R E V I E W

Economic Evaluations of Interventions to Optimize Medication Use in Older Adults with Polypharmacy and Multimorbidity: A Systematic Review

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Purpose: To conduct a systematic review of the economic impact of interventions intended at optimizing medication use in older adults with multimorbidity and polypharmacy.

Methods: We searched Ovid-Medline, Embase, CINAHL, Ageline, Cochrane, and Web of Science, for articles published between 2004 and 2020 that studied older adults with multimorbidity and polypharmacy. The intervention studied had to be aimed at optimizing medication use and present results on costs.

Results: Out of 3,871 studies identified by the search strategy, eleven studies were included. The interventions involved different provider types, with a majority described as a multidisciplinary team involving a pharmacist and a general practitioner, in the decision-making process. Interventions were generally associated with a reduction in medication expenditure. The benefits of the intervention in terms of clinical outcomes remain limited. Five studies were cost-benefit analyses, which had a net benefit that was either null or positive. Cost-utility and cost-effectiveness analyses resulted in incremental cost-effectiveness ratios that were generally within the willingness-to-pay thresholds of the countries in which the studies were conducted. However, the quality of the studies was generally low. Omission of key cost elements of economic evaluations, including intervention cost and payer perspective, limited interpretability.

Conclusion: Interventions to optimize medication use may provide benefits that outweigh their implementation costs, but the evidence remains limited. There is a need to identify and address barriers to the scaling-up of such interventions, starting with the current incentive structures for pharmacists, physicians, and patients.

Keywords: polypharmacy, economic evaluation, potentially inappropriate medication, cost-effectiveness, cost-utility, cost-benefit

Introduction

Population aging comes with an increase in older individuals living with multiple chronic conditions leading to a rise in the number of prescribed medications. Polypharmacy, the consumption of multiple medications simultaneously,[1] is associated with the risk of adverse drug events (ADEs), hospital admissions, the reduction of patients' functional capacity and quality of life,[2-6] and the prescription of potentially inappropriate medications (PIM). PIMs, although unstandardized in definition, generally refer to the prescription of medications that lead to higher risk

relative to clinical benefit or reasonable alternative therapies.[4,7] The term may refer to incorrect dosing or indication, prolonged medication use, and presence of interactions, among other suboptimal practices.[7,8] A recent review of systematic reviews suggests that interventions to decrease the prescriptions of PIMs are effective, even if the effect size was moderate.[7] Commonly employed interventions include medication reviews, wherein recommendations are made from a systematic assessment of medications, and pharmaceutical interventions, which incorporate formal clinical practice of pharmacists.[7] Yet, the costs of conducting interventions to optimize medications in older people with polypharmacy have to be offset by the added value for patients and for health care systems for the interventions to be scaled up. To the best of our knowledge, no systematic review analyzed the economic evaluations of such interventions.

The purpose of our study was to conduct a systematic review of economic evaluations of interventions intended at optimizing medication use in older adults with multimorbidity and polypharmacy to determine if such interventions are cost-effective.

Methods

Using the PICO framework,[9] we identified the population of interest as older adults with multimorbidity and polypharmacy. Multimorbidity was defined as the presence of at least two chronic conditions in a patient.[10,11] Although there is no consensus on the definition of polypharmacy, it is generally considered when a patient is prescribed at least five medications.[1] We, therefore, applied this common definition in our inclusion criteria when polypharmacy was not explicitly defined by the authors. When authors clearly defined polypharmacy (eg use of 10+ medications), we kept their definition. The intervention was aimed at optimizing medication use, the comparator being a group of individuals with similar characteristics but not receiving the intervention. Interventions were interpreted as optimizing medication use if they sought to evaluate patient medication lists in order to optimize prescription appropriateness and/or minimize medication-related problems (MRPs) and adverse drug events (ADEs).

Our systematic review is specific to studies including a full economic evaluation, that is a cost-effectiveness analysis (CEA), cost-utility analysis (CUA), or cost-benefit analysis (CBA). The outcome varied depending on the type of economic evaluation without any restrictive criteria on our side. While all three methods identify and measure the costs of at least two alternatives (for instance, an intervention and a control), they differ in how the outcomes are measured. In a CEA, a specific outcome related to the intervention is identified and measured in natural units for each alternative. For example, a study may measure cost-savings related to ADE avoided as a result of medication optimization.[12,13] The CUA is a special case of a CEA in which the effect is measured in quality-adjusted life years (QALY). In a CBA, each outcome is given a monetary value. For example, a CBA may examine reduction in medication costs or medical expenditures due to PIM reduction.[14–16]

Research Strategy

With the support of a librarian, we identified all the terms associated with the elements of the PICO and the combinations possible. Details of the terminology are provided in the Appendix. The search was conducted in March 2018 and updated in May 2020 on the following databases: Ovid-Medline, Embase, CINAHL, Ageline, Cochrane, and Web of Science. We hand-searched references of all identified systematic reviews as well as included articles to single out additional potentially relevant articles.

