



# Effectiveness and Cost Effectiveness of Pharmacist-led Deprescribing Interventions in Nursing Homes and Ambulatory Care Settings in Elderly Patients: A Systematic Review

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## Abstract

**Background:** Potentially Inappropriate Medications (PIMs) are drugs in which the adverse risks exceed the clinical benefits, lacking evidence-based indications, potentially interact with other medications. PIM use is common in older adults who are frequently treated with multiple medications. PIM use in older adults is associated with many complications. **Aim:** To critically appraise and systematically evaluate the existing studies on the effectiveness of pharmacist-led deprescribing in health service utilization, clinical effectiveness, cost effectiveness and cost utility. In nursing home and ambulatory care settings and patients aged 65 years and above. **Methods:** PubMed, Medline, CINAHL, Embase, and Cochrane Library were searched between 1st to 2nd July 2021 and updated on 25<sup>th</sup> December 2021 to select studies that compare pharmacist-led deprescribing in nursing home and ambulatory care settings with usual care. Outcomes related to health service utilization, clinical effectiveness, cost effectiveness and cost utility were evaluated. **Results:** A total of 3944 relevant records were identified through database searching. A further ten records were identified by following up citations and reference lists of the selected studies. After assessment, nine studies were included in the review. Four of the included studies reported outcomes relating to both health service utilization and clinical effectiveness, three studies reported only health service utilization, and the two economic studies reported cost effectiveness and cost utility respectively. Six out of seven studies that reported health service utilization outcomes found improvement in health service utilization after the implementation of the pharmacist-led deprescribing. However, there is no positive clinical effectiveness outcomes, and no worldwide studies for the economic outcomes. **Conclusion:** This evidence of moderate to high quality. Pharmacist-led deprescribing was effective only in reducing PIMs usage and medication burden for older adults in nursing home and ambulatory care setting, but with no clinical effectiveness outcomes. It is essential to evaluate the economic outcomes in different countries other than Canada (high-income country).

**Keywords:** Pharmacist-led; Deprescribing; Cost effectiveness; Effectiveness; Systematic review

## Introduction and Review of Literature

Deprescribing has been defined as “the process of withdrawal of an inappropriate medication, supervised by a health care professional with the goal of managing polypharmacy and improving outcomes” (1, p. 1262). The concept first appeared in Australian literature on 2003 and was then used internationally [1].

Potentially Inappropriate Medications (PIMs) are drugs in which the adverse risks exceed the clinical benefits, lacking evidence-based indications, potentially interact medications [2]. In Brazil, PIMs use by patients in nursing homes cause harm to the patients and are associated with increase in mortality (death) by 44% [3].

PIM use is common in older adults who are frequently treated with many medications [4]. Approximately 62% of older adults aged 65 to 70 years administered at least one PIM during hospitalization. These rates may reflect a significant prevalence of older adults with more comorbidities than others and thus administer many drugs that increase the risk of PIMs use [2]. PIM use in older adults is associated with prolonged hospitalization, increased death rates, increased incidence of adverse drug events and an increased economic burden [5]. One study concluded that 10-30% of older adult patients’ admission resulted directly because of PIMs usage [6].

Heider, et al. argues that PIMs use in older adult patients is linked to higher utilization of healthcare services and higher healthcare costs [7]. In addition, Moriarty, et al. agreed the previous argument and found that healthcare costs impact of PIMs usage is due to pharmaceutical expenditure and managing the adverse drug reactions that might result [8].

Around 96% of physicians and hospital admission drug lists are imprecise with at least one medication history mistake, and 24-59% of these errors relate to PIMs. However, pharmacist led medication history collection upon hospital admission has been shown to reduce medication costs, medication errors, length of stay, adverse drug reactions, and death rates [4].

Because of deprescribing challenges and barriers, pharmacists could help physicians in optimizing drug therapy in older adults [6]. There is increasing reliance on a pharmacist to review patient medications, by assessing regularly prescribed drugs, extraction of medical record information and patient interview. PIMs could be identified at any step of this process. Thus, all these steps are required [9]. Pharmacist medication review followed by physician communication have been shown to lead to safer prescribing practices [9]. Therefore, pharmacist should collaborate with physician and patient to formulate a plan of care which documents each PIM, the agreed goals and essential actions [9].

At the UK acute hospitals settings, pharmacist medication reviews reduced PIMs usage and improved prescribing [10].

Many studies have shown positive pharmacy clinical outcomes for different disease specific practice. However, the majority of the evidence showing pharmacist-led healthcare interventions has failed to include the economic analysis that support the implementation and adoption of these interventions more broadly [11]. Generally, new healthcare interventions are costlier than current interventions. However, these same interventions might add value or benefits over the usual care. Therefore, decision-makers have to determine affordability and an efficiency use of limited resources [11].

Deprescribing PIMs could significantly save healthcare provider budgets, even when PIMs display low prevalence rates [12]. Therapy duplication that is defined as prescribing of more than one drug for the same indication [13] may increase unnecessary costs and adverse events [12]. In older adults, potentially inappropriate medications are related with more adverse drug events [12]. Equally treating an unrecognized adverse event could also add new adverse events and increases costs [12].

In the United States and Europe, the prevalence of potentially inappropriate medications use is 20% and 43% among ambulatory care older adults and nursing home residents, respectively [14]. Effective strategies to improve drug prescribing in nursing homes are needed. Because of deprescribing challenges and barriers pharmacist could help physicians in optimizing drug therapy in older adults [6]. However, health service utilization, clinical effectiveness, cost effectiveness, cost utility in comparison with usual care have not been fully evaluated in a systematic review or meta-analysis.

A scoping search identified a systematic review that described the impact of pharmacists’ models of care in optimizing pharmacotherapy for older adults in European trials [6]. This review selected 15 European publications from 2001 to 2011 and in addition to nursing home and ambulatory care setting they selected acute care settings and continuity of care settings (transition across settings of care). However, the authors concluded that cost effectiveness, quality of life and health outcomes were mixed, and more research must be undertaken that focuses on pharmacist deprescribing intervention outcomes like adverse drug reactions. Also, they argued that opportunities remain to determine the clinical effectiveness and economic benefits of pharmacist deprescribing.

In a systematic review by Dills, et al. to evaluate the outcome of deprescribing compared to usual care, for adult patients 18 years and older in outpatient settings and acute care settings. As a result of broad inclusion criteria, by not limiting to pharmacist-led articles, they included 58 articles in this review [15]. However, they concluded that patient-specific medication recommendations and pharmacist-led educational interventions comprise the most successful interventions. This review situates older adult use of potentially inappropriate medications, together with its harm, within an international context. Therefore, the results of this review will reflect the global context in the pharmacist-led deprescribing process.

**Aim of the review:** To critically appraise and systematically evaluate the existing studies on the effectiveness of pharmacist-led deprescribing in health service utilization, clinical effectiveness, cost effectiveness and cost utility. In nursing home and ambulatory care settings and patients aged 65 years and above. Our main research question was “In patients aged 65 years and above, what is the effect of pharmacist-led deprescribing interventions in nursing home and ambulatory care settings on health service utilization, clinical effectiveness, cost effectiveness and cost utility when compared to usual care?” **Objectives:** To summarize the available evidence around pharmacist-led deprescribing effectiveness. Summarization will be achieved through a systematic review of the relevant studies.

## Methods

This study review was conducted in accordance with the Cochrane handbook and reported according to the recommended general principles by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [16].

