the economic impact of the intervention from any perspective, converted into 2019 US Dollars. The World Health Organization threshold of 1 gross domestic product per capita was used to define cost effectiveness. Studies were appraised for methodological quality using the extended Consensus on Health Economics Criteria checklist.

Results Of 6154 articles identified by the search strategy, 14 papers assessing 13 different interventions were included. Most deprescribing interventions included some type of medication review with or without a supportive educational component ($n = 11$, 85%), and in general were delivered within a pharmacist-physician care collaboration. Settings included community pharmacies, primary care/outpatient clinics and patients' homes. All economic evaluations were conducted within a time horizon varying from 2 to 12 months with outcomes in most of the studies derived from a single clinical trial. Main health outcomes were reported in terms of quality-adjusted life-years, prevented number of falls and the medication appropriateness index. Cost effectiveness ranged from dominant to an incremental cost-effectiveness ratio of $112,932 per quality-adjusted life-year, a value above the country's World Health Organization threshold. Overall, 85% of the interventions were cost saving, dominated usual care or were cost effective considering 1 gross domestic product per capita. Nine studies scored > 80% (good) and two scored ≤ 50% (low) on critical quality appraisal.

Conclusions There is a growing interest in economic evaluations of deprescribing interventions focused on community-dwelling older adults. Although results varied across setting, time horizon and intervention, most were cost effective according to the World Health Organization threshold. Deprescribing interventions are promising from an economic viewpoint, but more studies are needed.

Key Points for Decision Makers

Older adults are often exposed to inappropriate or unnecessary medication that can cause harm to patients and high costs to the health system.

Economic evidence of deprescribing interventions for community-dwelling adults is recent.

The results of this review suggest that deprescribing interventions for community-dwelling older adults are promising from an economic viewpoint.

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1 Introduction

Population ageing is one of the greatest social and economic challenges worldwide. Over the last two decades, the number of older people in the EU-27 has risen almost six times faster than the overall population [1]. Despite an increment in life expectancy, there is no guarantee of healthy ageing [2–4]. The prevalence of multimorbidity (presence of two or more chronic diseases in the same individual) among older adults is very high and continues to grow, exposing them to multiple medicines, commonly referred to as polypharmacy [5–7]. Polypharmacy is related to an increased risk of adverse drug events, use of potentially inappropriate medication (PIM), and greater health services utilisation, morbidity and mortality [8, 9]. About 30% of community-dwelling older European adults take at least one PIM [10], i.e., a medicine posing a risk of harm that outweighs the clinical benefit [10, 11]. Deprescribing, in a simple definition, is an intervention supervised by a health professional of reducing or withdrawing a medication that might be causing harm or might no longer be of benefit [12, 13]. Several strategies to deprescribe have been developed, including drug-specific guidelines, educational interventions, medication reviews and audits of prescription practices [14, 15].

This subject is gaining attention and various systematic reviews of deprescribing interventions and their effectiveness for older people have been published. Overall, deprescribing seems to be safe, with evidence suggesting that these interventions may result in small reductions in falls [16, 17], mortality [17–20], use of PIMs [17, 21] and hospital admissions [17–19]—all with little to no effect on health-related quality of life (HRQoL) [17–19, 22]. A recent overview of systematic reviews of interventions to reduce the prescription of PIMs suggested potential benefits, even if modest, of different interventions depending on the study design, intervention type and population characteristics [23]. Considering the ageing population, polypharmacy and associated healthcare costs, it is important to determine if these minor benefits are worth it from an economic viewpoint.

As deprescribing interventions are potentially complex and require highly skilled staff and time to be undertaken, high implementation costs can be expected. In a context of limited resources, economic evaluations (EEs) play an increasingly important role in decision making, informing the issue of whether interventions represent a cost-effective strategy. To the best of our knowledge, no systematic review has addressed the economic value of deprescribing interventions for community-dwelling older adults. Moreover, a review focused on this vulnerable population is valuable as their needs, preferences and behaviours may impact the deprescribing process and outcomes [24, 25]. This systematic review seeks to identify and synthesise available evidence of the economic value of deprescribing interventions among community-dwelling older adults in community or primary care settings.

2 Methods

This review followed current guidance for conducting and reporting systematic reviews, including guidance for undertaking reviews on healthcare interventions by the Centre for Reviews and Dissemination of the University of York [26] and recommendations from the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 statement, an updated guideline for reporting systematic reviews [27].

2.1 Eligibility Criteria

The population, intervention, comparator, outcome and study-design (PICOS) approach [26] was used to guide the search strategy and synthesis of evidence gathered from single studies:

- Population: community-dwelling (non-institutionalised) older adults (aged ≥ 65 years, the cut-off commonly defined in developed world economies [28]).
- Intervention: any intervention conducted in the community or primary care settings that includes deprescribing inappropriate medicines, i.e. identifying and reducing medicine dosage or discontinuing unnecessary medications in which existing or potential harms outweigh the potential benefits [12, 13]. Intervention procedures can include any educational approaches focused on patients and/or in doctors, medication reviews or any other framework that explores deprescribing medicines. Study investigators defined community setting as community pharmacies, primary care/general practices, outpatient care (clinics or hospitals) and patients' homes.
- Comparator: usual care as described by the study.
- Outcomes: the main outcome is the economic impact of the intervention regardless of how it is expressed (incremental cost-effectiveness ratios [ICERs], dominance, etc.), and regardless of the perspective.
- Study-design: full EEs as defined by Drummond et al., i.e. studies comparing both benefits and costs of alternative courses of action [29].

Studies were excluded if: (i) the effectiveness of the intervention among the older adults could not be isolated; (ii) the intervention was not focused on reducing the dose or withdrawing medicines (e.g. adherence medication reviews); (iii) the intervention was delivered in settings other than primary

care or community settings (e.g. hospital inpatient or acute care; assisted living, nursing homes or geriatric wards); (iv) the studies did not include a full EE (e.g. studies measuring costs only); (v) studies did not report the mean costs, benefits or resource data that enabled the authors to estimate the ICER; and (vi) studies were presented as letters to editor/editorials, health technology assessment reports not submitted to peer review, study protocols, academic theses, review articles and conference abstracts.

2.2 Literature Search and Study Selection

The following electronic databases were searched for journal articles and abstracts, from inception to February 2021: MEDLINE (PubMed), EconLit, Scopus, Web of Science, CEA-TUFTS registry and CRD York database (DARE, National Health Service EE Database; ceased to be updated in March 2015). Google Scholar was also searched. In addition, relevant grey literature was explored using the Google search engine and the International HTA Database. Complementary searches were made to identify possible additional articles through citation searches, reference checking and hand searching.

The search strategy was developed by one of the authors (SR) in consultation with the other authors (DF, IT, JP) using an iterative process, and comprised a variety of combinations of free-text synonymous and Medical Subject Heading (MeSH) terms. Although the main search terms were the same, the conventions of each database were adjusted accordingly. There were no date or language restrictions on the searches. The final search strings are presented in the Appendix 1 of the Electronic Supplementary Material (ESM). References identified as potentially eligible for inclusion were exported to an Excel® file. Duplicate articles were removed. Titles and abstracts were screened independently by two authors against the inclusion and exclusion criteria and labelled as include, exclude or uncertain (first screening). Two authors independently evaluated the full text of all articles classified as include and uncertain (second screening). In each step, discrepancies between reviewers were solved by discussion with a third author. The PRISMA flowchart as suggested by the PRISMA statement was used for the study selection report [27].

