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Evaluation of direct-to-patient educational approaches for reducing inappropriate sedative-hypnotic use in community-dwelling older adults

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Résumé

Cette thèse teste l'hypothèse selon laquelle l'initiation du processus de déprescription des benzodiazépines peut être facilité chez les aînés via l'utilisation de documents éducatifs fondés sur des données probantes, soulignant les risques associés à ces médicaments ainsi que les alternatives non pharmacologiques plus sécuritaires. Cette thèse détaille comment nous avons développé, testé et adapté des outils éducatifs destinés aux consommateurs de benzodiazépines en nous basant sur des éléments de la théorie sociale cognitive et de la théorie constructiviste de l'apprentissage. Notre recherche a révélé l'importance du soutien offert par les professionnels de la santé chez les patients intéressés à déprescrire. Les étapes subséquentes de notre programme de recherche visaient à fournir aux aînés l'information nécessaire pour initier la conversation sur la déprescription, et, de façon simultanée, améliorer le niveau de confiance et outiller les professionnel de la santé, pour leur permettre d'assister les patients motivés à arrêter leurs sédatif-hypnotiques.

Nous avons d'abord mené l'essai randomisé par grappes EMPOWER, où nous avons recruté 303 usagers chroniques de benzodiazépines âgés de 65 à 95 ans, dans 30 pharmacies communautaires (15 interventions, n = 148 participants, 15 témoins, n = 155). Une analyse préliminaire de l'effet de l'intervention sur la perception du risque associé aux benzodiazépines chez les participants a révélé que 45,1% de ceux ayant reçu l'intervention EMPOWER avaient signalé une augmentation du risque perçu, ce qui est associé à une meilleure acquisition des connaissances, à un changement des croyances, à une dissonance cognitive, à un sentiment d'auto-efficacité accru et à une plus grande intention d'entamer la conversation sur la cessation du médicament. Après 6 mois, 27% des patients du groupe d'intervention avaient cessé leur benzodiazépine contre 5% des témoins (différence de risque 23%, IC 95% 14-32%, ICC 0,008, NNT = 4). Aucun facteur de risque n'influençait l'effet de l'intervention.

Subséquemment, nous avons cherché à mieux comprendre les raisons pour lesquelles l'intervention avait échoué ou réussi chez certains participants, afin de guider la recherche future. Nous avons vérifié si les patients avec un déficit cognitif léger avaient autant bénéficié de l'intervention que les patients avec une cognition normale. Une analyse post hoc de tous les participants ayant complété l'étude EMPOWER (n =

261) n'a révélé aucune différence significative, l'arrêt des benzodiazépines ayant été noté chez 39 (32,0% [24.4,40.7]) participants avec déficit cognitif léger et chez 53 (38,1% [30.5,46.4]) participants avec une cognition normale (OR ajusté 0,79, IC 95% [0.45-1.38]). Nous avons ensuite mené une évaluation réaliste qui a révélé que l'intervention avait réussi à motiver 167 participants (n = 64%) à déprescrire, cela ayant été démontré par l'amélioration du niveau de connaissances et un sentiment d'inquiétude accru quant à la prise de benzodiazépines. La déprescription était plus souvent vouée à l'échec chez les participants s'il y avait un manque de support offert par un professionnel de la santé, si l'accent était mis sur la qualité de vie à court terme, ou en présence d'intolérance aux symptômes de sevrage ou de perception défavorable de son niveau de santé.

En se basant sur les défis observés dans l'essai EMPOWER, nous avons cherché à éliminer certains des obstacles à la déprescription de sédatif-hypnotiques, ciblant spécifiquement la réticence des professionnels de la santé à soutenir les patients dans le processus de déprescription. L'intervention dans l'essai D-PRESCRIBE consistait en une approche éducative en deux volets dirigés par le pharmacien auprès des patients et des médecins, via la distribution de la brochure EMPOWER aux patients et d'une opinion pharmaceutique destinée aux prescripteurs. Nous avons développé un modèle standard d'opinion pharmaceutique fondé sur des données probantes, testé auprès d'un échantillon de 32 médecins et de 61 pharmaciens. Via révision du prototype, un modèle final a été obtenu par consensus. Dans le cadre de l'étude randomisée par grappes D-PRESCRIBE, nous avons recruté 299 utilisateurs chroniques de sédatif-hypnotiques âgés de 66 à 96 ans, provenant de 68 pharmacies communautaires (34 interventions, n = 145 participants, 34 témoins, n = 154). Après 6 mois, 44% des patients du groupe d'intervention avaient cessé leur sédatif-hypnotique, contre 6,5% chez les contrôles (différence de risque 38%, IC 95% 24-48%, ICC 0,012, NNT = 3). Les taux de cessation de D-PRESCRIBE étaient significativement plus élevés que ceux observés dans l'étude EMPOWER. Les résultats suggèrent que l'ajout d'une composante éducative chez les prescripteurs réduit leur réticence à soutenir un patient motivé par le processus de déprescription.

Mots-clés : Benzodiazépine, personnes âgées, pharmacie communautaire, étude randomisée par grappes, éducation du patient, soins axés sur le patient, pratique collaborative, ordonnances potentiellement non-appropriées.

Abstract:

This thesis tests the hypothesis that older adults can enable the initiation of benzodiazepine deprescribing when equipped with evidence-based educational material about drug harms and safer non-pharmacological alternatives. The work described in this thesis explains how we developed, tested, refined and adapted educational tools for benzodiazepine consumers, based on elements of social cognitive theory and constructivist learning theory. Our research revealed that health care provider support is required to assist patients in following through on their initial desire to deprescribe. Subsequent steps in my research program aimed to simultaneously equip older adults with the information they need to drive deprescribing conversations, while also boosting health care provider support and self-efficacy for enabling motivated patients to successfully discontinue sedative-hypnotics.

We first conducted the EMPOWER cluster randomized trial, where we recruited 303 chronic users of benzodiazepine medication aged 65-95 years, recruited from 30 community pharmacies (15 intervention, n=148 participants; 15 control, n= 155). A preliminary analysis was conducted to evaluate the intervention's effect on participants risk perception about benzodiazepines through knowledge acquisition and change in beliefs. We showed that 45.1% of participants receiving the EMPOWER intervention reported an increased perceived risk, which was associated with better knowledge acquisition, change in beliefs, occurrence of cognitive dissonance, increased self-efficacy and increased intent to discuss discontinuation. Six-months outcomes from the trial revealed that 27% of the intervention group had discontinued benzodiazepine use compared to 5% of controls (risk difference 23%, 95% CI 14-32%, ICC 0.008, NNT=4) with no risk factor characteristics interacting with the effect of the intervention.