## Ethics and data

Ethical approval is not required for this study review because this is a review of the published literature. No research protocol was registered on the international database of prospectively registered systematic reviews with a health-related outcome (PROSPERO). However, before the start of the systematic review, a research protocol was developed and completed on May 2<sup>nd</sup>, 2021.

## Selection criteria

The systematic review inclusion and exclusion criteria are organized around the PICO eligibility criteria [17].

## Types of populations

Patients mean age 65 years and above in nursing home or ambulatory care settings were included. This age group was selected as approximately 62% of older adults aged 65 to 70 years administered at least one PIM during hospitalization [2]. Thus, patients mean age less than 65 years were excluded.

And the reason of selection nursing home or ambulatory care settings were PIMs use prevalence are 20% and 43% among community-dwelling elderly and nursing home residents, respectively [14]. Studies including hospitalized patients were excluded because these patients were studied earlier in a systematic review by Thillainadesan, et al. [18].

## Types of interventions

The included studies must assess the outcome of the pharmacist-led deprescribing process for potential inappropriate medications. In this process, pharmacist must be the initiative in assessing regularly prescribed drugs, extraction of medical record information, patient education and patient interview. PIMs could be identified at any step of this process. Thus, all these steps are required. Pharmacist medication review followed

by physician communication have been shown to lead to safer prescribing practices. The communication between pharmacists and the physicians could be either directly or indirectly by sending patients back to their physicians with the recommended notes. Studies assessing the outcome of interventions with no core role of the pharmacist like multidisciplinary team-led deprescribing process (with or without pharmacists' access [19]) and physician-led deprescribing were excluded, as these studies do not evaluate the pharmacist deprescribing properly.

## Comparator

Usual care process in general, subject to local variations between countries.

## Types of outcomes

Studies reporting data about health service utilization, clinical effectiveness, cost effectiveness and cost utility of pharmacist-led deprescribing process were deemed eligible. These outcomes must be compared between pharmacist-led deprescribing process and usual care process. The primary outcomes include health service utilization of potential inappropriate medications, clinical effectiveness, cost effectiveness and cost utility. Secondary outcomes include the effect of pharmacist-led deprescribing process on the total number of medications used by patients.

## Health service utilization and clinical effectiveness outcomes

Health service utilization reported as the reduction or change in the number of PIMs used by the patient after implementing pharmacist-led deprescribing process or pharmacist-led drug review. The pharmacist-led deprescribing process is expected to reduce the number of PIMs more than the usual care. Another way to report health service utilization is the reduction or change in the total number of medications used after implementing pharmacist-led deprescribing process or pharmacist-led drug review. The pharmacist-led deprescribing process is expected to reduce the total number of medications more than the usual care.

Clinical effectiveness reported as the difference in hospitalization or out of hours general practitioner visits between patients under pharmacist-led deprescribing intervention compared to usual care, in addition to the change in mortality rates (death rates) and fall rates after implementing pharmacist-led deprescribing process or pharmacist-led drug review. The pharmacist-led deprescribing process is expected to decrease hospitalization rate, mortality rate and risk of fall more than the usual care process.

## Cost effectiveness and cost utility outcomes

National Institute for Health and Clinical Excellence (NICE) has been defined cost-effectiveness analysis as “An economic study design in which consequences of different interventions are measured using a single outcome, usually in ‘natural’ units (for example, life-years gained, deaths avoided, heart attacks avoided, or cases detected). Alternative interventions are then compared in

terms of cost per unit of effectiveness” (20, p. 81)

Cost effectiveness reported as an incremental cost-effectiveness ratio (how much it costs to extend life by one year). However, to incorporate quality of life rather than quantity of life, we would assign a utility between 0 (poor quality of life) and 1 (perfect quality of life), and by dividing incremental cost-effectiveness ratio per life year to utility the quality-adjusted life-year (QALY) resulted. The pharmacist-led deprescribing process is expected to lower incremental cost-effectiveness ratio and QALY than the usual care. However, direct medication cost and direct pharmacist interventions cost (like pharmacists’ salary) will be excluded and will not be considered as a benchmark to compare between intervention and control groups.

### **Secondary outcomes**

Secondary outcomes include the reduction or change in the proportion of patients taking ten or more medications after implementing pharmacist-led deprescribing process or pharmacist-led drug review. The pharmacist-led deprescribing process is expected to reduce the proportion of patients taking ten or more medications more than the usual process.

### **Types of the included studies**

Interventional studies that compare pharmacist-led deprescribing with the usual care were eligible to be included. These studies include standard randomized, and cluster randomized controlled trials. Quasi-randomized controlled trials, non-randomized controlled trials, reviews, observational studies, prospective and retrospective cohort studies, guidelines, editorials, news articles and letters were excluded in this review. We will depend in the review on studies truly randomizing participants or group and control group. Despite excluding reviews, the reference lists of the reviews were examined to ensure no one eligible study to miss. Including studies published in languages other than English were excluded due to increasing resource challenges regarding expertise in non-English languages, costs and time [21]. For the cost effectiveness studies cohort subpopulation of randomized controlled trials are accepted.

### **Search strategy for identification of studies**

To identify relevant published studies, a detailed and comprehensive search accomplished in several electronic databases. The searched data bases were PubMed (1950 to 2021), Ovid (1946 to 2021), CINAHL via EBSCO (1981 to 2021), Embase (1974 to 2021) and Cochrane Library (2000 to 2021). The search process carried out between 1<sup>st</sup> to 2<sup>nd</sup> July 2021 and updated on 25<sup>th</sup> December 2021. Reeve, et al. mentioned that deprescribing term first appeared in Australian literature on 2003 and was then used internationally. Thus, the search was limited to publication year from 2003 to 2021, English language articles and human subjects [1]. In addition, searching on Google scholar citation and visual scanning conducted for the included studies reference lists to select other relevant studies. Through handsearching and EMBASE search, conference proceeding, and abstracts were searched to

select the unpublished articles. Also, world wide web (www), thesis and book chapters were searched to limit publication bias effect. EndNote desktop version was used to manage and record the references of all studies.

Based on the intervention process and population elements in the PICO format, the search terms were selected. No terms related to outcome or comparator were used as it reduces the search sensitivity [22]. The search used thesaurus terms, free text and combined synonyms relating to intervention (pharmacist-led deprescribing, pharmacy deprescribing, pharmacist-led review, and pharmacist review) and the population (nursing home, ambulatory care, community dwelling, old adults, and elderly). Moreover, in the searches of Cochrane Library, MEDLINE and EMBASE, related terms were included. In the combination of terms Boolean logic (AND/OR) was used.

### **Data collection**

Based on the inclusion and exclusion criteria, studies were selected for the systematic review. EndNote desktop version was used to remove the duplicated studies found from the several databases. By one reviewer, the study selection was conducted using a two-stage approach and by the second reviewer the steps double-checked to decrease the potential bias risk. In the first stage, after removing duplicate studies, the titles and abstracts of the selected studies were examined against the inclusion and exclusion criteria. Then, the full texts of the selected studies were examined to finalize the included studies list.

Study data were tabulated into Excel sheet using Microsoft Excel 365. The data were extracted and checked by the two reviewers. By using Cochrane handbook guidance [23], the extraction form included study identifiers (the name of the authors, publishing date and study country of origin), study characteristics (study design, setting, inclusion and exclusion criteria), population (sample size and participants’ mean age), intervention, comparator, outcome data (health service utilization, clinical effectiveness, cost effectiveness, and cost utility), and duration of the outcome evaluation were extracted.

