Medication Appropriateness in Community Dwelling Older Adults

by

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Abstract

Medication appropriateness is a fundamental target for the healthcare system, particularly in relation to older adults. Because polypharmacy and multimorbidity are prevalent in older adults, they are more prone to the risks of having an inappropriate medication. They are also more prone to adverse medication events, such as adverse drugs reactions, falls, morbidity, and mortality. Older adults represent a vulnerable community segment that requires a broad approach to healthcare planning, with intentional and structured follow up. The objective of this thesis was to describe two perspectives that healthcare practitioners can adopt for older adults' medication management; including the financial aspect of deprescribing inappropriate medications, and the healthcare outcomes of Home Medication Reviews (HMR). Accordingly, the first study objective was to determine the economic impact when deprescribing for older adults. The second study aim was to outline the effect of Home Medication Review (HMR) in older adults in the community on healthcare related outcomes, including clinical, medication, and humanistic outcomes.

For the first study, we established eight different deprescribing scenarios for a standard case of an average senior in Canada with common comorbidities and polypharmacy, reflecting the financial changes over one-year period in each province with its distinctive government plan. For the second study, we completed a systematic review and a quality appraisal where we screened 3585 studies to include and extract data from 18 relevant articles of HMR.

The findings of the first study showed a small financial loss impact of deprescribing on the pharmacy's gross margin but savings in most cases, of patients' share, with consistent savings to

government share. Additionally, we found that that medication regimens varied significantly across the country in terms of coverage and costs to the senior.

The second study showed minimal HMR role in reducing health services utilization, where only four out of the 18 included studies showed significant reduction of hospitalization readmission rates. On the other hand, HMR had a positive role in improving medication outcomes concerning adjustments of patients' treatment regimen, with little impact on patients' quality of life or mortality rates. The findings from this thesis indicated that deprescribing inappropriate medications may create financial burden that restrain the community pharmacy from accepting this approach; and the need for a future decision from policy makers that includes an integrated financial consideration of pharmacy, patients, and government when adopting deprescribing policies. Another finding in this thesis is that HMR is one of the suggested approaches to resolve polypharmacy and inappropriate medications, however, the effect of HMR on healthcare outcomes appears minimal.

Preface

This thesis document is an original work by myself under the supervision of Dr. Cheryl Sadowski.

Some of the research conducted for this thesis was done in collaboration with the Alberta SPOR SUPPORT Unit KT Platform with Dr. Sadowski being the lead collaborator at the University of Alberta.

Data collection for chapter 2 was done by myself and Jody Shkrobot.

Data collection for chapter 3 was done by myself and Sholeh Rahman

Data analysis for chapter 2 and 3 are my original work.

S Abu Fadaleh, J Shkrobot, T Makhinova, D Eurich, C Sadowski. [Medication deprescribing for seniors: Economic advantage or financial barrier?]. Poster presentation at Canadian Agency for Drugs and Technologies in Health April2019.

S Abu Fadaleh, T Charrois, SRahman T Makhinova, D Eurich, C Sadowski.[The impact of home medication review in older adults in the community: A systematic review]. HMR poster presentation at American Geriatrics Society Annual Scientific Meeting. California, USA May2020 [accepted for presentation February 3, 2020]

Dedications

This thesis is dedicated to the memory of my father, Mohammad Abu Fadaleh, from whom I learnt that we should pursue our dreams until come true. You are gone but your belief in me has given me the light to continue this journey.

To my mother, Fathieh Iskandarani, who continuously supports and encourages me. Her love and prayers helped me finish my studies successfully.

To my brother and sisters, who had been great supporters through hard times. Their believe in education and building a better future, is surely contagious.

To all my friends and family, Thank you.

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I would also like to acknowledge and thank my co-supervisors, Dr. Dean Eurich and Dr. Tatiana Makhinova for their valuable insights and expertise throughout my research.

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List of abbreviations:

PIM	Potentially Inappropriate Medications
MRH	Medication Related Harm
ADR	Adverse Drug Reaction
HMR	Home Medication Review
AGS	American Geriatric Society
PPI	Proton Pump Inhibitor
CIHI	Canadian Institute for Health Information
DIN	Drug Identification Number
MAC	Maximum Allowable Cost
OTC	Over The Counter
PANL	Pharmacy Association of Newfoundland
NIHB	Non-Insured Health Benefits
COPD	Chronic Obstructive Pulmonary Disease
HF	Heart Failure
CAD	Coronary Artery Disease
CHF	Congestive Heart Failure
DM	Diabetes
NR	Not Reported
PSQ	Patient Satisfaction Questioner
MAI	Medication Appropriateness Index
ER	Emergency Room
GP	General Practitioner
QoL	Quality of Life

CDM	Chronic Disease Management
PCS	Physical Component Scale
MCS	Mental Component Scale
GDS	Geriatric Depression Scale
PPT	Physical Performance Test
MMSE	Mini Mental Status Examination
VAS	Visual Analogue Scale
OPD	Out Patient Department

Chapter One
Introduction

1.1 Demographics and Older Adults

The demographics in Canada are shifting toward an aging population. In 2014/2015 the growth rate of the baby boomers (who had reached the age of 65 by 2011) was 3.5%; which was four times the growth rate of other age groups.[1] Consequently, by 2030 older adults will represent 23% of Canadians, the highest proportion in history.[2]

Older adults have a higher percent of medication use compared to any other age group.[3] In 2016, 65.7% of Canadian older adults were prescribed more than4 drug classes per year, with 26.5% prescribed more than 9 different drug classes. Furthermore, 35.4% had chronic use of a five or more of different drug classes.[3] Older adults are also using more drugs due to their predisposition to a higher number of chronic conditions.[3] In Canada, 90% of individuals over the age of 65 have one or more chronic disease.[2] Hypercholesteremia is common, diagnosed in 44% of older adults, which corresponds to statins being the most commonly prescribed drug class, with 48.4% use in older adults. [3,4]

The Canadian healthcare system was designed in the 1950s [5] to provide the acute care of a relatively young population.[6] With the escalation of the challenges to manage older adults' chronic conditions and related complex health issues, the healthcare needs to seniors are not being met.[6] Additionally, Canadian geriatric medicine is facing the critical challenge of geriatricians scarcity.[7] The definite number of geriatricians required to satisfy the healthcare need is not yet determined; however, estimates that up to 700 geriatricians could be a reasonable number to meet the current demands.[7] The Canadian Medical Association reported 304 specialists in geriatrics in 2018; which highlights a substantial shortage in most provinces.[8] This necessitates a national older adults' health strategy to optimize health services; and create an "age-friendly"[9] environment with improved physical and mental health, and reduced disease burden. [6]

1.2 Statement of problem

Chronic diseases require multifaceted intervention, often including pharmacotherapy. However, a number of variables must be considered when clinicians prescribe medications to older adults: physiological and psychosocial factors. Physiological changes represented by pharmacodynamic and pharmacokinetics processes, differ substantially between older patients and younger ones.[10] In addition, older adults have diseases or syndromes that are less common in younger populations, such as dementia or falls, which can affect medication choices.[11] The complexity of older adult's medication regimens requires healthcare practitioners to evaluate older adults' functional capacity for medication management, including the assessment of their physical and cognitive skills.[12] Furthermore, psychosocial factors such as mood, social support, or financial status can change with age and must be part of medication-related decision making for older adults.[13] For example, older adults are at greatest risk for social isolation and poverty, which increases the risk of depression, dementia and other poor health outcomes.[14,15]Considering all these factors is vital for avoiding inappropriate medications and healthcare burden.[13]

Since chronic disease is often managed with pharmacotherapy, it is common for older adults in the community to have multimorbidity and polypharmacy.[16]

Multimorbidity is defined as "the co-existence of two or more chronic conditions, where one is not necessarily more central than the others".[17] The incidence of multimorbidity becomes higher with age, affecting quality of life, imposing financial burden, in addition to increasing the risk of hospitalization and polypharmacy.[17] However, clinical practice guidelines are directed toward the management of single disease conditions, such as hypertension, or arthritis.[16] This leads to increasing complexity in decision making, which is why the American Geriatrics Society has published guidelines on multimorbidity, with more emphasis on individualization of patient care.[17]

Polypharmacy, defined by most researchers as using five or more medications simultaneously [18], has a large impact on older adults' health status.[19]According to 2016 national data in Canada, older adults prescribed 10 or more medications were five times at higher risk to be hospitalized as a result of related adverse drug reactions.[3] Polypharmacy increases risk for falls, frailty, hospital readmissions, and increased length of hospitalization.[19] The prevalence of polypharmacy

is attributed to many aspects, but mostly due to older adults having multiple of chronic conditions.[20]

Polypharmacy and multimorbidity both increase the risk of potentially inappropriate medications (PIM) in ambulatory older adults.[13,21] PIM is a term used when the harm outweighs the benefit from a medication, or when a safer alternative exists.[22] PIM are associated with increased morbidity, disability, increased use of health resources, and mortality [21]. The American Geriatrics Society (AGS) Beers Criteria was created in the early 1990's, and is now regularly updated by the AGS. It is an explicit list out of medications that are classified as PIMs. The medications are classified into different categories, including 1) medications where the harm always outweighs the benefit, 2) medications that should be avoided with particular disease states, 3) medications that have interactions, 4) mediations that should be avoided or have their dose reduced due to reduced kidney function .[23] In Canada, CIHI uses the Beers Criteria as their standard for classifying PIMs. The most recent report on medication use in seniors found that 49.4% of older adults had at least one claim for a medication listed as a PIM, with PPI (Proton Pump inhibitors) as the most commonly prescribed PIM in 23.6% of older adults.[3]

This highlights the need for strategies that would identify inappropriate medications , medications with evident interactions, and those that should be avoided with certain diseases.[24]Accordingly, tools to assess the appropriateness of prescribed medications include explicit tools (e.g. Beers, STOPP/START criteria) or implicit measures (e.g. Medication Appropriateness Index- MAI); these are used for the purpose of judging either the prescriptions' standards or risk for adverse outcomes. [25,26]

Another unique aspect of health in older adults is the presentation of geriatric syndromes. These are defined as "multifactorial health conditions that occur when the accumulated effect of impairments in multiple systems renders an older person vulnerable to situational challenges".[13] Syndromes that occur commonly include delirium, falls, frailty, or urinary incontinence.[27] They have multiple risk factors and require multifactorial intervention to address.[27] Medication related harm (MRH), that results from older adults' polypharmacy and multimorbidity, is classified as a geriatric syndrome. Both geriatric syndromes and MRH are associated with multimorbidity and frailty, lead to poor outcomes, and are highly prevalent among older adults.[13] A recent systematic review found that 17% to 51% of older adults experienced MRH within 30 days after hospital discharge.[28] Additionally, in 2017 the World Health Organization (WHO) announced a 5 year-

plan of reducing 50% of MRH by addressing three domains of patient safety, including high-risk situations, polypharmacy, and transitions of care, with emphasis on proper medication management.[29] Given this international call for action, and that older adults with more than 10 medications accounted for 58.6% of adverse drug reaction related hospitalization in Canada,[3] MRH and medication decision for older adults require coordinated and integrated healthcare.[13]

Therefore, optimizing older adults' medication regimens represents an opportunity, where tools can be developed, or currently available tools can be implemented to assess medications, and bring about changes necessary to prevent MRH.[24] Accordingly, medication management considerations include both deprescribing inappropriate medications and optimizing appropriate ones.[24]

1.3 Objectives

The overall objective is to determine the effect of two strategies to improve medication appropriateness for older adults. These two strategies are deprescribing and home medication reviews (HMR).

Specific objectives:

- To determine the financial implication of deprescribing of older adults' medications.
- To describe the effect of home medication reviews on health-related outcomes.

1.4 Thesis outline

Two milestones were developed to address the overall objective of the thesis. Table 1-1 summarizes these milestones.

Table 1-1: summary of thesis

Milestone	Research
1	Financial analysis of a case study of a senior with common multimorbidity and polypharmacy, addressing eight possible deprescribing scenarios over a one-

	year period.
2	Conducting a systematic review of home medication reviews' (HMR) articles to report the current evidence relating health outcomes of HMR for older adults.

Milestone 1: A standard case was developed to reflect an 'average' senior in Canada, at median income, with common multimorbidity, medications frequently used in seniors, and one high-cost medication. Eight different deprescribing scenarios were studied financially to calculate the annual average pharmacy margin difference and total government and patient share. (Milestone 1 detailed in chapter 2)

Milestone 2: The systematic review was done to determine HMRs' impact on older adults health related outcomes by extracting data related to clinical, medication, humanistic and economic outcomes. (Milestone 2 detailed in chapter 3)

Chapter Two

Financial advantage or barrier when deprescribing for seniors: A case-based cost analysis

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Abstract

OBJECTIVE: Polypharmacy is a trigger for potentially inappropriate medications (PIM), which may lead to poor outcomes for seniors. One solution is to use deprescribing. However, several barriers may oppose this process, including financial implications. The purpose of this study is to determine the financial impact of deprescribing on the pharmacy, public payer (government), and the patient, across Canadian provinces and territories.

METHODS: A standard case was developed to reflect an 'average' senior in Canada, at median income, with common multimorbidities, medications frequently used in seniors, and one high-cost medication. Eight different deprescribing scenarios were studied financially before and after each intervention. Detailed drug costs were obtained from the different government plans covered in each province or territory, and were used to calculate the annual average pharmacy margin dollar difference and total government and patient share. Costs were calculated for a 1-year period.

RESULTS: Before deprescribing, the patient share for the regimen ranged between $1511.47 (Quebec) and $4342.75 (British Columbia) per year. The scenario with the greatest cost saving to the patient and greatest loss to the pharmacy was switching to a lower cost medication from liraglutide to prefilled detemir, with highest savings in patient share of $3699.95and highest loss in pharmacy margin of $473.84 in Alberta**.**

CONCLUSION: There is a range in costs and coverage for medications across Canada. The deprescribing scenarios demonstrated a small impact on the pharmacy's gross margin, in some cases a significant financial impact on patient costs, but minimal impact to government.

Deprescribing initiatives and policies should include financial considerations for community pharmacies and patients.

Keywords:

Deprescriptions, Inappropriate Prescribing, Costs and Cost Analysis, Drug Costs, Cost-Benefit Analysis, Pharmacy Fee, Pharmacy Economics.

Highlights

- Deprescribing in older adults usually leads to cost savings for the patient.
- Deprescribing can lead to increased drug cost to the patient due to policies on drug pricing.
- Deprescribing in older adults usually leads to a small loss in gross margin to the dispensing pharmacy, which may pose a barrier to pharmacist practice to deprescribe.
- The government payer is generally sheltered from any drug cost implications from deprescribing.

2.1 Introduction

The definition for polypharmacy is not universally agreed upon, but many researchers accept the concept of using five or more medications simultaneously.[19] The prevalence of polypharmacy is highest amongst older adults (65.7%) over the age of 65, with 66.7% women and 64.5% men, using 5 or more medications in Canada.[3] Polypharmacy and complex medication regimens can be due, in part, to comorbidities in older adults. As the number of medications increase, the risk of potentially inappropriate medication (PIM) use is likely to increase, with a prevalence of 18%-79% in seniors.[21] Polypharmacy and PIM are associated with poorer outcomes, adverse events, increased hospitalization rates, and death.[21]

Beers Criteria was created and periodically updated to identify a number of medications or classes of medications that are potentially inappropriate to be prescribed for older adults; for the purpose of addressing patient safety, these criteria are routinely referenced in geriatric clinical practice .[23,30] To address PIMS and polypharmacy, deprescribing has been proposed and defined as: adjusting medications down to the minimum effective dosage or stopping them when that medication burden or potential for harm outweighs the benefit of the medication.[31] This includes stopping medications , tapering of doses, switching to a safer or convenient choice.[32,33] Deprescribing should be considered at each point in the patient's treatment strategy, and in all settings, including hospitals, clinics, and community pharmacies.[34] However, the implementation of deprescribing represents a clinical challenge, as there are barriers to deprescribing, including patient or prescriber beliefs, fear of adverse effect with drug withdrawal, clinical inertia, adherence to clinical practice guidelines, and financial disincentives from the community pharmacy.[34,35]

In Canadian community pharmacy practice environments, the dispensing of prescription medications is associated with a compensation model that includes the sale of a product and an accompanying professional service fee, typically referred to as a dispensing fee. The rationale for this study is that pharmacists, as regulated healthcare professionals, may be motivated to adopt deprescribing to support best patient care for older adults, but there is the potential for lost income due to loss of dispensing fees and product mark-up.[36]

This study will attempt to determine if there is a financial barrier to deprescribing. The primary objective of this study was to determine the financial loss to the community pharmacy when

deprescribing medications for a publicly funded senior scenario regimen. The secondary objectives were to determine the financial impact on the public payer (the government), and the senior.

2.2 Methods

A case scenario was developed by the research team (SA, CS, JS) to reflect an 'average' senior in Canada, with multimorbidity associated with the most common diagnoses, and the most common medication classes used in this population, based on national health information and prescription drug data. [3]We selected doses and over the counter products (OTC) based on practice experience. To highlight cost issues, we chose medications representing OTC and prescription, oral and non-oral formulations, combination and single product formulations, generic and innovator brand, and PIM and non-PIM.

2.2.1 Scenario

A male (70 years) diagnosed with hypertension, hypothyroidism, diabetes, and hypercholesterolemia. His median after-tax annual income was$56,000 based on the median value reported by Statistic Canada.[37] The patient's regimen: metformin 1000 mg twice a day, atorvastatin 40 mg tablet daily, omeprazole 20 mg tablet daily, irbesartan/hydrochlorothiazide (HCTZ)300 mg/25 mg daily, levothyroxine 50 mcg daily, atenolol 50 mg daily, liraglutide injection 1.8 mg daily, enteric coated acetylsalicylic acid (ASAEC) 81 mg daily, calcium 500mg/Vitamin D 1000 units twice a day, lorazepam 1 mg daily at bedtime.