We then aimed to gain a better understanding as to why the intervention failed or succeeded for certain participants in order to guide future research. We tested whether patients with mild cognitive impairment (MCI) received the same benefits from the intervention as patients with normal cognition. A post-hoc analysis of all participants

completing the EMPOWER study (n=261) revealed no significant differences, with benzodiazepine discontinuation occurring in 39 (32.0% [24.4,40.7]) participants with MCI and in 53 (38.1% [30.5,46.4]) with normal cognition (aOR 0.79, 95% CI [0.45–1.38]). We then conducted a realist evaluation, which showed that the intervention triggered the motivation to deprescribe among 167 (n=64%) participants, demonstrated by improved knowledge and increased concern about taking benzodiazepines. Contexts where the deprescribing mechanisms failed included lack of support from healthcare providers, short-term quality of life focus, intolerance to withdrawal symptoms and perceived poor health.

Based on the challenges observed in the EMPOWER trial, we aimed to address some of the observed barriers to sedative-hypnotic deprescribing, specifically targeting healthcare provider reluctance to support patients in the deprescribing process. The intervention in the subsequent D-PRESCRIBE trial consisted of a two-pronged educational approach brokered by the pharmacist to patients and physicians, through distribution of the EMPOWER brochure to patients and a pharmaceutical opinion to prescribers. We developed a standardized template for an evidence-based pharmaceutical opinion, which we tested in a convenience sample of 32 primary care physicians and 61 primary care pharmacists. The content and format of the prototype underwent revisions until a consensus was reached on a final recommended template. We then conducted the D-PRESCRIBE cluster randomized trial, where we recruited 299 chronic sedative-hypnotic medication users aged 66-96 years, from 68 community pharmacies (34 intervention, n=145 participants; 34 control, n= 154). Six-months outcomes yielded a 44% discontinuation rate in the intervention group compared to a 6.5% rate in the controls (risk difference 38%, 95% CI 24-48%, ICC 0.012, NNT=3) with risk profile characteristics interacting with the effect of the intervention. Discontinuation rates in D-PRESCRIBE were significantly higher than those observed in the EMPOWER trial. Process outcomes from the trial suggest that the added value of adding an educational component to prescribers is that it decreases reluctance to support motivated patients to attempt and succeed at deprescribing.

Keywords: Benzodiazepine, older adults, community pharmacies, cluster-randomized trial, patient education, patient-centered care, collaborative practice, inappropriate medications.

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List of acronyms

D-PRESCRIBE → **D**eveloping **P**harmacist-led **R**esearch to **E**ducate and **S**ensitize **C**ommunity **R**esidents to the **I**nappropriate prescription **B**urden in the **E**lderly

EMPOWER → **E**liminating **M**edications **T**hrough **P**atient **O**wnership of **E**nd **R**esults

List of abbreviations

aOR → Adjusted odds-ratio

aHR → Adjusted Hazards-ratio

BMQ → Beliefs about Medications Questionnaire

C-M-O → Context-Mechanism-Outcome

DSM → Diagnostic and Statistical Manual of Mental Disorders

DTSQ → Diabetes Treatment Satisfaction Questionnaire

FDA → Food and Drug Administration

GABA → Gamma-Aminobutyric acid

GAI → Geriatric Anxiety Index

GEE → Generalized Estimating Equations

HR → Hazards-Ratio

ICC → Intra-cluster Correlation Coefficient

ICD → International Statistical Classification of Diseases and Related Health Problems

ICPC → International Classification of Primary Care

MMSE → Mini-Mental State Examination

MoCA → Montreal Cognitive Assessment

NNT → Number-Needed-to-Treat

OR → Odds-ratio

PHQ → Patient Health Questionnaire

RE→ Realist Evaluation

RCT → Randomized Controlled Trial

RR → Relative Risk

SF → Short Fort Health Survey

SMAF → Functional Autonomy Measurement System

VES → Vulnerable Elders Survey

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In the same way that this thesis focuses on the concept of collaboration, these projects would have never been materialized without the help of many individuals. I would first like to thank Dr. Cara Tannenbaum who acted as my supervisor and the principal investigator of the studies in this thesis and who trusted to oversee the D-PRESCRIBE trial. I would like to thank Dr. Tannenbaum for her passion for research, for her expertise, for her constant support and for the many opportunities she has provided me. I would like to thank Dr. Lyne Lalonde and Dr. Sylvie Perreault for their support, encouragement, and oversight as members of my research committee. I would also like to thank Dr. Robyn Tamblyn, Dr. Andrea Benedetti and Dr. Sara Ahmed for the roles they played as co-investigators of the clinical trials in this study. It would have been impossible to accomplish these studies without the precious help of other members of the team. I would like to thank Joëlle Dorais, Isabelle Reid, Danielle Clément, Mira Jabour, Céline Morisette, Liliane Celifoni and Marie-Ève Lavoie who worked extremely hard to collect data from patients in both studies. Finally, I would like to thank Dr. Justin Turner, who shared my office in the final year of my thesis and for his support to finish my graduate studies.

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Chapter 1 – Introduction

The introduction provides a foreword and overview of this thesis and describes my contributions to the EMPOWER and D-PRESCRIBE randomized trials. The overarching aim of my thesis was to develop and evaluate novel patient-centered approaches to deprescribing inappropriate sedative-hypnotic use in older adults in the community.

1.1 Foreword

As medical treatments and living conditions improve, people are living longer, healthier lives. In North America, the number of men and women over the age of 65 is expected to double by 2050.[1] Economists estimate that seniors will account for 40% of all spending on prescribed drugs and 60% of public drug program spending, despite comprising only 15% of the Canadian population.[2] Due to a high prevalence of comorbidities and high medication consumption, older adults are more likely to use multiple medications (polypharmacy) and are at higher risk of drug-drug interactions, drug-disease interactions, and adverse drug events.[3] Sixty-six percent of Canadian seniors have claims for 5 or more drug classes with 27.2% having claims for more than 10 drug classes.[2] Data from Canadian population datasets indicate that more than one-third (38.9%) of seniors use a drug from the Beers list of medications to avoid in the elderly, with 12.4% of seniors having claims for multiple potentially inappropriate medications.[2]

The most commonly used class of potentially inappropriate prescriptions in Canadian older adults is benzodiazepines[2]. The use of benzodiazepine, as well as non-benzodiazepine sedative-hypnotics, is not recommended in older adults, due to an unfavourable ratio of potential benefit to potential harm incurred from use of these drugs. Benzodiazepine users develop psychological and physical dependence to benzodiazepines, and both physicians and consumers have difficulty implementing tapering protocols.[4 5] Interventions to discontinue benzodiazepines that have targeted physicians and pharmacists only, have been relatively unsuccessful, and have been deemed labour-intensive and unfeasible on a large scale.[6 7]

The aim of this thesis was to develop and evaluate new approaches to deprescribing benzodiazepines in older adults by targeting users directly with educational material. At the time of study inception, there were no published studies that targeted the patient as a driver of safer prescribing practices.