### **Quality assessment**

The quality assessment conducted by the two reviewers using the revised version of the Cochrane tool to assess risk of bias in randomized trials (RoB 2) [24], and the revised version of the Cochrane tool to assess risk of bias in cluster randomized trials (RoB 2) [25]. Farrah, et al. encouraged systematic review protocol that restricted to randomized controlled trials to use the Cochrane RoB 2 tools [26].

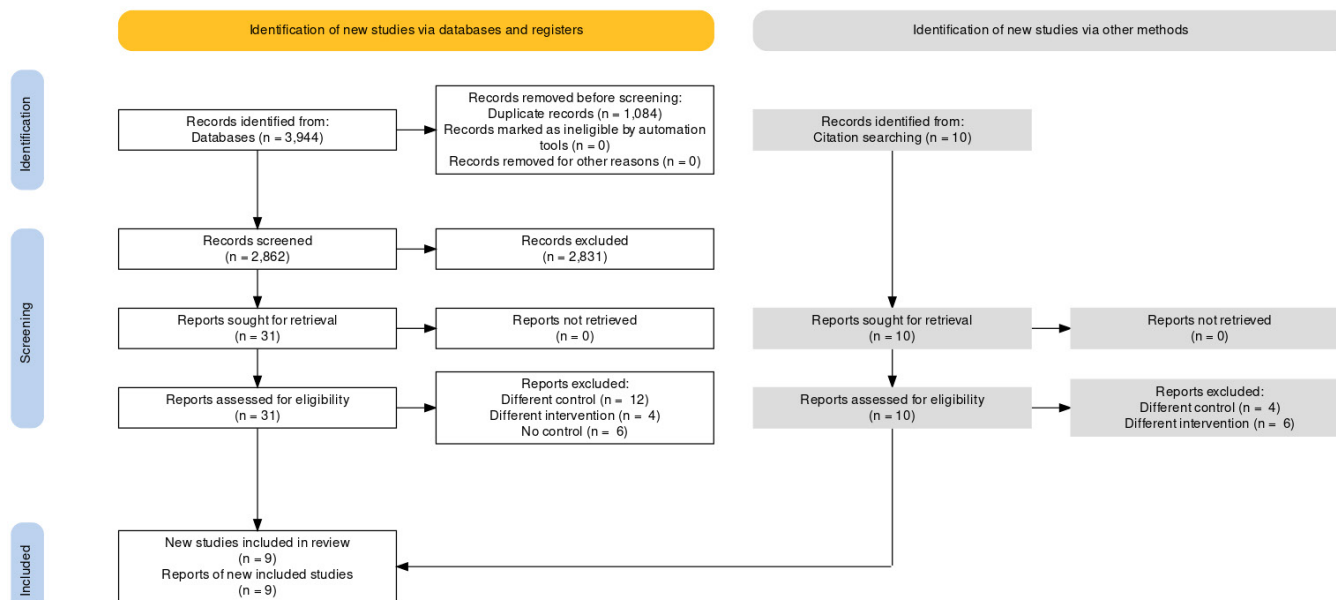
Quality assessment of the cost effectiveness and cost utility analysis articles (economic evaluation) would be conducted using Drummond, et al. checklist, that assess the methods of the economic articles rather than decision analysis [27,28]. Drummond, et al. ten main questions checklist was used to assess strengths and weaknesses of the articles, and elaborated judgement of the worth and suitability of the results for their objectives [28].

## Synthesis of results

Meta-analysis was not conceivable due to significant levels of heterogeneity of study designs and the variable outcome measures. Therefore, a narrative synthesis approach was carried out to synthesis the evidence using the Synthesis Without Meta-analysis (SWiM) guideline [29].

## Results

A total of 3944 relevant records were identified through database searching. A further ten records were identified by following up citations and reference lists of the selected studies. Of the 3944 records identified, 1082 duplicate records were removed before screening, leaving 2862 records for screening. According to the inclusion and exclusion criteria of this systematic review and after screening titles and abstracts, full text assessment of 31 reports were conducted. After assessment, nine studies were included in the review. The other 22 reports were excluded as they had different controls (n=12), a different intervention (n=4), or no control (n=6). Also, the ten records identified by the citation searching were assessed against the inclusion and exclusion criteria of this systematic review. After assessment, all ten studies were excluded because of different intervention (n=6) and different controls (n=4) (Figure 1).



**Figure 1:** The PRISMA flow diagram for the screening process.

## Characteristic of included studies

A total of nine studies were included in the review, published between 2006 and 2021 [30-38]. All nine studies compared the outcomes of interest between pharmacist-led deprescribing intervention in nursing home and/ or ambulatory care settings for patients of mean age 65 or above and the usual care. Table 1 summarizes the included study characteristics and table 2 summarizes the included economic study characteristics.

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Author, year of publication	Country, setting and study design	Study inclusion criteria and exclusion criteria	Participants	Outcome measured and duration of the outcome evaluation	Intervention and comparator
[30]	Country: United Kingdom (Leeds area). Setting: Nursing, homes, and mixed care homes for older adults. Study design: Randomized controlled trial.	<p>Inclusion:</p> <ul style="list-style-type: none"> <li>All care homes with 6 or more residents aged 65 years and more.</li> <li>Patients took one or more repeat medications.</li> <li>Demented patients were included.</li> </ul> <p>Exclusion:</p> <ul style="list-style-type: none"> <li>Participated in another clinical trial.</li> <li>Terminally ill patients with life expectancy less than one month.</li> <li>Received medication reviews by a pharmacist beforehand.</li> </ul>	<p>Sample size:</p> <ul style="list-style-type: none"> <li>Intervention arm: 331 patients.</li> <li>Control arm: 330 patients.</li> </ul> <p>Patients mean age: 85 years</p>	<p><b>Primary outcome:</b> The number of changes in medication per patient.</p> <p><b>Secondary outcome:</b></p> <ul style="list-style-type: none"> <li>hospital admissions <ul style="list-style-type: none"> <li>mortality</li> <li>falls.</li> </ul> </li> </ul> <p><b>Duration of the outcome evaluation:</b> 6 months</p>	<p>Intervention: the pharmacist review patients clinical records, then formulated recommendations to the physicians through written Performa. Comparator: usual care.</p>
[31]	Country: Netherlands. Setting: community pharmacies. Study design: Randomized controlled trial	<p>Inclusion:</p> <ul style="list-style-type: none"> <li>Patients aged <math>\geq 65</math> years</li> <li>Using <math>\geq</math> six medications.</li> </ul> <p>Exclusion:</p> <ul style="list-style-type: none"> <li>Nursing home residents who were hospitalized in the year preceding.</li> <li>Lack of cooperation by the general practitioners.</li> <li>removal to another pharmacy</li> <li>Death.</li> </ul>	<p>Sample size:</p> <ul style="list-style-type: none"> <li>Intervention arm: 98 patients.</li> <li>Control arm: 98 patients.</li> </ul> <p>Patients mean age: 76.6 years</p>	<p><b>Primary outcome:</b> The change in number of PIMs between the intervention and control arms.</p> <p><b>Secondary outcome:</b> The change in number of medications between the intervention and control arms.</p> <p><b>Duration of the outcome evaluation:</b> 4 months</p>	<p>Intervention: community pharmacist-led medication assessment to DE prescribe PIMS. The recommendations discussed with the physicians. Comparator: usual care.</p>