2.3 Data Extraction

Data from included papers were extracted by three authors (SR, DF, IT) and validated by a fourth investigator (JP), using a standardised data extraction template designed for this review. This template, based on the CRD recommendations for systematic reviews of EEs [26], was designed to systematically retrieve information from each included study on the following items: (1) general characteristics: first author, year of publication, country, title and funding sources; (2) effectiveness data: study design, population, intervention and comparator descriptions, setting, sample size, follow-up time, unit of effectiveness, effectiveness results and sources; (3) economic data: economic model/design, perspective, time horizon, costs items (or categories) and sources, currency/year of costing, outcomes measures for ICER, ICER, discount rate, deterministic, and probabilistic sensitivity analysis and scenario analysis (methods and main findings). When not provided in the studies, the incremental analysis was performed by the authors.

Selected studies were classified according to the type of intervention provided, namely, educational or medication reviews with or without a supportive educational (patients and/or practitioners) component. In order to allow comparisons of results across countries and years, the investigators converted costs, incremental costs, ICERs, and reported thresholds on a sensitivity analysis to a common currency and year ($US, 2019), through a web-based tool developed by the Campbell and Cochrane Economics Methods Group in collaboration with the Evidence for Policy and Practice Information and Co-ordinating Centre [30]. This tool uses the gross domestic product (GDP) deflator index to adjust the costs to a target price year and the purchasing power parities (PPP) to convert currencies. Purchasing power parities values of the International Monetary Fund were used. The international World Health Organization threshold for cost effectiveness was used as a reference [31]. For the purpose of this review, a strategy was considered cost effective only when the cost per disability-adjusted life-year (DALY) averted or quality-adjusted life-year (QALY) gained was less than 1 GDP per capita [31]. The threshold for each study was calculated considering The World Bank GDP per capita, PPP ($US, 2019), of the country for which it was performed [32].

2.4 Quality Assessment

Three authors (SR, DF, IT) independently appraised the methodological quality of the included studies, using the extended Consensus on Health Economics Criteria list (CHEC-extended) [33, 34]. In case of doubts or disagreement, a consensus was obtained by discussion with a fourth author (JP). The CHEC-extended includes an additional question regarding model-based EEs compared to the original CHEC checklist [33–35], and is recommended for the assessment of both trial-based and model-based EEs [36]. This checklist was chosen because it allows parameters and analysis appropriateness assessment and is considered to

entail a more detailed scrutiny than other common checklists [36, 37]. Twenty items were scored using: yes (1), no (0), unclear (0.5) or not applicable. The maximum score was 19 for trial-based EEs and 20 for model-based evaluations. The total score of each study was converted to a percentage, with values from zero to 100. Final scores were categorised into three grades: low, moderate or good quality, using cut-off values of ≤ 50, 51–75 and > 75, respectively. Higher scores denote higher quality.

3 Results

Figure 1 shows the PRISMA flowchart for the study selection. A total of 6149 records were identified through seven databases. After removing duplicates, 5382 records were eligible for review. In the first screening, 5298 records were excluded by applying the exclusion criteria, leaving 84 papers for full-text retrieval. An additional five papers were identified through citation search, obtaining 89 papers for the second screening. Of those, 74 were excluded and one was not retrieved. The remainder of 14 full EE papers [38–51] were included in the final review (Fig. 1). The main causes for the second screening exclusion were a population not exclusively aged 65 years or over, the type of intervention not focusing on deprescribing and the absence of a full EE analysis.

3.1 Characteristics of Studies

All of the included studies, with the exception of one from Taiwan [38], were conducted for Organization for Economic Co-operation and Development countries—three in the UK [39–41] and in the Netherlands [42–44], two in Spain [45, 46] and Canada [47, 48], and one in Ireland [49], Chile [50] and the USA [51]. Both EE studies conducted in Spain assessed the same service, the conSIGUE trial. Thus, 13 interventions assessed in 14 papers were reviewed. Of those, 11 interventions ascertained in 12 EE studies were some type of medication review of services covering heterogenous older people, with polypharmacy ($n = 7$) [38, 40, 41, 44–46, 50, 51], a history of falls and taking fall-risk-increasing-drugs [FRIDs] ($n = 2$) [42, 43], taking medications on a regular basis of specific class(es) of PIMs [49], and very old persons taking two or more medicines who were discharged to their homes after an emergency department visit ($n = 1$)

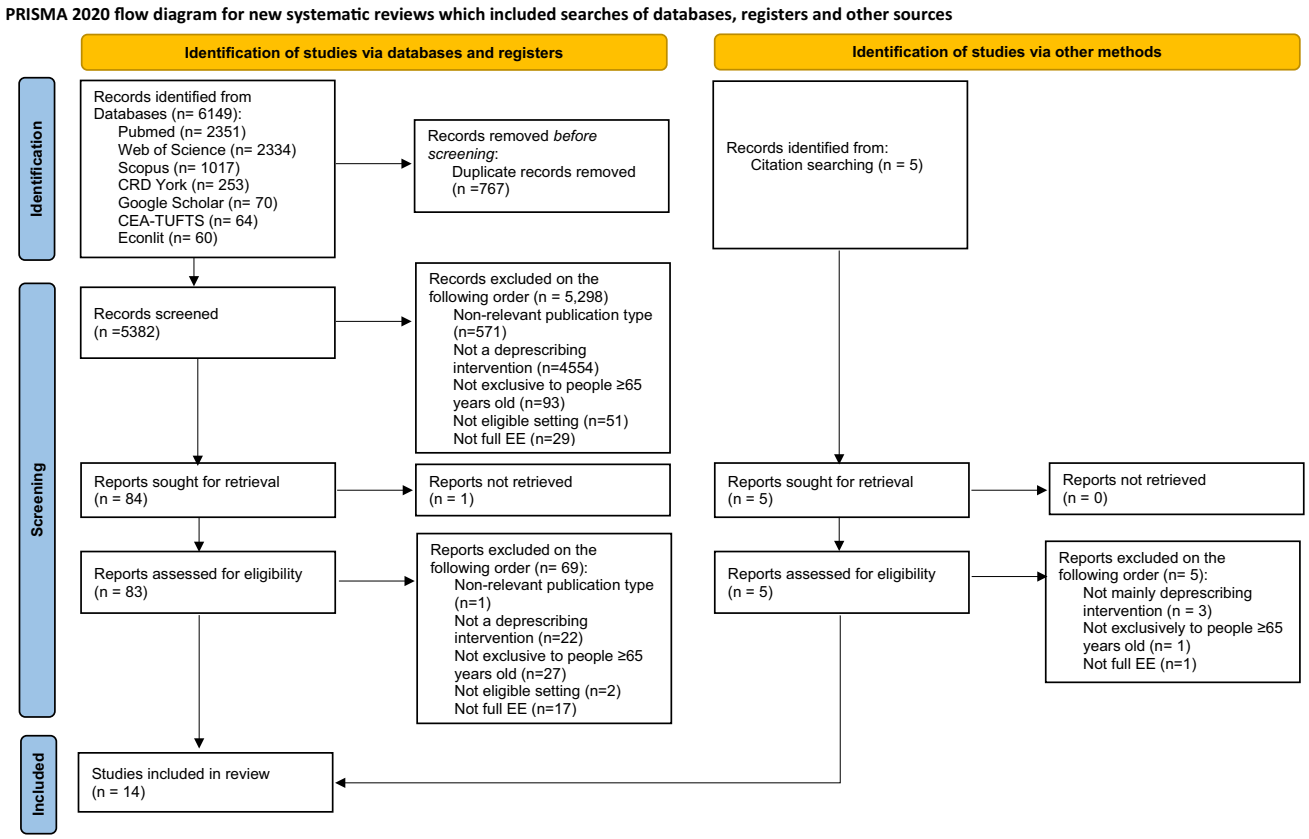

Fig. 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 flowchart of study selection. *EE* economic evaluation

[39]. The remaining two interventions were educational-only services delivered by pharmacists targeting patients taking a specific class of PIMs [47, 48].