1.2 Overview of this thesis

This thesis comprises 10 chapters. Chapter 1 consists of this introduction. Chapter 2 introduces the issues of polypharmacy and the concept of inappropriate prescribing in older adults. Chapter 3 reviews the historical and medicinal context of benzodiazepine use in the general population, including variations over time in the prevalence and predictors of use of these drugs, as well as their associated benefits and harms. Chapter 4 introduces the concept of and barriers to deprescribing and suggests a role for patients as drivers of deprescribing.

Chapter 5 outlines the general and specific objectives of this thesis. Chapter 6 describes detailed methodology related to the development of two novel deprescribing interventions, the design and analysis of the two associated randomized trials aimed at testing these interventions, and the protocol for conducting a realist evaluation alongside the first trial in order to better understand what worked and what failed for which participants, under which contexts.

Chapter 7 includes four published articles, highlighting the results from the EMPOWER (**E**liminating **M**edications **T**hrough **P**atient **O**wnership of **E**nd **R**esults) randomized trial. The first article is titled “A drug education tool developed for older adults changes knowledge, beliefs and risk perceptions about inappropriate benzodiazepine prescriptions in the elderly.” Published in the journal *Patient Education & Counselling* in July 2012, the paper reports changes in knowledge, beliefs, risk perception and self-efficacy among participants having received an educational brochure detailing the risks associated with benzodiazepine use. The second article, published in *JAMA Internal Medicine* in April 2014, titled “Reduction of Inappropriate Benzodiazepine Prescriptions Among Older Adults Through Direct Patient Education:

The EMPOWER Cluster Randomized Trial" compares the effect of the EMPOWER direct-to-consumer educational intervention against usual care on benzodiazepine therapy discontinuation in community-dwelling older adults. The third article, published in *BMC Geriatrics* in January 2017, describes a sub-group analysis of participants from the EMPOWER trial with mild cognitive impairment and is entitled "Use of the EMPOWER brochure to deprescribe sedative-hypnotic drugs in older adults with mild cognitive impairment." Finally, the fourth article, published in *BMJ Open* in May 2017 is titled "A realist evaluation of patients' decisions to deprescribe in the EMPOWER trial," and explores the mechanisms and contexts behind the success or failure of the educational intervention in order to identify potential barriers and enablers to deprescribing, and help direct the refinement of the intervention for the second trial of my thesis. I was the recipient of the Edmund V. Cowdry Award for best scientific presentation by a graduate student at the 34th annual Canadian Geriatrics Society meeting in April 2014 for oral presentation on the EMPOWER trial.

Chapter 8 includes 2 articles from the second randomized trial that I participated in during my thesis, called the D-PRESCRIBE trial (**D**eveloping **P**harmacist-led **R**esearch to **E**ducate and **S**ensitize **C**ommunity **R**esidents to the **I**nappropriate prescription **B**urden in the **E**lderly). The first article titled "Development of an Evidence-Based Pharmaceutical Opinion for Deprescribing" describes the theory and process of refining pharmaceutical opinions to assist in deprescribing. The article is currently accepted for publication in the *Canadian Pharmacists Journal*. The second article "Comparison of Interventions to Reduce Sedative-Hypnotic Prescriptions Among Older Adults in the Outpatient Setting: the EMPOWER vs. D-PRESCRIBE Pragmatic Cluster Randomized Trials" compares the results of the EMPOWER trial to those of the D-PRESCRIBE trial. The latter tested the added value of having the pharmacist send an evidence-based pharmaceutical opinion to the prescribing physician. This article is in preparation and will be submitted to the *Journal of the American Geriatrics Society*. Preliminary results of this analysis won the Best Clinical Abstract at the Annual Scientific Meeting of the American Geriatrics Society in May 2017.

Chapter 9 critically appraises the results from the EMPOWER and D-PRESCRIBE trials as well as the realist evaluation. I discuss the strengths and weaknesses of each study, and implications for community pharmacy practice to reduce the use of inappropriate medication among community-dwelling older adults. Areas for future research, and scale-up and spread of the interventions from a population impact perspective will be described. Finally, chapter 10 wraps up and concludes this thesis.

My thesis provides an original contribution the current body of literature on interventions to enhance medication appropriateness in older adults. The EMPOWER trial received significant acclaim as the first trial to ever investigate the effectiveness of a direct-to-patient educational approach to reducing the inappropriate use of benzodiazepines in older adults. Additionally, this thesis delves into the process and mechanisms underlying the success or failure of the EMPOWER intervention by using a mixed methods realist evaluation of the patient's point of view, another original contribution to the literature in this area. Finally, the subsequent D-PRESCRIBE trial builds on the pitfalls of the EMPOWER trial by involving the pharmacist in the distribution of evidence-based pharmaceutical opinions to physicians to overcome physician resistance to deprescribing. Altogether, my thesis builds on the growing body of evidence showing that pragmatic randomized trials are feasible for testing interventions to promote deprescribing among community-dwelling older adults and provides valuable information on novel educational interventions for reducing benzodiazepine use among seniors.

1.3 My Contribution to the Trials Described in this Thesis

1.3.1 The Empower Trial

I joined Dr. Tannenbaum's team in May 2012 as a Master's student. At that time, approximately two-thirds of the recruitment had been completed for the EMPOWER trial. I, therefore, had no role in the conception of this study. My Master's project (which I later transitioned into a Ph.D. thesis) was to complete enrolment of the remaining pharmacies, and code and analyze the data from the trial for publication.

More specifically, to gain practical experience in the conduct of clinical trials, I was in charge of personally recruiting the last 10 of the 30 pharmacies for the EMPOWER trial. I called pharmacies to assess their interest in participating and followed up with an in-person visit to explain and confirm their participation in the trial. I also acted as the medical liaison between pharmacies and the trial team. I also served as the intermediary between pharmacies and the Jean Coutu headquarters, who provided the list of eligible trial participants, once pharmacists consented to enroll in the trial. My main task, however, was data cleaning and data analysis. I coded the different outcomes (complete discontinuation of benzodiazepines versus dose reduction or substitution) using the pharmacy claims profiles, and conducted the main quantitative analysis for the study, with oversight from the statisticians on the team. On my own, I subsequently performed the sub-group analysis for participants with cognitive impairment. Having at this time converted my Master's thesis into a Ph.D. thesis (accelerated graduate program at the Faculty of Pharmacy at the Université de Montréal), I spent the next two years learning the methods to conduct a realist evaluation. I applied these quantitative and qualitative approaches for analyzing, interpreting and publishing a realist evaluation of the data from the EMPOWER trial. I am the first author on 3 of the 4 articles included in my thesis on the EMPOWER trial.