Eligibility Criteria

To be included, studies needed to meet the following criteria: the study population was composed of at least 80% of older adults (defined as being aged 65 and over) with multimorbidity and having polypharmacy; the study included an economic evaluation of an intervention to optimize medication use; the article was published between 2004 and 2020; and the article was published in English, French, German, Italian, Spanish or Dutch, languages understood by our team. Because the definition of polypharmacy changed over the last decades, we restricted the search from 2004 to 2020 to limit heterogeneity in the definitions used between the studies. The lower limit of 2004 was chosen in the other systematic reviews performed by our team.[17]

The following criteria were used to exclude studies: the study population did not consist of older adults, the study targeted a population with polypharmacy within a specific condition (for instance, polypharmacy described as the use of multiple psychotropic medications in schizophrenia), the study did not assess an intervention, costs were not measured. We nevertheless included studies in which the

intervention was on a specific medication class optimization, without identifying a specific condition. Studies that did not include a complete economic evaluation (CEA, CUA, or CBA) were excluded. We also excluded systematic reviews, study protocols and conference posters.

Study Selection

The first phase consisted of identifying articles eligible for full-review. First, one of the authors (MG) removed all the duplicates in the list. Then, four authors scanned titles and abstracts (CB, CS, MG, ML), with each title/abstract being independently assessed by two authors. Each author indicated whether an article should be included or excluded using the defined criteria. The authors discussed any discordance to reach a consensus on the list of articles. In the second phase, each article was independently fully read by at least two authors to confirm inclusion (CS, CL, MG, ML, YN). If, upon full review, the article met one of the exclusion criteria, it was removed, and the reason for the exclusion was noted. If multiple articles covered the same intervention, we selected the one deemed the most relevant based on the study objectives and inclusion/exclusion criteria and was usually the most recent. The list of references from systematic reviews and included articles were handsearched. Titles and abstracts of articles that were not in the initial search were reviewed by two authors (YN and ML) using the same process as described above.

Data Extraction

A table of variables was developed for data extraction with the following elements: authors, year of publication, title, study design, time horizon, number of patients, study setting (primary care clinics, pharmacies, long term care facilities, etc.), country, intervention characteristics, clinical outcomes of the intervention, costs elements measured (direct medical, direct non-medical, indirect), perspective (hospital, health care system, patient, pharmacist, society), and results of the economic evaluation (incremental cost-effectiveness ratio [ICER], net benefit, or cost-benefit ratio). Data were extracted and reviewed by at least two authors independently with a third author when there was uncertainty (CL, CS, MG, ML, YN).

At least two authors independently assessed the quality of each study retained and discussed discrepancies, with a third author providing input when needed to reach consensus (CL, CS, ML, MLL, YN). The Quality of Health Economics Studies (QHES) instrument[18] was used for the

assessment. In this instrument, a number of points are attributed for fulfilling certain criteria; evaluators can only give 0 or full points.

Data Synthesis

Studies were organized based on intervention and economic evaluation themes. Intervention themes included setting, type of intervention to optimize medication use (PIM identification tool, medication reviews), provider types involved, and incorporation of patient-provider discussions in decision-making. We determined the type of economic evaluation based on costs and outcomes measured in each study. We independently determined whether each study qualified as a CEA, CUA, or CBA, and discrepancies were discussed. Quantitative analyses were limited due to heterogeneity of study design and economic evaluations.

Results

Figure 1 shows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[19] flow diagram (Figure 1). A total of 3,871 distinct articles were identified from the search strategy across six databases. After including four articles identified through systematic review references, 68 articles were eligible for full-text review. Of the total full text articles, eleven studies (including three from the 2020 update) met the inclusion criteria. The characteristics of the studies are summarized in Table 1. The studies came from different countries [Spain, n=2; Australia, n=1; Ireland, n=2; Netherlands, n=2; Northern Ireland, n=1; Taiwan, n=1; and United Kingdom, n=1, United States=1]. The settings were distributed between primary care clinics (n=4),[12,14,15,20] nursing homes (n=1),[21] pharmacies (n=3),[22–24] one hospital,[13] one academic medical centre,[16] and one study included three different types of clinical sites.[25] The most common study design was cluster randomized controlled trial (n=6),[13,15,20,21,23,24] or randomized controlled trial (n=3).[12,14,16] One study conducted a before-and-after analysis[22] and one was a cohort study with a control group.[25]