2.2.2 Interventions

Medication Changes to represent a variety of deprescribing scenarios were tested, based on case studies and common practices discussed by leading deprescribing initiatives in Canada, and considering Beers criteria.
(www.deprescribing.org and www.deprescribingnetwork.ca)
Scenarios presented include:

1. Scenario 1: Discontinuation of an OTC medication (ASAEC).

2. Scenario 2: Abrupt discontinuation of a medication (atorvastatin – in this scenario, the patient presented with leg pain as a side effect)
3. Scenario 3: Slow taper of a PIM (lorazepam) over 4 quarters as follow:
   Q1 (90 tablets) – Q2 (45 tablets) – Q3 (30 tablets) – Q4 (0 tablets)
4. Scenario 4: Rapid taper of a PIM (proton pump inhibitor(PPI) omeprazole changed to lower dose) as follows:
   Q1 (90 tablets) of 20 mg - Q2 (90 tablets) of 10 mg- Q3 and Q4 (0 tablets)
5. Scenario 5: Patient switched to an alternate/safer medication (lorazepam to an OTC melatonin)
6. Scenario 6: Dose reduction (lorazepam 1 mg to 0.5 mg dose)
7. Scenario 7: Switched to a lower cost medication (based on patient request switched liraglutide to pre-filled detemir 10unit /day (1cartridge/month)).
8. Scenario 8: Changed from a combination drug to single drug (irbesartan/HCTZ 300 mg/25 mg to irbesartan 300 mg daily).

Publicly accessible data from provincial and territorial websites for the ministries of health were used to obtain information for the general seniors (age 65y and older) publicly funded drug programs.[38] When not available, the Ministry was contacted directly, and if a reply could not be obtained, the provincial pharmacy association was contacted for this information. If an association was not available, such in some of the territories, we contacted local pharmacies. The senior in the scenario was mostly covered under the provincial or territorial seniors drug plan, factoring in the median income based on the most recent Canadian Census data.[9]The medication related costs in all 10 provinces and 3 territories in Canada were determined, and this was defined as baseline costs. The total costs were calculated as the sum of medication cost, maximum allowable upcharges (i.e. mark-up), and dispensing fees. Median dispensing fees were used for this analysis, which were the same as the maximum allowable except for in Manitoba where the median fee was dramatically lower than the maximum allowable. Medication costs were obtained from published government drug plan formulary price maximums. For medications that were not included in the government formulary, medication costs were obtained from an established wholesaler's list price. Selling prices were determined by the same wholesaler's published manufacturer's suggested retail price which resulted in a 35% gross

margin to the pharmacy. Patient share and government share were calculated based on patient eligibility under the implemented drug plan in each area.

2.2.3Cost parameters

1. Drug selection - DIN (Drug Identification Number, uniquely assigned by health Canada for every dug product approved for the market) was chosen as the first drug on the Alberta Interactive Drug Benefit List .[40] If not available in other provinces' list, then the first DIN specific to that province was used.
2. Supply –90days /3 month supply, for 4 dispenses/year, which is standard for drug supply in Canada.
3. Drug cost or MAC(Maximum Allowable Cost - if it applies to the province). [39,41,42,43,44,45,46,47,48,49,50]
    A. For Manitoba and Prince Edward Island, levothyroxine 50 mcg is under formulary but no price listed. Accordingly, the mentioned price is estimated to the other provinces Levothyroxine 50 mcg price
    B. The only province that included liraglutide injection under the formulary was Quebec.
4. Mark-up - part of provincial pharmacy framework.
   The mark-up for prescription medications was determined from Ministry websites. [50,51,52,53,54,55,56,57,58] The OTC mark-up was calculated as the difference between an established wholesaler's list price (i.e. cost to pharmacy) and the same wholesaler's published manufacturer's suggested retail price. This resulted in a 35% gross margin to the pharmacy.
    A. For Newfoundland and Labrador this was confirmed by the Pharmacy Association of Newfoundland (PANL) that markup is 9% for generics and 8.5% for brands.
    B. For Northwest Territories and Nunavut the Department of Indigenous Services Canada were contacted to have the Non-Insured Health Benefits (NIHB) pricing structure.
5. Dispensing fee - if not fixed, then it was drug pricing related (using max government allowable fees). [50,51,54,55,57,59,60,61]

6. Government and patient share according to eligibility and drug cost. [41,62,63,64,65,66,67,68,69]
7. Margin for pharmacy - dispensing fee plus mark-up
8. The change in cost for the patient, pharmacy, and public payer was compared for each province or territory as each intervention was made to the regimen. Only one scenario was tested at a time, rather than looking at combinations of deprescribing interventions that could occur in practice.
9. The means of each patient, government and pharmacy margin differences were calculated to compare the data based on each scenario (costing information was gathered in Q4 2018 and Q1 2019).

2.2.4Limitations in costing

1. We did not add GST or HST.
2. The costs of OTC products vary across Canada as do the retail prices in pharmacies where they are sold. For this study, we used a defined cost of the OTC product to the pharmacy and a calculated gross margin to the pharmacy of 35%.
3. We only looked at medication costs associated with our sample patient.
4. Costs associated with government funded clinical services provided by pharmacists were not included (e.g. medication review).This was because chronic patients should have a review, whether they have deprescribing or not, and because services vary from jurisdiction to jurisdiction.
5. Pharmacies may not be able to purchase drugs at the formulary price. There are rebates to most generics, but these vary and their impact could not be measured.
6. The supplemental private insurance plans are not considered in this paper.

2.3 Results

The patient was covered under all provinces seniors' drug plans, but in British Columbia he didn't reach the annual deductible of $1700 required for the provincial plan (i.e. Pharmacare) and therefore did not qualify for the subsidy.[70] The baseline results calculated showed the highest total drug cost in Canada (patient share plus government share) is in Alberta ($4631.01per year),

while the least expensive regimen was in Quebec ($4023.73per year). The greatest cost to the patient was in British Columbia ($4342.75), where the senior's income limited the amount of publicly funded drug coverage. (Table 1)

The mean changes in the cost/payment share are presented in Table 2. The change in pharmacy margin is listed as a positive number, indicating loss to the pharmacy, while positive dollar values for the government or patient indicate cost savings. The scenarios showed a decrease in overall cost of the regimen, except for scenario 4. This is because the cost of a lower strength of omeprazole is generally at higher cost and not covered under most seniors' drug plans. (Table 2) However, the provinces of Newfoundland and Labrador and Saskatchewan do cover the higher cost of the lower strength which in turn was reflected as higher government share. (Table 3)

In terms of patient impact, scenario 7 showed the most cost savings for a patient and the greatest loss to the pharmacy.

Most scenarios showed the pharmacy would experience a direct financial loss. For each scenario, if we consider the average difference of pharmacy margin, government and patient share from baseline costs this would show a yearly loss of pharmacy income across seven of the eight scenarios from 0.04% up to 29.14%. (Table 2) Additionally, we found the different scenarios had some effect on government share with almost all scenarios resulting in yearly cost saving that ranged from 0.32% up to 15.77%. For the patient share, yearly savings ranged from 0.03% to 87.4%. For scenario 5 (OTC alternative) the patient cost was increased 0.6%, while in scenario 4 (rapid taper of a PIM), the patient cost increased 75%.

2.4 Discussion

This economic analysis of a typical patient case showed a loss to pharmacy income the majority of the time reaching a maximum annual loss of $473.84 in Alberta when an expensive medication is switched to lower cost medication. Only one scenario provided a small increase in pharmacy income of $0.83 annually when changing from combination to a single drug.

Our baseline patient share ranged from $1511.47 (Quebec) to $4342.75 (British Columbia) per year, with a range from $0 coverage in British Columbia to $2512.26 coverage in Quebec paid by the government plan.

These findings show that overall, deprescribing does reduce drug cost that the patient has to pay, with few exceptions (e.g. scenario 4). However, despite seniors having publicly funded coverage plans for their medications, they have to pay a portion of the cost of their medications in Canada. The use of medication not covered under the provincial/territorial plan will shift the amount they pay to a higher level, such as scenario 4. In this scenario, the lower dose of the medication wasn't covered by some plans, although covered in others, which also shows inconsistency in coverage across jurisdictions. Similar to other studies, our baseline data also highlights an issue of equity.[71,72,73]As where seniors reside matters, since there are differences across the provinces and territories with regard to medication coverage and the amount the seniors must pay. For instance, the British Columbia plan showed that using the standard of income can dramatically affect the cost to the senior.

Our study is the first, to our knowledge, to consider the cost implications of deprescribing on the community pharmacy, patient, and government payer. Although barriers to deprescribing have been listed previously [34,35], the extent of the impact has not been evaluated, and all barriers may not be equal in determining clinical decisions. It is important to consider financial barriers, as this could play a role in healthcare professional decision making. In the case of deprescribing, physicians, nurse practitioners, or clinic-based or hospital pharmacists receive a salary or are reimbursed for a service provided (e.g. clinic visit),although the long-term financial impact on clinician income in the case of deprescribing has not been studied (e.g. fewer patients visits for medications renewal). However, for a community pharmacy, the financial situation is such that the loss of dispensing prescriptions does mean a loss of income.[36] This is the only profession that is affected in such a way by deprescribing. Although there have been studies incorporating pharmacist intervention in Canadian communities in the province of Quebec, neither study evaluated economics or how decisions might have been impacted by financial loss to the pharmacy.[44] While the D-PRESCRIBE study relied on pharmacy funding of $19 Canadian for a Pharmaceutical Opinion, this is not consistent across the country, and this type of intervention is not unique to deprescribing.[74] Some provinces do provide reimbursement for a pharmacist medication review in a community pharmacy, but there are limits on the frequency, and the reviews are expected to be done regardless of deprescribing. While our study does not provide

insight on pharmacist behavior, financial disincentives to do the 'right thing' for a patient amount to perverse incentives and require further study.

We also noted the significant challenges in locating information, despite the transparent process that one would expect from taxpayer funded programs. While the information for seniors' programs was mostly available on the government websites, some was outdated, and in some cases we had to contact the pharmacy associations. For two jurisdictions we had to contact pharmacists directly, through a 'cold call' approach by browsing pharmacy names for a particular region or city. For one jurisdiction we had to speak with a government employee directly, as there was no online or printed documentation of the funding mechanisms that we could obtain. The public, healthcare professionals, policy makers, and researchers, should be able to locate this information without difficulty. Taxpayer funded programs require scrutiny, and the lack of transparency and inconsistency in access from one jurisdiction to another was unexpectedly opaque.

It must be pointed out that healthcare professionals ought to consider thoroughly when determining the drugs to be included in patients' treatment plan. Furthermore, the variation in costs and services available across Canada can be considered in discussions relating to a national province drug program.

Research on pharmacist behaviour and reimbursement for clinical services demonstrated that funding leads to pharmacist activity and improved disease measures.[36] As noted by Avery and Bell, cost effectiveness data is scarce and they suggest more research on the elements of cost effectiveness.[75] A review by Reeve and colleagues frames deprescribing in terms of cost savings.[76] These papers highlight that clinician behaviour and financial disincentives, particularly in community pharmacy setting are not currently on the research agenda. However, our study suggest that this require further research to address enablers and barriers for successful deprescribing.

The limitations of our study include the use of a scenario rather than actual patient cases, or pharmacy practice behavior in the community; this means that each of the scenarios will not be appropriate in all patients with this medication. We also standardized the timelines for dispensing as quarterly, but patients and pharmacists may choose to have medications dispensed more frequently (e.g. monthly).Another limitation relates to the overall cost to pharmacy and

government. The financial impact on the pharmacy related to deprescribing activities may be more substantial than the data presents. In many jurisdictions, community pharmacies are able to negotiate trading terms, also referred to as rebates, with manufacturers of medications that are no longer on patent. These terms are typically confidential and will vary from pharmacy to pharmacy. The financial implications of lost revenues to the pharmacy due to deprescribing activities in the scenarios we have presented are likely understated. In addition, governments also negotiate rebates and this information is not available, and could not be factored into the analysis. Further research is required regarding the impact of policies and funding in community pharmacy and cost implications regarding patients' behavior. In this study, we used national median income tax values, which may not be representative of the financial situation of many older adults. In addition, indirect costs such as laboratory tests and physician visits should be factored into the analysis.

2.5 Conclusion

Our study found that publicly funded medication regimens varied significantly across the country in terms of coverage and cost to the senior. The deprescribing scenarios typically lowered the pharmacy's income and reduced patient cost, while providing little impact on government cost.

Table 2-1: Baseline annual medication costs in Canadian dollars			
Pharmacy Margin	**Government share**	**Patient share**	**Total cost (Patient+Government shares)**
Alberta			
964.49	506.57	4124.45	4631.01
British Columbia			
683.71	0.00	4342.75	4342.75
Manitoba			
494.43	747.71	3430.81	4178.52
New Brunswick			
693.49	478.27	3882.11	4360.37
Newfoundland and Labrador			
872.38	547.26	3993.25	4540.51
Nova Scotia			
805.38	497.63	3974.49	4472.12
Ontario			
624.96	452.17	3839.54	4291.70
Prince Edward Island			
666.72	307.32	4025.92	4333.24
Quebec			
1104.43	2512.26	1511.47	4023.73
Saskatchewan			
546.51	106.59	4106.65	4213.25
Northwest Territories			
728.55	767.98	3627.09	4395.07
Nunavut			
882.70	905.21	3644.01	4549.22
Yukon			
783.35	870.75	3566.44	4437.20
National Average (SD)			

757.78 (169.54)	669.21 (616.36)	3697.61 (705.17)	4366.82 (166.89)

Table 2-2: The national average of the cost difference for each deprescribing scenario				
Average(SD) change	**Pharmacy Margin (i.e. losses) by scenario**	**Government share (Savings)**	**Patient share (Savings)**	**Total cost (Patient+ Government)**
Scenario 1 (stop ASA)	25.69 (11.32)	6.66 (24.00)	57.26 (17.81)	63.91(8.20)
Scenario 2 (abrupt discontinuation of atorvastatin)	62.17 (19.30)	105.54 (48.16)	41.30 (41.01)	146.84 (19.19)
Scenario 3 (slow taper of lorazepam)	14.38 (4.56)	15.18 (9.04)	7.88 (7.70)	23.05 (4.56)
Scenario 4 (rapid taper of omeprazole)	24.27 (12.98)	35.51 (79.25)	-64.64 (93.69)	-29.13 (86.16)
Scenario 5 (switch lorazepam to melatonin)	38.45 (18.15)	46.51 (28.93)	-22.85(22.73)	23.66 (18.16)
Scenario 6 (dose reduction of lorazepam)	0.33 (0.27)	2.13 (1.55)	1.15 (1.47)	3.28 (1.01)
Scenario 7 (switch liraglutide to pre-filled detemir)	220.78 (127.70)	19.92 (467.62)	3231.78 (736.46)	3251.70 (306.90)
Scenario 8 (switch irbesartan/HCTZ 300 mg/25 mg to irbesartan 300 mg)	-0.29 (0.24)	-2.89 (1.43)	-0.36 (0.57)	-3.26 (1.46)

Table 2-3: Economic change/impact of deprescribing scenarios from baseline								
Scenario Province data	**Scenario 1**	**Scenario 2**	**Scenario 3**	**Scenario 4**	**Scenario 5**	**Scenario 6**	**Scenario 7**	**Scenario 8**
Alberta								
Δ Pharmacy Margin(loss)	21.23	57.21	13.04	29.99	33.61	0.32	473.84	-0.36
Δ Government share(saving)	0.00	99.06	15.23	60.00	46.43	2.44	-99.76	-2.69
Δ Patient share(savings)	60.65	42.46	6.53	25.72	-27.62	1.05	3699.95	-1.15
British Columbia								
Δ Pharmacy Margin(loss)	42.76	46.74	10.70	11.42	24.66	0.25	250.11	0.00
Δ Government share(saving)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Δ Patient share(savings)	77.26	131.04	19.42	-95.79	9.87	3.42	3376.46	0.00
Manitoba								
Δ Pharmacy Margin(loss)	21.23	54.60	14.20	27.30	37.97	0.00	0.00	0.00
Δ Government share(saving)	0.00	143.12	23.24	105.78	72.31	3.49	0.00	-3.67
Δ Patient share(savings)	60.65	0.00	0.00	-184.11	-47.52	0.00	3126.35	0.00
New Brunswick								
Δ Pharmacy Margin(loss)	21.23	50.74	11.70	13.30	28.66	0.25	256.93	-0.28
Δ Government share(saving)	0.00	94.54	14.29	69.78	42.97	2.40	-90.67	-2.64
Δ Patient share(savings)	60.65	40.52	6.12	-165.19	-29.11	1.03	3473.63	-1.13
Newfoundland and Labrador								
Δ Pharmacy Margin(loss)	21.23	55.20	12.74	14.72	32.74	0.27	393.37	-0.30
Δ Government share(saving)	0.00	115.91	15.50	-106.49	41.53	3.46	0.00	-3.78

Δ Patient share(savings)	60.65	24.00	6.00	12.00	-23.52	0.00	3519.72	0.00
Nova Scotia								
Δ Pharmacy Margin(loss)	21.23	54.54	12.65	27.36	32.46	0.25	328.27	-0.28
Δ Government share(saving)	0.00	97.20	14.95	49.40	45.63	2.40	-99.37	-2.64
Δ Patient share(savings)	60.65	41.66	6.41	21.17	-27.97	1.03	3553.99	-1.13
Ontario								
Δ Pharmacy Margin(loss)	21.23	42.06	9.53	8.96	19.98	0.25	236.02	-0.28
Δ Government share(saving)	0.00	101.94	12.13	74.85	28.26	3.42	-293.12	-3.77
Δ Patient share(savings)	60.65	24.44	6.11	-174.60	-23.08	0.00	3479.37	0.00
Prince Edward Island								
Δ Pharmacy Margin(loss)	21.23	54.50	12.88	18.20	33.77	0.19	187.58	-0.21
Δ Government share(saving)	0.00	75.05	5.19	54.71	19.65	0.19	0.00	-3.70
Δ Patient share(savings)	60.65	63.76	16.41	-145.23	-0.67	3.17	3313.93	0.00
Quebec								
Δ Pharmacy Margin(loss)	21.23	113.48	27.57	46.93	92.41	0.21	144.87	-0.23
Δ Government share(saving)	0.00	128.76	23.62	95.54	81.46	2.20	1545.25	-2.42
Δ Patient share(savings)	60.65	69.03	12.66	-184.32	-3.85	1.18	828.41	-1.30
Saskatchewan								
Δ Pharmacy Margin(loss)	21.23	54.03	14.01	11.93	33.80	0.95	54.44	-0.35
Δ Government share(saving)	0.00	38.34	-0.04	-146.78	0.00	0.00	-226.81	-3.84
Δ Patient share(savings)	60.65	100.00	22.73	50.00	19.00	4.12	3237.16	0.00

Northwest Territories								
Δ Pharmacy Margin(loss)	21.23	66.36	14.32	35.67	37.20	0.58	184.35	-0.64
Δ Government share(saving)	0.00	150.67	23.04	91.40	69.93	3.75	-151.74	-4.13
Δ Patient share(savings)	60.65	0.00	0.00	0.00	-47.52	0.00	3462.44	0.00
Nunavut								
Δ Pharmacy Margin(loss)	21.23	87.83	19.02	47.14	54.99	0.75	179.75	-0.83
Δ Government share(saving)	0.00	172.14	27.74	102.87	87.72	3.92	-173.26	-4.32
Δ Patient share(savings)	60.65	0.00	0.00	0.00	-47.52	0.00	3479.36	0.00
Yukon								
Δ Pharmacy Margin(loss)	57.72	70.91	14.57	22.58	37.67	0.00	180.67	0.00
Δ Government share(saving)	86.52	155.22	22.39	10.59	68.70	0.00	-151.57	0.00
Δ Patient share(savings)	0.00	0.00	0.00	0.00	-47.52	0.00	3462.44	0.00

Chapter Three

The impact of home medication review in older adults in the community: A systematic review

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Abstract

BACKGROUND: Home medication reviews (HMR) is defined as a patient interview to discover all drug related problems in their home setting, along with detailed follow up of their medical and clinical records. The objective of this systematic review is to assess the implications of HMR on healthcare utilization and patient-related outcomes for older adults.