1.3.2 The D-PRESCRIBE Trial

Based on my involvement in the early analysis for the EMPOWER trial, I helped conceive the D-PRESCRIBE trial and contributed to the protocol development. I wrote several sections of the grant that was then funded by the Canadian Institutes of Health Research, with Dr. Tannenbaum as Principal Investigator. My Ph.D. project was to lead the D-PRESCRIBE trial from conception to implementation and analysis.

Under Dr. Tannenbaum's supervision and acting as the coordinator for the study, I was involved in all stages of the conduct and analysis of the D-PRESCRIBE trial, including ethics submission processes, development of the evidence-based pharmaceutical opinion, choice of validated measurement tools, questionnaire development, pharmacist recruitment, study flow, analysis of the data, interpretation of

the data, and drafting of both articles included in this thesis for publication as first author. As part of my leadership training, I supervised a team of 3 research assistants for the trial. Co-investigators contributed to this thesis by providing their comments and suggestions on the research methods, statistical analyses and published articles.

Chapter 2 – Polypharmacy and Inappropriate Medications for Older Adults

In this chapter, we briefly introduce the issue of polypharmacy and the concept of inappropriate prescribing in older adults. Over the past three decades, multiple classification schemes have been developed for inappropriate prescribing, including several lists of explicit and implicit criteria for drugs to avoid in the elderly. Benzodiazepines now figure prominently in all classification systems around the world, providing a compelling rationale for why benzodiazepines and their sister z-drugs should be targeted for deprescribing.

2.1 Older adults and polypharmacy

The number of people over the age of 65 in North America will double by the year 2050.[1] With increasing age comes an accumulation of comorbidities.[8] Individuals with 1-2 chronic conditions take 3-4 prescription medications on average, while seniors with three or more chronic conditions take six.[9 10] As a result, prescribing of medications is the most frequent medical intervention physicians perform for older people, and polypharmacy (multiple medications) is common.[11-13] Polypharmacy in older adults is associated with a higher risk of drug-drug interactions, drug-disease interactions, and adverse drug events.[3] Even when controlling for age and the number of chronic conditions, the number of prescription medications is associated with an increased rate of emergency department use in Canada.[10]

Currently, people aged 65 years and older constitute approximately 15% of the population, consume over one-third of all prescription medications,[13] account for 40% of all spending on prescribed drugs, and are responsible for 60% of public drug program expenditures.[2] Nearly two-thirds (65.9%) of seniors have claims for five or more drug classes, and more than one-quarter (27.2%) of seniors has claims for 10 or more drugs.[2] Almost two-thirds of seniors living in long-term facilities use 10 or more different drug classes per day.[2]

Both age and comorbidity-related physiological decline put older people at higher risk of harm from their medications.[14] Changes in pharmacokinetics (what the body does to the drug) and pharmacodynamics (what the drug does to the body) result in increased toxicity.[14 15] For instance, reduced glomerular filtration rate increases the risk of harm from long-acting sulfonylureas amongst others.[16] Higher fat mass can lead to an accumulation of lipid-soluble medications such as diazepam.[14 17] There is an increased susceptibility to cognitive effects from anticholinergic medication.[18] Drug-disease interactions are also common, e.g. the dopaminergic blocking effects of metoclopramide may cause an exacerbation of Parkinson's disease symptoms.[18-20] It comes as no surprise that older Canadians rank concerns about medication side effects highest on their list of health priorities. [21 22]

2.2 Potentially inappropriate medications

Medications are generally thought to offer benefits that outweigh the potential risks to a patient and are thus deemed appropriate to prescribe. However, when the ratio reverses, and potential harms outweigh potential benefits, a medication can be labeled as inappropriate for use in older adults. There are many definitions for drug inappropriateness, including the use of a medication that does not have an indication, the use of excessively large doses, a duration of use that exceeds what is recommended, underuse of a necessary medication, or the use of a medication where the risk of harm outweighs the potential for benefit.[23 24] In this thesis, we will use the following definition of potentially inappropriate medications: "Medications for which potential risks outweigh potential benefits and for which therapeutic alternatives that have a similar or superior efficacy exist."[23-25] In order to target and prevent the use of inappropriate medications, clinicians have to identify which medications may potentially be inappropriate for use in older adults. A number of different explicit and implicit criteria exist for identifying inappropriate medications. [26]

Explicit criteria are dichotomous lists of medications to be used or avoided in the elderly.[26] Explicit lists require less clinical information and have a higher interrater reliability than implicit criteria.[27] Explicit criteria are usually developed through a

modified Delphi technique using an expert panel.[3] Explicit criteria permit easy identification of potentially inappropriate medications in large datasets, as they do not require knowledge of the patient's diagnosis or other clinical information.[28] Inappropriateness in explicit criteria lists represent: medications with an unfavorable benefit to harm profile,[23] medications that are associated with specific measurable harmful outcomes,[29] or medications that once may have been useful, but due to changes in the patient's clinical condition, are now classified as unnecessary or 'futile'.[30] Seven main sets of explicit criteria have been developed internationally[18 25 31-35]. The Beers criteria are the most commonly used explicit criteria, first developed in 1991 in the United States to detect potentially inappropriate medications for elderly nursing home residents.[36] Several iterations ensued, and the list was updated and adapted to community-dwelling seniors. The most recent version released in 2015[18] has over 53 different drug classes listed as always being inappropriate to prescribe, or sometimes being inappropriate to prescribe depending on other clinical factors. Table 1 shows the prevalence of use of Beers list medication by seniors in Canada.

