A systematic review of case-series studies on the effectiveness of interventions to reduce polypharmacy and its adverse consequences in the elderly

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ABSTRACT

Background: Aging is frequently accompanied by chronic diseases; consequently, older people are exposed to polypharmacy, often with negative health-consequences. The aim of this study is to conduct a systematic review of the literature reporting on the effectiveness of different approaches to reduce polypharmacy in the elderly.
Methods: We conducted a comprehensive literature search of MEDLINE, Scopus and ISI Web of Knowledge databases. Eligible studies were case-series reporting outcomes of interventions aimed at reducing polypharmacy and its consequences in the elderly. A quality appraisal of the studies included was performed.
Results: Nineteen studies were included, of which seven conducted in hospital setting, six in community setting, six in nursing homes. Seventeen were judged as moderate quality, and two as poor quality. Majority of the interventions were carried out by pharmacists, alone (35%) or with other professionals (40%). Interventions consisted in pharmacotherapy reviews based on various tools and software; in some cases educational interventions were performed for review-performers and patients. Studies conducted in community-setting provided also a feedback to primary care physician. The outcomes included five categories: therapy's characteristics, quality of life, health-related outcomes, costs, healthcare services' utilization. Therapy-related outcomes were positively affected by all types of interventions, while results were contrasting for quality of life and services' use. Costs and health outcomes were reported by only few studies.
Conclusion: Interventions aimed at reducing polypharmacy are effective in optimizing the use of drugs. More research is needed regarding the effectiveness on quality of life, healthcare costs, services' utilization, and health-related outcomes.

Key words: polypharmacy; elderly; inappropriate prescribing

INTRODUCTION

Since the end of the nineteenth century, life expectancy continues to increase, especially in Western countries, due to medical discoveries and public health actions improving hygienic conditions [1]. The older population is therefore expanding, and is expected to represent almost 25% of the whole Western population by 2030 [2]. Aging is frequently accompanied by chronic-degenerative diseases, and as a consequence the elderly are often exposed to polypharmacy and drug-related problems. A Drug-Related Problem (DRP) is defined by the Pharmaceutical Care Network Europe as "an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes" [3]. Polypharmacy is defined by the World Health Organization as "the administration of many drugs at the same time or the administration of an excessive number of drugs" (≥5 is the most diffused definition, although consensus has not been reached yet) [4,5]. In various studies, the prevalence of polypharmacy in the elderly is estimated to be around 40% of outpatient population, and even higher in selected groups, such as hospitalized patients [6-9]. Polypharmacy has been associated with various negative health-consequences in the elderly. There is compelling evidence that the potential for adverse drug-related events increases with the number of medications used [10-12]. Moreover, pharmacokinetic is altered in the elderly, and the assumption of numerous drugs can lead to a decreased effect of some of them [13]. At last, compliance to therapy can be altered due to the difficulty to manage multiple drugs, which may lead to decreased quality of life [14].

Taking into account all the issues previously described, there is an ongoing international effort to find the most effective way to reduce polypharmacy and other drug-related problems in the elderly. One of the strategies that might bring positive results are medication reviews. The Pharmaceutical Care Network Europe defines a "medication review" as: ''an evaluation of patients' medicines with the aim of managing the risk and optimizing the outcome of medicine therapy by detecting, solving and preventing drug-related problems'' [15]. Many tools have been created with the aim to improve the decisional process of reducing the risk for drug-related problems. The first and most famous is the Beers list that has been updated several times [16]. A more recent tool is the Screening Tool of Older Persons (STOPP) criteria [17]. Multi-disciplinary approaches, involving pharmacists, doctors and other health professionals who collaborate, are widely studied as a way to reduce the health and economic impact of polypharmacy [18]. This study aimed to systematically review the literature on the effectiveness of different approaches targeting the polypharmacy and drug-related problems in elderly. Since the Cochrane Collaboration recently performed a systematic review on the same topic including clinical trials and controlled pre-post studies [19], we decided to limit our search to observational studies without control group, in order to compare different study designs on the same topic.

METHODS

Search Strategy

Eligible articles were identified in three databases: MEDLINE, SCOPUS, and ISI Web of Science.

