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 alteration 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 poly-prescription 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
Reduction of polypharmacy in the elderly

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.
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 EQSD 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.

<table>
<thead>
<tr>
<th>FIRST AUTHOR, YEAR</th>
<th>POPULATION</th>
<th>EFFECTIVENESS OUTCOME</th>
<th>EFFECT MEASURE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bellingan, 1996</td>
<td>85</td>
<td>Pre-post % of patients with polypharmacy 68% vs 27%, p&lt;0.01</td>
<td>Pre-post frequency of drug interactions 64% vs. 25%, p&lt;0.01</td>
</tr>
<tr>
<td>Chan, 2001</td>
<td>210</td>
<td>Pre-post mean number of medications/patient 4.65 vs 3.56, p&lt;0.001</td>
<td>Pre-post mean number of inappropriate medications/patient 0.50 vs 0.13, p&lt;0.001</td>
</tr>
<tr>
<td>Christensen, 2004</td>
<td>6344</td>
<td>Pre-post % of patients with inappropriate medications 34.8% vs. 12.4%, p&lt;0.001</td>
<td>Pre-post mean number of prescriptions per month (0.21), p&lt;0.001</td>
</tr>
<tr>
<td>Finkers, 2007</td>
<td>91</td>
<td>Pre-post reduction in PDTP occurrence p&lt;0.001</td>
<td>Pre-post drug cost saving by PDTP categories p&lt;0.001</td>
</tr>
<tr>
<td>Woodward, 2008</td>
<td>81</td>
<td>Pre-post mean reduction in number of claims (4.73), 95% CI (8.34) to (0.99), p=0.013</td>
<td>Pre-post mean reduction in number of drug interaction pairs (0.73), 95% CI (0.77) to (0.69), p&lt;0.0001</td>
</tr>
<tr>
<td>Brulhart, 2011</td>
<td>329</td>
<td>Pre-post mean number of total drugs/patient 12.8 [2-27] vs 11.8 [1-27], p&lt;0.01</td>
<td>Pre-post mean number of continuous use drugs/patient 9.8 [1-20] vs 9.1 [1-19], p&lt;0.01</td>
</tr>
<tr>
<td>Tamura, 2011</td>
<td>70</td>
<td>Pre-post mean number of medications with potential contraindicators 0.29 [0.74] vs. 0.13 [0.48], p=0.004</td>
<td>Pre-post mean number of medications without contraindicators 6.10 [±5.71] vs 4.83 [±4.19], p&lt;0.001</td>
</tr>
<tr>
<td>Chan, 2012</td>
<td>139</td>
<td>Pre-post mean number of high risk medications 0.94 [±1.39] vs 0.73 [±1.25], p&lt;0.001</td>
<td>Pre-post mean number of chronic medications/patient 9.0 vs. 8.6, p&lt;0.05</td>
</tr>
<tr>
<td>Kojima, 2012</td>
<td>70</td>
<td>Pre-post mean monthly medication costs 874.27$±859.01 vs 843.56$±853.23, p&lt;0.0001</td>
<td>Pre-post mean number of MRPs per patient 4.2 ± 2.1 vs 1.0 ± 1.5, p&lt;0.0001</td>
</tr>
<tr>
<td>Roth, 2013</td>
<td>55</td>
<td>Pre-post mean number of MRPs per patient 21 [1-4] vs 0 [0, 11], p&lt;0.001</td>
<td>Pre-post mean number of acute health services utilization (events/person-months) 8.3/100 vs 5.4/100, -35%</td>
</tr>
<tr>
<td>Yeoh, 2013</td>
<td>118</td>
<td>Pre-post mean number of MRPs with potential contraindicators 0.29 [0.74] vs. 0.13 [0.48], p=0.004</td>
<td>Pre-post mean number of MRPs 2 [1, 4] vs 0 [0, 11], p&lt;0.001</td>
</tr>
<tr>
<td>Tan, 2014</td>
<td>62</td>
<td>Pre-post mean number of medications with potential contraindicators 0.29 [0.74] vs. 0.13 [0.48], p=0.004</td>
<td>Pre-post mean number of acute health services utilization (events/person-months) 8.3/100 vs 5.4/100, -35%</td>
</tr>
<tr>
<td>Trenaman, 2014</td>
<td>136</td>
<td>Pre-post mean number of medications 10.3 ± 4.7 vs 9.8 ± 4.2, p=0.005</td>
<td>Pre-post mean number of medications 10.72 ± 4.74, p&lt;0.001</td>
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<tr>
<td>Chiang, 2015</td>
<td>459</td>
<td>Pre-post mean number of medications Ns</td>
<td>Ns</td>
</tr>
<tr>
<td>Ilic, 2015</td>
<td>104</td>
<td>Pre-post median number of inappropriate prescribed drugs according to Beers criteria 11 [1-43] vs. 1 [1-2], p&lt;0.001</td>
<td>Pre-post median number of inappropriate prescribed drugs according to STOPP criteria 3.5 [1-20] vs 1.5 [0, 6], p&lt;0.005</td>
</tr>
<tr>
<td>McKean, 2015</td>
<td>50</td>
<td>Pre-post median n° of medications 10 [9-12] vs 7 [5-9], p&lt;0.001</td>
<td>Pre-post median n° of inappropriate prescribed drugs according to Beers criteria 11 [1-43] vs. 1 [1-2], p&lt;0.001</td>
</tr>
<tr>
<td>Twigg, 2015</td>
<td>441</td>
<td>Pre-post mean n° of falls 0.25 ± 0.88 vs 0.13 ± 0.41, significant</td>
<td>Pre-post mean number of inappropriate prescribed drugs according to Beers criteria 11 [1-43] vs. 1 [1-2], p&lt;0.001</td>
</tr>
<tr>
<td>Hayashi, 2016</td>
<td>226</td>
<td>Pre-post median n° of total medications 7.83 ± 2.44 vs 6.69 ± 3.34, p&lt;0.01</td>
<td>Pre-post median n° of total medications 7.83 ± 2.44 vs 6.69 ± 3.34, p&lt;0.01</td>
</tr>
<tr>
<td>Mudge, 2016</td>
<td>17</td>
<td>Pre-post mean n° of total medications 14.3 ± 1.1 vs 11.2 ± 5.1, p&lt;0.001</td>
<td>Pre-post mean n° of total medications 14.3 ± 1.1 vs 11.2 ± 5.1, p&lt;0.001</td>
</tr>
</tbody>
</table>

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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