[32]	<p>Country: Northern Ireland. Setting: Nursing home. Study design: Cluster randomized controlled trial</p>	<p>Inclusion:</p> <ul style="list-style-type: none"> <li>All nursing home residents aged 65 years and above.</li> <li>Homes with &lt;30 beds.</li> </ul> <p>Exclusion:</p> <ul style="list-style-type: none"> <li>Terminally ill resident.</li> <li>Patients attending on a day-care basis only.</li> </ul>	<p>Sample size:</p> <ul style="list-style-type: none"> <li>Intervention arm: 11 nursing home with 173 patients.</li> <li>Control arm: 11 nursing home with 161 patients.</li> </ul> <p>Patients mean age: 82.7 years.</p>	<p><b>Primary outcome:</b> the proportion of patients on one or more inappropriate psychoactive drugs at 12 months after the start of the DE prescribing.</p> <p><b>Secondary outcomes:</b></p> <ol style="list-style-type: none"> <li>Change in the number of inappropriate psychoactive drugs between the intervention and control arms over 12 months.</li> </ol> <p>Difference in the rate of fall.</p> <p><b>Duration of the outcome evaluation:</b> 12 months</p>	<p>Intervention: monthly pharmacist home visit for 12 months. In the visit, the pharmacist identified PIMs (especially psychoactive medications: anxiolytic, hypnotic, or antipsychotic) and recommended for intervention:</p> <ol style="list-style-type: none"> <li>Discontinue the medication.</li> <li>Suggested for alternative medications.</li> </ol> <p>Comparator: usual care.</p>
[33]	<p>Country: Sweden. Setting: Public primary health care centers. Study design: Randomized controlled trial</p>	<p>Inclusion:</p> <ul style="list-style-type: none"> <li>Patients on multi dose drug dispensing system aged 75 years and above.</li> <li>Patients live in nursing homes or their own homes with home care services.</li> </ul> <p>Exclusion:</p> <ul style="list-style-type: none"> <li>NA</li> </ul>	<p>Sample size:</p> <ul style="list-style-type: none"> <li>Intervention arm: 185 patients.</li> <li>Control arm: 189 patients.</li> </ul> <p>Patients mean age: 87.4 years.</p>	<p><b>Primary outcome:</b> change in the proportion of patients administering PIMs.</p> <p><b>Secondary outcome:</b> proportion of patients taking ten or more medications.</p> <p><b>Duration of the outcome evaluation:</b> 2 months</p>	<p>Intervention: pharmacist-led medication reviews to identify PIMs and recommending medication changes. Comparator: normal routine</p>
[34]	<p>Country: Spain (Barcelona). Setting: community dwelling elderly people (non-institutionalized). Study design: Randomized controlled trial.</p>	<p>Inclusion:</p> <ul style="list-style-type: none"> <li>Patients aged 70 years and above</li> <li>On eight or more drugs (except topically administered ointment).</li> </ul> <p>Exclusion:</p> <p>Patients with:</p> <ul style="list-style-type: none"> <li>Nursing home residents</li> <li>Active cancer</li> <li>Participated in another clinical trial.</li> </ul> <ul style="list-style-type: none"> <li>An estimated life expectancy &gt;6 months</li> </ul>	<p>Sample size:</p> <ul style="list-style-type: none"> <li>Intervention arm: 252 patients.</li> <li>Control arm: 251 patients.</li> </ul> <p>Patients mean age: 79 years.</p>	<ol style="list-style-type: none"> <li>Number of medications prescribed for the patients at 3, 6, and 12 months.</li> <li>Emergency department and primary care consultation rate for acute conditions.</li> <li>Mortality rate.</li> <li>Hospitalization rate.</li> </ol> <p><b>Duration of the outcome evaluation:</b> 3, 6 and 12 months</p>	<p>Intervention: three phases:</p> <ol style="list-style-type: none"> <li>A pharmacist review patient medication and classify medication based on STOPP/START criteria.</li> <li>A pharmacist discusses the recommendations with the patient's physician.</li> <li>A physician discusses the recommendation with the patient through face-to-face visit.</li> </ol> <p>Comparator: routine clinical practice.</p>

[35]	Country: Canada. Setting: outpatient settings. Study design: Cluster randomized controlled trial.	Inclusion: Patients aged 65 years and above on one of four Beers Criteria medications (nonsteroidal anti-inflammatory drugs, first-generation antihistamines, sedative-hypnotics, or glyburide). Exclusion: <ul style="list-style-type: none"> <li>• Dementia.</li> <li>• Significant mental illness.</li> <li>• Severe cognitive impairment.</li> </ul>	Sample size: <ul style="list-style-type: none"> <li>• Intervention arm: 34 pharmacies received intervention immediately and 248 patients.</li> <li>• Control arm: 35 Pharmacies wait-listed and 241 patients.</li> </ul> Patients mean age: 74.7 years.	<b>Primary outcome:</b> complete discontinuation of prescriptions for any of the 4 Beers criteria medications after 6 months of randomization, measured at participant level. Discontinuation defined as: no prescription renewal at six months, continued for at least three consecutive months and no substitution to another PIM. <b>Duration of the outcome evaluation:</b> 6 months.	Intervention: research assistants provided pharmacies with: <ul style="list-style-type: none"> <li>• Patient educational brochures.</li> <li>• Prototype pharmaceutical opinion.</li> </ul> To distribute to both patients and their prescribers. Comparator: usual care
[36]	Country: Canada (Newfoundland and Labrador). Setting: nursing home. Study design: Randomized controlled trial.	<ul style="list-style-type: none"> <li>• Inclusion:</li> <li>• Residents aged 65 years or older.</li> <li>• All patients located in one floor that consisted of three units.</li> <li>• Exclusion:</li> <li>• Residents with no regular scheduled medications.</li> <li>• Palliative.</li> <li>• Patient, family, or care team refused participation.</li> </ul>	Sample size: <ul style="list-style-type: none"> <li>• Intervention arm: 22 patients.</li> <li>• Control arm: 23 patients.</li> </ul> Patients mean age: 84.4 years.	<b>Primary outcome:</b> The change in the number of medications at 3 and 6 months. <b>Secondary outcomes:</b> <ul style="list-style-type: none"> <li>• Changes in patients' survival.</li> </ul> <b>Duration of the outcome evaluation:</b> 3 and 6 months.	Intervention: deprescribing recommendation after in-depth medication review by pharmacist to detect PIMs. Comparator: usual care.

**Table 1:** The included Studies characteristics.

### Setting

All seven effectiveness studies included in the review were conducted in developed countries. Two of the studies were carried out in Canada [35,36]. A further one study was carried out in each of England [30], Netherlands [31], Northern Ireland [32], Sweden [33], and Spain [34]. Four of the studies were conducted in ambulatory care settings [31,33-35] and three studies in nursing homes [30,32,36]. The two included economic studies were conducted in a high-income country, namely Canada [37,38]. Both studies were conducted in community-dwelling settings [37,38].

### Design

Five of effectiveness studies were standard randomized controlled trials [30,31,33,34,36] with two being cluster randomized controlled trials [32,35]. All the seven studies included in the review reported exclusion criteria with the exception of one study conducted by Milos, et al. [33]. The most common reasons for exclusion of patients were terminally ill patients with a short life expectancy, participation in another clinical trial or lack of

cooperation with the assigned physician. Both included studies were cohort subpopulations of cluster randomized trials [37,38], linked to a single cluster RCT conducted by Martin, et al. [35]. One study was a cost effectiveness analysis [37] and the other study was cost utility analysis [38].