Intervention Characteristics

Characteristics of the interventions are reported in Tables 1 and 2. The stated purpose of interventions was variable. Seven studies examined interventions explicitly aimed at identifying PIMs.[12–14,16,20–22] Five studies included interventions with a stated goal of optimizing prescribing to address MRPs or ADEs.[13,16,23–25] One study evaluated medications reviews as a form of monitoring "prescription-related points of concern", such as benzodiazepines use in older adults.[15]
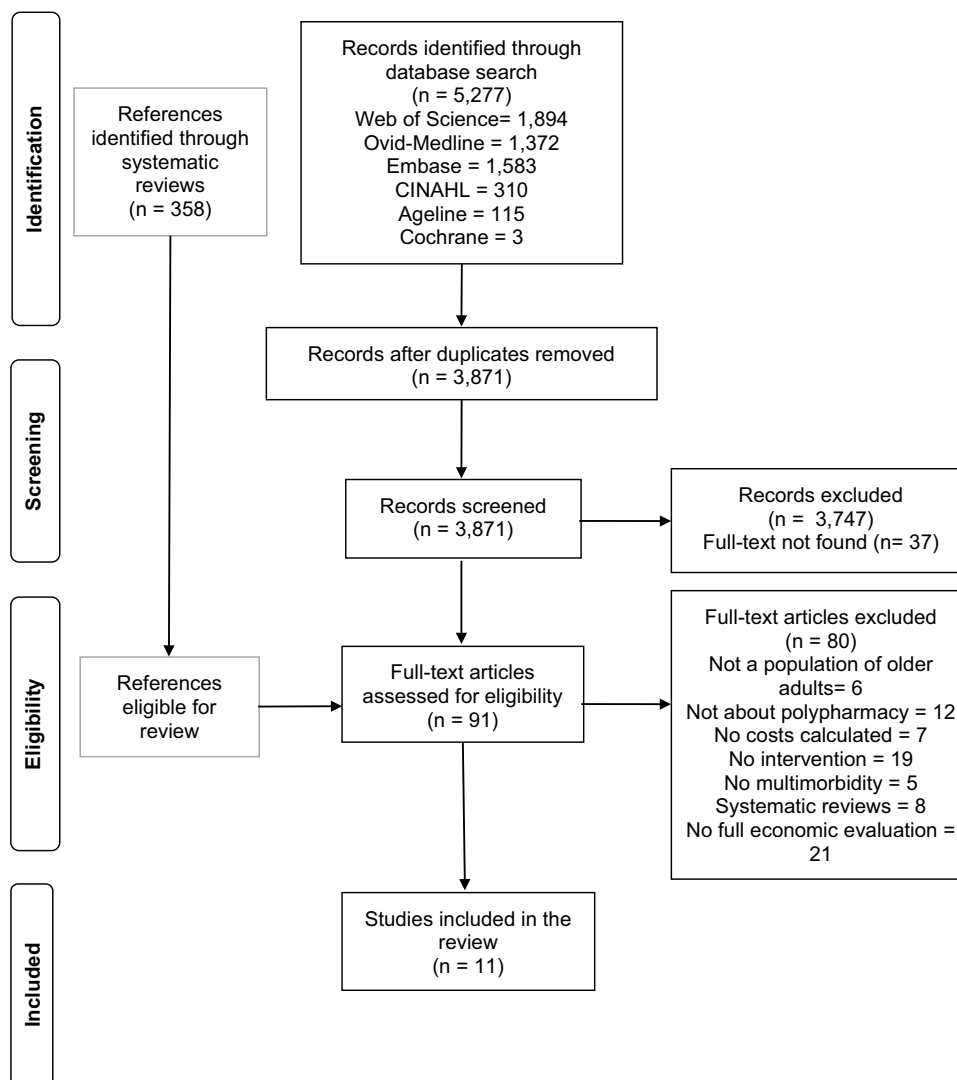
Figure 1 Flow diagram for screening and selection processes. Updated search conducted in May 2020 resulted in 1,145 new records screened, 36 full-text articles assessed, and three studies included in the review.
Notes: Adapted from: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med*. 2009;6(7):e1000097. doi:10.1371/journal.pmed1000097.[37] Copyright: © 2009 Moher et al Creative Commons Attribution License. For more information, visit www.prisma-statement.org.