The interventions were conducted at the community pharmacy ($n = 6$) [40, 41, 44–48], primary care centres/general practices/geriatric/outpatient clinics ($n = 6$) [38, 42, 43, 49–51] or at the patient's home ($n = 1$) [39]. Across settings, most interventions were delivered by a community or clinical pharmacist working in collaboration with a physician, mostly general practitioners [38–41] [44–51]. Exceptions were the van der Velde et al. [42] and Polinder et al. studies [43], whose interventions were conducted at a geriatrics outpatient clinic and at multicentre outpatient clinics, respectively. Both interventions were led by geriatricians who consulted the prescribing physician if medication withdrawal was intended. The details of the included studies are summarised in Table 1.

3.2 Methods and Inputs

Most ($n = 10$) EE studies were published recently, between 2015 and 2021 [38, 40, 43–50]. The oldest study was published in 1998 [51]. Eleven studies [38–41, 43, 44, 46–50] reported health outcomes in terms of QALYs, three of these also reported additional effectiveness measures—life-years gained, reduction in health-related complaints and mean number of PIPs [39, 44, 49]. One study reported as an additional outcome the total avoided medical expenditure [38], two expressed results in terms of clinical effectiveness measures only [42, 51] and one in terms of monetary benefit [45]. There were two studies with a societal perspective [43, 44], one with a hospital perspective [38] and 11 with a third-party payer perspective (public or private). Three studies did not state the perspective explicitly [38, 40, 43]. Most studies were undertaken alongside the effectiveness trial. One EE used data from a two-arm (fallers with and without a medication change) non-randomised observational study supported by a literature review and expert estimates [42]; another used a before-and-after comparison analysis, with intervention patients used as historical controls [40]; and a third one used a randomised, multiple interrupted time series [41]. Except for the two studies conducted in Canada [47, 48], which in addition to the randomised controlled trial (RCT) data, derived utility and cost values from the literature, the remaining studies used single RCTs (or cluster RCTs) as the basis for undertaking the EE [38, 39, 43–46, 49–51]. The two Canadian studies [47, 48] used a decision analytical model, combining a decision tree that represents treatment pathways (based on the 6-month RCT D-PRESCRIBE trial) with a Markov model (representing state transitions for older adults following the trial) in a 1-year time horizon for all analyses.

Regarding funding sources, four of the 14 studies had no sources of funding to declare [40, 47, 48, 50], one did not include any statement [51], five were supported by a combination of two entities—pharmaceutical industry and academia [42], pharmaceutical industry and Pharmaceutical Society [45, 46], association of pharmacies and Pharmaceutical Society [44], and Medical Research Council and primary care trusts [41]. Three studies received funding from research organisation grants [39, 43, 49] and one from the Department of Health [38].

All studies except two considered some type of intervention costs and included medication expenses [38, 40]. Hospital admissions were also considered in all studies, as well as emergency department visits with the exception of the RESPECT trial [41]. Laboratory or diagnostic tests were reported in four studies [41, 48, 50, 51], and the two studies with the societal perspective [43, 44] considered institutional care (e.g. rehabilitation centres, nursing homes).

Regarding the type of interventions, two studies did not include potentially relevant costs, namely the cost of general practitioner visits [45, 46]. Most studies used countries' official data for cost valuation. Time horizons of the EEs were no longer than 12 months, and therefore discounting was not applicable. As for ICERs, one had to be recalculated because the original estimation considered only the drugs and intervention costs, failing to include other retrieved relevant medical costs (e.g. emergency room visits) [51], and another had to be estimated because it was not reported in the original paper [43]. Table 2 summarises the study findings.

3.3 Quality Assessment

Nine studies had a "good" [39, 41, 44–50] quality score, three were "moderate" [40, 42, 43] and two a "low" [38, 51] quality assessment (Table 2). Overall, costs were measured appropriately in all studies. Moreover, their valuation was adequate in all studies except one [38]. The economic study design was considered appropriate in 12 studies, excluding two [38, 42] that did not include an appropriate comparison of mean benefits and costs. An appropriate incremental analysis of costs and outcomes of alternatives was also performed in 11 of 14 studies. The quality items assessed with lower scores were: (i) the time horizon, which varied between 2 and 12 months, was not sufficiently long to incorporate all potentially important differences in costs and consequences [53] (lifetime horizon is the most appropriate approach to the interventions under comparison, as events can occur over patients' lifetimes, according to most international guidelines [53–55]); (ii) the ethical and distributional issues, which were addressed satisfactorily in only one study [50], such as prioritising high-risk groups, or considering an equitable distribution of benefits across socioeconomic or other groups [29]; and (iii) the generalisability of the results

Table 1 Characteristics of included studies

Authors, year	Country, data retrieval	Data source of effectiveness measurement	Study population	Intervention type	Setting	Intervention description	Comparators
Malet-Larrea et al., 2017 [45]	Spain, 2011–13	Cluster RCT (consigue) IG: 688 CG: 715	Patients aged ≥ 6 5 years taking ≥ 5 medications for at least 6 months	Medication review	Community pharmacies, multicentre	MRF provided by trained community pharmacists. Patients attended the pharmacy on a monthly basis. In the first month, an action plan was developed by the pharmacist, agreed with the patient and shared with the patient's GP	Usual care
Jódar-Sánchez et al., 2015 [46]	Spain, 2011–13	Cluster RCT (consigue) IG: 688 CG: 715	Patients aged ≥ 65 years taking ≥ 5 officially registered medicines	Medication review	Community pharmacies, multicentre	MRF, provided by trained community pharmacists. Patients attended the pharmacy on a monthly basis. In the first month, an action plan was developed by the pharmacist, agreed with the patient, and shared with the patient's GP	Usual care

Table 1 (continued)

Authors, year	Country, data retrieval	Data source of effectiveness measurement	Study population	Intervention type	Setting	Intervention description	Comparators
Van der Velde et al., 2008 [42]	The Netherlands, 2003–5	Non-randomised observational study n = 141 (6 months: IG: 75; CG: 64)	Patients aged ≥ 65 years with as history of falling, a MMSE score of ≥ 21 points, ability to walk 10 m without a walking aid	Medication review	Geriatric outpatient clinic and diagnostic day centre, single centre	A treating geriatrician checked the medication list of newly referred patients who had fallen at least once during the previous year, for the use of FRIDs. The prescribing physician was consulted if drug changes were intended. Patients were informed about the withdrawal and consulted by telephone on a 2-weekly basis during the 1-month withdrawal period	Patients who did not withdraw or reduce the dose of FRIDs
Polinder et al., 2016 [43]	The Netherlands, 2008–12	RCT (IMPROveFALL trial) [65] IG: 319 CG: 293	Community-dwelling adults aged ≥ 65 years who visited the ED because of a fall, use ≥ 1 FRIDs, MMSE score of ≥ 21 out of 30 points, ability to walk independently	Medication review	Outpatient clinics, multicentre	Systematic FRID assessment by a research physician, combined with FRID withdrawal or reduction. A research nurse offered counselling, evaluated possible negative effects via a telephone follow-up, and discussed any problems regarding the drug modification with the research physician and geriatrician	Usual care