### Population

A total of 2602 patients were included in the review with sample sizes ranging from 45 patients [36] to 661 patients [30]. Five of the studies included older adults aged  $\geq 65$  years [30-32,35,36], one study included older adult patients aged  $\geq 70$  years [34] and one study included older adult patients aged  $\geq 75$  years [33]. The mean age of the patients in the included studies ranged from 74.7 years [35] to 87.4 years [33].

Sanyal, et al. studied 56 patients on nonsteroidal anti-inflammatory drugs [37], and Turner, et al. studied 301 patients on sedative medications to treat insomnia [38]. Both studies were subpopulation from Martin, et al. [35], that included 69 pharmacies in the cluster and a total of 489 patients, with patients mean age 74.7 years.



## Intervention

All seven effectiveness studies included in the review evaluated pharmacist led deprescribing intervention in nursing homes and/or ambulatory care settings for patients mean age 65 years and above. Five studies evaluated pharmacist-led medication reviews to identify PIMs recommending medication changes to the general practitioner and/or patients [31-34,36]. The pharmacist in Vinks, et al. discussed the recommendations with the general practitioner within 2 weeks of the inclusion date (5-15 minutes of discussion) [31], and the pharmacists in Balsom, et al. [36] implemented and documented the deprescribing plan over weeks to months. Moreover, The pharmacist in Patterson, et al. visited the patients monthly for 12 months [32].

One study evaluated the clinical records of patients who had undergone pharmacist review followed with formulated recommendations to the physicians through written proforma [30]. The pharmacists in Zermansky, et al. trial conducted medication review within 28 days of randomization [30]. Martin, et al. evaluated pharmacist-led deprescribing through patient educational brochures and prototype pharmaceutical opinion to distribute to both patients and their prescribers [35]. Sanyal, et al. evaluated pharmacist-led educational deprescribing intervention for nonsteroidal anti-inflammatory drugs [37]. Turner, et al. evaluated pharmacist-led educational deprescribing intervention for chronic sedative medications [38].

## Comparator

In all the trials, the comparator was usual care with no special medication review by pharmacists to discontinue potentially inappropriate medications. The comparator for the economic studies was no medication review by pharmacist for patients taking nonsteroidal anti-inflammatory drugs [37] and patients taking sedative medications to treat insomnia [38].

## Outcome measures

Four of the included studies reported outcomes relating to both health service utilization and clinical effectiveness [30,32,34,36], three studies reported only health service utilization [31,33,35], and the two economic studies reported cost effectiveness and cost utility respectively [37,38].

Study period included in the analysis: In the five randomized controlled trials, Zermansky, et al. [30] evaluated both health service utilization and clinical effectiveness outcomes over 6 months, Vinks, et al. [31] and Milos, et al. [33] evaluated health service utilization outcomes over 4 months and 2 months, respectively. Campins, et al. [34] evaluated both health service utilization and clinical effectiveness outcomes over 3, 6 and 12 months, and Balsom, et al. evaluated both health service utilization and clinical effectiveness outcomes over 3 and 6 months [36].

In the two cluster randomized controlled trials, Patterson et al. [32] study evaluated both health service utilization and clinical effectiveness outcomes over 12 months, and Martin, et al. [35] evaluated the health service utilization outcomes over 6 months. Both economic studies included evaluated economic outcomes over 6 months [37,38].

**Health service utilization outcomes:** All seven effectiveness studies included in the review reported health service utilization outcomes, many studies described the health service utilization using different measurements. Four of these studies described the health service utilization as the change in number of potentially inappropriate medications between the intervention and control arms [31-33,35], and the change in the number of medications described in four studies [30,31,34,36]. Whereas one study described the health service utilization as the proportion of patients taking ten or more medications [33].

**Clinical effectiveness outcomes:** Four included studies reported clinical effectiveness outcomes. The selected studies described the clinical effectiveness using different measurements. Three studies described the clinical effectiveness as the change in mortality rate [30,34,36] while the change in hospitalization rate described in two studies [30,34]. Two studies reported the clinical effectiveness as risk of fall reduction by measuring the number of falls per patient [30] or the difference in the rate of fall [32]. Cost effectiveness and cost utility outcomes: The selected two economic studies reported cost effectiveness outcomes as the incremental cost effectiveness ratio (\$/QALY gained), while the QALYs and the incremental QALYs represented cost utility outcomes (Table 2).

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Author, year of publication	Country, setting and study design	Study inclusion and exclusion criteria	Sample size	Duration of the outcome evaluation	Intervention and comparator
[37]	Country: Canada (Quebec). Setting: community-dwelling. Study design: cost effectiveness analysis, cohort subpopulation of cluster randomized conducted by Martin, et al. [35].	Inclusion: Patients aged $\geq 65$ years. On chronic oral nonsteroidal anti-inflammatory drug users (more than 90 days supplied in the previous 120 days). Exclusion: None.	<ul style="list-style-type: none"> <li>Intervention arm: 33 patients.</li> <li>Control arm: 23 patients.</li> </ul>	6 months	Intervention: pharmacist-led educational deprescribing intervention for nonsteroidal anti-inflammatory drugs. Comparator: usual care.
[38]	Country: Canada (Quebec). Setting: community-dwelling. Study design: cost utility analysis, cohort subpopulation of cluster randomized conducted by Martin et al. [35].	Inclusion: Patients aged $\geq 65$ years. Chronic users ( $>3$ months) of sedative medications to treat insomnia. Exclusion: None.	<ul style="list-style-type: none"> <li>Intervention arm: 146 patients.</li> <li>Control arm: 155 patients.</li> </ul>	6 months	Intervention: pharmacist-led educational deprescribing intervention for chronic sedative medications. Comparator: usual care.

**Table 2:** The included economic studies characteristics.

### Quality of included studies

Risk of bias assessment for the standard randomized controlled trials see Table 3. The risk of bias of five standard randomized controlled trials selected for the review [30,31,33,34,36] were assessed using the revised version of the Cochrane tool to assess risk of bias in randomized trials (RoB 2) [24].

Study ID	Randomization process	Deviations from the intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall <sup>2</sup>
[30]	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
[31]	Some concerns	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Some concerns
[33]	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
[34]	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
[36]	Some concerns	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Some concerns

<sup>1</sup>Risk of bias for each domain judged based on the signaling questions. <sup>2</sup>**Low risk of bias:** at low risk of bias for all domains. **Some concerns:** at least one domain judged with some concerns, with no one domain judged with high risk of bias. **High risk of bias:** at least one domain judged with high risk of bias, or multiple some concerns judgment.

**Table 3:** Risk of bias assessment for the randomized controlled trials<sup>1</sup>.

Three studies received similar low risk scores in all domains [30,33,34]. Risk of bias in randomization process was rated low for Zermansky et al., Milos, et al. and Campins, et al., as random sequence distribution and allocation concealment were labeled in detail [30,33,34].

Risk of bias in randomization process held some concerns for Vinks, et al. and Balsom, et al., as no random element was used in distributing the allocation sequence or there are some imbalances between the intervention and the control group that maybe caused because of the randomization process [31,36]. Moreover, risk of bias in deviations from the intended interventions in all selected RCTs was low, as they were using appropriate analysis to estimate the result of assignment to deprescribing.