Table 1: *Rate of use of Beers list medication among Canadian older adults in 2012*[2]

Age group	Percentage of older adults with any Beers use		Percentage of older adults with chronic Beers use		Percentage of older adults with multiple Beers Drugs	
	Long-Term Care Facility	Community	Long-Term Care Facility	Community	Long-Term Care Facility	Community
65-74	68.3%	32.7%	46.6%	17.9%	40.9%	9.4%
75-84	64.1%	38.2%	39.4%	22.8%	35.2%	11.5%
85+	62.7%	42.7%	34.5%	25.4%	30.7%	13.3%
Total	**63.8%**	**35.8%**	**37.5%**	**20.5%**	**33.3%**	**10.6%**

Implicit criteria, on the other hand, take into account individual patients' clinical situations including patients' comorbidities as well as their beliefs, values and treatment goals. Unfortunately, implicit criteria are time-consuming to apply, as they must be applied by a clinician with good knowledge of the patient and their treatment goals. As a consequence, implicit tools have lower interrater reliability when compared to explicit tools.[27] There exists a wide range of implicit criteria that have been developed, including the Medication Appropriateness Index[37 38], Screening Medications in Older Drug Users

(SMOG)[39], Assess, Review, Minimise, Optimise, Reassess (ARMOR)[40], the Tool to Improve Medications in the Elderly via Review (TIMER)[41], the Good Palliative-Geriatric Practice Algorithm (GPGPA)[42 43] and Assessing Care of Vulnerable Elders-3 (ACOVE-3)[44]. The Medication Appropriateness Index, developed by Hanlon et al. in 1992, is the most frequently used. [38] Ten questions each address different aspects of appropriateness: effectiveness, dosage, directions, practicality, drug-drug interactions, drug-disease interactions, unnecessary duplication, duration, and cost. Each question can be scored as being (a) appropriate, (b) marginally appropriate, and (c) inappropriate.[37] The sum of the scores is added to provide a score for each medication, with the scores of each medications being summed to provide an overall score for the patient.[37 38] The main disadvantage is that the Medication Appropriateness Index takes up to 10 minutes to apply to one patient.[38 45] This can limit its feasibility of use in a clinical setting. The practical limitations around implicit criteria render them unfeasible in most large clinical trials which use administrative drug claims datasets as the primary outcome measure.

2.3 Benzodiazepines and Z-drugs as inappropriate prescriptions

Benzodiazepines (BZDs) first appeared on an explicit list of inappropriate prescriptions in 1991 when Mark Beers, a geriatrician working in long-term care, noticed an association between sedative-hypnotic use and cognitive impairment.[46] The original 1991 Beers criteria categorically recommended avoiding the use of long-acting benzodiazepines; but permitted short-acting benzodiazepines to be used for 4 weeks or less.[36] The most recent version of the Beers list, released in 2015 by the American Geriatrics Society, now recommends avoiding any use of long or short-acting benzodiazepines and Z-drugs in older adults[18]. Table 2 shows the evolution of the status of sedative-hypnotics as an inappropriate prescription since the development of explicit criteria in 1991.

Table 2: *Evolution of the status of sedative-hypnotics as an inappropriate prescription*

Explicit Criteria	Country	Long-acting BZDs	Intermediate-acting BZDs	Short-acting BZDs	Z-drugs	Strength of recommendation	Rationale
Beers 1991[36]	United-States	All use should be avoided	Nightly use for >4 weeks should be avoided	Nightly use for >4 weeks should be avoided	Not included as an inappropriate prescription	Agree that use is inappropriate	Prolonged sedation and increased risk of falls and fractures in older adults
McLeod 1997[25]	Canada	Long-term use should be avoided	Not included as an inappropriate prescription	Not included as an inappropriate prescription	Not included as an inappropriate prescription	Agree that long-term use of long-acting BZDs is inappropriate	May cause falls, fractures, confusion, dependence and withdrawal
Beers 1997[47]	United-States	All use should be avoided	Use preferable to long-acting BZDs	Use preferable to long-acting BZDs	Not included as an inappropriate prescription	Strongly agree that use of long-acting BZDs is inappropriate	Prolonged sedation and increased risk of falls and fractures in older adults.
Zhan 2001[48]	United-States	Most use should be avoided	Not included as an inappropriate prescription	Not included as an inappropriate prescription	Not included as an inappropriate prescription	Use of long-acting BZDs is likely inappropriate	Prolonged sedation and increased risk of falls and fractures in older adults
Beers 2003[49] **+ Norwegian**	United-States + Norway	All use should be avoided	Lower doses recommended, should not exceed	Lower doses recommended, should not exceed	Not included as an inappropriate prescription	Strongly agree that use of long-acting BZDs and high doses of other	Prolonged sedation and increased risk of falls and fractures in older adults. Lower doses

General Practice Criteria 2009 [35]			suggested maximums	suggested maximums		BZDs is inappropriate	recommended due to increased sensitivity in older adults.
Rancourt 2004[31]	Canada	All use should be avoided	Nightly use for >4 weeks should be avoided	Nightly use for >4 weeks should be avoided	Not included as an inappropriate prescription	Agree that use is inappropriate	Prolonged sedation and increased risk of falls and fractures in older adults
Laroche 2007[32]	France	All use should be avoided	Lower doses recommended, should not exceed half the normal dose	Lower doses recommended, should not exceed half the normal dose	Not included as an inappropriate prescription	Strongly agree that use of long-acting BZDs and high doses of other BZDs is inappropriate	Increased likelihood of adverse events in older adults
Winit-Watjana Criteria 2008[50]	Thailand	All use should be avoided	Long-term use associated with risks but can be appropriate	Long-term use associated with risks but can be appropriate	Not included as an inappropriate prescription	Agree that long-term use of all BZDs contains risk but is sometimes appropriate	Increased risk of sedation and fall in older adults
STOPP/START 2008[51]	Ireland	Use over 4 weeks should be avoided	Not included as an inappropriate prescription	Not included as an inappropriate prescription	Not included as an inappropriate prescription	Strongly agree that use of long-term BZDS exceeding 4 weeks is inappropriate	Increased risk of sedation and fall in older adults

Beers 2012 [52]	United-States	All use should be avoided	All use should be avoided	All use should be avoided	Not included as an inappropriate prescription	Strongly agree that use of BZDs is inappropriate other than exceptional circumstances	Increased risk of cognitive impairment, delirium, falls fractures and motor vehicle crashes in older adults
STOPP/ START 2015[33]	Ireland	Use over 4 weeks should be avoided	Use over 4 weeks should be avoided	Use over 4 weeks should be avoided	Use over 4 weeks should be avoided	Strongly agree that use exceeding 4 weeks is inappropriate	Increased risk of sedation and fall in older adults
Beers 2015[18]	United-States	All use should be avoided	All use should be avoided	All use should be avoided	All use should be avoided	Strongly agree that use is inappropriate	Increased risk of cognitive impairment, delirium, falls fractures and motor vehicle crashes in older adults

It is important to note that several of the explicit criteria lists have not been updated since their inception. For example, the McLeod criteria[25] were published in Canada in 1997, but have not been updated since, which is why Canada now uses the Beers criteria. While developed specifically for the American healthcare system, the use of the Beers criteria can be easily adapted to medications available in the Canadian healthcare system, so offers the best comparison across published studies.

With benzodiazepines and their sister z-drugs are now featured on every single list of drugs to avoid in the elderly, from Thailand to North America, it behooves us to take a closer look at the rise and fall of these highly prevalent sedative-hypnotic medications among older adults, from both a historical, medicinal and drug safety context.