Table 1 (continued)

Authors, year	Country, data retrieval	Data source of effectiveness measurement	Study population	Intervention type	Setting	Intervention description	Comparators
Verdoorn et al., 2021 [44]	The Netherlands, 2016–17	RCT (DREAMeR study) [52] IG: 294 CG: 294	Patients aged ≥ 70 years taking ≥ 7 long-term drugs	Medication review/ educational (patient)	Community pharmacies and general practices, multicentre	Pharmacist led a CMR with a patient-centred approach, focused on patient's preferences, personal goals and health-related complaints. Actions agreed with the GP were implemented gradually in two follow-ups within approximately 3 months	Usual care
Pacini et al., 2007 [39]	UK, 2000–3	RCT (HOMER trial) [66] IG: $n = 415$ (LYG); $n = 354$ (QALY) CG: $n = 414$ (LYG); $n = 344$ (QALY)	Patients aged > 80 years, who had an EA (any cause), returning to their own home or warden-controlled accommodation, taking ≥ 2 drugs daily on discharge	Medication review/ educational (patient)	Home visit, multicentre	Pharmacist-led two home visits to educate patients about their drugs, remove out-of-date drugs, inform GPs of drug reactions or interactions and inform the local pharmacist if an adherence aid was needed. Initial referral to the pharmacist included a copy of the patient's discharge letter	Usual care

Table 1 (continued)

Authors, year	Country, data retrieval	Data source of effectiveness measurement	Study population	Intervention type	Setting	Intervention description	Comparators
Twigg et al., 2015 [40]	UK, 2012–13	Before and after analysis Participants: 620	Patients aged ≥ 65 years taking ≥ 4 medicines	Medication review	Community pharmacies, multicentre	Prior to first appointment, pharmacist assessed the patient's medication using their pharmacy medication record and STOPP/START criteria. Pharmacist then discussed and agreed the assessment with the patient. GP was contacted when necessary. Patients met with the pharmacist on a regular basis	Usual care (same patients before the intervention)
RESPECT trial team, 2010 [41]	UK, 2002–5	Randomised multiple interrupted time series [67] $n = 598$	People aged ≥ 75 years, who were living at home and receiving repeat prescriptions for ≥ 5 drugs	Medication review	Community pharmacies and general practices, multicentre	Pharmaceutical care that aimed to ensure that medication was prescribed and used appropriately. Medication review was provided by trained pharmacists in collaboration with GPs and involved patients and caregivers. Drug-related problems were resolved through continuous visits	Usual care

Table 1 (continued)

Authors, year	Country, data retrieval	Data source of effectiveness measurement	Study population	Intervention type	Setting	Intervention description	Comparators
Cowper et al., 1998 [51]	USA, 1991	RCT [68] IG: 105 CG: 103	Patients aged ≥ 65 years taking ≥ 5 prescribed medicines, who received primary care from Veterans General Medicine Clinic	Medication review	General Medicine Clinic at Durham Veterans Affairs Medical Center, single centre	Pharmacist-led comprehensive medication review with patients. Medicine appropriateness was assessed using MAI. Written recommendations were sent to the GP	Usual care (clinic nurse reviewed prescription drugs before and after physician visits). Recommendations by the pharmacist were not provided or discussed with the physician
Ahumada-Canale et al., 2021 [50]	Chile, 2018–19	Cluster RCT IG: 146 CG: 145	Patients aged ≥ 65 years taking ≥ 5 prescription medications, enrolled in a CVD prevention programme and deemed as independent (Barthel Index for activities of daily living)	Medication review/ educational (patient)	Primary care centres, multi-centre	MRF service provided by trained pharmacists with a practice change facilitator regular follow-up. It followed a stepwise approach: medical record review, patient interview, pharmacotherapy assessment, patient educational interview, recommendations to the GP and implementation of the prescription's changes agreed with GP	Primary care healthcare team (GPs, nurses and dietitians) who carry out interdisciplinary work with other allied health professionals. Pharmacists were mainly performing administrative duties

Table 1 (continued)

Authors, year	Country, data retrieval	Data source of effectiveness measurement	Study population	Intervention type	Setting	Intervention description	Comparators
Lin et al., 2018 [38]	Taiwan, 2009–11	RCT IG: 87 CG: 91	Patients aged ≥ 65 years with ≥ 3 chronic diseases, > 6 prescription items, and > 4 outpatient visits or ≥ 2 visits to different specialties in the hospital	Medication review/ educational (patient)	Outpatient clinics of a medical university hospital, single centre	Clinical pharmacist provided MTM interventions focused on potentially inappropriate medications, including identifying MRPs. Complex cases were discussed within the physician-pharmacist MTM team. Clinical pharmacist contacted the patient's prescribing physician regarding the action plan and provided face-to-face and telephone counselling to patients on health education and medication adherence. A brochure about safe medication use was distributed	Usual care with an additional brochure about safe medication use for elderly patients was delivered
Gillespie et al., 2017 [49]	Ireland, 2012–13	Cluster RCT (OPTISCRIPT study) [69] IG: 99 CG: 97	Patients aged ≥ 70 years, being prescribed ≥ 1 PIPs on a repeat basis	Medication review/ educational (GP, patient)	General practices, multic-entre	Multifaceted intervention incorporating academic detailing with a pharmacist on how GPs can review medicines with patients. Medicines reviews were supported by web-based pharmaceutical treatment options to PIP, and delivery of tailored information leaflets to patients	Usual care with an additional simple, patient-level PIP postal feedback summarising the class to which the patient's PIP belonged

Table 1 (continued)

Authors, year	Country, data retrieval	Data source of effectiveness measurement	Study population	Intervention type	Setting	Intervention description	Comparators
Turner et al., 2020 [47]	Canada, 2014–18	Cluster RCT (D-PRESCRIBE Trial) [70] IG: 248 CG: 241	Community-dwelling adults aged ≥ 65 years, long-term sedative users (> 3 months prescription claims) for insomnia management	Educational (patient)	Community pharmacies	Community pharmacist delivered to patients an evidence-based educational brochure that outlined the risks associated with the use of sedatives and safer alternative strategies to manage insomnia. Pharmacists were also encouraged to provide similar evidence-based opinion to the participant's primary care providers	Usual care
Sanyal et al., 2020 [48]	Canada, 2014–18	Cluster RCT (D-PRESCRIBE Trial) [70] IG: 248 CG: 241	Hypothetical community-dwelling adults ≥ 65 years, long-term oral NSAID users (> 90 days supplied in the previous 120 days)	Educational (patient)	Community pharmacies	Community-pharmacist delivered to patients an evidence-based educational brochure that outlined the risks associated with the long-term use of NSAIDs and alternative management strategies. Pharmacists were also encouraged to provide similar evidence-based opinion to the participant's GP	Usual care

CMR clinical medication review, *CG* control group, *CVD* cardiovascular disease, *EA* emergency admission, *ED* emergency department, *FRIDs* fall-risk-increasing drugs, *GP* general practitioner, *IG* intervention group, *MAI* Medication Appropriateness Index, *MMSE* Mini-Mental State Examination, *MRF* medication review with follow-up, *MRP* medication-related problems, *MTM* medication therapy management, *NSAIDs* non-steroidal anti-inflammatory drugs, *PIP* potentially inappropriate prescription, *QALY* quality-adjusted life-year, *RCT* randomised controlled trial