All interventions included a medication review performed by a pharmacist except for one study in which the intervention consisted of pharmacogenetic testing coupled with a clinical decision support tool.[25] The interventions involved different provider types; some described multidisciplinary teams, while others had providers as informal collaborators. The pharmacists' recommendations were most often discussed with a general practitioner (GP) (n=8),[12,14–16,20–22,25] or/and specialists (geriatricians, cardiologists, nephrologist) (n=1).[16] The Screening Tool of Older Persons Prescriptions/Screening Tool to Alert doctors to Right Treatment (STOPP/START),[13] and the Good-Palliative-Geriatric Practice (GP-GP) tools were

mentioned as means to identify PIMs.[14,22] Seven studies also mentioned the use of an algorithm that was either developed by the team and explained, using existing tools, or not further defined.[12,15,16,20,21,23–25] The duration of the interventions and the study period varied between four[25] and 12 months,[14,16,20,21,24] with the exception of one study in which the time horizon was the 10 days following a patient's discharge.[13]

Intervention Clinical Outcomes

The benefits of the intervention in terms of clinical outcomes remain limited. Only two studies specifically reported a decrease in PIM use,[20,21] including one

Table 1 Characteristics of Included Studies

Authors (Ref #)	Year	Intervention	Country	Study Design	No. of Patients
Brixner et al[25]	2016	Pharmacogenetic testing and clinical decision support tool identifies drug-drug and drug-gene interactions. -Discussion: Pharm + MD -Setting: cardiology, primary care, and internal medicine clinics	United States	Cohort +control group	1,025
Campins et al[14]	2017	MR conducted by a pharmacist -Discussion: Pharm + MD, MD + patient -Setting: 7 primary care centres	Spain	RCT	490
Denneboom et al[15]	2007	2 MR intervention groups involving MD, Pharm: -Case-conferences to discuss PIM -Written recommendations to GPs -Setting: Primary care	Netherlands	Cluster RCT	738
Gillespie et al[20]	2017	MR by research team pharmacist -Discussion: Pharm + MD -Setting: 21 general practices	Ireland	Cluster RCT	196
Lin et al[16]	2018	MR conducted by a pharmacist -Discussion: Pharm + patient, Pharm + MD -Setting: Academic medical centre	Taiwan	RCT	178
Malet-Larrea et al[23]	2017	MR conducted by a pharmacist -Action plan: Pharm + patient -Setting: Community pharmacies	Spain	Cluster RCT	1,403
O'Brien et al[13]	2018	MR conducted by research physician -Discussion: research MD + hospital MD -Setting: University teaching hospital	South Ireland	Cluster RCT	732
Patterson et al[21]	2011	MRF conducted by a pharmacist. Monthly pharmaceutical care visits. -Discussion: Pharm + MD -Setting: 22 nursing homes	Northern Ireland	Cluster RCT	253
Sorensen et al[12]	2004	Home program including: -MR and patient home visit by a pharmacist -GP education, primary care team conferences -Action plans: GP + patients Setting: Primary care (through GPs)	Australia	RCT	400
Twigg et al[22]	2015	MR conducted by a pharmacist -Discussion: Pharm + MD + patient -Setting: Community pharmacies	United Kingdom	Before-and-after	620
Van der Heijden et al[24]	2019	MR conducted by a pharmacist -Discussion: Pharm+MD, Pharm +patient -Setting: Community pharmacies	Netherlands	Cluster RCT	340

Abbreviations: GP, general practitioner; MD, medical doctor; MR, medication review; MRF, medication review with follow-up; RTC, randomized controlled trial; Pharm, pharmacist.

restricted on antipsychotics use.[21] Two studies reported decreases in ADEs.[13,24] Two studies reported recommendations for changes in medication,[15,22] with one documenting those implemented during the intervention, but the changes between groups were no longer significant nine months after the intervention.[15] Two studies

Table 2 Select Characteristics of Intervention

Study (Ref #)	PIM Tool	Time Horizon	Clinical Outcomes (Intervention vs Control)	Costs Elements Measured	Perspective	QHES
Brixner et al[16]	Clinical Decision Support tool	4 months	Hospitalizations: 9.8% vs 16.1%; ED visits: 4.4% vs 15.4%; outpatient visits: 71.7% vs 36.5% (all SS)	Costs of the test; Costs for physician visits, ED visits, and hospitalizations	Not stated (appears to be health care system)	89
Campins et al[14]	GP-GP algorithm STOPP/START	12 months	Mean reduction in # of prescriptions (%): 12.5% vs 8.9%, p=0.091	Health care providers: pharmacists' and physicians' time* hourly wage; Drug costs	Not stated (appears to be health care system)	95
Denneboom et al[15]	Computerized screening tool	9 months	Number of medication changes following recommendations (at 9 months): 19 vs 33, p=0.070	Health care providers: pharmacists + MD; Drug costs	Not stated; (appears to be health care system)	52
Gillespie et al[20]	Web-based algorithm	12 months	Before/after: Number of PIMs per patient: 1.31/0.61 vs 1.39/1.08; EQ5D score: 0.628/0.665 vs 0.689/0.652	Costs of the intervention; Costs related to PIMs; Health care costs	Health care system	99
Lin et al[16]	Not specified	12 months	Laboratory data and EQ5D scores (half were SS)	Health care costs: ED, Outpatient, Inpatient	Not stated	51
Malet-Larrea et al[23]	Not specified	6 months	Before/after: Number of medicines used:7.7/7.5 vs 7.4/7.3; Patients in ED: 193/90 vs 211/173; Patients hospitalized: 89/38 vs 68/65.	Direct medical costs: drugs, ED visits, hospital admissions; Intervention costs (pharmacists' time and investments)	Health care system	85
O'Brien et al[13]	STOPP/START	10 days	Decrease in adverse drug reactions (−0.164, 95% CI:-0.257;-0.070)	Intervention costs (physician time and remuneration); Hospitalization costs	Public health care provider	71
Patterson et al[21]	Algorithm	12 months	Proportion of residents with psychoactive PIM at 12 months: 19.5% vs 50.4%	Drug costs; Total patient-level health care costs	Health care system	92
Sorensen et al[12]	Not specified	6 months	Duke's severity of illness reduced by 4.92 vs 1.34 (not SS); No differences for number of hospital admissions and GP visits.	Health care costs; Drug costs; Intervention costs (Pharmacist & MD remuneration)	Not stated (appears to be health care system)	72
Twigg et al[22]	START/STOPP	6 months	142 recommendations made; decrease in total falls (−0.116, 95% CI: −0.217; −0,014); increase in adherence (SS); no SS differences in pain and day-to-day activity	Intervention costs: time for pharmacist, healthcare assistant, GP HCC: hospital inpatient and outpatient days, A&E visits, specialist consults, out of hours with GP/RN	Not stated (appears to be health care system)	72