METODE: We searched electronic databases from 1990-2019, including: Ovid databases, CINAHL, Cochrane library, Health Technology Assessment and Economic Evaluation databases, and grey literature. We included only prospective, quasi- experimental (including a control group) or randomized, controlled trials. Two authors independently screened titles and abstracts, evaluated eligibility, extracted data, and assessed the risk of bias. The primary outcome was healthcare utilization defined by ER visits and hospitalization.

RESULTS: We identified 3558 articles that led to 18 included studies. The number of participants ranged from 66 to 855 subjects, and studies ran from 6-15 months. Studies included between 1-9 scheduled visits, with 3 studies allowing for variation in visits depending on patient need. Subjects were recruited primarily from hospital discharge. HMR showed significant reduction in healthcare utilization in 4 of 12 studies that reported this outcome. However, one study reported increased hospital readmissions of the intervention group. As for mortality, 1 of 13 studies reported a significant decline in favour of the intervention group. Similarly, 1 of 7 studies showed an improvement in patient's quality of life. Of the 5 studies reporting adherence, 2 showed improvement. Two studies showed a reduced number of medications. There was a limited scope for meta-analysis due to the range of different outcomes measured across the trials. Overall risk of bias ranged between "unclear" and "High" and none showed "low" risk.

CONCLUSION: We found that HMR provides modest benefit in improving healthcare utilization and some medication measures. However, the studies were quite variable in how HMR was delivered, and in the outcome measures reported. The magnitude of benefit for HMR appears insufficient for convincing policy change at this time.

Highlights:

1. HMR shows a minimal benefit in reducing the use of health care services.
2. HMR is a strategy for improved medication management.
3. HMR shows marginal effect on improving quality of life, and mortality

3.1 Introduction

The demographic trend in Canada is moving toward an aging population, with an average number of drugs between 5 and 9 per individual age 65 years and older.[3,77] Polypharmacy (generally accepted as the use of 5 or more drugs at once[78] is a contributor to potentially inappropriate medications (PIM) and is associated with adverse events such as falls, hospitalization and death.[78] The high prevalence of polypharmacy is attributed to many factors, primarily aging with increased number of comorbidities, in addition to, the application of disease-based clinical guidelines which often increases the number of drugs.[79]

Addressing polypharmacy and PIMs requires collaborative work amongst health care practitioners. This can be done through a number of processes, including medication reviews, which may take place in a community pharmacy, clinic, hospital setting, or home.[80] Home medication reviews (HMR) are defined as a thorough patient interview to discover all drug related problems, in their home setting, along with detailed follow up of their medical and clinical records post initial medication review.[80,81]

Research has been carried out to estimate the effect of HMR for older adults. These individual studies have been done in a variety of countries including Germany, UK, and Australia, with different health care professionals, settings, and a diversity of outcome measures.[81,82,83,84,85,86] The Australian model review reported that HMRs conducted by pharmacists reduced the use of anticholinergic and sedative drugs among older adults, an impact that would lessen the risk of falls and poor cognitive function.[82] A study in Germany estimated that HMR helped in identification of potential drug-drug interactions.[81]

In Australia, for example, HMR became part of Medicare Benefit Schedule [MBS] starting from 2001.[87,88] Studies such as Castelino et al,, conducted in Australia, demonstrated an improvement of Medication Appropriateness Index (MAI) score, which, along with the community pharmacy policy agreement supported the decision of HMR becoming publicly funded.[89,90]

Although it is presumed that HMRs done by healthcare professionals improve outcomes for seniors, the magnitude of HMR contribution remains uncertain.[83] However, two landmark trials challenged the assumptions regarding HMR effects. The HOMER study showed increased hospital admissions with reduced quality of life,[84] and the POLYMED study did not show any

significant improvement in clinical outcomes.[85] In addition, the economic evaluation of HOMER demonstrated low cost effectiveness.[86]

Our systematic review will attempt to answer this uncertainty by reviewing literature related to HMR studies including HMR done by any healthcare professionals, with at least 6 month follow-up time to determine the effect on outcomes. The objective of this systematic review will determine the value of HMR and whether such a review will contribute to significant change in health service utilization or not.

3.2 Methods

3.2.1 Information source, Search strategy

The MEDLINE search strategy was drafted by an information specialist with expertise in systematic review literature searching, and the final search was conducted by a librarian (LA) with literature searching experience.

We searched electronic databases between March 15 and 19, 2019: MEDLINE (Ovid), Embase (Ovid), PsycINFO (Ovid) Cochrane Library (Wiley), and CINAHL (Ebsco). Search results were limited to publications from 1990 to present. See appendix for the MEDLINE strategy.

Other sources searched for grey literature: Conference Proceedings Citation Index (Clarivate Analytics) and Dissertations & Theses Global(ProQuest).

3.2.2 Selection of studies, Data extraction and management

Literature search results were recorded in an Excel file formatted for screening through level 1(titles and abstracts) and level 2 (detailed full text) based on pre-defined inclusion and exclusion criteria. This was accomplished independently by two review authors (SA and SR). When there was uncertainty or any disagreement between reviewers, it was resolved by a discussion and whenever a consensus could not be reached, a third member of the research team made the decision (CS). The reasons for excluding studies were recorded. For data extraction, SA extracted the data from the included studies on a pre-specified data collection form, and SR

completed data extraction for 20% the total included studies; both SA and SR finalized the quality appraisal of the included studies.

For data synthesis, we pooled the results of the included randomized controlled studies for the primary outcome of hospitalization readmission, using a random-effects meta-analysis with risk ratios for binary outcomes; generated forest plot and funnel plot to also estimate the publication bias.

3.2.3 Study selection criteria

Inclusion and exclusion criteria were identified a priori in the study protocol. [91]

Studies were included if they were prospective, quasi- experimental (including a control group) or randomized, controlled trials; for the purpose of providing a high level of evidence with minimal bias about HMR effects. In observational studies, such as [92] patients were assigned to the intervention group for HMR, due to increased illness, frailty, or past history of medication problems, thus leading to the intervention group being significantly different than a control group.

The HMR had to be a structured process, conducted in patients' place of residence in the community and provided by healthcare professional where all patients' medications were included. We excluded HMR studies that were carried out in hospitals, clinics, or assisted living facilities. There was no restriction on languages. Studies had to have at least 6 months of follow up after the medication review was completed. Studies were excluded if they focused on palliative care, involved peer to peer reviews, or if the home medication reviews were done with family caregivers; as our target was ambulatory older adults capable of self-care activities with the possible target of wellness improvement in their own homes.

As an exclusion, research papers concerning home medication reviews should have been issued no earlier than 1990; as research on this topic notably started around the year 2000.

3.2.4 Study population

We included studies of community-dwelling older adults. During the primary screening, and to have a wider understanding of HMR effect on older adults, we included studies with study population of older adults with no age cut-off. During secondary screening we solidified the age cut-off as 65 years, consistent with many studies for older adults. When studies included a range of ages, we only extracted data on those individuals who are over this cut-off and older. The comparator group was patients who received usual care with no medication review.

3.2.5 Outcome measures

Healthcare outcomes were identified a priori in the study protocol. [91]

The primary outcome of the study was hospitalization or emergency room (ER) admission rates. Secondary outcomes were mortality, quality of life, economic outcomes and medication outcomes.

Medication outcomes were reported based on adverse drug event, complexity of medication regimen, change in the number of medications, medication appropriateness using explicit criteria (e.g. Beers Criteria, STOPP) or implicit criteria (e.g. Medication appropriateness index).

3.2.6 Assessment of risk of bias in included studies

We used Cochrane risk of bias assessment tool available in Cochrane Handbook for Systematic Reviews of Interventions and judged risk of bias as either low, high, or unclear. [93]

Two reviewers (SA and SR) independently performed the risk of bias assessment. Disagreements were resolved upon discussion, when needed.

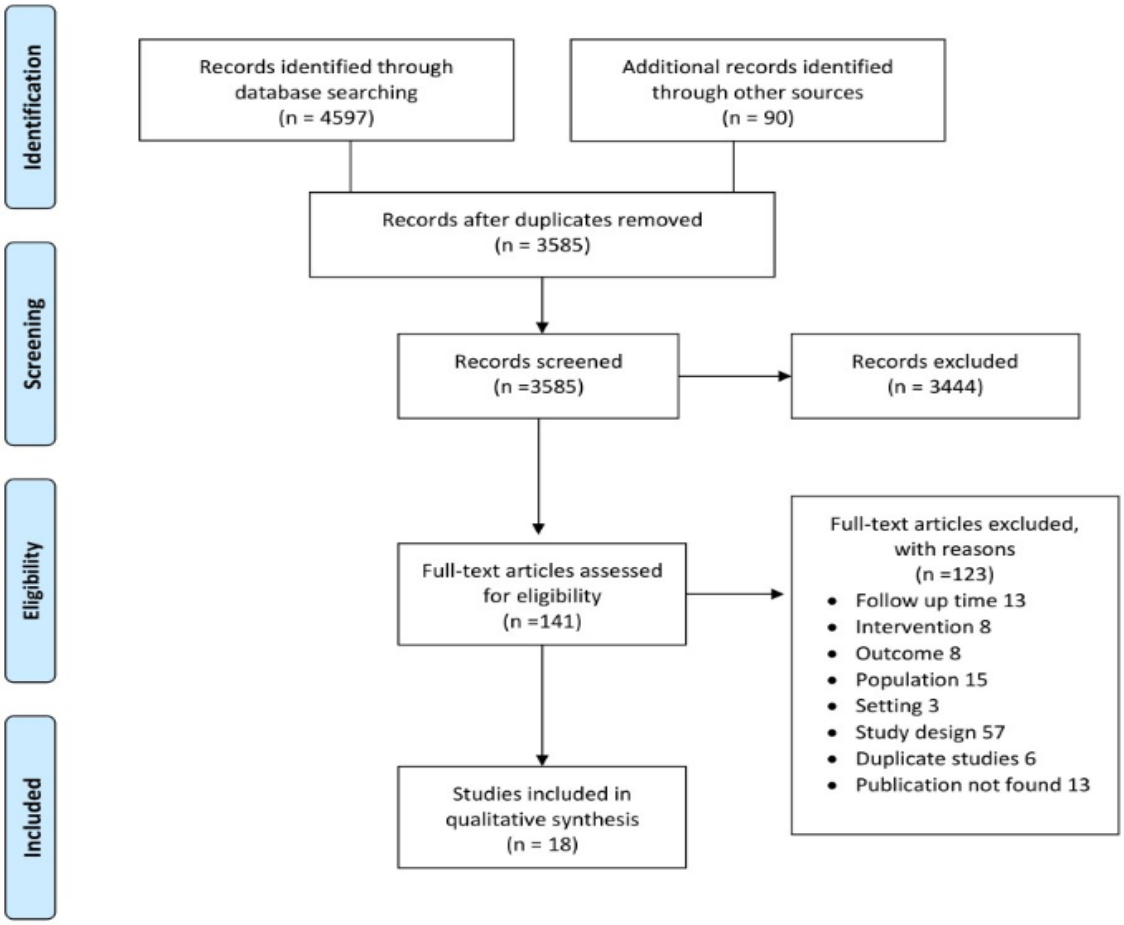
The final judgment was reported along with the support for each chosen decision. [Table 4]

3.3 Results

3.3.1 Results of the search (Figure 1)

After searching databases and grey literature, and removing duplicate studies, 3585 records were included in primary screening. Of these, 141 full articles were retrieved and reviewed, to finally identify18 studies that met the inclusion criteria. [84,84, (94-109)]

Figure 1. PRISMA Flow Diagram of search strategy



3.3.2 Study characteristics

The included HMR studies (N=18)were quite diverse, coming from 8 different countries. [Appendix D] The sample size ranged from 66 subjects to 855 subjects, and follow-up time was from 6 to 15 months. For our primary outcome of healthcare system utilization, 12 studies included this.[84,85,94,95,98,100,102,104,105,106,107,109] There was variability of other study outcomes, including adherence [94,95,102,103,109], quality of life, or combined cumulative incidence of

readmission and death as primary outcome measures.[98] We found (n=3) studies did not include the number of drugs taken by patients.[98,99,104] There were 3 studies with unique designs, each with 3 study arms.[96,103,108] All other studies involved comparison of a control to an intervention group.

Nine studies recruited hospital discharged patients,[84,94,98,99,100,102,103,105,107] one study referral was from both hospital and emergency room (ER) lists.[106] GP or pharmacy lists constituted the referral pool for 5 studies.[85,97,104,108,109] [Marek,2013] recruited patients from three Medicare certified home health agencies,[96] [Olesen,2014] referral was from National Health Insurance Population register.[95]

The broadest recruitment of participants was by Sidel et al, where the researchers [Sidel,1990] recruited from a list of 3340 patient names from of Medicare recipients supplied by the Health Care Finance Administration, with additional names provided by local agencies such as senior centers, horses of worship, Meals-on-wheels programs, hospital admissions records and voter registration rolls.[101]

3.3.3 Interventions (Appendix E):

In all studies the clinicians had access to patients' records and conducted an assessment. These services were primarily delivered by multidisciplinary teams that were comprised of physicians, pharmacists, or nurses. In one study from Germany, 3 home-care specialists (social pedagogue with diploma certificate, gerontologist, and healthcare scientist) were involved to run the first assessment of patients' conditions and then communicated with corresponding pharmacists and physicians.[108] One study had a trained research occupational therapist to interview patients.[107]Half of the studies included an intervention done by both pharmacists and physicians,[84,85,94,97,101,102,103,106,108] 4 included physicians and nurses,[98,104,105,107] and the remaining 5 were collaboration of three professions (physicians, pharmacists, and nurses).[95,96,99,100,109]

Five studies had a specific disease-related intervention, rather than a general medication review. These included COPD[94], heart failure[98,99,100], and a few different disease states (e.g. heart disease, COPD, heart failure, diabetes) combined in one study.[109]

3.3.4 Outcome data (Appendix F)

Our primary outcome of health service utilization was reported in 12 studies.[84,85,94,95,98,100,102,104,105,106,107,109] Four studies showed statistically significant decrease in hospitalization rates in favour of the intervention arm,[94,100,105,107] while one study found that the intervention led to an increase in hospitalization.[84] As for the emergency room readmissions, four of five studies that looked at this outcome showed no significant reduction [98,105,106,109] but one found a statistically significant reduction in favour of the intervention.[100]

Mortality was an outcome reported in 13 studies[84,85,94,95,97,98,99,100,102,105,106,107,109], but it was reduced in only 1 of the studies. [99]

Medication outcomes were reported in11studies.[84,85,94,95,97,101,102,103,107,108,109] Medication outcomes included the number of adverse drug reactions (ADR),[84,94,95,108] which was improved in 4 studies. Five studies assessed patients' adherence,[94,95,102,103,109] with 2 of the 5 showing that patients had statistically significant improvements in adherence after the HMR intervention.[103,109] Medication changes (e.g. doses reduced, medications stopped or changed). [85,94,97,101,103,107,108] were included in 7 studies, with improvements found in 5 of those 7 studies; Improvements included the difference of the mean number of medications from baseline[85], risk assessment interviews before and after intervention[101], percentage of stopped medications[103], number of adjusted medications[107], and Medication Appropriateness Index [MAI] score which decreased significantly (i.e. improved) after the intervention[108]. Only one study [Marek, 2013] used Beers Criteria to identify PIM.[96]

Eight studies provided outcomes that related to humanistic measures including quality of life and satisfaction.[84,85,96,97,102,104,105,109] The studies that reported quality of life outcome used different tools of measurements (e.g. SF-36, EQ-5, etc.) detailed in table 3. One study reported statistical significant improvement in quality of life, and this study showed that the use of the pill organizer, implemented after the initial HMR, improved participants' quality of life.[96]

Cost analysis was reported in four studies, all showing significant cost savings in the intervention arm.[94,100,105,107]

3.3.5 Quality appraisal (Table 3-2)

We found the registered protocols for five included studies.[85,96,102,108,109] The studies overall risk of bias ranged between "unclear" or "High" and none showed "low" risk. (see Appendix G)

3.4 Discussion

Our systematic review found that HMR did not consistently decrease healthcare utilization. Of the 12 studies that looked at this outcome. [84,85,94,95,98,100,102,104,105,106,107,109] Four of these studies showed statistically significant improvement in favour of HMR in reducing hospital readmissions rate.[94,100,105,107] However, seven studies found no difference compared to the usual care group and one study reported increased hospital admission of the intervention group.[84] Additionally, only one study found significant reduction in ER visits.[100]

For the studies that focused on specific disease management, they still reviewed all medications the patient was taking, which resulted in patients becoming more aware about their conditions,[94] improved medication adherence,[98]and reduced LOS in hospital.[99,100] However, this type of disease-focused review is limited in terms of addressing multimorbidity, the most common situation in geriatrics.[110]

In contrast, most HMR studies involved a general medication review. This type of HMR does not require the patient to have a particular disease for enrolment, and in theory could provide a thorough medication assessment in terms of multimorbidity and polypharmacy, however, the results of these studies were heterogeneous. For example, one study looking at adherence, hospitalization, and mortality showed non-significant results[95]; but this study had a higher drop out in the intervention compared to the control group. Another study reported a statistically significant increase in hospitalization rate the intervention arm.[84] As noted by Holland et al, the increase in hospitalization was possibly due to patients becoming more aware about their clinical conditions with resultant increase in hospital visits; or that the longer the time the pharmacists spend with patients, the more the patients become confused and dependent on the healthcare system.