Key words used in the search were based on the implemented PICO model which was first defined for use in MEDLINE and subsequently adapted for the other databases. The example of MEDLINE

research query was: (Polypharmacy OR Polytherapy OR polymedication OR polymedicine OR polymedicinal OR polyprescription OR poly-pharmacy OR poly-therapy OR poly-medication OR poly-medicine OR poly-medicinal OR poly-prescription) AND (Elderly OR Aged OR "Aged, 80 and over" OR Elder OR Elders OR "Older adults") AND (Organization OR Management OR Administration OR Program OR Pathway OR Model OR Software OR Database OR "Managed care" OR "Care, managed" OR tool OR review OR reconciliation).

The search has been limited to articles written in English and published until August, 30th, 2016. An extensive cross-check of the references from the original studies was performed in order to identify potential additional papers.

Inclusion and exclusion criteria

The eligibility criteria for inclusion required that: the study design was observational and without control group; the study population was composed by individuals older than 64 years old, or with mean age >70 years old, or recruited in a geriatric ward/ institution; the study reported the pre-post measures of the outcomes of any type of intervention targeted at reducing polypharmacy or inappropriate medications or drug-related problems. The exclusion criteria were: case reports; studies regarding intervention directed at single categories of drugs or single diseases.

Characteristics of the studies

After removing duplicates, we identified a total of 3752 articles in our initial search. Of these, 3366 were excluded as reviews or unrelated to the research topic after title and abstract screening . The remaining 386 articles were assessed for eligibility, and 367 were excluded because they did not meet the inclusion criteria.

Data extraction and analysis

After completion of the searches and excluding the duplicate studies, the initial screening of publications included reviewing titles and abstracts independently by two researchers (MBM and SM). Any discrepancy between researchers was resolved through consensus. For documents fitting the inclusion criteria, we collected the following information: first author, publication year, country, definition of polypharmacy adopted, study setting, study population, DRP evaluation system, performer of the corrective intervention, effectiveness outcomes, and effect measures. Descriptive statistic was used to resume the study results. This systematic review was reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guideline [20].

Quality assessment

Two investigators independently performed a quality assessment of the selected studies. Differences in scoring were resolved by consensus. The evaluation criteria for the quality assessment were derived from the checklist for quality appraisal of case series studies produced by the Institute of Health Economics [21].

The original quality assessment checklist consisted of 20 items, out of which 17 were considered applicable to the present study. Table 1 reports the modified checklist.

Each item was independently rated as "present", "partially present," or "absent". Consequently, each study was assessed for high, moderate, or low quality. In particular, a study was evaluated as "high quality" if there were at least 15 criteria were rated present. A rating of "moderate quality" was achieved if at least 11 criteria were rated present. A rating of "low quality" was given if less than 11 items were present.

RESULTS

Figure 1 reports the flowchart of the bibliographic search strategy and the results.

Table 2 reports the main characteristics of the 19

TABLE 1. Elements evaluated in the quality assessment.

Study objective
Was the hypothesis/aim/objective of the study clearly stated?
Study design
Was the study conducted prospectively?
Were the cases collected in more than one centre?
Were patients recruited consecutively?
Study population
Were the characteristics of the patients included in the study described?
Were the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated?
Intervention
Was the intervention of interest clearly described?
Outcome measures
Were relevant outcome measures established a priori?
Were outcome assessors blinded to the intervention that patients received?
Were the relevant outcomes measured using appropriate objective/subjective methods?
Were the relevant outcome measures made before and after the intervention?
Statistical analysis
Were the statistical tests used to assess the relevant outcomes appropriate?
Results and conclusions
Was follow-up long enough for important events and outcomes to occur?
Was the loss to follow-up reported?
Did the study provided estimates of random variability in the data analysis of relevant outcomes?
Were the conclusions of the study supported by results?
Competing interest and sources of support
Are both competing interests and sources of support for the study reported?