(Continued)

Table 2 (Continued).

Study (Ref #)	PIM Tool	Time Horizon	Clinical Outcomes (Intervention vs Control)	Costs Elements Measured	Perspective	QHES
Van der Heijden et al[24]	Amsterdam CMR tool	6–12 months	Hospital re-admissions: 46.4% vs 20.9%. Decrease in drug-related problems (−0.2, 95% CI: −0.4; −0.1)	HCC: GP visits, specialist visits, physical therapy, hospital readmissions, home care; Indirect costs: Help by family and friends, paid housekeeping; Cost of CMR	Society	84

Abbreviations: ADR, adverse drug reaction; A&E, ambulatory & emergency; CMR, clinical medication review; ED, emergency department; GP, general practitioner; GP-GP algorithm, Good palliative-geriatric practice algorithm; HCC, health care costs; MD, medical doctor; PIM, potentially inappropriate medications; QHES, Quality of Health Economic Study; RN, registered nurse; SS, statistically significant.

that evaluated the decrease in the total number of medications did not obtain statistically significant results between groups.[14,23] Further, no statistically significant difference was noted in the Duke's severity of illness score, the number of hospital admissions or GP visits in the study by Sorensen et al.[12] Hospital re-admissions were higher in the intervention group than they were in the control group in van der Heijden et al's study.[24] The number of hospitalizations and of emergency room visits were reduced in the study by Brixner et al, but outpatient visits increased, although not statistically significantly.[25] Finally, mixed results were obtained on laboratory data in the study by Lin et al, where about half of the many tests performed were not statistically significant.[16]

Nine studies included the costs of the interventions. One included only the cost of a pharmacogenetic test.[25] The other eight included the time of pharmacists, and of physicians.[12–15,20,22–24] When included, non-medication expenditures, and specifically costs of hospitalizations, drove total patient expenditures down following the intervention.[16,20,23,25] In one study, the factors driving the reduction in medication expenditure costs were identified as, first, the reduction in the total number of prescribed medications, second, the reduction of newer (more expensive) prescribed medications, and lastly, the change in dosages.[14]

Economic Evaluations

Five studies were cost-benefit analyses where the outcomes were medication expenditure[14,15] or health care costs.[16,23,25] They reported either a non-significant benefit[15] or cost-benefit ratios between 2.38[14] and 6.22.[23] Cost-utility analyses with QALYs were conducted in two studies.[20,22] Estimates of the cost per QALY gained varied

from £11,885 to £32,466 in the UK[22] and were €30,535 in Ireland.[20] Cost-effectiveness analyses were conducted in five studies and used either the proportion of patients having a PIM,[21] the number of PIM avoided[20] or the number of ADE avoided.[12,13,24] The cost per PIM avoided was estimated at €1,269 (95% CI=€-1,400-€6,302).[20] The cost per ADE avoided varied between AUS $69[12] and €8,270.[24] Patterson et al found the intervention to be associated with non-significant lower cost as well as a reduction in patients having at least one PIM.[21] Complete results are reported in Table 3.

Quality of the Studies

The QHES score of each study is indicated in Table 4 and ranges from 51 to 99 out of 100. Only five studies stated the perspective.[13,20,21,23,24] Sensitivity analyses were reported in six studies.[14,20,21,23–25] Similarly, seven studies transparently displayed the components for the economic evaluation[13,14,20–22,24,25] and six explained the potential sources of bias.[14,15,20,21,24,25] The type of economic evaluation was not always explicit, and there were key cost elements that were often omitted, notably the cost of the intervention itself (physician time, training of providers, etc.).