We found that the studies overall did not significantly improve patients' quality of life or mortality rates,[111] Perhaps a 6 month follow-up, the timeframe used in most of the studies, is simply not long enough to see a difference between groups. In addition, interventions that improve disease measures may lead to added burden or reduced quality of life for older adults.[112] Given that there are numerous tools to address medication appropriateness, adherence, or safety, it is surprising that the outcomes in these studies were not more profound. For example, an outcome such as medication adherence could be incorporated with more detailed results into three studies as they already reported medications' changes.[97,101,107] Two studies could have analyzed adverse drugs reactions as an important medication outcome especially for older adults with polypharmacy.[97,107]

One systematic review of HMR done in patient homes, aged care homes, and nursing homes, found that these medication reviews helped in identifying and avoiding drug related problems, in addition to optimizing drug choices; but not mortality/hospitalization, etc. [113] This is similar to our findings that HMR can help in adjusting an older adult's treatment regimen. However, our systematic review is novel in addressing different selected health-related outcomes with confined setting of patients' home.

Intensive interventions, or more interactions with healthcare professionals, and a sense of being cared for, can improve one's sense of wellbeing.[114] Therefore, it may be surprising that over this period of months in the studies, with some studies including many visits, there was not a consistent improvement in QoL. However, this could also reflect the complexity and disease burden experienced by the participants; for instance, [Hogg,2009] reported that their selected population were at high risk of irreversible functional decline and that could account as a factor in QoL outcomes.[109] Another study done by [Holland] justified this decline in QoL as patients had better understanding of their cases, which precipitated anxiety, and reporting a worsened medical situation.[84] Third study by [Godwin] had done their home reviews for older adult having a high quality of life, so there was little room for further improvement.[104]

We do not believe that humanistic outcomes were robust enough to draw conclusions regarding HMR role in improving patients' satisfaction, as only four studies reported this outcome.[97,102,104,105]

As each intervention of the included studies represented a detailed medication review with a minimum six month follow up, we imagined that each study would cover more outcomes of interest, however, this was not the case especially for medication and humanistic outcomes. On the other hand, cost analysis was done only in four of the included studies, done in four different countries, with distinctly different healthcare systems and payment models.[94,100,105,107] Their measures were highly variable, with one study focusing on the costs of hospitalization, clinic attendance, pharmacy and consultant time, and nurses salaries .[94] Another study included reimbursement of acute care visits, home health aide, health practitioners visits' post discharge.[105] Additionally, one reported the costs of medicine, GPs and district nurse first home visit, and cost of intervention at hospital .[107] However, all of these showed a benefit in reducing cost of HMR compared to the control group. In the future, economic analyses should be required for health services research, including measures relating to all discharged but unused medications, non-prescription drugs costs, insurance and governmental drugs' coverage plans, and indirect costs.[115]

Engaging healthcare professionals for HMR activities requires a number of considerations. For example, the healthcare workforce in Canada has few available geriatricians, and healthcare professionals are dealing with increased complexity of disease burden does not appear to be prepared for caring for an aging population.[116] There is also an expense and potential inefficiency in doing HMR, versus healthcare professionals working in a clinic setting. For pharmacies, dispensing medications may be the greatest source of income, and reviewing medications, where some medications may be discontinued, is not efficient or enhancing their business case. None of the studies included measures about satisfaction or experiences of the healthcare professionals; as this may impact continued provision of these services. In addition, job satisfaction may play a role in improving patients' outcomes.[117] In order to engage healthcare professionals to provide a time-consuming service such as an HMR, there must be some sort of compensation, such as finances, or other professional rewards. The process of the intervention, such as mileage, time taken, or efficiency compared to other clinic medication reviews should be compared in the future.

All studies showed high risk of bias, which highlights the need for applying proper measures when planning an intervention (such as randomization or blinding of participants.) and providing

the study protocol. However, it is a difficulty to maintain blinding (participants, assessors, or practitioners) and some measures such as allocation concealment, reporting bias when the interventions are medication reviews. Ways researchers could reduce their risk of bias include third party assessors, complete data collection and follow up, randomization to reduce baseline characteristic differences between study arms and having balanced groups.

The studies included a range of patient groups, ranging from frail patients with multimorbidity[105] to older adults with good health.[104] For instance, the study that provided advanced nurse services for generally healthy older adults and cognitive MMSE score above 25 as eligibility criteria, showed no significant differences in term of the use of medical services, QoL, or satisfaction.[104] On the other hand, another study targeted multimorbid patients that had poor outcomes after discharge and with the HMR intervention there were significant differences in admissions' rate and costs savings.[105] From a policy perspective, consideration should be given for HMR's for patients that are older, frailer, have more comorbidities and more medications.

HMRs are one step closer to patients, especially for frail seniors in need and who may find these reviews inaccessible especially in the case of no care giver. However, in-pharmacy medication reviews reduced medication related hospitalization in older adults.[118] Medication reviews done in clinics or other healthcare settings showed improved chronic disease management and medication use. [119] None of the studies we included in our review compared HMR to another form of medication review, only to 'usual care'. It appears that HMR may not be that different than a regular medication review, and evidence to date does not support this becoming a standard policy.

The limitations of our study were that we excluded peers or caregiver reviews, we only included studies with long-term outcomes at a minimum of 6 months, and we may have missed some studies that had benefit in the short term. In addition, we excluded palliative studies and reviews conducted in hospitals, clinics, or other assisted living facilities, which should be the subject of future research to have a broader prospective of HMR effect on healthcare outcomes in those settings. The strengths of our study were that we looked into different health related outcomes rather a single outcome, we included any healthcare professional on the team, there was neither a restriction to a language nor limitation to a single country of the research setting, adding an international point of views to our results.

3.5 Conclusion

HMR is proposed to resolve polypharmacy and prevent drug related adverse outcomes, but the magnitude of the effect of HMR on healthcare utilization appears minimal; only four studies related to our primary outcome showed a clinical and statistical significance in reducing hospitalization rate. Accordingly, future research should be directed to answer further in-depth questions of HMR role in older adult's health improvement, and if such approach should be stated as a future healthcare policy, especially for the benefit of frail older adults.

Table 3-1 Summary table

Study	Number of participants at randomization	Results Health System Utilization	Results Mortality	Results Medication outcomes	Results Humanistic outcomes
Hunt,2018 (UK)	I- 88 C- 87	Hospitalization 45% (I) vs 76% (C) (p<0.001)	14 (I) vs 19 (C) (p 0.53)	NR for (C) I – identification of 2 DRP, 3 adherence issues 62had dose changes 45 had medication changes	
Hogg,2009 (CA)	I- 120 C- 121	Hospitalization[1] 40% (C) vs 46% (I) = reduced 6% (p 0.67) ER 63% (C) vs 73% (I) = reduced 10% in (I) vs (C) (p 0.48)	3 (I) vs 0 (C)	Adherence to chronic disease management guidelines 9.8% (I) vs .8% (C) = improved 9% in (I) vs (C) (p 0.0013)	SF-36 physical component 1.6% improved (I) vs (C) (p 0.18) SF-36 mental component 1.1% decline (I) vs (C) (p 0.44)

[1] Represented as percentage difference between end of study and baseline data

Aldamiz-Echevarria Iraurgui,2007 (Spain)	I-137 C- 142	Hospitalization cumulative incidence 43.1%(I) vs 50% (C) (p 0.28) ER admission during the first 6 months of follow up 59 (I) vs 57 (C)	cumulative incidence 16.1% (I) vs 14.8 (C) (p 0.769)		
Stewart,2002 (AU)	I-33 C- 33		6 (I) vs 13(C) ($p< 0.05$)		
Stewart,1998 (AU)	I- 49 C- 48	Primary composite end point for the mean incidence of hospital readmission and out of hospital death per patient 0.8 (I) vs 1.4 (C) (p 0.03) ER admission 48 (I) vs 87 (C) (p .05)	6 (I) vs 12 (C) (p 0.11)		

Marek,2013 (USA)	Pill organizer- 154 Medication dispenser- 174 Control- 128				SF-36 mean PCS quarterly improvement pill organizer vs. control 1.39 (p<0.0001) SF-36 mean MCS quarterly improvement pill organizer vs. control 1.686 (p<0.0001)
Olesen,2014 (Denmark)	I- 315 C- 315	Hospitalization 30% (I) vs 28% (C) (p 0.47)	19 (I) vs 14 (C) (HR 1.41- 95% CI (0.71- 2.82))	Identification of 183 DRP (I) vs NR (C) Non- adherence 28 (I) vs 26 (C) (OR 1.14)95% CI (0.62-2	
Hugtenburg,2009 (NLD)	I- 336 C- 379		22% (I) vs 22% (C) (p >0.05)	Discontinuation of drugs newly prescribed at discharge 64% (I) vs 58% (C) (p>0.05)	Satisfaction 87% "very satisfied" (I) vs 50% "satisfied" (C) (p <0.001)
Lenaghan,2007 (UK)	I- 69 C- 67	Hospitalization 36% (I) vs 43% (C) (p 0.8)	7 (I) vs 6 (C) (p 0.81)	Mean change in the number of medications (-0.31) (I) vs 0.56 (C) (p 0.03)	Mean change EQ-5D (-0.1) (I) vs (-0.02) (C) (p 0.1) Mean change VAS (-2.0) (I) vs 2.9 (C) (p 0.21)

Holland,2005 (UK)	I-429 C- 426	Hospitalization 56% (I) vs 43% (C) (p 0.009)	49 (I) vs 63 (C) (p 0.14)	NR (C) vs 81 patients with ADR (I)	Mean change EQ-5D (-0.13) (I) vs (-0.14) (C) (p 0.84) Mean change VAS (-7.36) (I) vs (-3.24) (C) (p 0.042)
Sidel, 1990 (USA)	I- 141(113 consented) C- 143			Change in medication risk score (negative means improvement) (-8.35) (I) vs (-10.84) (C) (p 0.44) Change in normative scores: Requesting information from physician (P-value 0.041) as follows I- 23.8% Improvement I- 25% Decline C- 13.3% Improvement C- 16.7% Decline	

Nazareth, 2001 (UK)	I- 181 C- 181	Hospitalization 27.9% out of 136 (I) vs 28.4% out of 151 (C) (p > 0.05)	22 (I) vs 19 (C) (p > 0.05)	Adherence 0.78 (I) vs 0.78(C) (p>0.05) Mean value of adherence (0=none, 1=total/highest level)	Mean value of general well being 2.5 (I) vs 2.4 (C) (p>0.05) Mean value of general well-being (1= ill health, 5= good health) Mean value of satisfaction 3.4 (I) vs 3.2 (C) (p >0.05) Mean value of satisfaction questionnaire scores (1= dissatisfied, 4= satisfied)
Begley,1997 (UK)	I-74 C- 75 NV- 73			Mean compliance 86% (I) vs 75% (C) vs 69% (NV) (p 0.0001) Percentage of patients where one or more of their medications stopped 31.1% (I) vs 16% (C) vs 8% (NV) (p 0.001)	

Godwin,2016 (CA)	I-121 C-115	Hospitalization 19% (I) vs 13% (C) (p 0.23)			SF-36 (General health) 70 (I) vs 69.2 (C) (p 0.79) CASP-19, 44.5 (I) vs 44.7 (C) (p 0.84) Mean patient satisfaction with physician care 4 (I) vs 3.9 (C) (p 0.74)
Naylor,1999 (USA)	I- 177 C- 186	Hospitalization 40% (I) vs 78% (C) (p <0.001) Mean ER visits 0.1 (I) vs 0.2 (C) (p 0.21)	11 (I) vs 11 (C)		Mean functional status (I) vs (C) (P-Value = 0.33); Measured using Enforced Social Dependency Scale (higher scores on a 10 to 51 scale equal disability) Mean patient satisfaction score (C) vs (I) (p 0.92)

Hanna,2016 (AU)	I- 487 C-131	Hospitalization rate increased 9.4% from pre-intervention rate (I) vs 14.4% increase (C) (p 0.45) ER rate decreased 34.7% from pre-intervention rate (I) vs 44.2% decrease (C) (p 0.16)	19 (I) vs 3 (C)		
Rytter,2010 (Denmark)	I- 166 C-165	Hospitalization 45% (I) vs 59% (C) (p 0.03)	15 (I) vs 20 (C) (HR 0.72 - 95%CI (0.37-1.41))	Number of patients with adjusted medications 84 (I) vs 63 (C) (p 0.01)	

Köberlein-Neu,2016 (DE)[2]	Total 162 Cohort 1: 66 Cohort 2: 49 Cohort 3: 47			Mean DRP per patient 5.87 (I) vs 6.98 (C) (p 0.014) MAI sum score per patient 22.27 (I) vs 29.21 (C) (p ≤0.001)	

[2]This study was evaluated in a cluster-randomized controlled trial with stepped wedge design.

Abbreviations: USA-United States of America, NLD-Netherland, UK-United Kingdom, CA-Canada, AU- Australia, DE- Germany, DRPs-drug related problems, C- Control group, I-intervention group, NV- No visit Control group, NR-not reported, ER- Emergency Room, OR- Odd Ratio, HR- Hazard Ratio, PCS-Physical Component Scale ,MCS-Mental Component Scale

Table 3-2: Summary Quality appraisal

Reviewer	Verifier	Ref ID	Author, Year	Selection bias	Selection bias	Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias	Overall Risk of bias	
				Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other sources of bias	Judgment	Support for judgment
SM	SR	140	Hunt,2018	High	Unclear	High	Unclear	Low	Unclear	Low	High	At least one domain is high.
SM	SR	347	Olesen,2014	Low	Low	High	Unclear	High	Unclear	Unclear	High	At least one domain is high.
SM	SR	366	Merek,2013	Low	Low	High	Unclear	Low	Low	High	High	At least one domain is high.
SM	SR	545	Hugtenburg,2009	High	Unclear	High	Unclear	Low	Unclear	High	High	At least one domain is high.
SM	SR	603	Aldamiz-Echevarria Iraurgui,2007	Low	Low	High	Low	Low	Unclear	Low	High	At least one domain is high.
SM	SR	615	Lenaghan,2007	Unclear	Unclear	High	Unclear	Low	Unclear	Low	High	At least one domain is high.
SM	SR	667	Holland, 2005	Low	Low	High	Unclear	Low	Low	Unclear	High	At least one domain is high.

SM	SR	713	Stewart, 2002	Low	Low	Unclear	Unclear	Low	Unclear	High	High	At least one domain is high.
SM	SR	756	Stewart,1998	Unclear	Low	High	Unclear	Low	Unclear	Low	High	At least one domain is high.
SM	SR	805	Sidel, 1990	Low	Unclear	Unclear	Unclear	Low	Unclear	Low	Unclear	One or more domains are unclear. No domain is high.
SM	SR	1674	Nazareth,2001	Low	Low	High	Low	Low	Low	Low	High	At least one domain is high.
SM	SR	1709	Begley,1997	Low	Low	High	Unclear	Low	Unclear	Low	High	At least one domain is high.
SM	SR	1766	Godwin, 2016	Unclear	Low	High	High	High	Unclear	High	High	At least one domain is high.
SM	SR	2304	Naylor,1999	Low	Low	Unclear	Low	Low	Unclear	Low	Unclear	One or more domains are unclear. No domain is high.
SM	SR	2746	Hanna,2016	High	High	High	Unclear	High	Unclear	High	High	At least one domain

												is high.
SM	SR	2909	Rytter,2010	Low	Low	Low	Low	Low	Unclear	High	High	At least one domain is high.
SM	SR	3586	Köberlein-Neu,2016	Unclear	Low	High	Low	Low	Low	High	High	At least one domain is high.
SM	SR	3587	Hogg,2009	Low	Low	Low	Unclear	Low	Unclear	High	High	At least one domain is high.

Chapter Four
Discussion

Medication management with its considerations for older adults' health maintenance and wellness, is a patient centered plan. The role of healthcare practitioners in medication management, implies the use of their expertise in implementing a comprehensive care plan that delivers safe and effective medication choices. Several medication management strategies can be put into practice; this includes deprescribing inappropriate medications, in addition to reviewing and making decisions regarding ongoing medications. The first part of this thesis considered the cost implications when deprescribing that could add financial strains on the community pharmacy, while reducing the government and patient share of cost. The second part of this thesis showed a minimal effect of Home Medication Review (HMR) on healthcare system utilization with variable results on other health related outcomes.