FIGURE 1. The search strategy and flow diagram for databases search.
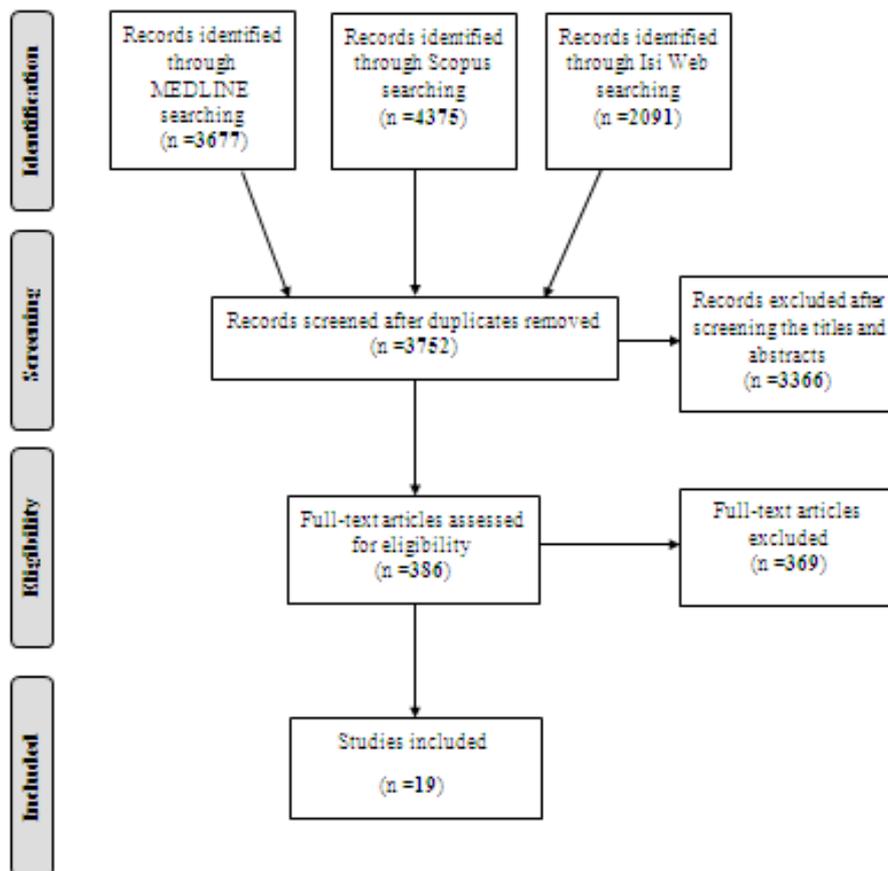
studies included [22-40]. Of these, six were conducted in community setting [27,33,34,36,38,39], seven in hospital setting [24-26,29,32,37,40], and the remaining six in nursing homes [22,23, 28,30,31,35]. The most common definition of polypharmacy was the contemporary assumption of at least five drugs (four studies, 21,1%) [25,29,34,36]. The majority of the interventions (73,7%) to reduce polypharmacy or medication inappropriateness were performed by pharmacists, alone [22,27,34,36,38,40] or in cooperation with other healthcare professionals (nurse, general practitioner, geriatrician, medical student, pharmacologist) [23-25,28,29,32,33,37]. The remaining studies analyzed interventions conducted by pharmacologists alone [30], geriatricians alone [31,35], physicians alone [26], and general practitioners alone [39].

In 12 studies, the performers of the interventions provided a feedback to patients' general practitioners [22,24,27,35-37, 23,31-34,40]; six interventions provided educational sessions on therapy changes for patients[24,28,32,33,36,37]. Regarding the tools used by the performer of therapy review, the most used were the STOPP/START criteria, the Beers criteria, the Medication Appropriateness Index, and several informatic softwares (Micromedex, Epocrates, Lexi-Interact).

Main results of the included studies are presented in Table 3. For the purpose of this systematic review, detailed results are presented within the following five sections: drugs (any modification of drug therapy's characteristics), quality of life, health-related outcomes, costs, and healthcare services' utilization.

Drug-related outcomes

Eighteen of 19 included studies reported at least one outcome related to therapy's modifications [22-30,32-40].

Eleven studies [23-29,32,33,37,39] reported results on the reduction of number of drugs per patient, expressed as mean or median number of drugs per patients, mean number of prescriptions per month, mean tablets per day, or mean number of claims; of these, all but one study [26] reported significant reductions.