Table 2 Summary of study findings

Authors, year	Effectiveness outcome	Original currency/year	Economic model assumptions	Perspective	Time horizon (months)	Cost categories	Incremental costs (intervention vs control) (US$, 2019)	Incremental effectiveness (intervention vs control)	Cost effectiveness	Uncertainty	Quality score
Malet-Larrea et al., 2017 [45]	QALYs valued at monetary values	Euros (€)/2014	Trial-based analysis	Third-party payer (public)	6	Intervention costs (pharmacists' time, pharmacists' training, investment of the pharmacy, cost of the practice change facilitator); medication; ED visits; hospital admissions	$− 157.69	0.0233 QALYs valued at $522.94 or $977.21	Benefit:cost ratio = 3.33:1 to 6.22:1 Dominant intervention	DSA: 14 scenarios: upper and lower variation costs (medication, ED visits, pharmacy time and investment of the pharmacy), logical values (hospital admissions without cause-effect screening and the number of patients who could be attended by each pharmacy in actual practice) and arbitrary and conservative values in remaining ones (length of follow-up and practice change facilitator time). MRF saved costs in 13 of the 14 scenarios	87% Good
Jódar-Sánchez et al., 2015 [46]	QALYs	Euros (€)/2014	Trial-based analysis	Third-party payer (public)	6	Intervention cost (pharmacist training, intervention time and infrastructure); medication ED department visits; hospital admissions	$− 405.58 (95% CI − 877.17 to 0.006)	0.0156 QALYs (SD = 0.004) (95% CI 0.008–0.023)	Dominant intervention	PSA, CEAC (bootstrapping) MRF 100% CE ($48,570.52 and $72,855.78 per QALY)	82% Good

Table 2 (continued)

Authors, year	Effectiveness outcome	Original currency/year	Economic model assumptions	Perspective	Time horizon (months)	Cost categories	Incremental costs (intervention vs control) (US$, 2019)	Incremental effectiveness (intervention vs control)	Cost effectiveness	Uncertainty	Quality score
Van der Velde et al., 2008 [42]	Prevented number of falls	Euros (€)/2005	Trial-based analysis, literature review and expert estimates	Third-party payer	2	Intervention costs (extra time for fall history assessment, drug use and patient education, extra telephone consultations, overhead and housing); medication; prescription costs; personnel costs (medical staff)	$− 2526.74 (95% CI − 3258.92 to − 989.18)	Fall risk reduction: 0.89 (95% CI 0.33–0.98) Number of prevented falls: 3.4 (95% CI 1.4–4.5)	Dominant intervention	DSA: reduce by 50% the number of injurious falls. Cost savings remained significant $1201.36 (95% CI 427.35–1562.97)	66% Moderate
Polinder et al., 2016 [43]	QALYs	Euros (€)/2009	Trial-based analysis	Societal (not reported)	12	Intervention (systematic fall-related drugs assessment); Medication; GP and physiotherapist visits; ED admissions; hospital admissions, outpatient visits; institutional care (intermediate care and rehabilitation centres, home care and nursing home visits) Indirect costs: travel (patient)	$54.29 (calculated by researchers)	0.05 QALYs	$1085.84/QALY (estimated by researchers)	Not reported	61% Moderate

Table 2 (continued)

Authors, year	Effectiveness outcome	Original currency/year	Economic model assumptions	Perspective	Time horizon (months)	Cost categories	Incremental costs (intervention vs control) (US$, 2019)	Incremental effectiveness (intervention vs control)	Cost effectiveness	Uncertainty	Quality score
Verdoorn et al., 2021 [44]	QALYS and reduction in health-related complaints	Euros (€)/2017	Trial-based analysis	Societal	6	Intervention (pharmacist, pharmacy technician and GP); medication; GP, practice nurse, physiotherapist and other visits; ED admissions; hospital admissions; outpatient visits; institutional care (day visits and admissions rehabilitations clinics, psychiatric wards, nursing homes); home care Indirect costs: informal care	$− 236.21	QALYs (EQ-5D): − 0.00217 QALYs (VAS): 0.003 Health-related complaints: − 0.34	$112,703 (EQ-5D)/QALY Dominant intervention: VAS Reduced complaints Intervention was cost saving	PSA, CEAC: likelihood of > 90% cost-saving intervention and > 63.7% of QALY loss DSA: all cost parameters, CMR remain cost saving	84% Good

Table 2 (continued)

Authors, year	Effectiveness outcome	Original currency/year	Economic model assumptions	Perspective	Time horizon (months)	Cost categories	Incremental costs (intervention vs control) (US$, 2019)	Incremental effectiveness (intervention vs control)	Cost effectiveness	Uncertainty	Quality score
Pacini et al., 2007 [39]	LYG and QALYs	Pound sterling (£)/2000	Trial-based analysis	Third-party payer (public)	6	Intervention (training, pharmacist time, adherence aid and filling); hospital admissions and emergency ambulance; Primary care (GP and nurse clinic appointment, telephone calls, home visits, prescription items), only for a small subset of patients from which data were collected	Cost (LYG): $489.44 ($95% CI 20.74–960.21) Cost (QALY): $844.08 (95% CI 371.23–1316.92)	LYG: 0.0070 (95% CI − 0.0068 to 0.0209) QALYs: 0.0075 (95% CI − 0.0064 to 0.0214)	$69,560/LYG $112,932/QALY Intervention was not cost effective	DSA, 5 scenarios: (i) hospital stay cost, (ii) community hospital and primary care costs, (iii) imputing missing quality-of-life data for those patients alive, (iv) intervention costs only, (v) baseline minus ambulance costs. 4 in 5 >WHO CE threshold ($49,931) PSA, CEAC (bootstrapping): less than 25% probability of the ICER being <WHO CE threshold	87% Good
Twigg et al., 2015 [40]	QALYs	Pound sterling (£)/2011–2012	Trial-based analysis	Third-party payer (not reported)	6	Intervention costs (training, consultations and service material); GP visits; hospital admissions; ED visits; hospital specialist consultation; out of hours contact with GP/nurse	$353.96 (95% CI 270.95–440.84)	0.007 QALYs (95% CI 0.0010–0.012)	$52,389/QALY Intervention was not cost effective	PSA, CEAC ($32,777.79 and $49,166.69 per QALY) 6-month intervention CE probability of 13.8% and 43.5% respectively; 12-month (assuming EQ-5D score and costs constant) $19,178.66/QALY, CE probability of 81.0% and 90.5%, respectively	66% Moderate

Table 2 (continued)

Authors, year	Effectiveness outcome	Original currency/year	Economic model assumptions	Perspective	Time horizon (months)	Cost categories	Incremental costs (intervention vs control) (US$, 2019)	Incremental effectiveness (intervention vs control)	Cost effectiveness	Uncertainty	Quality score
RESPECT trial team, 2010 [41]	QALYs	Pound sterling (£)/2004–2005	Trial-based analysis	Third- party payer (public)	12	Intervention cost (pharmacists' time); medication; GP consultations; nurse consultations; outpatient visits; hospital admissions; laboratory tests	$359.19 (90% CI − 280.61 to 1083.17)	0.019 (90% CI − 0.023 to 0.102)	$18,708 per QALY	PSA, CEAC, Monte Carlo simulation ($38,370.58 and $57,555.87/QALY) CE probability of 0.775 and 0.812, respectively. Scenario analysis, with alternative methods of costing visits. CE results not changed. Subgroup analysis: age 75 years with 5 medications; age 80 years with 7 medications, age 85 years with 10 medications, age 90 years with 15 medications. More CE for younger patients taking fewer drugs	82% Good
Cowper et al., 1998 [51]	MAI	US dollar (US$)/1991	Trial-based analysis	Third-party payer	12	Intervention: (a) fixed costs (orienting the study pharmacist, intervention protocol, beeper), (b) variable costs (personnel time, supplies); medication, outpatient visits; ED visits; inpatients; diagnostic tests; nursing home	$3527.80 (estimated by researchers)	− 4 (estimated by researchers)	MAI score: $881.95/1 unit change (estimated by researchers)	Not reported	47% Low