Deprescribing

Deprescribing inappropriate medications (this includes stopping medications, tapering of doses, switching to a safer or convenient choice[32,33] had cost implications on pharmacies, patients, and government based on our case scenarios. Although 42% and 31% Canadian women and men over the age of 65, respectively, are using PIMs with an estimated total cost of $419 million;[120] the cost saving effect of deprescribing on patients and government shares had not been studied before, and supports that there is a potential for these costs to impact decision making by patients or pharmacists. However, pharmacy loss of income may create restraints on community pharmacies when adopting deprescribing. Our research is novel to report the costs effect of deprescribing on three payers; pharmacies, patients, and government.

A number of studies demonstrated that economics may drive clinical decisions in the community pharmacy setting. One article demonstrated how the engagement of pharmacists in a merit-based incentive service led to an expansion of their clinical role otherwise the pharmacy profits relied solely on the cost of medications and dispensing fees.[36] Another study involved the

pharmacists with a patient centered medical home intervention, where they provided comprehensive healthcare services in a multidisciplinary approach to high risk patients (e.g. life style recommendations, disease education, medication reviews), and the pharmacists received a capitated payment/ patient per month, clinical outcomes, such as flu vaccination rate, A1c and blood pressure all improved.[121]The financial incentives led to improved patient outcomes, because pharmacists were able to expand their role and become more involved in clinical services.[121]

A literature review done by Kazungu, et alincluded 16 studies, aiming to analyze which characteristic of provider payment mechanisms (PPM) drives health care providers' behaviour.[122]Capitation, fee for service, and payments for performance were the most common PPM studies.[122] The key factor that affected providers' behaviour and incentives for quality was the payment rate.[122] Higher payments rate means less budgeting constrains and a consequent performance improvement.[123]

That being said, the pharmacy loss of income when deprescribing may create financial disincentive and discourage the community pharmacy from implementing this model; which ranged in our case scenarios on yearly basis from 0.04% up to 29.14%. Nevertheless, looking into deprescribing model from a patient standpoint, one of the scenarios (scenario 7) was switching from a high cost medication to a lower cost one. The rational for presenting this scenario was to emphasize on the burden of medication costs to patients; which could be promoted as one of the possible reasons for deprescribing, and for starting a cost conversation between patients and healthcare practitioners.[124] Medication cost burden may create a challenge for the patient to adhere with the treatment regimen, or what is commonly referred to as cost-related medication underuse (CRMU); with resultant poor health-related outcomes.[124]
A second deprescribing enabler wascost savings demonstrated across most of the scenarios when considering the patient cost, which on yearly basis showed cost saving that ranged from 0.03% to 87.4%. The patient's medication cost saving implies a win-win situation when it comes to reducing healthcare expenditure and avoidance of PIM.[125]An American deprescribing study involved 27 older adults with cancer from the Geriatric Oncology Clinic at the University of Virginia Health System Cancer Centre. The main outcome was to compare three medications assessment tools (Beers Criteria, START/STOPP criteria, and MAI) to Beers criteria alone in

identifying PIM, and the secondary outcomes included addressing the effect of a pharmacist-led deprescribing intervention on medication numbers deprescribed, and medications costs. The study reported improved healthcare outcomes and cost savings to the patients, and a mean of 3 medications deprescribed per patient. Costs were calculated based on: minor and major adverse events prevention with assigned costs value of $220and $2200 respectively, medication education with assigned cost value of $208, and detailed medication history with assigned cost value of $642.00; the results were cost saving of healthcare expenditure of $4282.27 in US dollars per person.[126]

The cost implications of deprescribing on government share was another objective covered in our study. Canada healthcare expenses were expected to reach $264 billion by 2019; with the highest healthcare spending on older adults ($6,656 for the age range 65to 69).[127]Provincial and territorial governments cover 70% of these healthcare expenses,[127]where funding of medications is supported for older adults primarily through public funding delivered at the provincial level. Our case scenarios proved a modest government savings when deprescribing, ranging from 0.32% up to 15.77% from baseline annually. Accordingly, this government medication cost saving may provide a possible solution for health funding and reinvestment. Further analysis is required to determine the pharmacoeconomic impact of deprescribing on governments, and that such savings can be reallocated to improve several health services provided to seniors.[76]

Yet, it must be noted that coverage for older adults under the public senior government plans varies across the provinces and territories. In the study case scenarios, several factors played role in determining old adult's share of payments; such as reaching the deductible, medication coverage, and mediation strength. These factors are inconsistent across Canada. This inequity may be partly addressed with the call for national pharmacare, that answers patients' need regardless of where he/she reside.[128]

Additionally, locating medication coverage and cost information during the electronic search of the government ministry of health websites, was sometimes not feasible.[129]As a result, we had to apply other approaches such as calling the pharmacy association, or directly calling pharmacies. This highlights a gap in transparency and access. In the future, the provincial governments

should work on developing a transparent tax funded programs that the healthcare providers and patients can use and refer to.

Home medication review (HMR)

In our second study, we did a systematic review to determine the impact of home medication reviews (HMRs) as an approach to determine medication appropriateness on older adults' health-related outcomes. We found 18 studies that reported their HMR intervention impact on either clinical, medication, humanistic, or economic outcomes.

All included studies had done an assessment of patients' health conditions and reviews of the medication lists. However, the outcomes of HMRs varied considerably across the included studies. In addition, there was a limited scope for meta-analysis because of the range of different outcomes measured across the small number of existing trials.

There have been multiple articles and studies concerning HMR. However, we chose to conduct a systematic review. We found only one other HMR systematic review, which just considered the pharmacist role in addressing drug related problems in patients' home setting or home care facilities, with no restrictions on follow-up times.[130] We addressed this gaps in the literature by including studies that had at least 6 months of follow-up.Another overview of systematic reviews was carried by [Silva, 2019], the study included 17 systematic reviews; the objective they targeted was to search and compare for different systematic reviews of medication reviews done by pharmacists in different practice settings. None of the included systematic reviews was done solely in the older adult's home setting but were done as well in other practice settings such as community pharmacy or hospital.[131]

Hospital services use including admissions and readmissions are highest among older adults.[132] Interventions that help older adults adapting to their daily life at home, and managing their medications, with the objective of reducing hospital admissions are essential.[132] Our primary outcome was health system use; this was chosen as the primary outcome of interest because no other systematic reviews analyzed this outcome of HMR for older adults as a possible strategy to reduce readmissions (Hospitals and emergency rooms), and this may be the driver for policy change in terms of adopting HMR. Of the 18 studies we included, four studies out of 12 (33%) showed statistically significant differences in terms of hospitalization rate

reduction in favor of the intervention groups compared to usual care groups (the hospitalization reduction risk were reduced more than 20% in these four studies- this ranged from 24% to 49%), however, one study reported 30% increased hospitalization risk of the intervention group[84]. [Holland] study had shown an increase in hospitalization after intervention possibly due to patients increased knowledge about their cases, which precipitated more dependency on healthcare services. These findings contrast with the review by Gudi, which focused on the primary outcome of ADR, and did not specify a follow-up time.[113]

Investigating the effect of HMR on older adult's medication outcomes, mortality, and humanistic measures were the secondary objectives of our systematic review. The results varied among these outcomes, and the overall effect of HMR was minimal with regard to mortality and humanistic outcomes. However, the medication outcomes through the identification of ,frail comorbid older adult patients may harvest the benefits of HMR more readily than healthier patients with high quality of life

Strengths of the study

Our research has many strengths. For our deprescribing paper, firstly, we chose the case study based on the Canadian Institute for Health Information[3] , where the number and type of medications/conditions chosen represent what is common for Canadian seniors. Additionally, our research had considered deprescribing scenarios based on Beers Criteria and examples and priorities from The Canadian Deprescribing Network. Beers Criteria is a guide to identify PIMs, while the Canadian Deprescribing Network provides process, guidance and recommendations for deprescribing as well as pharmacologic and non-pharmacological treatment approaches.[23,133] Second, our sources of data for analyzing the annual costs are referenced from publicly accessible data from provincial and territorial websites for the ministries of health to obtain information for the general seniors' (age 65y and older) publicly funded drug programs; which makes our calculations replicable when needed.

For our systematic review of HMR we followed the 6 stages recommended by Cochrane Handbook for Systematic Reviews of Interventions: (1) identifying the research question; (2) defining eligibility criteria; (3) searching for the studies; (4) selecting the included studies; (5) assessing the risk of bias; (6)collating, summarizing, and reporting results. Additionally, we had

two reviewers for study selection, risk of bias assessment (using Cochrane risk of Bias tool), and for data extraction verification; for the purpose of reducing the risk of selection and reporting bias. Furthermore, our search was not restricted by language, which enabled us to capture and include all relevant studies that reported the effect of HMRs that were conducted in different countries. We also provided a more robust follow-up timeframe for benefit, 6 months, to give an optimal time in order to determine the validity of the review effect on developing the outcomes. We know that many interventions can result in rapid improvements, but some of these interventions fail to show persistence in benefit, which should be considered when designing health policy.

Limitations of study

There were limitations to our study that should be reported. For the deprescribing analysis, healthcare in Canada is socialized and individual cost for physician visits and laboratory tests are not charged to patients or insurance, and not publicly available, accordingly, the indirect costs such as laboratory tests and physician visits were not included.As well, the use of a scenario rather than actual patient cases, or pharmacy practice behaviour in the community represent another limitation. We also tested only 1 scenario at a time, and in practice multiple interventions could potentially take place at once.

For our systematic review of HMR; although our search was not restricted by language, for searching methodologies we used English language, that could have precipitated some language bias. We included four foreign language's studies in our secondary screening, however, they were excluded as they did not meet our inclusion criteria. Additionally, we excluded palliative studies or the ones with peer to peer or caregivers' reviews, accordingly, the effect of HMR in these cases were not reported.

Contribution to existing knowledge

To our knowledge, this the first study that reports the cost impact of deprescribing on pharmacies, patients, and governments, all three in relation to one case study. This highlights the need to have policies that consider all deprescribing outcomes from different perspective aspects. In addition, our study revised all possible outcomes of home medication reviews from clinical,

medication, humanistic, and costs perspectives. This study adds to the field of pharmacy practice research in the following ways:

- It has reviewed two strategies for medication management to overcome challenges in older adults relating to an optimum therapeutic regimen; deprescribing and home medication reviews.
- It has identified a financial disincentive to deprescribing, specifically a financial barrier on the part of the pharmacy
- It has identified a financial disincentive to deprescribing in some cases, for the patient.
- It has identified the costs implication of deprescribing as a possible loss to pharmacies and as a savings to patients and governments.
- It has reported the challenges in locating cost information for seniors' publicly funded drug programs from ministries of health provincial and territorial websites.
- It has reported the effect of home medication reviews on older adults' health related outcomes
- It has spotlighted the need for stricter quality measures when planning studies of HMR, as when the quality assessment was applied to the included HMR studies, risk of bias results ranged between "unclear" and "High" .

Chapter Five
Conclusions and recommendations

Aging is often accompanied by multimorbidity and polypharmacy.[134] These two conditions are the primary drivers for potentially inappropriate medications (PIMs) and consequent poor health related outcomes.[134] Given the increasing geriatric population, it is imperative that this growing problem of medication related harm secondary to PIMs be addressed.

Inappropriate treatment regimens are often associated with adverse drug reactions (ADR), drug-drug interactions, drug-disease interactions. Often the original indication for the drug no longer exists or it is causing harm and its use does not align with the goals of care, which eventually results with morbidity and/or mortality.[135]

In such cases, interventions require more than just an understanding of geriatric pharmacotherapy. Interventions require efforts between the healthcare team, caregivers, and patients themselves.[136] Interventions must be supported in good policy, and must be economically feasible, with meaningful outcomes for seniors and the healthcare system.

This thesis work described older adult's medication management with two different strategies: the financial implication of deprescribing potentially inappropriate medications on three payers (community pharmacy, patients, and government); and the second approach of understanding Home Medication Review (HMR) on older adult's health related outcomes.

The findings of the previous two projects in this research showed that for *deprescribing* strategies, most often the cost burden of deprescribed medications is reduced for older adults' medication expenses and reduces the government cost. On the other hand, this approach leads to financial loss to the community pharmacy.

As for HMR, the outcome of doing such a medication review on older adults' healthcare-utilization showed little effect in terms of reducing hospitalization rate or emergency room admissions (the primary outcome), mortality, and humanistic outcomes. However, the concept of older adult's medication review by healthcare practitioners was of value when the treatment

regimen was revised and amended. (e.g. identifying adverse drugs reactions, changing or stopping inappropriate medications.)

5.2 Future direction

5.2.1 Deprescribing

Our cost analysis study was novel concerning highlighting the outcomes deprescribing inappropriate medications for older adults on the community pharmacy, the patients, and government. Studies that considered the financial implications of deprescribing were limited to one payer group; subsequently, more research is needed to confirm the financial implications of deprescribing models from a wider angle that includes pharmacies, patients and government; which can lead to integrated financial decision from the policy makers when developing deprescribing policies and models.

Additionally, we chose for our research to build case scenarios rather than actual patients' cases, since we wanted to explore this model financially through all Canadian provinces and territories. Nevertheless, more research is needed to incorporate actual cases of patients and to focus on the pharmacist behaviour towards deprescribing in a community. In addition, indirect costs such as laboratory tests and physician visits should be factored into the analysis. Deprescribing may also lead to more non-pharmacologic interventions which can be a cost burden on patients. The role of other prescribers, or other participants in pharmacy practice (e.g. pharmacy managers, pharmacy franchisees) should also be considered in future research.

5.2.2 Home Medication Review

Our systematic review to determine the effect of older adults' Home Medication Review, was novel concerning analyzing the reviews done in the patients' home setting and reporting the results of clinical, humanistic, and medications outcomes for any healthcare professional involved. The value of reducing medication related problems through HMR needs further study to determine if the costly home-based team interventions add enough value, or if other forms of medication reviews are equivalent. For example, future research is needed to report the effect of HMR in palliative studies and studies concerning peers or caregiver reviews, for the purpose of

expanding our knowledge about HMR in these distinctive conditions. Furthermore, the articles that reported the costs implication of HMR were measured by a small number of the included studies; accordingly, the financial aspect of HMR should be a priority in future research.

Finally, this thesis described two strategies of medication management from two different perspectives; the financial perspective of deprescribing inappropriate medications, and the health outcomes perspective of implementing HMR. However, the outcomes of older adults receiving an appropriate treatment regimen, and the consequence of that on related health outcomes, should be the target of further studies to confirm.

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Appendix A: Deprescribing study supplemental table

Supplemental table: %The national average of the cost difference for each deprescribing scenario.			
	Pharmacy margin	Government share	Patient share
Scenario 1	3.39	0.99	1.55
Scenario 2	8.20	15.77	1.12
Scenario 3	1.90	2.27	0.21
Scenario 4	3.20	5.31	-1.75
Scenario 5	5.07	6.95	-0.62
Scenario 6	0.04	0.32	0.03
Scenario 7	29.14	2.98	87.40
Scenario 8	-0.04	-0.43	-0.01

Appendix B: HMR study protocol

The impact of home medication review in older adults in the community:

Protocol for a systematic review

Background

The average number of medications prescribed and used by older adults people range between 5 and 9 drugs.[1] In addition, the demographic trend in Canada is toward an aging population with significant growth in the age group over 65years.[2]This would demand a comprehensive clinical practice concerning seniors' health.

Another concern in older adults is polypharmacy, generally accepted as the use of 5 or more medications at once.[3]Polypharmacy can lead to potentially inappropriate medications (PIM), and is associated with adverse events such as falls, hospitalization and death.[3]Increasing prevalence of polypharmacy is attributed to many factors, primarily aging with increased number of comorbidities that require administering more than a single remedy. In addition, the application of disease-based clinical guidelines often increases the number of medications.[4]

Investigating polypharmacy and PIMs requires collaborative work amongst health care practitioners. This can be done through a number of processes, including medication reviews, which may take place in a community pharmacy, clinic, hospital setting, or home. Home medication reviews (HMR) are defined as a thorough patient interview to discover all drug related problems like adverse drug reactions, non-adherence, or unclear dosing instructions, in their home setting, along with detailed follow up of their medical and clinical records post initial medication review.[5,6]

Research has been carried out to estimate the effect of home-based medication reviews for older adults. These individual studies have been done in a variety of countries including Germany, UK, and Australia, with different health care professionals, settings, and a diversity of outcome measures. [6,7,8,9,10,11] The Australian model review study showed that HMRs conducted by pharmacists reduced the use of anticholinergic and sedative drugs among elderly,an impact that would lessen the risk of falls and poor cognitive function.[7] Another study in Germany estimated that HMR helped in identification of potential drug-drug interactions.[6]

Although it is presumed that HMRs done by healthcare professionals improve outcomes for seniors, the impact of HMR remains uncertain.[8] Two of the landmark trials showed conflicting results, with the HOMER study showing increased hospital admissions with reduced quality of life,[9] and POLYMED study not showing any significant improvement in clinical outcomes. [10]In addition, the economic evaluation of HOMER study presented low cost effectivess.[11]

There are inconsistent international policies on the support for this intervention, For instance, the Australian government pays for HMR and reviews done in residential aged care,[7] but this is not the case in all jurisdictions.

Our systematic review will attempt to answer this uncertainty by reviewing literature related to HMR studies including HMR done by all healthcare professionals, with a meaningful follow-up time to determine the impact on outcomes. This will provide reliable evidence to clarify the outcome of such intervention on public measures and to be used by international health policies. This systematic review will determine the significance of home medication review and whether such a review will contribute to significant change in health service utilization or not.

PICOS question:

In community-dwelling older adults, what is the result of a HMR (conducted in their home) compared to usual care, in terms of health system use, in controlled clinical trials.