Regarding the prevalence of potential inappropriate medications (PIMs), four studies [25,30,35,37] reported a significant reduction of the frequency of inappropriate medication or of the mean number of patients taking inappropriate drugs.

Three studies [27,34,36] investigated the prevalence of drug-related problems, and all of them reported significant reductions after the intervention period.

TABLE 2. Main characteristics of the 19 studies included.

FIRST AUTHOR, YEAR	COUNTRY	DEFINITION OF POLYPHARMACY	SETTING	TOOLS USED	PERFORMER
Bellingan et al., 1996 [22]	Republic of South Africa	≥6 drugs	Nursing home	Micromedex	Pharmacist
Chan et al., 2001 [25]	China	≥5 drugs	Hospital	N/D	Physician, pharmacist
Christensen et al., 2004 [27]	North Carolina	N/D	Community	N/D	Pharmacist
Finkers et al., 2007 [28]	Netherlands	≥9 drugs	Nursing home	N/D	Pharmacist, physician
Woodward et al., 2008 [39]	Australia	≥20 drugs	Community	N/D	General practitioner
Brulhart et al., 2011 [23]	Switzerland	N/D	Nursing home	N/D	Pharmacist, physician, nurse
Tamura et al., 2011 [35]	Hawaii	≥9 drugs	Nursing home	Beers criteria; Epocrates	Geriatric fellows
Chan et al., 2012 [24]	Taiwan	≥8 drugs	Hospital	N/D	Geriatricians, pharmacists, research assistants
Kojima et al., 2012 [31]	Hawaii	≥9 drugs	Nursing home	Beers Criteria; Epocrates	Geriatric fellow, faculty geriatrician
Roth et al., 2013 [34]	North Carolina	≥5 drugs	Community	MRP classification tool	Pharmacist
Yeoh et al., 2013 [40]	Singapore	N/D	Hospital	Lexi-Interact™	Pharmacist
Tan et al., 2014 [36]	Australia	≥5 drugs	Community	Criteria by Strand et al.§	Pharmacist
Trenaman et al., 2014 [37]	Nova Scotia	N/D	Hospital	MAI	Pharmacist, geriatrician
Chieng et al., 2015 [26]	New Zealand	N/D	Hospital	Pill Pruner	Physician
Ilic et al., 2015 [30]	Serbia	N/D	Nursing home	Beers criteria; STOPP criteria	Pharmacologists
McKean et al., 2015 [32]	Australia	≥8 drugs	Hospital	National support tool for deprescribing	Physician, pharmacist
Twigg et al., 2015 [38]	UK	≥4 drugs	Community	STOPP criteria	Pharmacist
Hayashi et al., 2016 [29]	Japan	≥5 drugs	Hospital	N/D	Physician, nurse, pharmacist
Mudge et al., 2016 [33]	Australia	N/D	Community	STOPP criteria	Physician, pharmacist, nurse

§ Strand LM, Morely PC, Cipolle RJ, Ramsey R, Lamsam GD. Drug-related problems: their structure and function. Ann Pharmacother 1990;24:1093–1097. [41]

MAI: medication appropriateness index. MRP: medication related problem.

Finally, three studies reported a significant improvement of patients' adherence to therapy, as well as in their satisfaction and knowledge on drugs [34,38,36].

Quality of life

Three studies considered outcomes related to quality of life. Chan et al. used a rating scale, and observed a significant increment of patients rating their quality of life as "good" or "better" [24]. Another study [36] used a five-points Likert scale, reporting instead non-significant results. Twigg et al. used the EuroQol EQ5D 3L questionnaire,

finding a significant improvement in the score [38].

Health-related outcomes

Only one study investigated the effect of the intervention on a health-related outcome, observing a significant reduction in the mean number of falls [38].

Costs

Two studies referred to cost-outcomes [27,31].

TABLE 3. Main results of the 19 studies included.