Risk of bias in missing outcome data and measurement of the outcome was found to be low in all RCTs selected as the outcome data for the studies available for all or nearly all randomized patients and the method of measuring the outcome appropriate and the outcome assessors were blinded to intervention status, respectively. Risk of bias in selection of the reported result was found to be low in all RCTs selected as the analysis of the data according to the prespecified analysis plan.

Risk of bias assessment for cluster randomized controlled trials (Table 4). The risk of bias of two cluster randomized controlled trials selected in the review [32,35] were assessed using the revised version of the Cochrane tool to assess risk of bias in cluster randomized trials (RoB 2) [25].

Study ID	Randomization process	Timing of identification or recruitment of participants	Deviations from the intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall <sup>2</sup>
[32]	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Some concerns	Low risk of bias	Some concerns
[35]	Some concerns	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Some concerns

<sup>1</sup>Risk of bias for each domain judged based on the signaling questions. <sup>2</sup>**Low risk of bias:** at low risk of bias for all domains. **Some concerns:** at least one domain judged with some concerns, with no one domain judged with high risk of bias. **High risk of bias:** at least one domain judged with high risk of bias, or multiple some concerns judgment.

**Table 4:** Risk of bias assessment for cluster randomized controlled trials<sup>1</sup>.

Risk of bias in randomization process was found to be low for Patterson, et al. as random sequence distribution and allocation concealment were labeled in detail [32]. Risk of bias in the randomization process held some concerns for Martin, et al. given that there was some imbalance between the intervention and the control group that maybe caused because of the randomization process. Risk of bias in timing of identification or recruitment of participants was considered low for both cluster RCTs as all patients recruited before randomization of clusters [35].

Risk of bias in missing outcome data and measurement of the outcome was recorded as low in all cluster RCTs selected as the outcome data for the studies available for all or nearly all randomized patients and the method of measuring the outcome appropriate and the outcome assessors were blinded to intervention status, respectively. Risk of bias in selection of the reported result was rated as low in all cluster RCTs selected as the analysis of the data according to the prespecified analysis plan. The quality of the economic studies [37,38] was assessed according to Drummond et al. [27] 10-item checklist, that assess strengths and weaknesses of the articles, and elaborated judgement of the worth and suitability of the results for their objectives [28] (Table 5).

Yes/ no/ can't tell	Sanyal, et al. [37]	Turner, et al. [38]
Was a well-defined question posed in an answerable form?	Yes	Yes
Was a comprehensive description of the competing alternatives given?	Yes	Yes
Was the effectiveness of the programs or services established?	Yes	Yes

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Were all the important and relevant costs and consequences for each alternative identified?	Yes	Yes
Were costs and effects measured accurately in appropriate physical units (e.g., QALYs)?	Yes	Yes
Were costs and effects valued credibly?	Yes	Yes
Were costs and effects adjusted for differential timing?	Yes	Yes
Was an incremental analysis of costs and effects of alternatives performed?	Yes	Yes
Were allowances made for uncertainty in the estimates of costs and effects?	No	No
Did the presentation and discussion of study results include all issues of concern to users?	Yes	Yes
Total score	9	9

**Table 5:** Drummond’s 2015, 10-item checklist for quality assessment of the economic studies.

Both studies received similar evaluation and total score (9 points). Appraised uncertain in the estimate of cost and outcomes was the common failed point, by not explaining the justification for the chosen key parameters ranges. While the strength of both studies is that they mentioned the alternatives and examined the costs and effects. The alternative was described as usual care for both studies. Also, the effectiveness of the intervention was evaluated through cluster randomized controlled trial. For both studies, all relevant perspectives were considered to be covered as well as capital costs and operating costs. Moreover, the effects measured using QALYs. Also, the discount rate used and justified for both studies. Outcomes finding summarized in Table 6.

Author, year of publication	Health service utilization outcomes			Clinical effectiveness outcomes		
	The change in number of potentially inappropriate medications	The change in the number of medications	The proportion of patients administering ten or more medications	The change in mortality rate	The change in hospitalization rate	Risk of fall reduction
[30]	Not reported	Significant change in the intervention arm compared to control arm 3.1 and 2.4, respectively. (P < 0.0001).	Not reported	No statistically significant difference in mortality, with 51 deaths in intervention arm and 48 deaths with control arm, (P = 0.81).	Lower rate of hospitalization (not statistically significant), with mean values 0.2 (intervention arm) and 0.3 (control arm), P = 0.11	Significant reduction in the fall rate (0.8 vs 1.3), (P < 0.0001).
[31]	Significant reduction with mean difference -16.3%; 95% CI -24.3, -8.3	No significant change with mean difference -4.7%; 95% CI -9.6, 0.2.	Not reported	Not reported	Not reported	Not reported
[32]	After adjustment for clustering within homes, the percentage of patients on PIMs was much lower than in the control. (19.5 % for intervention group and 50.0% for control group) (odds ratio= 0.26, 95% CI = 0.14-0.49)	Not reported	Not reported	Not reported	Not reported	No difference in the fall rate (277 falls for intervention group and 186 falls for control group (P =0.09).

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[33]	Significant reduction with 6 % in intervention arm; p = 0.007) but not in the control arm (p = 1.0)	Not reported	Significant reduction with 58.7% of patients in intervention group used ten or more medications vs 64.1 patients in the control group, P = 0.001.	Not reported	Not reported	Not reported
[34]	Not reported	Significant reduction with 10.03 medications/patient (used by intervention group) and 10.91 medications/patients (used by control group), (P = 0.001).	Not reported	Non-statistically significant difference with 7 deaths (2.8%) in intervention group and 6 deaths (2.4%) in control group, P= 0.784	No difference with hospitalization rate 23.3 % (intervention group) and 25.2% (control group), P= 0.616	Not reported
[35]	Intervention arm: Complete discontinuation occurred among 106 of 248 patients (42.7%). The relative risk was 3.55 (95%CI, 2.45-5.15). Control arm: Complete discontinuation occurred among 29 of 241 (12.0%). mean difference: 31% (95%CI, 23%-38%)	Not reported	Not reported	Not reported	Not reported	Not reported
[36]	Not reported	Mean number of medications administered per patient significantly reduced at three and six months. Intervention group used a mean value 2.68 medications less than control arm (p < 0.02) at 3 months and 2.88 less (p = 0.02) at 6 months.	Not reported	No deaths recorded in intervention or control group.	Not reported	Not reported

**Table 6:** Outcomes from the included studies.

## Health Service Utilization Outcomes

### The Change in Number of Potentially Inappropriate Medications (PIMs)

All four studies that reported the change in number of PIMs found a significant reduction in the number of PIMs used by the intervention groups compared to control groups [31-33,35]. Vinks, et al. [31] reported significant reduction with mean differences -16.3%; 95% Confidence Interval (CI) -24.3, -8.3, Patterson, et al. reported that after adjustment for clustering within homes, the percentage of patients on PIMs was much lower than in the control group [32] (19.5 % for intervention group and 50.0% for control group) (odds ratio= 0.26, 95% CI = 0.14-0.49), Milos, et al. [33] reported significant reduction with 6% in intervention group;  $p = 0.007$ ) but not in the control group ( $p = 1.0$ ), and Martin, et al. [35] reported that complete discontinuation that occurred among 106 of the intervention group (42.7%), the relative risk was 3.55 (95%CI, 2.45-5.15) compared to complete discontinuation occurred among 29 of control group (12.0%), mean difference: 31% [95%CI, 23%-38%].