Outcomes

Primary: To determine the impact of HMRs on hospitalization or ER admission rates

Secondary outcomes: number of medications, number of potentially inappropriate medications, health related quality of life, economic outcomes

Methods

Eligibility criteria

- Study design: prospective, quasi-experimental (including a control group) or randomized, controlled trials
- Publications: electronic databases and grey literature as per the search strategy
- Participants: We will include studies examiningcommunity-dwellingolder adults
    - We will solidify the age cut off as 60 or 65 years during secondary screening
    - we will include only data on those individuals who are over this cut-off and older if the study involves individuals across many age groups
- Intervention: Home based medication review provided by health care professional where all medications are included.
- Comparators: Usual care with no medication review
- Primary Outcome: Health service utilization represented in:
    - Hospitalizations
    - ER visits
- Secondary outcomes:
    - Economic outcome: monetary value
    - Humanistic outcome: standardized or validated quality of life measures
    - Clinical outcomes: mortality
    - Medication outcomes: adverse drug event, complexity of medication regimen, change in the number of medications, medication appropriateness using explicit

criteria (e.g. Beers Criteria, STOPP) or implicit criteria (e.g. Medication appropriateness index)

- Setting: The medication review should be conducted in patient place of residence in the community.
- Follow up: at least 6 months of follow-up after the med review conducted
- Language: No restriction

Exclusion criteria

- Studies conducted in hospitals, clinics, or assisted living facility.
- Studies involving peer to peer or family caregiver reviews
- Palliative studies
- Health policies concerning home medication reviews no earlier than 1990

Information source

The electronic databases search includes Ovid databases (PsycINFO, MEDLINE, and EMBASE), in addition to Cochrane library (Wiley platform), CINAHL (Ebsco platform), and HTA & Economic Evaluations DBs.

Other sources include conference proceedings Citation Index (Clarivate Analytics) and Dissertations & Theses Global (extracted from ProQuest).

Search Strategy

The specific search strategies will be created by Librarian (Ms. Robin Featherstone)with expertise in systematic review searching. The MEDLINE strategy will be peer reviewed by a second librarian.

Strategy

1 Drug Therapy/ut [Utilization] (452)
2 Drug Utilization Review/ (3564)
3 Inappropriate Prescribing/pc [Prevention & Control] (778)
4 Medication Adherence/ (15409)
5 Medication Reconciliation/ (873)
6 Polypharmacy/ (4031)
7 ((adhere* or complian* or nonadhere* or noncomplian*) adj6 (drug* or medication* or regimen* or treatment*)).tw,kf. (52124)
8 ((assess* or check* or evaluat* or manage* or review*) and (medication load* or poly-medication* or poly-pharmacy* or polymedication* or polypharmacy*)).tw,kf. (4100)
9 (de-prescribing or deprescribing).tw,kf. (334)
10 ((drug utili#ation* or drug regimen*) adj1 review*).tw,kf. (415)
11 inappropriate prescri*.tw,kf. (1562)
12 ((medication* or medicines) adj2 (management* or reconcil* or review*)).tw,kf. (8259)
13 (pharmacist* adj1 consult*).tw,kf. (417)
14 or/1-13 [Combined MeSH& text words for medication reviews] (77276)
15 Community Pharmacy Services/ and (home* or house*).mp. (315)
16 Home Care Services/ (31607)
17 Home Care Services, Hospital-Based/ (1820)

18	Home Health Nursing/ (215)
19	House Calls/ (3158)
20	(home adj (based or service* or visit*)).tw,kf. (16644)
21	hospital at home.tw,kf. (385)
22	house call*.tw,kf. (612)
23	((doctor* or health professional* or nurse* or pharmacist* or physician*) adj2 visit*).tw,kf. (9696)
24	or/15-23 [Combined MeSH& text words for home visits] (56974)
25	Age Factors/ (426805)
26	exp Aged/ (2867149)
27	Aging/ (216894)
28	Geriatric Assessment/ (24490)
29	((adult* or citizen* or individual* or people or person* or resident*) adj1 (older* or senior*)).tw,kf. (104703)
30	community dwelling*.tw,kf. (19582)
31	elderly*.tw,kf. (226162)
32	frail*.tw,kf. (17455)
33	((post-menopausal or postmenopausal) adj women).tw,kf. (36925)
34	or/25-33 [Combined MeSH& text words for older adults] (3368367)
35	and/14,24,34 [Combined concepts for medication review, home-based & older adults] (714)
36	limit 35 to yr="1990-Current" (701)
37	remove duplicates from 36 (696)

Study Records

Literature search results will be recorded in an excel file formatted for screening through level 1(titles and abstracts) and level 2 (detailed full text) based on inclusion and exclusion criteria.

The review authors (SA, and a research assistant) will independently screen the titles and the abstract of the articles included according to specified criteria, after that the chosen full articles will be reviewed.

If any disagreement between reviewers happen, it will be resolved by discussion. If a consensus cannot be reached, a third member of the research team will make the decision (CS). The reasons for excluding trials will be recorded.

Data Items

All the medications used by and prescribed for the patient will be included in the review.

Risk of bias

We will use Cochrane " Risk of bias " assessment tool in Cochrane Handbook for Systematic Reviews of Interventions and will judge "risk of bias" as either "low", "high", or "unclear".

Strategy for data synthesis

We will provide a synthesis of the findings from the included studies and will provide summaries of interventions effects for each study by calculating risk ratios (for dichotomous outcome) or standardized mean differences (for continuous outcomes), where possible.

We anticipate that there will be limited scope for meta-analysis because of the range of different outcomes measured across the small number of existing trials. However, where studies have used the same type ofintervention and comparator, with the same outcome measure, we will pool the results using a random-effects meta-analysis, with standardized mean differences for continuous outcomes and risk ratios for binaryoutcomes, and calculate 95% confidence intervals and two sided P values for each outcome. We will conduct sensitivity analysis based on study quality.

Conflict of interest

None known

References

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3. Mangin D, Bahat G, Golomb BA, Mallery LH, Moorhouse P, Onder G, et al. International group for reducing inappropriate medication use & polypharmacy (IGRIMUP): Position statement and 10 recommendations for action. Drugs Aging 2018;35(7):575-587.Payne RA. The epidemiology of polypharmacy. Clin Med (Lond) 2016 Oct;16(5):465-469.
4. Payne RA. The epidemiology of polypharmacy. Clin Med (Lond) 2016 Oct;16(5):465-469.
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8. Hallberg IR, Kristensson J. Preventive home care of frail older people: A review of recent case management studies. J ClinNurs 2004;13:112-120.
9. Holland R, Lenaghan E, Harvey I, Smith R, Shepstone L, Lipp A, et al. Does home based medication review keep older people out of hospital? the HOMER randomised controlled trial. BMJ 2005;330(7486):293.
10. Lenaghan E, Holland R, Brooks A. Home-based medication review in a high risk elderly population in primary care—the POLYMED randomised controlled trial. Age Ageing 2007;36(3):292-297.
11. Pacini M, Smith RD, Wilson EC, Holland R. Home-based medication review in older people. Pharmacoeconomics 2007;25(2):171-180.

Appendix C: HMR search strategy

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to March 15, 2019

Date conducted: 15 March 2019

Strategy:

1 Drug Therapy/ and utli?ation.tw,kf. (369)
2 Drug Utilization Review/ (3600)
3 Inappropriate Prescribing/pc [Prevention & Control] (842)
4 Medication Adherence/ (16002)
5 Medication Reconciliation/ (908)
6 Polypharmacy/ (4173)
7 ((adhere* or complian* or nonadhere* or non-adhere* or noncomplian* or non-complianc*) adj6 (drug* or medication* or regimen* or treatment*)).tw,kf. (53628)
8 exp "Treatment Adherence and Compliance"/ (223927)
9 ((assess* or check* or evaluat* or manage* or review*) adj2 (multiple medication* or medication load* or poly-medication* or poly-pharmacy* or polymedication* or polypharmacy*)).tw,kf. (193)
10 (de-prescribing or deprescribing).tw,kf. (406)
11 ((drug utili#ation* or drug regimen*) adj1 review*).tw,kf. (418)
12 (inappropriate prescri*).tw,kf. (1631)
13 (potentially inappropriate medication*).tw,kf (819)
14 Inappropriate Prescribing/ (2523)
15 Potentially Inappropriate Medication List/ (269)
16 ((medication* or medicines) adj2 (management* or reconcil* or review*)).tw,kf. (8539)
17 (pharmacist* adj3 consult*).tw,kf. (770)
18 or/1-17 [Combined MeSH& text words for medication reviews] (78738)
19 Community Pharmacy Services/ and (home* or house*).mp. (320)
20 Home Care Services/ (31984)
21 Home Care Services, Hospital-Based/ (1836)
22 Home Health Nursing/ (264)
23 House Calls/ (3243)
24 (home adj2 (based or service* or visit*)).tw,kf. (16644)
25 hospital at home.tw,kf. (393)
26 house call*.tw,kf. (618)
27 ((doctor* or health professional* or nurse* or pharmacist* or physician*) adj3 visit*).tw,kf. (12822)
28 or/19-27 [Combined MeSH& text words for home visits] (63313)
29 Age Factors/ (431231)

30 exp Aged/ (2914938)
31 Aged, 80 and over (836942)
32 Aging/ (219147)
33 Geriatric Assessment/ (24974)
34 ((adult* or citizen* or individual* or people or person* or resident*) adj1 (older* or senior* or geriatric*)).tw,kf. (108781)
35 community dwelling*.tw,kf. (20304)
36 elderly*.tw,kf. (229742)
37 frail*.tw,kf. (18360)
38 ((post-menopausal or postmenopausal) adj3 wom?n).tw,kf. (40986)
39 or/29-38 [Combined MeSH& text words for older adults] (3424210)
40 and/18,28,39 [Combined concepts for medication review, home-based & older adults] (838)
41 limit 40 to yr="1990-Current" (823)
42 remove duplicates from 41 (822)

Appendix D: HMR Study Characteristics

Author, date acronym (Country)	Follow-up (months)	Number of patients at randomization	Number of patients who completed the study	Mean age (years, SD)	Gender %	Number of medications at baseline	Study Outcomes	HMR (other specification)
Hunt,2018 (UK)	12	I- 88 C- 87	I- 86 C- 87	I-(67.9, 9.8) C-(72.1, 9.4)	Female %: I- 67.1% C- 66.7%	• Median respiratory repeat (maintenance) prescription: P-value <0.001 I- 6 c- 4 • Median non-respiratory repeat (maintenance) prescription: P-value 0.92 I- 7 c-7	1. Respiratory hospitalization rate 2. Respiratory clinic attendance 3. Respiratory Specialized nurse visits	• Disease-specific: COPD patients
Hogg,2009 (CA)	12 to 18 months (mean of	I- 120 C- 121	I-112 C-116	I-(69.6, NR) C-(72.8,	Female%: I- 52%	Mean number of medications:	1. Differences in the quality of care for chronic disease	• Disease-specific: COPD patients

	14.9 months in each arm)			NR)	C- 63%	I- 4 • C- 3.7	management. (D)	DM patients CAD patients CHF patients
Aldamiz-Echevarria Iraurgui,2007 (Spain)	12	I-137 C- 142	I-137 C-142	I-(75.3, 11.1) C-(76.3, 9.4)	Female%: I- 61.3% C- 59.9%	NR	1.One year combined cumulative incidence of readmissions following release from hospital. 2. Cumulative readmission, duration of readmission 3. Cumulative death rates 4. Use of emergency services during the first 6 months	• Disease-specific: HF patients
Stewart,2002 (AU)	6	I-33 C- 33	I- 33 C- 33	I-(77, 7) C-(76, 6)	Men: Women I- (20:13) C- (20:13)	NR	1. Days of hospitalization. 2. Mortality	• Disease-specific: HF patients

Stewart,1998 (AU)	6	I- 49 C- 48	I- 49 C- 48	I-(76, 11) C-(74, 10)	Men: Women I- (22:27) C- (25:23)	Mean number of medications: I- 6.9 C- 6.5	1. Mean incidence of unplanned readmission plus out of hospital death. 2. Duration of hospital stay. 3. Overall mortality.	• Disease-specific: CHF patients
Marek,2013 (USA)	12	Pill organizer-154 Medication dispenser-174 Control- 128	Pill organizer-102 Medication dispenser-98 Control-101	Pill organizer (79.6, 7.64) Medication dispenser (79.6, 7.92) Control (78.2, 7.25)	Female%: Pill organizer 67.9% Medication dispenser 68.4% Control 61.6%	Medication complexity index: Pill organizer 37.3 Medication dispenser 40.8 Control 32.2 P-value 0.01	Quality of life: PCS –Physical component scale MCS- Mental component scale	• General review
Olesen,2014 (Denmark)	12	I- 315 C- 315	I- 253 C- 264	Median age (year, Range) I-(74, 65-94) C-(74, 65-91)	Female%: I- 53% C- 51%	Median number of prescriptions: I- 7 C- 7	1. Adherence 2. Hospitalization 3. Mortality	• General review
Hugtenburg,2009	9	I- 336	I- 336	Mean age±	Female:	Mean number	1.Patient	• General review

(NLD)		C- 379	C- 379	SE I-(69.7± 15) C-(72.7±11.2)	I- 172 C- 202 Male: I- 164 C- 177	of medications: I- 7.8 C- 7.1 P- value <0.001	satisfaction 2. Mortality	
Lenaghan,2007 (UK)	6	I- 69 C- 67	I-56 C- 49	I-(84.5, NR) C-(84.1, NR)	Female% I- 67.6% C- 63.6%	Mean number of medications: I- 9 C- 9.9	1. Total number of non-elective hospital admissions. 2. Mortality. 4. Number of drugs prescribed. 5. Quality of life.	• General review
Holland,2005 (UK)	6	I-429 C- 426	I-415 C- 414	I- (85.4, 4) C-(85.5, 4)	Female% I- 61.1% C- 63.8%	Mean number of medications: I- 6.4 C- 6.3	1. Total emergency readmissions to hospitals. 2. Mortality. 3. Quality of life	• General review
Sidel, 1990 (USA)	6	I- 141(113 consented) C- 143	I- 92 C- 104	• Age 65-75: I - 48.4% C- 48.1% • Age 75-84: I- 38.5%	Female% I- 76.9% C- 77.9%	Quote: "Overall, 92.8% of the population reported use of prescription and/or OTC medications with a mean of	1. change in Medication management. 2. Use of ambulatory care in the past 3 months. (From baseline to 36-month Re-	• General review

				C- 41.4% • Age 85+ I- 13.2% C- 10.6%		4 medications among medication users project during the preceding month with a mean of four medications per medication user...”	interview)	
Nazareth, 2001 (UK)	6	I- 181 C- 181	I- 149 C- 157	I-(84, 5.2) C-(84, 5.4)	Female% I- 62% C- 66%	Quote:” Each patient had a mean of three chronic medical conditions and was on a mean of six drugs (SD=2) on discharge from hospital.”	1. Hospital readmission 2. Mortality 3. Attendances at hospital outpatient clinics and general practice. 5. Patient satisfaction with the service. 6. Adherence to and knowledge of prescribed medication.	• General review

Begley,1997 (UK)[3]	12	I-74 C- 75 NV- 73	I- 61 C- 63 NV- 66	Median age (year, Range) I-(84, 75-94) C-(81, 75-96) NV-(82, 76-92)	Female % I-61% C- 65% NV- 56%	• Mean number of prescribed medications: I- 4.6 C- 4.8 NV- 5.5 • Mean number of OTC medications: I- 2.6 C- 4.1 NV- 2.2	Patient compliance	• General review
Godwin,2016 (CA)	12	I-121 C-115	I-95 C-86	I-(85.3, 4.5) C-(85.7, 3.6)	Female% I- 62% C- 71.3%	NR	1.Quality of life measured by SF-36 & CASP-19 2. Patients satisfaction measured by PSQ-18	• General review
Naylor,1999 (USA)	6	I- 177 C- 186	I- 124 C-138	I-(75.5, 6.3)	Female% I- 46%	• Mean number of daily prescription	1. Readmissions. 2. Time to first	• General review

[3] This study included 3 groups of comparison: Intervention group, Control group which received visits only and no counseling, and second control group (designated NV) which received traditional pharmaceutical services with no visits except for beginning and end of the study.

				C-(75.3, 6)	C- 54%	medication: I- 5.3 C- 5.2	readmission. 3. Acute care visits after discharge. 4. Costs.	
Hanna,2016 (AU)	12	I- 487 C-131	I- 398 C- 118	I-(72.8, 14.1) C-(73.7, 14.2)	Female % I- 50.3% C- 54.2%	• Eligible study participant should have at least 4 medications	1. Hospitals admission. 2. Emergency room admission.	• General review
Rytter,2010 (Denmark)	6	I- 166 C-165	I-148 C-145	Median age I-(84, NR) C-(83, NR)	Female % I- 66% C- 66%	• Median number of medications: I- 6 C- 6	1. Hospital admission. 2. Mortality. 4. Healthcare cost.	• General review
Köberlein-Neu,2016 (DE)[4]	15	Total 162 Cohort 1: 66 Cohort 2: 49 Cohort 3: 47	Total 142 Cohort 1: 59 Cohort 2: 40 Cohort 3: 43	Total (76.8, 6.3) Cohort 1: (76.4, 6.1) Cohort 2: (78.5, 6.2) Cohort 3:	Female % Total: 53.3% Cohort 1: 47.5% Cohort 2: 75%	Mean drugs documented by primary care physician Total: 9.4 Cohort 1: 10.3 Cohort 2: 9	1. Quality of pharmacotherapy defined by MAI. 2. Number of DRP per patients.	• General review

[4] This study was evaluated in a cluster-randomized controlled trial with stepped wedge design. Compared with the usual parallel group structure, the design allows for each cluster to start in the control group and the intervention is introduced into the clusters at intervals. The clusters of the participating general practices were randomized into three cohorts that switched to the intervention phase at intervals of three months each.
Cohort 1 (Start of intervention after end of recruitment period)- Cohort 2 (Start of intervention after 3 months)- Cohort 3 (Start of intervention after 6 months)

				(75.5, 5.4)	Cohort 3: 41.9%	Cohort 3: 8.8		

Abbreviations: UK- United Kingdom, COPD- Chronic obstructive pulmonary disease, HF- Heart failure, CAD- Coronary Artery Disease, CHF- Congestive Heart Failure, DM- Diabetes, HF- Heart failure, NLD- Netherland, USA-United States of America, AU- Australia, DE-Germany, CA- Canada, I-intervention group, C-control group,NV- No visit Control group, NR-not reported, PSQ- Patient satisfaction questioner , MAI- Medication Appropriateness Index, DRP- Drug related problems.