FIRST AUTHOR, YEAR	POPULATION	EFFECTIVENESS OUTCOME	EFFECT MEASURE
Bellingan, 1996	85	Pre-post % of patients with polypharmacy	68% vs 27%, p<0.01
		Pre-post frequency of drug interactions	64% vs. 25%, p<0.01
Chan, 2001	210	Pre-post mean number of medications/patient	4.65 vs 3.56, p<0.001
		Pre-post mean number of inappropriate medications/patient	0.50 vs 0.13, p<0.001
		Pre-post % of patients with inappropriate medications	34.8% vs. 12.4%, p<0.001
Christensen, 2004	6344	pre-post mean number of prescriptions per month	(-0.21), p<0.001
		pre-post reduction in PDTP occurrence	p<0.001
		pre-post drug cost saving by PDTP categories	p<0.001
		pre-post paid prescription claims, 2002 US $	(-30.33), p<0.001
Finkers, 2007	91	Pre-post mean number of drugs/patient	13.5 vs 12.7, p<0.0001
Woodward, 2008	81	pre-post mean reduction of unique medications	(-2.22); 95%CI (-3.54) to (-0.90), p=0.0013
		pre-post mean reduction in number of claims	(-4.67); 95% CI (-8.34) to (-0.99), p=0.013
		pre-post mean reduction in number of drug interaction pairs	(-0.73); 95% CI (-0.77) to (-0.69), p<0.0001
Brulhart, 2011	329	Pre-post mean number of total drugs/patient	12.8 (2–27) vs 11.8 (1–27), p<0.01
		Pre-post mean number of continuous use drugs/patient	9.8 (1–20) vs 9.1 (1–19), p<0.01
		Pre-post mean number of on-demand use drugs/patient	ns
Tamura, 2011	70	Pre-post mean number of high risk medications	0.94 (±1.39) vs 0.73 (±1.25), p<0.001
		Pre-post mean number of medications with potential contraindications	0.29 (±0.74) vs 0.13 (±0.48), p=0.004
		Pre-post mean number of medications with drug-drug interactions	6.10 (±5.71) vs 4.83 (±4.19), p<0.001
		Pre-post mean number of medications without indications	3.34 (±3.36) vs 3.29 (±3.36), p=0.045
Chan, 2012	139	Pre-post mean number of chronic medications/patient	9.0 vs. 8.6, p<0.05
		Pre-post % of participants rating their general health as good or better	22% vs. 38%, p<0.001
		Pre-post functional decline in Nagi index	p=0.048
		Pre-post decline in mean IADL scores	p=0.019
Kojima, 2012	70	Pre-post mean monthly medication costs	874.27$±859.01 vs 843.56$±853.23, p<0.0001
Roth, 2013	55	pre-post mean number of MRPs per patient	4.2 ± 2.1 vs 1.0 ± 1.5, p<0.0001
		pre-post mean number of acute health services utilization (events/person-months)	8.3/100 vs 5.4/100, -35%
Yeoh, 2013	118	Pre-post mean improvement in patient satisfaction and knowledge of drugs and side effects	p<0.001
Tan, 2014	62	Pre-post mean number of MRPs	2 (1, 4) vs 0 (0, 1), p<0.001
		Pre-post Morisky Scale score for medication adherence	26 vs 37, p=0.035
		Pre-post Tool for Adherence Behaviour Screening score	21 vs 34, p=0.019
		Pre-post self-reported use of health services	ns
		Pre-post patients self-reported general health and wellbeing	ns
Trenaman, 2014	136	Pre-post mean number of medications	10.3 ± 4.7 vs 9.8 ± 4.2, p=0.005
		Pre-post mean MAI	10.72 vs 4.74, p<0.001
Chieng, 2015	459	Pre-post mean number of medications	Ns
Ilic, 2015	104	Pre-post median number of inappropriately prescribed drugs according to Beers criteria	11 (1-43) vs. 1 (1-2), p<0.001
		Pre-post median number of inappropriately prescribed drugs according to STOPP criteria	3.5 (1-20) vs 1.5 (0-6), p<0.005
		Pre-post mean number of inappropriate drugs/patient according to Beers and STOPP criteria together	3.4±0.5 vs 0.6±0.7, p<0.001
McKean, 2015	50	Pre-post median n° of medications	10 (9-12) vs 7 (5-9), p<0.001
Twigg, 2015	441	Pre-post mean total n° of falls	0.251±0.88 vs 0.135±0.41, significant
		Pre-post mean adherence score	7.348±1.06 vs 7.861±0.48, significant
		Mean change in EQ-5D score	+0.025 (95%CI 0,007-0.042), significant
Hayashi, 2016	226	Pre-post mean n° of total medications	7.83±2.44 vs 6.69±3.34, p<0.01
Mudge, 2016	17	Pre-post mean n° of total medications	14.3±6.1 vs 11.2±5.1, p<0.001
		Pre-post mean n° of tablets per day	20.5±9.1 vs 16.9±7.7, p<0.01

PDTP: potential drug therapy problem. MRP: medication related problems. MAI: medication appropriateness index.