Chapter 3 – Benzodiazepines

This second chapter provides an overview of the benzodiazepine drug class from a biopsychosocial perspective. We describe the prevailing historical and social context at the time benzodiazepines were first introduced to the market. We also review the pharmacological properties of benzodiazepines and their medical indications. Our aim is to explain how benzodiazepines came to be, what they are, how they work, and why their use is so prevalent. We then summarize the pharmacoepidemiology literature to illustrate a growing awareness of the risk of harms associated with this drug class. A thorough understanding of the cultural context behind the rise and fall of benzodiazepines is critical for addressing the challenges associated with the current overuse of these drugs in the older population, and many of the barriers to deprescribing.

3.1 Benzodiazepines – Historical and medicinal context

3.1.1 The rise of benzodiazepines

In the 1940s and 50s pharmaceutical companies were keenly interested in finding better tranquilizers. Until then, the only drugs available to treat depression, insomnia and anxiety were reserpine, chloral hydrate and barbiturates.[53] Use of all three of these drug classes was associated with many side effects, ranging from mild symptoms such as nausea or confusion to fatal accidental and suicidal overdoses in the case of barbiturates.[54] [55] Additionally, chloral hydrate and barbiturate use was limited due to concerns about dependence.[55]

In 1955, Leo Sternbach discovered the first benzodiazepine, chlordiazepoxide, while working as a chemist for Hoffman-La Roche.[54] Chlordiazepoxide had sat on his workbench for more than 20 years and had never been tested as a sedative-hypnotic.[54] [56] When asked to find a new sedative-hypnotic to replace the barbiturates, Sternbach decided to test this compound, RO-5-0690, and within a few days, he found that it demonstrated properties as an anticonvulsant, sedative and muscle relaxant. By 1960, Hoffman-La Roche marketed this new drug as Librium® while also experimenting with

molecular modifications for enhanced activity.[56] [57] Sternbach's efforts at Hoffman-La Roche resulted in the development and marketing of an improved and stronger benzodiazepine known as Valium® (diazepam) in 1963.[56]

Sales of benzodiazepines soon skyrocketed, fuelled by two main factors: 1) enthusiasm for these new tranquilizers based on their relative safety profile and 2) social and cultural pressure. Physicians quickly found indications other than anti-seizure therapy for benzodiazepines including informal use for insomnia, panic disorders, and phobias as well as the management of alcohol and barbiturate withdrawal.[58-60] Benzodiazepines proved effective for previously untreated conditions such as stress, general anxiety, and nervousness.[61] By 1970, benzodiazepines had largely replaced older sedative-hypnotics due to their improved safety profile with respect to causing respiratory depression.[62]

Physicians' enthusiasm for using benzodiazepines was further spurred by societal and cultural pressure. The untimely deaths of Marilyn Monroe in 1962[63] and of Judy Garland in 1969[64] from barbiturate overdoses were highly mediatized, driving patients to seek safer alternatives and underpinning much of the clamour for benzodiazepine prescriptions (see Image 1). The Rolling Stones even wrote a song titled "*Mother's Little Helper,*" depicting the common housewife's new reliance on benzodiazepines during this time period.

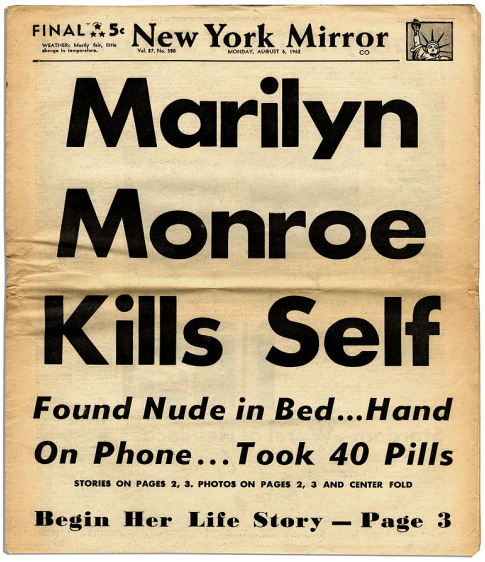

FINAL 5¢ New York Mirror
MONDAY, AUGUST 6, 1962
Marilyn Monroe Kills Self
Found Nude in Bed...Hand On Phone...Took 40 Pills
STORIES ON PAGES 2, 3. PHOTOS ON PAGES 2, 3 AND CENTER FOLD
Begin Her Life Story — Page 3

Image 1: *Front page of the New York Daily Mirror on August 6, 1962*

The representation of benzodiazepines as a miracle drug in movies, books and advertisements on TV, led to the belief that benzodiazepines were a "happiness pill", idealized by mothers and women in particular (see image 2).[65]

Image 2: *Typical benzodiazepine ad from the 1960s*

You can't set her free. But you can help her feel less anxious.

You know this woman.

She's anxious, tense, irritable. She's felt this way for months.

Beset by the seemingly insurmountable problems of raising a young family, and confined to the home most of the time, her symptoms reflect a sense of inadequacy and isolation. Your reassurance and guidance may have helped some, but not enough.

SERAX (oxazepam) cannot change her environment, of course. But it can help relieve anxiety, tension, agitation and irritability, thus strengthening her ability to cope with day-to-day problems. Eventually—as she regains confidence and composure—your counsel may be all the support she needs.

Indicated in anxiety, tension, agitation, irritability, and anxiety associated with depression.

May be used in a broad range of patients, generally with considerable dosage flexibility.

Contraindications: History of previous hypersensitivity to oxazepam. Oxazepam is not indicated in psychoses.

Precautions: Hypotensive reactions are rare, but use with caution where complications could ensue from a fall in blood pressure, especially in the elderly. One patient exhibiting drug dependency by taking a chronic overdose developed upon cessation questionable withdrawal symptoms. Carefully supervise dose and amounts prescribed, especially for patients prone to overdose; excessive prolonged use in susceptible patients (alcoholics, ex-addicts, etc.) may result in dependence or habituation. Reduce dosage gradually after prolonged excessive dosage to avoid possible epileptiform seizures. Caution patients against driving or operating machinery until absence of drowsiness or dizziness is ascertained. Warn patients of possible reduction in alcohol tolerance. Safety for use in pregnancy has not been established.

Not indicated in children under 6 years; absolute dosage for 6 to 12 year-olds not established.

Side Effects: Therapy-interrupting side effects are rare. Transient mild drowsiness is common initially; if persistent, reduce dosage. Dizziness, vertigo and headache have also occurred infrequently; syncope, rarely. Mild paradoxical reactions (excitement, stimulation of affect) are reported in psychiatric patients. Minor diffuse rashes (morbilliform, urticarial and maculopapular) are rare. Nausea, lethargy, edema, slurred speech, tremor and altered libido are rare and generally controllable by dosage reduction. Although rare, leukopenia and hepatic dysfunction including jaundice have been reported during therapy. Periodic blood counts and liver function tests are advised. Ataxia, reported rarely, does not appear related to dose or age.