Discussion

Despite a rich literature on interventions to optimize medication uses in older individuals with polypharmacy, only eleven studies met the criteria of the presence of a full economic evaluation. Cost-effectiveness of the intervention may depend on contextual factors of the intervention and willingness-to-pay thresholds for a marginal improvement in medication use or a marginal reduction in ADEs. Due to heterogeneity in reported outcomes and suboptimal

Table 3 Economic Evaluation Characteristics

Study	Type of Economic Evaluation	ICER (95% CI), or Cost-Benefit Ratio or Net Benefit	Costs	Outcome
Brixner et al[25]	CBA (not explicit)	Median cost: US$126 per patient (NB) Mean cost: US$218 per patient (NB)	Median ΔC hospitalizations: US$ 168,896 Median ΔC ED visits: US$ 15,390 Testing costs: US$ 187,370	Health care costs
Campins et al[14]	CBA (not explicit)	€2.38 per patient (NB)	Drug costs reduction: IG: €233.75 (CI=170–298) CG: €169.40 (CI=103–235) Intervention cost: €27.03	Drug costs
Denneboom et al[15]	CBA (not explicit)	0 (NB)	ΔC: €5.27 (CI= 2.21–8.34) ΔE: €4.44 (CI= −6.90–12.81)	Drug costs
Gillespie et al[20]	1)CEA 2)CUA	1) €1,269 (CI=−1,400–6,302) 2) €30,535 (CI=−334,846–289,498)	ΔC: €407 (CI= −357–3,040)	1) PIM avoided 2) QALY
Lin et al[16]	CBA (not explicit)	3.51:1	ΔC: −29,821 TWD	Total medical expenditure
Malet-Larrea et al[23]	CBA	1) €420 (NB); 3.33:1 2) €701 (NB); 6.22:1	ΔC: €-97 (6 months) IG €946; CG: €1,043	1) QALY WTP= €18,247 2) QALY WTP= €34,097
O'Brien et al[13]	CEA	€5358	ΔC: €877 (CI= −1807–3561)	ADR averted
Patterson et al[21]	CEA	ΔC US $-130.39/ΔE 0.309 (CI=−1,150.16–889.38) (negative ICER)	IG: US $4,923 (CI=4,206–5,640) CG: US $5,053 (CI=4,328–5,779)	Proportion of residents receiving one or more PIM
Sorensen et al[12]	1)CEA 2)CEA	Marginal benefit: AUS$54 1)AUS$69 2)AUS$65	IG: AUS $5,401 CG: AUS $5,730 Intervention: AUS $275	1)ADE avoided 2)Gain on the DUSOI-A score
Twigg et al[22]	CUA	£11,885 to £32,466	Intervention: £98.72 ΔC: £219.35	QALY
Van der Heijden et al[24]	CEA	€8270	ΔC: €1654 (CI= −520–3828)	Drug-related problem reduction

Abbreviations: ADE, Aadverse drug event; ADR, adverse drug reaction; CBA, cost-benefit analysis; CEA, cost-effectiveness analysis; CG, control group; CI, confidence interval; CUA, cost-utility analysis; ΔC, difference in costs; ΔE, difference in effects; DUSOI-A, Duke's Severity of Illness Visual Analogue Scale; ICER, incremental cost effectiveness ratio; IG, intervention group; NB, net benefit; PIM, potentially inappropriate medication; QALY, quality adjusted life year; WTP, willingness-to-pay.

quality of the economic evaluations, we cannot draw a clear conclusion on the cost-effectiveness of interventions to optimize medication use.

Only four studies evaluated the cost per PIM avoided or ADE avoided as result of the interventions.[13,20,21,24]

Specifically, Gillespie et al included both a cost-effectiveness analysis (CEA) and a cost-utility analysis (CUA) with estimates of the cost per PIM avoided and per QALY gained (measured using the EQ5D-3L instrument), respectively.[20] This study provided a more

Table 4 Quality Assessment of Included Studies

	Quality of Health Economic Studies (QHES) Criterion[18]	Points	Number of Studies
1	Was the study objective presented in a clear specific, and measurable manner?	7	10
2	Were the perspective of the analysis (societal, third-party payer, etc.) and reasons for its selection stated?	4	5
3	Were variable estimates used in the analysis from the best available source (ie RCT best; expert opinion, worst)	8	10
4	If estimates came from a subgroup analysis, were the groups prespecified at the beginning of the study?	1	0
5	Was uncertainty handled by (1) statistical analysis to address random events, (2) sensitivity analysis to cover a range of assumptions?	9	6
6	Was incremental analysis performed between alternatives for resources and costs?	6	8
7	Was the methodology for data abstraction (including the value of health states and other benefits) stated?	5	10
8	Did the analytic horizon allow time for all relevant and important outcomes? Were benefits and costs that went beyond 1 year discounted (3% to 5%) and justification given for the discount rate?	7	9
9	Was the measurement of costs appropriate and the methodology for the estimation of quantities and unit costs clearly described?	8	8
10	Were the primary outcome measure(s) for the economic evaluation clearly stated and did they include the major short-term, long term, and negative outcomes?	6	10
11	Were the health outcomes measures/scales valid and reliable? If previously tested valid and reliable measures were not available, was justification given for the measures/scales used?	7	9

(*Continued*)

Table 4 (Continued).