Table 2 (continued)

Authors, year	Effectiveness outcome	Original currency/year	Economic model assumptions	Perspective	Time horizon (months)	Cost categories	Incremental costs (intervention vs control) (US$, 2019)	Incremental effectiveness (intervention vs control)	Cost effectiveness	Uncertainty	Quality score
Ahumada-Canale et al., 2021 [50]	QALYs	US dollar (US$)/2019	Trial-based analysis	Third-party payer (public)	12	Intervention (pharmacists, GP and practice change facilitators' time); medications; pathology tests; ED visits; hospital admissions; medication-related outpatient visits	$27.37 (95% CI 0.65–54.09)	0.063 QALYs (95% CI 0.044–0.082)	$434.40 (95% CI 64.20–996.03) per QALY	PSA, CEAC (bootstrapping): all interactions CE, <US$1700/QALY 3 scenarios were analysed: (i) per-protocol analysis with patients that complied with all four visits and had complete HRQoL; (ii) maximum likelihood approach for QALY regressions as the restricted maximum likelihood approach limits variance and therefore uncertainty; (iii) included only centres that provided cost data of medication-related hospitalisations, specialists' visits and ED visits. Dominant ICER iterations increased to 31.8% with (iii). Subgroup analysis: CHD risk > 10%, BMI > 32 kg/m^2, age ≥ 75 years, T2DM diagnosis, > 9 medicines. Dominant ICER iterations increased to 41.0% with > 9 medicines	89% Good

Table 2 (continued)

Authors, year	Effectiveness outcome	Original currency/year	Economic model assumptions	Perspective	Time horizon (months)	Cost categories	Incremental costs (intervention vs control) (US$, 2019)	Incremental effectiveness (intervention vs control)	Cost effectiveness	Uncertainty	Quality score
Lin et al., 2018 [38]	QALYs and total medical expenditure	Taiwan dollar (TWD$)/2011 (assumed by researchers)	Trial-based analysis	Hospital (not reported)	12	Intervention (pharmacist salary) for savings:cost ratio calculation Hospital outpatient visits; hospital inpatient; ED visits	$− 2259.35 per patient in MTM group	IG: 0.216 (± 0.16) CG: − 0.01 (± 0.18) QALYs: 0.217 (estimated by researchers)	Dominant intervention Savings:cost ratio = 3.42:1	Not reported	50% Low
Gillespie et al., 2017 [49]	QALYS and mean number of PIPs	Euros (€)/2013	Trial-based analysis	Third- party payer	12	Intervention (GPs and pharmacists' time, travel expenses, materials and consumables); medication; GP and nursing visits; outpatient clinic visits; hospital day-case and inpatient admissions; ED visits	$544.43 (95% CI − 477.55 to 1565.08)	Number of PIPs/patient: –0.379 (95% CI − 0.666 to − 0.092) QALYs/patient: 0.013 (95% CI − 0.016 to 0.042)	$40,846 (95% CI − 447,91 to 387,25) per QALY $1697.51 (95% CI − 1872.74 to 8430.0) per PIP avoided	PSA, CEAC: PIP avoided: λ = €0/p[CE] 0.143; λ = $6019.52/p[CE] 0.951; QALY gained: λ = €0/p[CE] 0.138; λ = $60,195.23/p[CE] 0.602 7 Scenario analysis: (I) regression models estimated controlling for treatment arm only (ii) imputed QALYs for missing values; (iii) PIP costs (baseline cost by 6m + follow-up cost by 6m); (iv) PIP costs (baseline cost by 9m + follow-up cost by 3m); (v) reduce medication costs; (vi) increase intervention costs per patient; (vii) excluding PIP costs. Higher probability of CE intervention when QALYs were inputted λ = $60,195.23/p[CE] 0.764	82% Good

Table 2 (continued)

Authors, year	Effectiveness outcome	Original currency/year	Economic model assumptions	Perspective	Time horizon (months)	Cost categories	Incremental costs (intervention vs control) (US$, 2019)	Incremental effectiveness (intervention vs control)	Cost effectiveness	Uncertainty	Quality score
Turner et al., 2020 [47]	QALYs	Canadian dollar (CAN$)/ 2019	Decision tree (D-PRESCRIBE trial) combined with a Markov 5-states transition probabilistic model	Third- party payer (public)	12	Pharmacist intervention (fixed fee); sedative medication; GP visits; ED visits; hospital admission (non-hip fracture and hip fracture)	$− 1153.31 (95% CI − 1895.55 to − 642.41)	0.0769 (95% CI 0.0434–0.1191)	Dominant Intervention	PSA, CEAC, Monte Carlo simulation: 100% CE ($41,425.02/QALY and 82,850.04/QALY). 3 Scenario analysis: (i) all patients made an extra visit to the GP and the community pharmacist sent an opinion to the GP; (ii) pharmacist fee to provide the pharmaceutical opinion to the GP was increased; (iii) varied the success rate of sedative deprescribing: the intervention remained the dominant strategy	85% Good

Table 2 (continued)

Authors, year	Effectiveness outcome	Original currency/year	Economic model assumptions	Perspective	Time horizon (months)	Cost categories	Incremental costs (intervention vs control) (US$, 2019)	Incremental effectiveness (intervention vs control)	Cost effectiveness	Uncertainty	Quality score
Sanyal et al., 2020 [48]	QALYs	Canadian dollar (CAN$)/2018	Decision tree (D-PRESCRIBE trial) combined with a Markov model 6-states transition probabilistic model	Third- party payer (public)	12	Pharmacist intervention (fixed fee); medications; GP visits; ED visits; diagnostic tests; hospital admissions	$− 850.34 (95% CI − 1805.15 to − 232.26)	0.1078 (95% CI 0.0639–0.1658)	Dominant Intervention	PSA, CEAC, Monte Carlo simulation: 100% CE ($42,154.23/QALY and $84,308.46/QALY). 5 Scenario analysis: (i) all patients made an extra visit to the GP and the community pharmacist sent an opinion to the GP; (ii) pharmacist fee to provide the pharmaceutical opinion to the GP was increased; (iii) assumed 10% or 20% of patients who experienced a GI bleed underwent surgical management; (iv) examined the impact of less optimistic scenarios of NSAIDs discontinuation rates in IG; (v) examined the impact of low and high co-utilisation of gastroprotective agents: the intervention remained the dominant strategy	83% Good

BMI body mass index, *CE* cost effectiveness, *CEAC* cost-effectiveness acceptability curve, *CG* control group, *CHD* coronary heart disease, *CI* confidence interval, *CMR* clinical medication review, *DSA* deterministic sensitivity analysis, *ED* emergency department, *GI* gastrointestinal, *GP* general practitioner, *HRQoL* health-related quality of life, *ICER* incremental cost-effectiveness ratio, *IG* intervention group, *LYG* life-years gained, *MAI* medication appropriateness index, *MRF* medication review with follow-up, *PIP* potentially inappropriate prescription, *PSA* probabilistic sensitivity analysis, *QALY* quality-adjusted life-year, *T2DM* type 2 diabetes mellitus, *VAS* visual analogue scale, λ indicates threshold value

to other settings or patient groups was absent [43, 49, 51] or was poorly discussed [38, 40–42, 46] in several studies — an important issue from a policy viewpoint so that decision makers can use evidence in different contexts [56]. No study scored 100% and two studies scored ≤50% (low) on quality assessment. In addition, the ESM presents the studies with scores of 1, 0.5 or 0 for each item of the CHEC-extended checklist.