Christensen et al. [37] reported a significant reduction in paid prescription claims, while Kojima et al. found a reduction in mean monthly medication costs [31].

Utilization of healthcare services

Two studies reported outcomes related to healthcare services' utilization [34,36]. Roth et al. reported a reduction in acute health services utilization of 35%, defined as combined hospitalizations and emergency department visits [34]. The other study reported non-significant difference in the self-reported use of healthcare services [36].

Quality assessment

Based on the results obtained from the "Quality Appraisal Checklist for Case Series Studies" (institute of Health Economics, Alberta, Canada), the methodological quality resulted poor for two studies [22,25], and moderate for all the others [23,24,26-40]. The scores ranged from 10 to 14, none of the papers having attained the maximum score.

DISCUSSION

The aim of this study was to review the results of case-series studies in terms of effectiveness in the reduction of polypharmacy and its adverse effects in the elderly. We decided to include only case-series studies since the Cochrane collaboration recently updated a review on the same subject including clinical trials and observational studies with control groups [19].

Our review included 19 studies. Our inclusion criteria were less restrictive than those chosen for the Cochrane review, since we considered that many studies could be lost using a strict definition of polypharmacy and a limitation to older population (i.e. 65 years-old). Several included studies were performed in geriatric wards or institutions, and involved a geriatric population even if an age-threshold was not defined.

We categorized the outcomes in five groups: those related to therapy, quality of life, health-related events, costs, and utilization of healthcare services.

The majority of studies had outcomes related to therapy modifications. Particularly, all the studies but one reported significant reduction in the number of drugs administered to patients. The Cochrane review [19] did not consider this outcome as important since the rough number of drugs per patients is not necessarily a marker of inappropriateness.

We retrieved four studies evaluating the modification of therapy appropriateness. Among them, three studies used validated instruments of appropriateness, while one simply based on experts opinion. All the studies reported a significant improvement in therapy appropriateness. This result is similar to that of the Cochrane review [19], considering that all but one of their studies investigating this outcome reported significant results, and it was possible to perform meta-analysis for some of them. The Cochrane review [19] did not include those studies focusing only on experts' opinion, and we can agree that, in order to improve comparability between studies, validated tools are required.

As for the other categories of outcomes, they were investigated by a smaller number of studies both in our review and in the Cochrane review [19], yielding contrasting results.

On the whole, the results observed in the two reviews, although obtained through studies with a completely different design, were comparable.

Our study has some strengths and some limitations, compared to the Cochrane review [19].

As for the strengths, we adopted more inclusive criteria that allowed us to retrieve a certain number of studies that would have been excluded by the Cochrane criteria. Moreover, we collected all the outcomes analysed by the included studies, in order to have more comprehensive perspective of the different types of results obtained by these interventions to reduce polypharmacy and its adverse effects. On the other hand, being more inclusive can certainly represent a limitation, since this may introduce the issue of comparability between different studies.

The most important limitation of our study was the inclusion of case-series studies exclusively. Although the aim of this decision was to compare the results of different study designs, a case-series study design is considered to be of scarce quality compared to the others [42]. In the presence of studies of higher-quality (e.g. clinical trials, controlled pre-post studies), case-series studies should be considered/interpreted with caution, due to the impossibility to check what would have happened in control groups.

CONCLUSION

We can state that the effectiveness of interventions to reduce polypharmacy and its adverse effects has been currently studied more in terms of therapy modifications than of other outcomes related with quality of patients life, costs, health services utilization and health outcomes.

It is recommended to evaluate these outcomes in studies with intervention and control groups, in order to obtain an higher level of scientific evidence.

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