### The change in the number of medications

Three of the four studies that reported the change in the number of medications found that a significant reduction in the number of medications used by the intervention arm compared to control arm [30,34,36]. Zermansky, et al. [30] reported that the number of medication withdrawn in the intervention arm was significantly greater than that in the control arm 3.1 and 2.4, respectively ( $P < 0.0001$ ), Campins, et al. reported significant reduction with 10.03 medications/ patient (used by intervention group) and 10.91 medications/ patients (used by control group) [34], ( $P = 0.001$ ), and Balsom, et al. [36] reported that the mean number of medications administered per patient significantly reduced at three and six months, the intervention arm used in a mean value 2.68 medications less than the control arm ( $p < 0.02$ ) at 3 months and 2.88 less ( $p = 0.02$ ) at 6 months. On the other hand, Vinks et al. reported a non-significant reduction with mean difference -4.7%; 95% CI -9.6, 0.2 [31].

### The Proportion of Patients Administering Ten or More Medications

The single study that reported the proportion of patients administering ten or more medications found a significant reduction with 58.7% of patients in the intervention arm used ten or more medications compared to 64.1% of patients in the control arm,  $P = 0.001$  [33]. Overall, sex of the seven studies that reported health service utilization outcomes of the pharmacist-led deprescribing intervention in nursing home and ambulatory care settings found that pharmacist-led deprescribing significantly reduced health service utilization through reduction in the number of PIMs used, reduction in the number of medications used, and reduction in the proportion of patients administering ten or more medications. Only the study of Vinks, et al. reported a non-significant reduction in the number of medications used while same study reported a

significant reduction in the number of PIMs used [31].

### Clinical effectiveness outcomes

In contrast to health service utilization outcome, the studies reporting the clinical effectiveness outcome of the pharmacist-led deprescribing intervention in nursing home and ambulatory care settings displayed more variation.

#### a. The change in mortality rate

Two of the three studies that reported the change in mortality rate found a non-significant difference in mortality rate between the intervention arms and control arms [30,34]. Zermansky, et al. [30] reported a non-statistically significant difference in mortality, with 51 deaths in the intervention arm and 48 deaths in the control arm ( $P = 0.81$ ), and Campins, et al. [34] reported a non-statistically significant difference with 7 patient deaths (2.8%) in the intervention arm and 6 patient deaths (2.4%) in the control arm ( $P = 0.784$ ). while the third study did not record any deaths in the intervention and control arms [36].

#### b. The change in hospitalization rate

Both studies reporting a change in hospitalization rate found a non-significant reduction in hospitalization rate for the intervention groups compared to the control groups [30,34]. Zermansky et al. reported a lower rate of hospitalization (not statistically significant), with mean values 0.2 (intervention group) and 0.3 (control group) [ $P = 0.11$ ], and Campins, et al. reported a no difference with hospitalization rate 23.3 % (intervention group) and 25.2% (control group) [ $P = 0.616$ ] [30,34].

#### c. Risk of fall reduction

One of the two studies reported the risk of fall reduction found a significant reduction in the number of falls (0.8 vs 1.3 falls per patient) with  $P < 0.0001$  [30]. Conversely, the second study found no difference in the fall rate (277 falls for intervention arm and 186 falls for control arm ( $P = 0.09$ )) [32].

### Economic studies outcomes

#### a. Cost utility

Sanyal, et al. reported that a deprescribing intervention was associated with more QALYs (0.75) compared to control group (associated with 0.65 QALYs) and incremental QALYs associated with the deprescribing intervention compared to control group was 0.11 [37]. Moreover, Turner, et al. reported that deprescribing intervention associated with more QALYs (0.7232) compared to control group that associated with 0.6463 QALYs and incremental QALYs associated with the deprescribing intervention compared to control group was 0.0769 [38].

#### b. Cost effectiveness

Sanyal et al. reported that compared to control group, deprescribing was a dominant strategy (lower cost and more effectiveness). The incremental net benefit (INB) value at

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willingness-to-pay (WTP) thresholds of 50 000 Canadian dollars (CAD) and 100 000 CAD (39160 to 78320 United States dollars (USD)) was 6398 CAD (5000 USD) and CAD11 788 (9232 USD), respectively [37]. Also, Turner et al. reported that compared to control group, deprescribing was a dominant strategy (lower cost and more effectiveness). INB value at WTP thresholds of CAD50 000 (39160 USD) and CAD100 000 (78320 USD) was CAD5237 (4100 USD) and CAD9082 (7113 USD), respectively [38].

Overall, both economic studies reported the cost effectiveness and cost utility of the pharmacist-led deprescribing intervention in nursing home and ambulatory care settings finding that pharmacist-led deprescribing improve the QALYs, incremental QALYs, and incremental cost effectiveness ratio (\$/QALY gained). Both studies' authors concluded that the deprescribing intervention in community-dwelling older adults is a cost-effective strategy. However, linked to a single cluster RCT conducted by Martin, et al. [35]. Table 7 summarizes the economic studies outcomes.

Author, year of publication	QALYs.	Incremental QALYs.	Incremental cost effectiveness ratio (\$/QALY gained).
[37]	Deprescribing intervention associated with more QALYs (0.75) compared to control group that associated with 0.65 QALYs.	Incremental QALYs associated with deprescribing compared to usual care was 0.11.	Compared to control group, deprescribing was a dominant strategy (lower cost and more effectiveness). INB value at WTP thresholds of CAD50 000 (39160 USD) and CAD100 000 (78320 USD) was CAD6398 (5000 USD) and CAD11 788 (9232 USD), respectively. Thus, the deprescribing intervention in community-dwelling older adults is a cost-effective strategy.
[38]	Deprescribing intervention associated with more QALYs (0.7232) compared to control group that associated with 0.6463 QALYs.	Incremental QALYs associated with deprescribing compared to usual care was 0.0769.	Compared to control group, deprescribing intervention was a dominant strategy (lower cost and more effectiveness). INB value at WTP thresholds of CAD50 000 (39160 USD) and CAD100 000 (78320 USD) was CAD5237 (4100 USD) and CAD9082 (7113 USD), respectively. Thus, the deprescribing intervention in community-dwelling older adults is a cost-effective strategy.

**Table 7:** Outcomes' summary table for cost effectiveness and cost utility studies.

## Discussion

This systematic review evaluated pharmacist-led deprescribing in nursing home and ambulatory care settings on health service utilization, clinical effectiveness, cost effectiveness and cost utility compared to usual care in patients aged 65 years and above. A total of nine studies (five standard randomized controlled trials, two cluster randomized controlled trials, one cost effectiveness analysis and one cost utility analysis) were included.

Health service utilization was evaluated in three main ways. Firstly, the ability to reduce the number of PIMs. The four studies that evaluated this outcome found that pharmacist led deprescribing intervention reducing PIMs more than the usual care [31-33,35]. Secondly, the ability to reduce the total number of medications. Three of the four studies that evaluated this outcome found that pharmacist-led deprescribing reduced the total number of medications more than the usual care [30,34,36]. Only the study of Vinks et al. [31] reported that the reduction of total number of medication was non-significant. Thirdly, the ability to reduce the proportion of patients administering ten or more medications. One study reported this outcome and found that pharmacist led

deprescribing was better in reducing the proportion of patients administering ten or more medications than the usual care [33].