3.4 Main Findings

Of the seven EE studies conducted in the community pharmacy setting [40, 41, 44–48], four studies of three interventions [45–48] found that the intervention dominated usual care by improving health outcomes and reducing costs. One intervention was a pharmacist-led medication review with a 6-month follow-up conducted in Spain (conSIGUE trial) [45, 46], and the other two were a patients' educational service focusing on patients taking sedatives [47] and non-steroidal anti-inflammatory drugs [48] conducted in Canada. Cost savings for the intervention group compared with usual care were mainly driven by a reduction in hospital admissions related to the reduction in drug-related events. Interventions remained dominant in all scenarios and/or sensitivity analyses. The remaining three EE studies of pharmacist-led medication review services for people on polypharmacy found that interventions were either cost effective with an ICER of $18,708 per QALY [41], cost saving ($− 236.21) [44] or not cost effective compared with usual care ($52,389 per QALY) [40], considering the World Health Organisation's threshold.

The "RESPECT" study [41] evaluated a medication review service conducted on people aged ≥ 75 years taking five or more medicines. Compared with the base case, a sensitivity analysis revealed that intervention was more cost effective for younger patients (aged 75–84 years) with fewer medications (five to seven medicines) and less cost effective or even dominated usual care for older patients (aged ≥ 85 years) taking more medicines (ten or more medicines). The study that was not cost effective [40] evaluated a trial with a before-and-after study design of UK patients prescribed with four or more medicines. Pharmacists reviewed the medication for 6 months and discussed the risk of falls, pain management, adherence and general health with patients. A small but significant decrease in the number of falls, gains in quality of life and medicine adherence was observed. Overall, the mean costs per patient were higher in the 6-month follow-up compared with the pre-intervention period, mostly derived from the intervention and other (non-detailed) National Health Service costs. A further 12-month ICER estimation was made on the assumption that the 6-month gains would remain constant with no further costs, resulting in a cost-effective strategy compared with usual care ($19,179 per QALY). The intervention found to be cost saving [44] was a clinical medication review focused on patients' preferences, delivered to older Dutch adults aged ≥ 70 years using seven or more long-term medicines. Intervention gains were inconsistent with no benefits on HRQoL measured with the generic EQ-5D-5L instrument, and small benefits on health-related complaints, and HRQoL measured with the EQ-Visual Analogue Scale. However, the intervention compared with usual care led to cost savings, resulting in a > 90% likelihood of the intervention to be cost saving from a societal perspective. The highest savings were derived from a reduction in institutional and informal care in the intervention group at the 6-month follow-up [44].

Overall, regarding incremental effectiveness, there were no major variations between studies. Incremental QALYs varied from − 0.00217 [44] to 0.108 [48]. Greater differences were found regarding incremental costs, varying between $− 1153 [47] and $359.19 [40]. Variations were largely derived from a reduction in hospital admissions and informal care for the intervention group compared with the control group, and from wide-ranging intervention costs. Costs of intervention ranged between $16.6 (CAN$20) [47, 48] and $259.7 (€199) [44].

Regarding the six studies [38, 42, 43, 49–51] conducted in outpatient, general practices, primary care and geriatric clinics, two interventions dominated usual care [38, 42], three were cost effective [43, 49, 50], and one reported a value of $881.95 per 1 unit of medication appropriateness index change [51], a measure of appropriateness prescription rather than a measure of outcome. Cowper et al. [51] is the oldest study included, and presented the lowest quality in methodology.

In detail, the study from Taiwan [38], assessing a pharmacist-led medication review for people on polypharmacy conducted in an outpatient academic medical centre, reported positive incremental QALYs and cost savings in the intervention group compared with the control group (intervention dominated usual care). Additionally, a savings: cost ratio of 3.42:1 for a 12-month intervention was found, when total medical expenditure savings were compared with the annual salary of the clinical pharmacist enrolled in the intervention [38]. Note that this study was assessed with low methodological quality, for example, mean costs per patient in each arm were not reported, nor were details of the resource costs. The other dominant intervention compared with usual care was a medicine review focused on the withdrawal of FRIDs [42]. The intervention was associated with a risk reduction in falls and cost savings because of medical treatments avoided. The Polinder et al. [43] study also assessed the cost effectiveness of FRID withdrawal or reduction, and found that the intervention was cost effective with an estimated cost of $1085.84 per QALY gained. The total fall-related healthcare costs did not differ significantly between groups; however, the FRID withdrawal reduced the medication costs. Furthermore, differences

in effectiveness were significant and positive (incremental effectiveness = 0.05 QALYs) [43]. The intervention was delivered by a research physician supported by a research nurse who was responsible for a patient's follow-up via the phone. The two 12-month medication reviews, delivered in Chile [50] for people on polypharmacy enrolled in a cardiovascular disease prevention programme, and in Ireland for people taking specific classes of PIMs [49], were both assessed as cost effective compared with usual care, with ICERs of $434.4 and $40,846 per QALY, respectively. A scenario and subgroup analysis performed by Ahumada-Canale et al. [50] found that all iterations cost less than $1700 per QALY, and that dominant iterations increased to 41.0% when considering only patients taking more than nine medicines. In the case of the Irish study, a higher probability of the intervention being cost effective was found when QALYs were inputted for missing data [49]. Overall, no major variations in incremental QALYs (0.013 [49], 0.05 [43] and 0.063 [50]) were found across studies conducted in outpatient, primary care, general practices or geriatric clinics with the exception of the Lin et al. study [38]. Regarding costs, greater differences were observed among studies driven mainly by inpatient admissions and medication and intervention total costs. This latter item ranged between $77.6 (€58) [49] and $167 (€120) [43].

The study assessing the cost effectiveness of a pharmacist-led medication review intervention at a patient's home [39] showed that this service was not cost effective ($112,932 per QALY). The intervention was delivered to patients aged ≥ 80 years who had an emergency visit for any cause. Patients in the intervention group had higher community, primary and hospital care costs, with a slight mean positive difference in QALYs compared with the control group (incremental QALYs = 0.0075).

4 Discussion

This systematic review was conducted to identify and summarise available evidence of the economic value of deprescribing interventions among community-dwelling older adults. To the best of our knowledge, this is the first review gathering economic evidence of interventions that seek to reduce or withdraw medications that might be causing harm or might no longer be of benefit. Fourteen full EE studies assessing 13 interventions were identified.

Of these, nine interventions assessed in ten papers found that deprescribing interventions either dominated ($n = 5$) [38, 42, 45–48] or were cost effective ($n = 4$) [41, 43, 49, 50] compared with usual care, considering the World Health Organization threshold of 1 GDP/capita. One other EE reported cost savings with the intervention being at least as effective as usual care [44], and another found a cost of $881.95 per medication appropriateness index unit change in the intervention compared with usual care, concluding that the deprescribing intervention assessed can improve prescription and reduce inappropriate medications [51]. However, this conclusion can be challenged, as the cost effectiveness depends on each authority's willingness to pay for this type of outcome, and there is no standard acceptable threshold for a medication appropriateness index. Only two deprescribing interventions were found not to be cost effective compared with usual care [39, 40], the one delivered at a patient's home [39], and the other conducted at the community pharmacy [40]. Nonetheless, for the latter, a 12-month scenario found the intervention compared with usual care to be cost effective ($19,178.66 per QALY) within the country's World Health Organization's threshold [57].