These side reactions, noted with related compounds, are not yet reported: paradoxical excitation with severe rage reactions, hallucinations, menstrual irregularities, change in EEG pattern, blood dyscrasias (including agranulocytosis), blurred vision, diplopia, incontinence, stupor, disorientation, fever, euphoria and dysmetria.

Availability: Capsules of 10, 15 and 30 mg. oxazepam.

To help you relieve anxiety and tension

Serax®
(oxazepam)

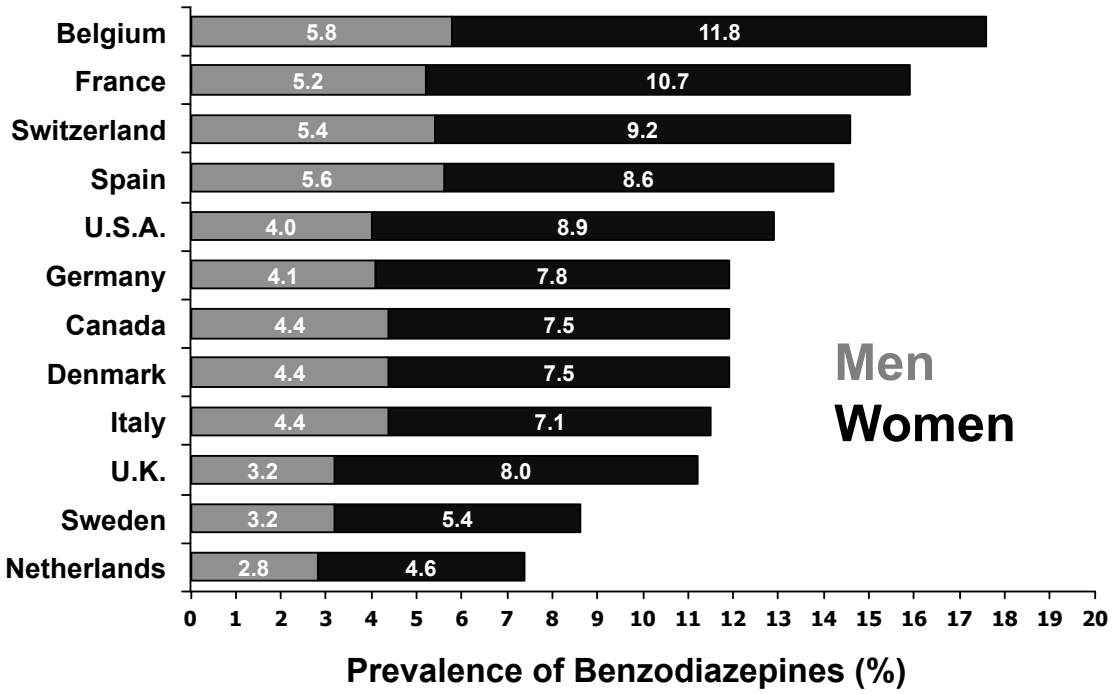
Wyeth Laboratories
Philadelphia, Pa.

Wyeth SERVICE TO MEDICINE

Printed in U.S.A. "Professional" model...

It comes as no surprise that in the mid to late 1970s, benzodiazepines would top the most frequently prescribed drug list, with approximately 40 billion doses consumed annually.[66] Figure 1 depicts a cross-country comparison of benzodiazepine use internationally, published during the early 1980's[67].

Figure 1: *Global sedative-hypnotic use in the early 1980's by sex**



* Adapted from Balter M.B., et al. A cross-national comparison of anti-anxiety/sedative drug use. *Curr Med Res Opin 1984*;8:5-20.

3.1.2 Mechanism of action and indications for benzodiazepines

Fifteen years elapsed before scientists fully understood the mechanism of action of benzodiazepines. Benzodiazepines exhibit an affinity for benzodiazepine receptors which act as a specific site for gamma-aminobutyric acid, the major inhibitory neurotransmitter in the central nervous system.[68-70] Benzodiazepines' central nervous system effects are produced through interaction with a macromolecular protein complex in the neuronal membrane which includes gamma-aminobutyric acid (GABA) receptors, high-affinity benzodiazepine receptors, and chloride channels.[68] Four alpha-receptor subtypes have been identified as benzodiazepine sensitive. Properties of each of these receptors are described in Table 3 [69 70]. The other two alpha-receptor subtypes, alpha 4 and alpha 6, are benzodiazepine insensitive.[71] Overall, benzodiazepines achieve their effects by facilitating GABA-ergic synapses,[72 73] which in turn causes a central reduction of the effect of excitatory neurotransmitters such as serotonin, dopamine, acetylcholine and norepinephrine.[69 70]

Table 3: *Effects of benzodiazepine on GABA receptor by alpha subtype*

Effects	Alpha 1	Alpha 2	Alpha 3	Alpha 5
Sedative	X			
Amnestic	X			
Anxiolytic		X	X	
Muscle-relaxant		X	X	
Anti-convulsive	X			X
Pain relief				X

The pharmacokinetics of benzodiazepines are such that these drugs are widely distributed in the body and accumulate preferentially in lipid-rich areas such as the central nervous system and adipose tissue.[68] Benzodiazepines are categorized as either short-, intermediate-, or long-acting. This refers to how fast the drug or its active metabolites are eliminated from the body.[68] [74] For short acting-benzodiazepines approximate half-lives of the parent compound and its active metabolite range from 1-5 hours; the half-life of intermediate acting benzodiazepines ranges from 5-80 hours, and those of long-acting benzodiazepines can exceed 100 hours.[68] [74] This last point is critical as benzodiazepines or active metabolites with longer elimination half-lives can accumulate with chronic dosing and produce prolonged effects, especially in elderly or obese patients, those with liver disease or with concurrent use of other medications competing for hepatic oxidation.[68]

There are currently 32 different benzodiazepine molecular entities, 14 of which are approved for use in Canada (see table 4).[68] Official indications include the treatment of anxiety disorders, seizure disorders, insomnia, alcohol-withdrawal, panic disorders, perioperative conditions and skeletal muscle spasticity.[68] However, benzodiazepines are also commonly used off-label for the following indications: agitation, restless leg syndrome and in the management of nausea and vomiting associated with chemotherapy or prior to surgical or diagnostic procedures.[68] Other off-label uses mentioned in the literature include the treatment of major depressive disorders[75], parasomnias[76], schizophrenia[77], extrapyramidal syndromes[78] as well as symptomatic

treatment of muscle stiffness, aggression, agitated depression and general pain sensation.[79]