	Quality of Health Economic Studies (QHES) Criterion[18]	Points	Number of Studies
12	Were the economic model (including structure), study methods and analysis, and the components of the numerator and denominator displayed in a clear, transparent manner?	8	7
13	Were the choice of economic model, main assumptions, and limitations of the study stated and justified?	7	10
14	Did the author(s) explicitly discuss direction and magnitude of potential biases?	6	6
15	Were the conclusions/recommendations of the study justified and based on the study results?	8	11
16	Was there a statement disclosing the source of funding for the study?	3	11

Notes: Quality of Health Economic Studies (QHES) Criterion reproduced from: Ofman JJ, Sullivan SD, Neumann PJ, et al Examining the value and quality of health economic analyses: Implications of utilizing the QHES. *J Manag Care Pharm*. 2003;9-(1):53–61. doi:10.18553/jmcp.2003.9.1.53.[18]

complete estimate of costs, including health care services utilization (visits with nurses and physicians in the primary care clinic as well as in other settings, hospital visits and admissions).[20] The outcome in the study was also the QALY, and the intervention was found to be costlier and more effective. Its cost-effectiveness depends on the willingness-to-pay for each additional QALY, with a marginal cost here estimated at € 30,535.[20] However, one could put such an ICER in perspective with treatments that have much higher ICER and that are covered in other jurisdictions. O'Brien et al estimated the ICER per ADE due to suboptimal prescribing at 5,358 and van der Heijden at 8,270. Both authors conclude that the interventions are not cost-effective. Yet, the cost-effectiveness depends on the willingness-to-pay for these outcomes. While a few jurisdictions have (implicit or explicit) thresholds for QALYs, such thresholds do not exist for ADEs.

Studies do carry limitations that render any generalization of such results difficult. The economic evaluation profile of interventions to optimize medication use in older adults with polypharmacy depends on several factors in terms of context, cost elements included, and details of the

intervention itself. For instance, in one study, implementation costs consisted of only the pharmacist salary, not taking the remuneration of physicians into account even though they were also involved in the intervention.[23] Albeit, according to authors, the limited time involved would not make a significant difference. One study did estimate the average time of both the physician's and the pharmacist's involvement in the intervention and used the time to estimate costs and found that the intervention costs were more than compensated for with a reduction in medication costs, resulting in a net benefit.[14]

In the studies identified in this review, reduction in PIM and in ADE due to suboptimal prescribing were the main effect measured in 2 studies each. One found a negative ICER[21] while the other three found that interventions, although effective, came with an ICER varying between €1,269[20] and €8,270.[24] When a cost-utility analysis is conducted, the estimates for the incremental cost per QALY suggest that the intervention is cost-effective if decision-makers are willing to pay £32,466[22] in one case and €30,535[20] in the other, for a QALY.

Perspectives and Outcomes of Interventions

Most studies did not rigorously follow the methods for economic evaluations as explained by Drummond et al[26] and failed to report important elements. Such is the case for the perspective, which was not explicitly stated in most studies (n=7). Payers for different types of health services and medications were rarely mentioned. If we assume that medications for older adults are mostly paid by public health insurers, which also pay for other health services (hospitalizations, physician visits, etc.), the public health insurers would have an interest in decreasing costs related to all such services, versus shifting services or medication expenditure to another payer. Community pharmacists may have no stake in reducing medication use in patients from a strictly economic perspective (which, of course, differs from the clinical and ethical perspectives), whereas nursing homes or hospitals that are covering the costs within their own budget would. In all cases, it is likely that there are also costs for patients, in the form of co-pays for health care services and medications, yet the patient perspective was never included. Acknowledging the out-of-pocket costs for patients would add value to such interventions.