The deprescribing interventions ($n = 9$) were mostly some type of medication review conducted on overall medication [38–41, 44, 46, 49–51], and performed largely by a community or clinical pharmacist [38–41, 44–46, 50, 51] with multidisciplinary cooperation, an approach that has been described as advantageous for the success of this type of intervention [58]. The positive findings for these interventions are mostly in line with those reported in a recent systematic review of cost effectiveness of advanced pharmacy services [59]. The review concluded that advanced services, where deprescribing interventions fit, appear to be cost effective when delivered in community and primary care settings, but not in home-based settings [59]. However, it is important to note that these interventions can be complex and depend on contextual factors, such as the existence of an efficient multi-professional cooperation, available communication channels and integration of care. For some interventions, such as the one described in the conSIGUE studies [45, 46], despite the dominance of the intervention, the level of cooperation and communication between the community pharmacists and the general practitioners did not seem structured. Although these interventions were carried out with professional cooperation, the studies highlighted the fragmentation and lack of structured integration of care, as well as an excessive pharmacological approach to health problems.

The other four interventions targeted specific class(es) of medicines through a directed physician-led medication review [42, 43] and a pharmacist-led patient educational intervention [47, 48]. Overall findings suggest that these strategies can be an efficient method to reduce costs with positive gains in health-related outcomes, especially on a large scale, as discussed previously by Bloomfield et al. [17]. Moreover, these conclusions based on experimental studies are strengthened with results presented in other studies with different study designs. For example, in a theoretical modelling study, Moriarty et al. [60] concluded that interventions to reduce the long-term use of non-steroidal

anti-inflammatory drugs, benzodiazepines and proton-pump inhibitors are cost-effective strategies; and in a similar study based on pharmacy dispensing data, Chau et al. [61] estimated cost savings and effect gains (QALYs) for a successfully inappropriate proton-pump inhibitor withdrawal, after non-steroidal anti-inflammatory drugs and low-dose acetylsalicylic acid cessation. Overall, with the exception of one moderate-quality study [40], deprescribing interventions delivered in the community pharmacies or general practices/outpatients clinic settings were cost saving, cost effective or dominant despite some differences in how and to whom they were delivered.

Nevertheless, these findings should be considered with some caution. Five studies were considered to have low or moderate methodological quality, failing to report and assess important aspects. Regarding the time horizon, all studies in the review adopted a short-term perspective (≤ 12 months), which may be inadequate to capture all potential long-term effects of medicine withdrawal. The type of intervention includes therapy discontinuation that may affect, for example, disease progression or the occurrence of long-term side effects [29], and at the same time, the effect of the intervention may have a limited effect in time, particularly after it is ended. Thus, the cost-effectiveness findings of these studies might be overrated or underrated, considering that the health might improve or deteriorate, and related adverse events might occur or be avoided over time. However, in studies with long-term horizons, investigators must anticipate outcome progression over time for treatment and control groups, which can be difficult to do. Another issue to consider is that private payer's perspective studies generally require relatively short-term horizons (1–2 years) [62]. Still, another aspect that needs to be considered is that most EEs are based on one experimental trial, subject to major or minor biases and confounding variables related to the study design, and that does not cover all evidence in the research area. The lack of large real-world-evidence is an issue, especially when considering that complex interventions greatly depend on the context in which they are delivered (e.g. cultural characteristics, socioeconomic status, patients' literacy, patients and healthcare provider engagement).

A positive fact is that most of the studies [38–41, 43–50] reported cost-effectiveness ratios using QALYs as the effectiveness measure, assessed by the EQ-5D generic instrument, which thereby facilitates comparisons between services for decision-making assessment and resource allocation. However, across studies, a low magnitude of QALY gains was observed even if other outcomes with an expected positive impact on patients' HRQoL were significantly improved (e.g. number of PIPs per patient, reduced health-related complaints). This raises the question of whether there is a lack of sensitivity in the EQ-5D instrument for elderly patients or the intervention is not sufficiently impactful to improve the quality of life in a short period of time [63, 64]. As incremental effectiveness was similar across studies, the variations in ICERs depended mostly on the incremental costs. Thus, an important concern is the type and valuation of resources included in each economic analysis, even the intervention costs. In most studies, the impact of varying these parameters was assessed in a scenario analysis, showing no substantial changes in conclusions drawn.

Heterogeneity between interventions, differences in population characteristics, methodology limitations, country-specific context, variety of settings, and type of healthcare system organisation and funding hinders a clear conclusion on the cost effectiveness, and on the generalisation and transferability of these findings. Nevertheless, it can be argued that there is economic evidence that supports the positive value of deprescribing interventions across countries and settings. In an era when an ageing population and multimorbidity are rising, small gains applied to a large proportion of people can become significant. However, for this to happen, it is necessary to implement country-wide measures.

Overall, it is important to point out that the studies included in this review reported ad-hoc interventions delivered in a specific context and/or region. Despite their relevance, there is a lack of wider evidence regarding these interventions. On a larger scale, the outcomes can be different from those found in a specific locality or region because PIM prevalence, level of professional cooperation, patients' characteristics, acceptance of the intervention and other factors may vary across regions. Additionally, there are no international comparisons of the same intervention that allow a conclusion to be drawn on which context is the most favorable to cost effectiveness. Moreover, a subgroup analysis should be explored and target patients who would most likely benefit from deprescribing interventions, as its effects may vary across therapeutic classes, number of medicines taken, and patients' age and lifespans, as discussed elsewhere [20, 22].

4.1 Limitations

There are some potential limitations to this study. First, it is restricted to peer-reviewed studies, which may have caused bias by excluding health technology assessment reports not submitted to this process, for example. Furthermore, papers from European countries not published in the English language could have been missed, as we could not access Embase, which is the most likely to cover such papers. However, seven electronic databases (generic and key databases) were searched with the goal of identifying as many relevant studies as possible. Second, the possibility of publication bias may have affected the review findings,

as negative results are less likely to be published. Third, the appraisal of the methodological quality of the studies using the CHEC-extended checklist was susceptible to the subjective judgements of the reviewers. However, the assessment was always conducted and agreed upon by at least two reviewers, which may have reduced individual discernment. Despite these limitations, the findings of this systematic review are valuable and contribute to a more comprehensive knowledge of the economic value of deprescribing interventions for community-dwelling older adults.

5 Conclusions

Despite the growing interest and research on the effectiveness of deprescribing interventions, economic evidence has been studied only recently. Different outcomes were found among studies, but overall findings point to the cost effectiveness of interventions, which in some cases are even dominant. Population-based studies considering different geographies, other targeted medications and equity concerns, as well as more robust EEs regarding a long-term impact assessment, are needed to support evidence-based decisions on the implementation of interventions to deprescribe inappropriate medicines for community-dwelling older adults. Considering contextual factors and observed heterogeneity among studies, transferability assessment of relevant interventions also needs to be addressed before their adoption by other countries.

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Consent for publication Not applicable.

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Code availability Not applicable.

Authors' contributions SR conceived the study and performed the literature search. Data collection and analysis were performed by all authors (SR, DF, IT and JP). The first draft of the manuscript was written by SR, and all authors reviewed and edited all versions of the manuscript. All authors read and approved the final manuscript.

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