On the other side, the clinical effectiveness was evaluated in three main ways. Firstly, the ability to improve the mortality rate. Two of the three studies that evaluated this outcome found a non-significant difference in mortality rate between pharmacist-led deprescribing and the usual care [30,34]. The third study did not record any death in the intervention and control groups [36]. Secondly, the ability to hospitalization rate. Both studies reported this outcome found that the differences in hospitalization rate between the pharmacist-led deprescribing and usual care were insignificant [30,34]. Thirdly, the ability to reduce risk of fall. Two studies evaluated this outcome, one study found that pharmacist-led deprescribing was better in reducing the risk of fall than the usual care [30], and the second study found no difference between intervention and control arms [32]. In the side of economic studies outcome, both studies evaluated this outcome found that pharmacist-led deprescribing is a cost-effective strategy by improving the QALYs, incremental QALYs, and incremental cost effectiveness ratio (\$/QALY gained) [37,38].

## Interpretation of Results

The studies reported outcomes regarding health service utilization, clinical effectiveness, cost effectiveness and cost utility. While most of the outcomes were in favor of the pharmacist-led deprescribing, many considerations must be borne in mind while applying the findings.

All the nine studies included in this review were conducted in developed countries, which would affect the generalizability of the findings for many reasons. Firstly, there are significant differences between the developed countries health systems and other health systems. Secondly, developed countries are rich countries with high-income resources where healthcare systems can handle new high-cost interventions. Thirdly, developing countries can apply the usual care and pharmacist-led deprescribing in a different way, differences in any of these steps may significantly affect the outcome. Finally, deprescribing need computerized decision support system for better outcome [39], which is not widely available in other countries especially developing countries. Unfortunately, the cost and economic analysis studies evaluated in this review conducted in one country, which is Canada, and are cohort subpopulation of one study led by Martin, et al. [35], that would affect the evidence generalizability because of significant variation in health system and costs between a rich country like Canada and other countries around the world.

In the included studies, there were different pharmacist-led deprescribing intervention that were evaluated such as pharmacist review patients' clinical record, regularly home visits, or patients' education brochures. However, these interventions share the same borders of pharmacist-led deprescribing interventions and aims to withdraw PIMs from the patients.

Mortality measurement after any variable in patients' health profile is better measured over 1 to 2 years [40]. In the included studies, clinical effectiveness outcomes measured after 3 to 12 months. Which could affect the findings accuracy. It was clear that the included studies established reliable findings regarding the health service utilization of pharmacist-led deprescribing interventions in nursing home and ambulatory care settings in elderly patients. These findings would help healthcare organizations to improve and modify their deprescribing and integrating the pharmacist to lead the intervention because of the deprescribing challenges discussed in chapter one. On the other hand, clinical effectiveness outcomes are not encouraging for the implementation of pharmacist-led deprescribing intervention, in addition to the lack of economic studies on a large scale.

## Quality of evidence

All the included studies were confirmed as randomized controlled trials to provide the highest level of evidence. Three studies with low risk of bias [30,33,34] and four studies with some concerns [31,32,35,36]. The methodological quality assessment for the two economic studies were of high quality and low risk of

bias [37,38]. Overall, the evidence of this review is of moderate to high quality due to studies design, moderate to high quality of the included studies, and variant outcome measurements. Assessment of studies quality are important to draw conclusions from the systematic review [24]. In this systematic review, the moderate to high quality of the studies indicates that the results and conclusion in the review are reliable.

## Strength and Limitation of the Review

This review possesses many strengths that include the use of randomized controlled trials. This is the first review to study the effect of pharmacist-led deprescribing in nursing home and ambulatory care settings on health service utilization, clinical effectiveness, cost effectiveness and cost utility. Descriptive statistics were also reported to provide insight into the topic's limited evidence base, and concerns about the data validity. An extensive search strategy was performed that included electronic databases, manual search references for embedded articles, citation searches, and other sources. Moreover, this review studied both the effectiveness and cost effectiveness of the intervention, which answered the economic question that would be raised if any new intervention would be implemented. Another strength of this review was the good methodological quality of the studies included. Studies were at low risk of bias or at concern that led to the assessment of a moderate to high-quality evidence.

However, this review included some limitations. Only one reviewer conducted the review instead of two reviewers because of the nature of the university dissertations. To reduce the human errors and the risk of bias, the systematic review must be performed by two reviewers. Therefore, the reviewer managed this limitation by one reviewer double-checking the relevant steps. While the reviewer performed extensive search strategy, the reviewer didn't contact the authors because of limited timeline for the dissertation. Moreover, meta-analysis would not be conducted because of the high levels of heterogeneity between studies and the variable outcomes. In addition, all the included studies were conducted in developed and high-income countries that would affect the generalizability of this evidence because of the variation between developed and developing countries health system. Finally, the two economic analysis studies were cohort subpopulation of one of the clusters randomized controlled trials included in the review [35].

## Comparison with Previous Reviews

This systematic review is the only review that limited the included articles to pharmacist-led deprescribing interventions in outpatient settings and excluded other types of intervention and setting. Spinewine et al. [6] evaluated pharmacist led deprescribing in European publications without setting limitation and found that pharmacist-led deprescribing reduced significantly the mean number of medications used by the patients, with no positive effect on cost effectiveness quality of life and health outcomes. This systematic review confirms Spinewine et al. [6] findings but



concluded that pharmacist led deprescribing is a cost effective strategy. Spinewine et al. [6] included two articles from this review conducted by Zermansky et al. [30] and Patterson et al. [32].

Dills, et al. evaluated deprescribing intervention in general and found that pharmacist-led educational deprescribing is the most successful intervention that had positive effect on reducing medication burden, with no positive effect on cognition, falls rate, admission rate and quality of life [15]. This systematic review agrees Dills, et al. findings about medication burden, falls rate and admission rate [15]. However, Dills, et al. included one article from this review conducted by Patterson, et al. [15,32].

## Conclusion

Potential inappropriate medications use is common in older adult patients, which have adverse risks that exceed the clinical benefits that cause harm to the patients and are associated with increase in mortality. Pharmacists could help physicians in optimizing drug therapy in older adults by reviewing patient medications, assessing regularly prescribed drugs, extraction of medical record information and patient interview. When compared with usual care, pharmacist-led deprescribing was effective in reducing PIMs usage and medication burden for older adults in nursing home and ambulatory care settings. On the other hand, pharmacist-led deprescribing has no positive effect in reducing mortality, hospitalization, and risk of fall. Moreover, the economic studies in this review concluded that pharmacist-led deprescribing is a cost-effective strategy in Canada only. However, it is essential to evaluate the economic outcomes in different countries to evaluate the cost effectiveness of the intervention. Overall, the evidence of this review is of moderate to high quality due to study design, moderate to high quality of the included studies, and variant outcome measurements.

## Implication for Practice and Future Research

The evidence identified in this systematic review could be used as a basis of new research for the effectiveness and cost effectiveness of pharmacist-led deprescribing. Pharmacists in the developing and low-income countries are encouraged to implement and evaluate their interventions using pharmacist-led deprescribing, that would improve the generalizability of the findings. Economic analyses from countries other than Canada are encouraged to publish to improve the generalizability of the outcomes. Moreover, it is essential to study the clinical effectiveness of pharmacist-led deprescribing in 2 years duration to improve the accuracy of the findings. It is important to conduct new and high-quality systematic review for clinical effectiveness of pharmacist-led deprescribing for older adults in nursing home and ambulatory care settings.

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