Another way of considering the issue of suboptimal medication use is through its impact on patients' quality of life. Five studies measured quality of life and used the QALY as an outcome measure of the intervention.[12,16,20,22,23] Although it is essential to consider the impact of suboptimal medication use in multimorbid older adults with polypharmacy on quality of life, the low average effect may reflect dilution from heterogeneity of the effect. One study examined cost-effectiveness of reducing prescriptions for some categories of medications and found that interventions to reduce long-term use of non-steroidal anti-inflammatory medications seemed to be the most likely to be cost-effective compared to benzodiazepines and proton pump inhibitors.[27]

Contextual Factors: Pharmacists' and Physicians' Incentives

On the context aspect, whether the intervention happens in the community or in an institutional setting represents an important difference. In an institutional setting, the pharmacists are generally salaried employees. In contrast, owners of pharmacies may be receiving dispensing fees and higher discounts when increasing the volumes of medications purchased.[28] Hence, from an economic perspective, the incentives in such an environment would motivate the continued dispensing of medications, and not support a conversation with physicians to deprescribe medications. From the cost calculation of pharmacists' remuneration in studies conducted in Spain, it appears that community pharmacists were paid by salary, and there was no indication as to the business model of community pharmacies.[14,29,30] Aside from the intervention implemented in Spain, there was no or limited information as to the remuneration models of pharmacists and how different payment schemes could affect the effectiveness of such interventions. For instance, the Canadian province of Ontario implemented a fee-for-service type remuneration for pharmacists' medication therapy management (MTM) services, including medication reconciliation. The uptake of MTM services may depend not only on the remuneration levels, but also on the capacity of a pharmacy to adapt and transform its business model.[31] In Ontario, the uptake required changes to pharmacists' practices[32] that may have been stimulated by a bill reducing pharmacists' income from generic medication manufacturers' rebates.[33]

Although pharmacists have an important role in identifying suboptimal medication use, physicians, as

prescribers, have an equally important role. Physicians may not consider the costs to patients or to the healthcare system of their prescriptions, and they have no incentive to review their patients' prescriptions to remove any prescriptions that may not have any benefit to patients. Some of them also receive benefits from the pharmaceutical industry to increase prescription.[34,35]

Methodological Limitations of the Included Studies

The studies included in this review had a number of limitations. First, the cost elements included varied among studies and the total cost of the intervention was not always estimated. Without such information, it is difficult to assess the value of the interventions and their potential for scaling up. Second, the design in some studies limited the validity of the results. For instance, one study did the randomization at the patient level with physicians treating both control and intervention patients, which may have led to contamination.[14]

Most studies had a small sample size, which does not enable estimating how patient characteristics could affect the cost-effectiveness of an intervention. Yet, from an economic perspective, it is questionable whether pharmacists should review all patients' medications, or if such an intervention is only cost-effective at a given level of patient complexity. This is illustrated in the study by Brixner et al[25] who conducted CBA separately on median and average costs. Using median costs resulted in a net loss while using average costs resulted in a net benefit. The results suggest that the higher reductions in expenditures happen in the tail, ie in patients with very high expenditure. Therefore, there is a need to investigate further the characteristics of the patients for whom such interventions are more likely to be cost-effective so that payers could determine selection criteria for patients that would be eligible.[36]

A factor that is seldom considered in the interpretation of the results is the self-selection of health care providers (mainly pharmacists and physicians) into studies. Not only was there attrition of participation in one study,[12] but researchers reported having difficulty recruiting providers to participate in the studies, suggesting that the interest is limited and that scaling-up such interventions would prove challenging. In addition, pharmacists and physicians participating into studies could differ from non-participants, which could lead to overestimating the benefits of the interventions. Moreover, although RCTs are considered the gold standard, results in real context may differ from those of the RCT.

Strengths and Limitations

One strength of this review is the fact that we applied an in-depth search strategy following the PICO framework in different databases to identify all the suitable studies. Nevertheless, we cannot exclude that relevant studies may have been missed, especially if they were published only in languages other than those spoken by the authors of this review. We considered all studies that included an economic evaluation of an intervention aimed at optimizing medication use in the context of polypharmacy, including all kinds of interventions and without restricting the definition of polypharmacy, referring to the way it was defined by the authors. This means that we did not evaluate the relevance of the interventions and the correctness of the definitions of polypharmacy. It is indeed known that, especially for polypharmacy, different definitions are proposed across the studies.[1]

Conclusion

Our review revealed very few studies with a full economic evaluation on interventions to optimize medication use, which is particularly surprising when considering the high number of studies in which such interventions are conducted. Whether interventions to optimize medication use are cost-effective may depend on a number of contextual factors. More importantly, it requires that the intervention be scalable in its given context.

The quality of the studies was not optimal. One of the striking elements of the studies identified is that none includes the patient perspective. The burden of prescription medications is increasing for patients. As such, optimizing medication use may have benefits not only to health care systems, but also to patients, and not only in terms of health care status.

Future research is needed with more thoughtful estimates of total intervention cost and rigorous methodology applied to economic evaluations of interventions in order to assess the economic impact of such intervention in large-scale environments.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to

which the article has been submitted; and agree to be accountable for all aspects of the work.

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