Appendix E: HMR Referral structure, provider information, and home-based medication review intervention process

	Referral				Provider Structure				Intervention								
Author, acronym, date (Country)	ER	Hospital discharge	GP or pharmacy list	Other source	Physician	Nurse	Pharmacist	Other	Number of visits per patient	Access to patient records	Formal assessment	Provided education on medication	Assessed conditions	Identify DRPs	Encourage adherence	Organize medication	Communicate with GP and/or pharmacist
Hunt, 2018 (UK)		√			√		√		Median of 3 Home visits	√	√	√	√	√	√		√
Marek,2013 (USA)				√[5]	√	√	√		Every 2 weeks to fill the Rx and more frequent when needed	√	√	√	√	√	√	√	√
Olesen,2014 (Denmark)				√[6]	√	√	√		1 Home visit and 3 follow up calls	√	√	√	√	√	√	√	√
Hogg,2009 (CA)			√		√	√	√		NR	√	√	√	√	√			√
Hugtenburg, 2009 (NLD)		√	√		√		√		1 Home visit	√	√	√	√	√	√	√	√
Aldamiz-		√			√	√			4 Home	√	√	√	√		√		√

[5] Three Medicare-certified home health agencies
[6] National Health Insurance Population Register

Echevarria Iraurgui,2007 (Spain)									visits and the follow up as a phone call carried out 3, 6, 12 months after discharge								
Lenaghan,2007 (UK)			√		√		√		2 Home visits	√	√	√	√	√	√	√	√
Holland,2005 (UK)		√			√		√		2 Home visits	√	√	√	√	√	√	√	√
Stewart,1998 (AU)		√			√	√	√		1 Home visit	√	√	√	√	√	√	√	√
Stewart,2002 (AU)		√			√	√	√		1 Home visit	√	√	√	√	√	√		√
Sidel, 1990 (USA)				√[7]	√		√		At least 2 home visits	√	√	√	√	√	√	√	√
Nazareth, 2001 (UK)		√			√		√		Home visits were recorded in 98 patients: • 58 Patients received 1 home visit • 32 Patients received 2 home visits.	√	√	√	√	√	√	√	√

[7] Total 3340 Names basically of Medicare recipients supplied by the Health Care Finance Administration. Additional names were provided by local agencies such as senior centers, horses of worship, Meals-on-wheels programs, hospital admissions records and voter registration rolls.

									• 5 Patients received 3 home visits • 3 Patients received 4 home visits									
Begley,1997 (UK)		√			√		√		5 Home visits	√	√	√	√	√	√	√	√
Godwin,2016 (CA)			√		√	√			9 Home visits	√	√	√	√				√
Naylor,1999 (USA)		√			√	√			2 Home visits, additional visits were made based on patients' needs with no limit on the number.	√	√	√	√		√		√
Hanna,2016 (AU)	√	√			√		√		1 Home visit	√	√	√	√	√			√
Rytter,2010 (Denmark)		√			√	√		√[8]	One home visit and another two contacts either at patients' home or	√	√	√	√			√	√

[8] Research occupational therapist

									in GPs' clinic depending on patients' condition.								
Köberlein-Neu,2016 (DE)			√		√		√	√[9]	1 Home visit	√	√	√	√	√	√	√	√

Abbreviations: UK- United Kingdom , NLD- Netherland, USA-United States of America, AU- Australia, DE- Germany, CA- Canada, DRPs-drug related problems, ER- emergency room, GP-general practitioner, HF-heart failure, NR-not reported.

[9]3 Home-care specialists (social pedagogue with diploma certificate, gerontologist, and healthcare scientist)

Appendix F: HMR Outcome data

	Clinical			Medication			Humanistic	
Author, date acronym (Country)	Mortality	Unplanned use of health services (Hospital readmissions)	Other clinical outcomes	Number of DRPs	Adherence	Medication change	Quality of Life (QoL)	Satisfaction
Hunt, 2018 (UK)	I-14 C- 19 P-value 0.53	I- 39 C- 66 P-value <0.001	• Respiratory clinic attendance I- 70 C- 50 P-value <0.001 • Respiratory specialist nurse home visits I- 44 C- 84 P-value <0.001	I-2 had DRPs C-NR	I-3 with adherence issues C- NR	I: 62 had dose changed 45 had drug changed 39 had new drug initiated 46 had existing drug discontinued 28 had restart previously prescribed drug 16 had formulation changed 39 had inhaler technique corrected through demonstration 9 had oxygen prescription changed 9 had repeat prescription reordering 7 had changed inhaler device 4 had dose	NR	NR

						timing changed C- NR		
Marek,2013 (USA)	NR	NR	• Depression: Mean GDS Quarterly improvement • Medication dispenser vs. Pill organizer (-0.045) P-value 0.56 • Pill organizer vs. control 0.322 P-value 0.0002 • Physical Performance: Mean PPT Quarterly improvement • Medication dispenser vs. Pill organizer 0.118 P-value 0.31 • Pill organizer vs. control 1.009 P-value <0.0001 • Cognition: Mean MMSE Quarterly improvement • Medication dispenser vs. Pill organizer 0.119 P-value 0.06 • Pill organizer vs. control 0.311 P-value <0.0001	NR	NR	NR	• Mean PCS Quarterly improvement: • Medication dispenser vs. Pill organizer 0.095 P-value 0.73 • Pill organizer vs. control 1.39 P-value <0.0001 • Mean MCS Quarterly improvement: • Medication dispenser vs. Pill organizer 0.241 P-value 0.50 • Pill organizer vs. control 1.686 P-value<0.0001	NR
Olesen,2014 (Denmark)	I- 19 C- 14 HR 1.41 95% CI (0.71-2.82)	I-77 C- 73 P-value 0.47	NR	I-183 had DRPs C-NR	I- 28 non adherent C- 26 non adherent OR 1.14 95% CI (0.62-2)	NR	NR	NR

Hogg,2009 (CA)	I-3 C-0	Average number of hospital admission D_I 0.4 D_c 0.46 D_I- D_C (-0.06): *Hospital admission was reduced 6% in intervention group compared to control group.* P-value 0.67	• Average number of emergency department visits D_I 0.63 D_C 0.73 D_I-D_C (-0.10) P-Value 0.48	NR	• **Quality of care- Chronic disease management, proportion of patients** D_I .098 D_C 0.008 D_I-D_C 0.091: *Chronic disease management quality of care was improved by 9.1% compared with control group* P-value 0.0013[10] • **Quality of care- Diabetes, proportion of patients** D_I 0.144 D_C 0.013 D_I-D_C 0.131 P-Value 0.0074 • **Quality of care- CAD, proportion**	NR	SF-36: (out of 100) Physical component D_I 2.7 D_C 1.1 D_I-D_C 1.6 P-value 0.18 Mental component D_I (-1.2) D_C (-0.1) D_I-D_C (-1.1) P-value 0.44	NR

[10] D_I and D_C: This outcome measure represents adherence to disease management guidelines and the difference between them represent intervention effect. D_I is difference between end of study and baseline data for intervention group; Dcis difference between end of study and baseline data for control group

					of patients D_I 0.075 D_C 0.025 D_I-D_C 0.05 P-Value 0.09 • **Quality of care- COPD, proportion of patients** D_I 0.08 D_C 0.017 D_I-D_C 0.063 P-Value 0.3			
Hugtenburg, 2009 (NLD)	I- 22% C- 22% No difference	NR	NR	NR	NR	Discontinuation of drugs newly prescribed at discharge: I- 64% C- 58% No difference	NR	I: 87% of the 112 analyzed with median score of" very satisfied". C: 50% of 146 analyzed with median score of "satisfied". P-value <0.001 [11]
Aldamiz-Echevarria Iraurgui,2007 (Spain)	Cumulative incidence I- 16.1% C- 14.8% P-value 0.769	Cumulative incidence I- 43.1% C- 50% P-Value 0.28	• Cumulative incidence of combined readmission or death: I- 45.3% C- 52.8% P-value 0.232 • Number of admissions to emergency during the first 6 months of	NR	NR	NR	NR	NR

[11] 112 of intervention group and 146 of the control group were analyzed regarding satisfactions' questioner due to 22% death and loss to follow up

			follow up: I- 59 C- 57					
Lenaghan,2007 (UK)	I- 7 C- 6 P-value 0.81	I- 20 C- 21 P-value 0.8	• Care home admissions: I- 1 C- 3 P-value 0.3	NR	NR	Mean change in total medication items score: I- (-0.31) C- 0.56 P-value 0.03	• Mean change EQ-5D: I- (-0.1) C- (-0.02) P-value 0.1 • Mean VAS: I- (-2.0) C- 2.9 P-value 0.21	NR
Holland, 2005	I- 49 C- 63 P-value 0.14	I- 234 C- 178 P-value 0.009	• Total number admitted to residential home I- 21 C- 17 P-value 0.61 • Total number admitted to nursing home I- 16 C- 15 P-value 0.97	I- 81 patients had possible drug reaction/interaction reported. C- NR	NR	NR	• Mean change EQ-5D: I- (-0.13) C- (-0.14) P-value 0.84 • Mean change VAS: I- (-7.36) C- (-3.24) P-value .042	NR
Stewart,1998 (AU)	I- 6 C- 12 P-value 0.11	I- 24 C- 31 P- value 0.12	• Composite end point for the mean incidence of hospital readmission and out of hospital death per patient: I- 0.8 C- 1.4 P-value 0.03 • Duration of hospital stay: I- 261 days C- 452 P- value 0.05 • Attendance to emergency department I- 48 C- 87	NR	NR	NR	NR	NR

			P-value .05					
Stewart,2002 (AU)	I- 6 C- 13 P-value < 0.05	NR	• Days of hospitalization per month per patient: I- 1.6 C- 3.6 P- value =0.05	NR	NR	NR	NR	NR
Sidel, 1990 (USA)	NR	NR	Change in frequency of Medical visits from baseline to 36-month Repeat-interview (In *the past 3 months*): • Physician office visit: I- (-0.16) C- (-0.56) P-value 0.18 • OPD clinic visits: I- (-0.69) C- (0.22) P-value 0.01 • Total ambulatory care visits: I- (-1.16) C- (0.25) P-value 0.08	NR	NR	• Change in medication risk score: (negative means improvement)[12] I- (-8.35) C- (-10.84) P-value 0.44 • Change in normative scores: [13] I- 36% Improvement I- 41.6% Decline C- 40.4% Improvement C- 43.3% No difference except in one category: *Requesting information from physician (P-value 0.041) as follow* *I- 23.8%*	NR	NR

[12] Calculated by subtracting the score on RAP (Risk assessment profile) from the score on REAP (Reassessment Profile)
[13] Based on changes in the answers to a number of individual questions on RAP and REAP during the study period that were scored normatively.

						Improvement *I- 25% Decline* *C- 13.3%* *Improvement* *C- 16.7%* *Decline*		
Nazareth, 2001 (UK)	I- 22 C- 19 P-value> 0.05	I- 38 C- 43 P-value> 0.05	• Outpatient clinic visit I- 39 C- 40 P-value> 0.05 • GP visit I- 76 C- 82 P-value> 0.05 s	NR	Mean value of adherence (0=none, 1=total/highest level): I- 0.78 C- 0.78 P-value>0.05	NR	Mean value of general well-being (1= ill health, 5= good health) I- 2.5 C- 2.4 P-value>0.05	Mean value of satisfaction questionnaire scores (1= dissatisfied, 4= satisfied) I- 3.4 C- 3.2 P-value>0.05
Begley,1997 (UK)	NR	NR	• Proportion of patients who had a contact with their GP during study I- 54 C- 74 NV- 79 P-value (<0.01)	NR	Mean compliance[14] I-86 C- 75 NV- 69 P-value 0.0001	% patients where one or more of their medications stopped I-31.1% C- 16% NV- 8% P- value 0.001	NR	NR
Godwin,2016 (CA)	NR	I-18 C- 11 P-value 0.23	NR	NR	NR	NR	• SF-36 (General health) I- 70 C- 69.2 P-value 0.79 • CASP-19 I- 44.5 C- 44.7 P-value 0.84	Mean patient satisfaction with physician care I- 4 C- 3.9 P-value 0.74
Naylor,1999 (USA)	I-11 C-11	I- 49 C- 107 P-value	• Percentage of patients readmitted at least once	NR	NR	NR	• Both groups were similar in mean functional status	Both groups were similar in mean

[14] Mean compliance: mean of the percentages of drugs taken with acceptable compliance by each patient.

		(<0.001)	I- 20.3% (n=36) C- 37.1% (n=69) P-value (<0.001) • Time to first readmission for any reason (for 25% of patients) I- within 133 days C- within 48 days P- value (<0.001) • Total Length of hospitalization I- 270 days C- 760 days P-value (<0.001) • Mean acute care visits: • Physician's office I- 1.5 C- 1.6 P-value 0.59 • Emergency department I- 0.1 C- 0.2 P-value 0.21				measured (P-Value = 0.33) • Measured using Enforced Social Dependency Scale (higher scores on a 10 to 51 scale equal disability) • Mean scores were slightly improved over baseline (from 21.5 to 19.2)	patient satisfaction score (P-value 0.92)
Hanna,2016 (AU)	I-19 C- 3	I- 1850 C- 913 P-value 0.45	• Emergency room admission I- 690 C- 153 P-value 0.16	NR	NR	NR	NR	NR
Rytter,2010 (Denmark)	I-15 C- 20 HR 0.72 95% CI (0.37-1.41)	I- 67 C- 86 P- value 0.03	NR	NR	NR	• Number of patients with adjusted medications: I- 84 C- 63 P- value 0.01	NR	NR

Köberlein-Neu,2016 (DE)	NR	NR	NR	Mean DRP per patient: I- 5.87 C- 6.98 P-value 0.014	NR	• MAI sum score per patient I- 22.27 C- 29.21 P- value (≤0.001) • Mean MAI reduction after 15 months from baseline: ***Cohort1***: from 30.15±24.14 to 14.09±14.80 ***Cohort2***: from 43.27±30.39 to 24.47±16.17 ***Cohort3***: from 26.07±17.33 to 18.44±14.67±	NR	NR

Abbreviations: USA-United States of America, NLD-Netherland, UK-United Kingdom, CA-Canada, DE- Germany, DRPs-drug related problems, C- Control group, I-intervention group, NV- No visit Control group, NR-not reported, , QoL-quality of life, CDM-Chronic Disease Management, D- Difference between end of study and baseline data, CAD- Coronary artery disease, COPD- Chronic obstructive pulmonary disease, CHF- Congestive heart failure, OR- Odd ratio, CI -Confidence interval, PAIS- Pharmacy administration and information system, PCS- Physical component scale, MCS- Mental component scale, GDS- Geriatric depression scale, PPT- Physical performance test, MMSE- Mini mental status examination , VAS- Visual analogue scale, OPD- Out patient department, GP- General practitioner , MAI- Medication appropriateness index.

Appendix G: HMR Quality appraisal data

Reviewer Verifier	Ref ID	Author, Year
SM SR	140	Hunt,2018
Risk of bias		
Bias	**Authors' Judgment**	**Support for judgment**
Random sequence generation (Selection bias)	High	• Non randomized design. • The baseline characteristics between groups were significantly comparable in terms of age and number of comorbidities (younger and fewer in the intervention group), also the intervention group had more baseline exacerbations.
Allocation concealment (Selection bias)	Unclear	Insufficient information on how participants were actually allocated to the intervention.
Blinding of participants and personnel (Performance bias)	High	• The intervention group were aware of their assignment to the intervention. • No information on blinding of the personnel.
Blinding of outcome assessment (Detection bias)	Unclear	Insufficient information
Incomplete outcome data (Attrition bias)	Low	90% of the intervention group completed the study. However, it should be noted that there was no power calculations made to estimate the needed sample size of the study and duration of follow up.

Selective reporting (Reporting bias)	Unclear	No protocol found
Other sources of bias	Low	No other sources of bias.
Overall Risk of bias	High	At least one domain is high.

Reviewer Verifier	Ref ID	Author, Year
SM SR	347	Olesen,2014
Risk of bias		
Bias	**Authors' Judgment**	**Support for judgment**
Random sequence generation (Selection bias)	Low	Randomization by means of sealed envelopes.
Allocation concealment (Selection bias)	Low	Quote: " a total of 945 envelopes (315 per patient subgroups) was prepared with each containing a study inclusion code. At the first home visit by a project nurse, patients were asked to select one envelope."
Blinding of participants and personnel (Performance bias)	High	The identity of participants was not blinded to pharmacists and nurses for the complexity of the reported intervention.
Blinding of outcome assessment (Detection bias)	Unclear	Insufficient information
Incomplete outcome data (Attrition bias)	High	Drop out were more frequent and higher for the pharmaceutical care group (n= 62) than control group (n= 51), as a result the needed sample size was not achieved. Also, dropout was more in the intervention group due to " lack of interest".
Selective reporting (Reporting bias)	Unclear	No protocol found
Other sources of bias	Unclear	Dropouts were different in relation to age.
Overall Risk of bias	High	At least one domain is high.

Reviewer Verifier	Ref ID	Author, Year
SM SR	366	Merek,2013
Risk of bias		
Bias	**Authors' Judgment**	**Support for judgment**
Random sequence generation (Selection bias)	Low	Computer assisted randomization
Allocation concealment (Selection bias)	Low	Quote: "Participants were randomly assigned to one of the three study arms, using a computer program developed by the study statistician, before research staff contacted potential participants."
Blinding of participants and personnel (Performance bias)	High	Healthcare providers were not blinded due to the nature of the intervention.
Blinding of outcome assessment (Detection bias)	Unclear	Insufficient information
Incomplete outcome data (Attrition bias)	Low	ITT approach was used for analysis. Quote: "an additional 100 participants were enrolled to account for the expected participant attrition."
Selective reporting (Reporting bias)	Low	Registered protocol: NCT01321853. All outcomes have been reported.
Other sources of bias	High	Potential bias due to higher attrition rate in medicine dispensing machine arm during the first quarter of the study.
Overall Risk of bias	High	At least one domain is high.

Reviewer Verifier Verifier	Ref ID	Author, Year
SM SR	545	Hugtenburg,2009
Risk of bias		
Bias	**Authors' Judgment**	**Support for judgment**
Random sequence generation (Selection bias)	High	Pharmacies were not randomized and were able to choose if in the intervention or usual care group. Successive patients were selected for the study.
Allocation concealment (Selection bias)	Unclear	Insufficient information
Blinding of participants and personnel (Performance bias)	High	• The pharmacies are not blinded to the intervention provided. • Quote " The basic pharmaceutical care given by an intervention pharmacist might already have been organised in a more structured fashion."
Blinding of outcome assessment (Detection bias)	Unclear	Insufficient information
Incomplete outcome data (Attrition bias)	Low	• Analysis was performed for all patients enrolled in each group. • Quote: " In both the intervention group, as the control group, no data were missing with respect to the basic characteristics and the intervention measurements."
Selective reporting (Reporting bias)	Unclear	No protocol found
Other sources of bias	High	The pharmacies were not randomized.
Overall Risk of bias	High	At least one domain is high.

Reviewer Verifier	Ref ID	Author, Year
SM SR	603	Aldamiz-Echevarria Iraurgui,2007
Risk of bias		
Bias	**Authors' Judgment**	**Support for judgment**
Random sequence generation (Selection bias)	Low	Randomization by stratification based on services involved: internal medicine, cardiology and short stay.
Allocation concealment (Selection bias)	Low	• Allocation done through closed envelops. • Quote: " The sequence was concealed until interventions were assigned."
Blinding of participants and personnel (Performance bias)	High	Quote: " By the very nature of the intervention being tested, neither the patients taking part in this study nor the homecare unit personnel were blinded to their treatment,.."
Blinding of outcome assessment (Detection bias)	Low	Quote: " ...the staff attending them in other services were aware of whether patients belonged to programme or control group. Events assignment was, therefore, blinded."
Incomplete outcome data (Attrition bias)	Low	ITT approach was used. There were no dropouts from the study
Selective reporting (Reporting bias)	Unclear	No protocol found
Other sources of bias	Low	No information for other bias
Overall Risk of bias	High	At least one domain is high.

Reviewer Verifier	Ref ID	Author, Year
SM SR	615	Lenaghan,2007
Risk of bias		
Bias	**Authors' Judgment**	**Support for judgment**
Random sequence generation (Selection bias)	Unclear	Randomization by third party, insufficient information.
Allocation concealment (Selection bias)	Unclear	Insufficient information
Blinding of participants and personnel (Performance bias)	High	Due to the nature of the intervention, participants were not blinded. However, no information regarding personnel blinding.
Blinding of outcome assessment (Detection bias)	Unclear	Insufficient information
Incomplete outcome data (Attrition bias)	Low	ITT approach was used. Primary outcome data were available to 99%.
Selective reporting (Reporting bias)	Unclear	No protocol found
Other sources of bias	Low	No information for other bias
Overall Risk of bias	High	At least one domain is high.

Reviewer Verifier	Ref ID	Author, Year
SM SR	667	Holland, 2005
Risk of bias		
Bias	**Authors' Judgment**	**Support for judgment**
Random sequence generation (Selection bias)	Low	Quote: "we used third party telephone randomization on a computer generated sequence in blocks of varying length. Randomization was stratified by abbreviated mental test score and whether the patient was living alone."
Allocation concealment (Selection bias)	Low	Third party did the randomization.
Blinding of participants and personnel (Performance bias)	High	Quote: " Because of the nature of the intervention, no "placebo" could be provided. Participants were told after randomization which group, they were in."
Blinding of outcome assessment (Detection bias)	Unclear	Insufficient information. Data for primary outcome was obtained from hospital statistics, but no information if the statistician was aware of group assignment.
Incomplete outcome data (Attrition bias)	Low	ITT approach was used for analysis. 3% of participants were lost to follow up or withdrew.
Selective reporting (Reporting bias)	Low	Registered protocol: ISRCTN0681317. All outcomes have been reported.
Other sources of bias	Unclear	The two groups showed possible baseline imbalance related to comorbidities
Overall Risk of bias	High	At least one domain is high.

Reviewer Verifier	Ref ID	Author, Year
SM SR	713	Stewart, 2002
Risk of bias		
Bias	**Authors' Judgment**	**Support for judgment**
Random sequence generation (Selection bias)	Low	Information related to randomization was given in their original publication (reference no. 4: randomization by a third-party using computer generated system).
Allocation concealment (Selection bias)	Low	Randomization by a third party who was not aware of patients' profile.
Blinding of participants and personnel (Performance bias)	Unclear	Insufficient information
Blinding of outcome assessment (Detection bias)	Unclear	Insufficient information
Incomplete outcome data (Attrition bias)	Low	Analysis included more than 80%.
Selective reporting (Reporting bias)	Unclear	No protocol found
Other sources of bias	High	Potential selection bias due to the fact that sample was from a population with disproportionate number of elderly, socially disadvantaged persons with higher admission rate.
Overall Risk of bias	High	At least one domain is high.

Reviewer Verifier	Ref ID	Author, Year
SM SR	756	Stewart,1998
Risk of bias		
Bias	**Authors' Judgment**	**Support for judgment**
Random sequence generation (Selection bias)	Unclear	No information on how randomization was actually achieved.
Allocation concealment (Selection bias)	Low	Third party did the randomization.
Blinding of participants and personnel (Performance bias)	High	Due to nature of intervention participants were probably aware of their group assignment. No information on blinding of personnel.
Blinding of outcome assessment (Detection bias)	Unclear	Insufficient information
Incomplete outcome data (Attrition bias)	Low	• ITT approach was used. • Quote:" Seven assigned to HBI (14%) did not receive a home visit because of early readmission or withdrawal of consent."
Selective reporting (Reporting bias)	Unclear	No protocol found
Other sources of bias	Low	No information for other bias
Overall Risk of bias	High	At least one domain is high.

Reviewer Verifier	Ref ID	Author, Year
SM SR	805	Sidel, 1990
Risk of bias		
Bias	**Authors' Judgment**	**Support for judgment**
Random sequence generation (Selection bias)	Low	They used randomization tables to assign the participants into control or intervention groups
Allocation concealment (Selection bias)	Unclear	Insufficient information
Blinding of participants and personnel (Performance bias)	Unclear	Insufficient information
Blinding of outcome assessment (Detection bias)	Unclear	Insufficient information
Incomplete outcome data (Attrition bias)	Low	• Quote: "Intervention by pharmacist visiting the home was accomplished in 80% of the high risk group." • Assessment was accomplished for 81% of intervention group and 73% of control group.
Selective reporting (Reporting bias)	Unclear	No protocol found
Other sources of bias	Low	No information for other bias
Overall Risk of bias	Unclear	One or more domains are unclear. No domain is high.

Reviewer Verifier	Ref ID	Author, Year
SM SR	1674	Nazareth,2001
Risk of bias		
Bias	**Authors' Judgment**	**Support for judgment**
Random sequence generation (Selection bias)	Low	Quote: "Patients were independently randomized by the heath authority's central community pharmacy office using computer- generated random numbers. We used block randomization, stratified by trial centre, to ensure equal numbers of participants in each randomized group."
Allocation concealment (Selection bias)	Low	Quote: "The research assistant remained blinded to the allocation of the patient. The allocation code held by the randomization centre was revealed only at the end of the study."
Blinding of participants and personnel (Performance bias)	High	Participants were not blinded, no information on blinding of personnel.
Blinding of outcome assessment (Detection bias)	Low	Research assistant collected hospital/outpatient data. Outcome related to medication review was assessed by a blinded pharmacist.
Incomplete outcome data (Attrition bias)	Low	Research assistant followed up with the physicians at each follow up and with letters or phone calls when no answer was received. Also, the mortality data was retrieved from the patients' carers, their general practitioner and health authority.

		91% of follow up data were collected and recorded. More than 80% were analyzed in each group.
Selective reporting (Reporting bias)	Low	Registered trial: ISRCTN66700837
Other sources of bias	Low	No information for other bias
Overall Risk of bias	High	At least one domain is high.

Reviewer Verifier	Ref ID	Author, Year
SM SR	1709	Begley,1997
Risk of bias		
Bias	**Authors' Judgment**	**Support for judgment**
Random sequence generation (Selection bias)	Low	They used randomization groups A,B, and C rather than the actual identity of the group
Allocation concealment (Selection bias)	Low	Quote: "The recruiting member of staff was blinded to the identity of the groups and was required to allocate consecutive patients into group A,B, OR C ".
Blinding of participants and personnel (Performance bias)	High	Given the nature of the intervention, participants were not blinded, no information on blinding of personnel.
Blinding of outcome assessment (Detection bias)	Unclear	Insufficient information
Incomplete outcome data (Attrition bias)	Low	• Quote: " When patients who completed the study were compared with those who did not, no statistically significant differences were found between the groups regarding the number of prescribed drugs, their home circumstances or responsibility for medication." • More than 80% in each group completed the study and were included in analysis.
Selective reporting (Reporting bias)	Unclear	No protocol found
Other sources of bias	Low	No information for other bias
Overall Risk of bias	High	At least one domain is high.

Reviewer Verifier	Ref ID	Author, Year
SM SR	1766	Godwin, 2016
Risk of bias		
Bias	**Authors' Judgment**	**Support for judgment**
Random sequence generation (Selection bias)	Unclear	Randomization schedule was used, but no information about the details.
Allocation concealment (Selection bias)	Low	The randomization was carried by the project coordinator rather than the research assistant that interviewed the patients
Blinding of participants and personnel (Performance bias)	High	• Participants dropped out of the study because they knew they are in the control arm. • Research assistant was aware of group assignments.
Blinding of outcome assessment (Detection bias)	High	Outcomes were assessed by the RA who was aware of group assignments.
Incomplete outcome data (Attrition bias)	High	Lost to follow up was high in both groups at 6 months (23.3%). Analysis was done for 78.5% in the intervention arm and 74.8% in the control arm.
Selective reporting (Reporting bias)	Unclear	No protocol found
Other sources of bias	High	• Low response rate (45%). • Physicians chose who to approach. • Intervention arm was more educated and satisfied with their healthcare than control arm.
Overall Risk of bias	High	At least one domain is high.

Reviewer Verifier	Ref ID	Author, Year
SM SR	2304	Naylor,1999
Risk of bias		
Bias	**Authors' Judgment**	**Support for judgment**
Random sequence generation (Selection bias)	Low	The project manager randomized the participants to the study groups using a computer-generated algorithm
Allocation concealment (Selection bias)	Low	Quote: " Patients were enrolled in the study within 48 hours of hospital admission by research assistants (RAs) blinded to study groups and hypothesis."
Blinding of participants and personnel (Performance bias)	Unclear	Insufficient information
Blinding of outcome assessment (Detection bias)	Low	Quote: " Outcome data were collected by RAs blinded to study groups and hypothesis ."
Incomplete outcome data (Attrition bias)	Low	• ITT approach was used. • Quote: " The 262 patients who completed the study didn't differ significantly from the 101 persons in the attrition group whether in sociodemographic variables and severity of illness measures." • Intervention group attrition rate was 30% compared with 26%for the control group with P-value of 0.26
Selective reporting (Reporting bias)	Unclear	No protocol found
Other sources of bias	Low	No information for other bias
Overall Risk of bias	Unclear	One or more domains are unclear. No domain is high.

Reviewer Verifier	Ref ID	Author, Year
SM SR	2746	Hanna,2016
Risk of bias		
Bias	**Authors' Judgment**	**Support for judgment**
Random sequence generation (Selection bias)	High	No randomization
Allocation concealment (Selection bias)	High	No allocation concealment given the design of the study.
Blinding of participants and personnel (Performance bias)	High	Participants in the intervention arm agreed to receive the intervention, so they were aware. No information on blinding of personnel.
Blinding of outcome assessment (Detection bias)	Unclear	Insufficient information
Incomplete outcome data (Attrition bias)	High	81% (398/487) in the intervention arm completed the study, but less than 50% (118/253) in the control arm did.
Selective reporting (Reporting bias)	Unclear	No protocol found
Other sources of bias	High	Other bias arising from non-randomization and lost to follow up reasons.
Overall Risk of bias	High	At least one domain is high.

Reviewer Verifier	Ref ID	Author, Year
SM SR	2909	Rytter,2010
Risk of bias		
Bias	**Authors' Judgment**	**Support for judgment**
Random sequence generation (Selection bias)	Low	Quote:" Randomization was done using a computer generated algorithm with numbers in closed envelopes which were opened at the inclusion interview."
Allocation concealment (Selection bias)	Low	Hospital staff were not informed about randomization. The GPs did not know about the enrolment of control patients until the evaluation.
Blinding of participants and personnel (Performance bias)	Low	Neither the doctors nor the nurses were blinded. However, since primary outcome was hospital readmission this is unlikely to bias the results.
Blinding of outcome assessment (Detection bias)	Low	Data on readmission rate and economic data were based on register data which were obtained for all randomized patients
Incomplete outcome data (Attrition bias)	Low	ITT approach. Analysis included more than 87% in each group.
Selective reporting (Reporting bias)	Unclear	No protocol found
Other sources of bias	High	• The data is highly dependent on patients interview which in that case exclude frail elders. • Potential bias due to baseline imbalances: more CVD in intervention group. • Dropout had significantly lower functional ability and lower self-rated health. • Since GPs and nurses were not blinded could have compromised the results.
Overall Risk of bias	High	At least one domain is high.

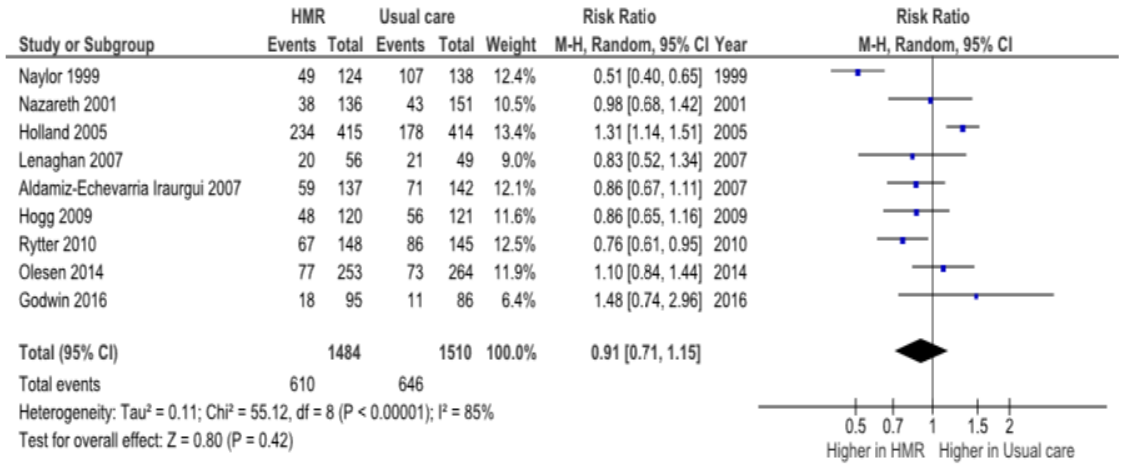
Reviewer Verifier	Ref ID	Author, Year
SM SR	3586	Köberlein-Neu,2016
Risk of bias		
Bias	**Authors' Judgment**	**Support for judgment**
Random sequence generation (Selection bias)	Unclear	Details of randomization not given.
Allocation concealment (Selection bias)	Low	The cohort allocation was disclosed only at the time of the changeover
Blinding of participants and personnel (Performance bias)	High	In determining the MAI score, Quote: "the pharmacist had been blinded when calculating scores as to which cohort a patient was allocated to, but they were involved in some cases in conducting the medication reviews."
Blinding of outcome assessment (Detection bias)	Low	Quote: " Two pharmacists separately evaluated each patients' MAI score. They were blinded with regard to the patients' group allocation."
Incomplete outcome data (Attrition bias)	Low	ITT approach was used. More than 81% in each group were included in ITT analysis (eFigure 2).
Selective reporting (Reporting bias)	Low	Registered protocol (ISRCTN41595373). Primary outcome reported as per protocol. Secondary outcomes reported partially.
Other sources of bias	High	• Selection bias is possible, Quote:" The study does , however, include a random regional sample, which includes medical practices that were willing to participate. " • The case number was not sufficient (below the target of 240 patients) for the evaluation of the patient-relevant secondary end points. • Low response rate - only 13/70 GPs (18.6%) responded to invitation. Patients' participation rate was 18.9%.
Overall Risk of bias	High	At least one domain is high.

Reviewer Verifier	Ref ID	Author, Year
SM SR	3587	Hogg,2009
Risk of bias		
Bias	**Authors' Judgment**	**Support for judgment**
Random sequence generation (Selection bias)	Low	Patients were randomized through an automated central telephone system.
Allocation concealment (Selection bias)	Low	Allocation list was generated electronically by TrialStat Corporation and was concealed from all study personnel.
Blinding of participants and personnel (Performance bias)	Low	Quote: "All care providers and patients were blind to the primary outcome measure of the study. Where more than 1 individual in a household was enrolled, all were randomized together to the same arm."
Blinding of outcome assessment (Detection bias)	Unclear	Secondary outcomes (instrumental activities of daily living and self-reported ED department visit) were assessed by a research associate blinded to treatment arms, but insufficient information on outcome assessment for primary outcomes.
Incomplete outcome data (Attrition bias)	Low	• ITT approach was used. • The number of lost to follow up patients were low in both groups.
Selective reporting (Reporting bias)	Unclear	Registered protocol (NCT00238836). Unclear because outcomes are not reported in the protocol.
Other sources of bias	High	Potential bias due to baseline difference between the two groups in terms of age (intervention group were significantly younger, p-value=0.018), self-rated health and receiving home care service (table 3). Potential recall bias.
Overall Risk of bias	High	At least one domain is high.

Appendix H: HMR Meta-analysis (Forest plot)

Hospitalization readmission (Primary outcome)

Forest plot of RCT (included studies)



Appendix I: HMR Meta-analysis (Funnel plot)

Funnel plot of RCT (included studies): Publication bias