Table 4: *List of benzodiazepines available in Canada*

Drug	Approximate Half-life (hours)	Health Canada approved indications
Long-acting benzodiazepines		
Chlordiazepoxide	100	Anxiety disorders
Clorazepate	100	Anxiety disorders, Panic disorders, Seizure disorders and Alcohol-withdrawal
Diazepam	100	Anxiety disorders, Perioperative medication, Seizure disorders, Skeletal muscle spasticity and Alcohol-withdrawal
Flurazepam	100	Insomnia
Intermediate-acting benzodiazepines		
Alprazolam	12-15	Anxiety disorders and Panic disorders
Bromazepam	8-30	Anxiety disorders
Clobazam	10-46	Seizure disorders
Clonazepam	20-80	Seizure disorders
Lorazepam	10-20	Anxiety disorders, Perioperative medication and Seizure disorders
Nitrazepam	16-55	Insomnia and Seizure disorders
Oxazepam	5-15	Anxiety disorders and Alcohol-withdrawal
Temazepam	10-20	Insomnia
Short-acting benzodiazepines		
Midazolam	1-4	Perioperative medication
Triazolam	1.5-5	Insomnia

Guidelines state that benzodiazepines should be used with caution, and preferably for no longer than 4-6 weeks.[23 51 80 81] Long-term use may rarely be indicated for certain treatment resistant and/or severe chronic psychiatric conditions or in terminal illness. As a general rule, however, long-term use should not have a role in practice as it carries significant risks.[68 82]

3.1.3 Fall from grace

While benzodiazepines enjoyed a long honeymoon period of almost 20 years where they were perceived as a miracle drug, doubts eventually arose concerning their addiction potential and safety profile. The late 1970s and early 1980s saw the rise of multiple reports of benzodiazepine addiction, abuse of large doses, an increase in the risk of serious outcomes and the creation of a black market for these drugs.[83-86] Today, benzodiazepine abuse and dependence issues are well known and documented.[87] Concurrently, clinicians raised concerns about the side effects associated with these medications and more specifically their side effects in older adults.[88] We now know that both short and long-term use of benzodiazepines is associated with an increased risk of cognitive impairment, falls and fractures, dementia, and motor vehicle accidents[23], described in more detail later in this chapter. The negative shift in perception about benzodiazepines as a miracle drug was paralleled in the media by reports of addiction and death due to benzodiazepines in celebrities such as Elizabeth Taylor[89], Anna Nicole Smith[90], and Heath Ledger[91]. Benzodiazepines were also villainized in the media and many popular crime shows featuring their addiction potential and their use as a date-rape drug.[92 93] Despite all this, high rates of benzodiazepine use persisted in the population, especially among older adults who lived through the era when benzodiazepines were being touted as the safest possible option for anxiety and insomnia. [2 94 95] Despite countless attempts to reduce the use of benzodiazpines,[96] long-term use of these medications in older adults has not diminished over time.[97] This overuse has often

***Image 3**: Mediatisation of high profile actor deaths from overdoses including benzodiazepine causes*

been attributed to dependence issues and reticence from both patients[4] and their physicians[5] to discontinue use despite guidelines and evidence-driven data about harms.

3.1.4 Z-hypnotics

Non-benzodiazepines, also referred to as "Z-hypnotics", are a class of psychoactive drugs that are very benzodiazepine-like in nature, introduced to the market in the late 1980s and early 1990s in response to concerns about benzodiazepine use. Z-hypnotics were developed in an attempt to improve benzodiazepines by creating new specific agonists of the GABA receptors but with a safer pharmacokinetic profile.[98] Their clinically attractive properties include short duration of action, non-disturbance of overall sleep architecture, and diminished residual effects during daytime hours.[99] Z-hypnotics have dissimilar or entirely different chemical structures and are therefore unrelated to benzodiazepines on a molecular level. They are divided into three primary groups: imidazopyridines (zolpidem), cyclopyrrolones (zopiclone) and pyrazolopyrimidines (zaleplon).[68] Z-drugs were initially believed to have a better safety profile than benzodiazepines. However, we now know that nonbenzodiazepines pharmacodynamics are almost entirely the same as benzodiazepine drugs because they bind to the same GABA-ergic complex and as such manifest similar benefits, side-effects, and risks.[98]

3.2 Current prevalence of use of benzodiazepines

3.2.1 Prevalence of use in the general population

Concerns about the safety of benzodiazepines, and issues linked to dependence[23], have curbed the rising rate of use in many countries except for the United States and Canada, where increasing trends persist[100-103]. In some countries such as the United Kingdom, the use of benzodiazepines has been replaced by an increase in Z-drug prescriptions.[104] General population prevalence of benzodiazepine use internationally likely ranges between 2.2% to 17.6%[104 105].These estimates vary greatly depending on the population studied and the definition of benzodiazepine use.[104] Long-term use is most commonly defined as six months or longer during a year[106] and

occurs in approximately 25-76% of consumers, which represents 2-7% of the overall general population.[107] [108] A recent study on sedative-hypnotic use in Israel from 2013-2015 found that while only 7% of adults aged 21-64 received at least one prescription for this type of medication, this increased to 32% in those aged 65 and over, and to 49% in those aged 85 and over.[109] As illustrated by this study, as well as most studies on the prevalence of sedative-hypnotics, adults aged 65 and over are the major consumers of such medications[104] and as such will be the focus of the discussion here.

3.2.2 Prevalence of use in older adults

Prevalence of use among older adults is consistently high in developed countries and has been estimated to range from 7% to 43% among adults 65 years and older.[101] [104] [110-114] These estimates have some limitations as they sometimes do not include Z-hypnotics. While some countries such as the United Kingdom[104] and Australia[115] have reported a reduction in the overall use of benzodiazepines in recent years, they note an increase in z-hypnotic use, and as such, long-term use of sedative-hypnotics remains stable. On the other hand, countries such as Israel[109], the United-States[100] [116], Canada[97] and other developed countries have seen a rise in use in recent years. Although a lot of information is available on general incidence and prevalence of benzodiazepine use in the general population at the national level, there is limited information from a lot of these sources as to details on sub-populations such as older adults and/or whether the use was maintained over the long-term. Table 5 presents a sample of varied estimates reported during the past decade of short and long-term sedative-hypnotic use in older adults in various countries.

These snapshots are by no means an all-encompassing picture of sedative-hypnotic use by older adults across the world, however, they clearly illustrate that endemic levels of sedative-hypnotic use exist among older adults in developed countries. Rates of sedative-hypnotic use in older adults remain high and long-term use is most prevalent, particularly among adults aged 85 years and older.

Table 5: *Prevalence of sedative-hypnotic use in older adults in the past decade*

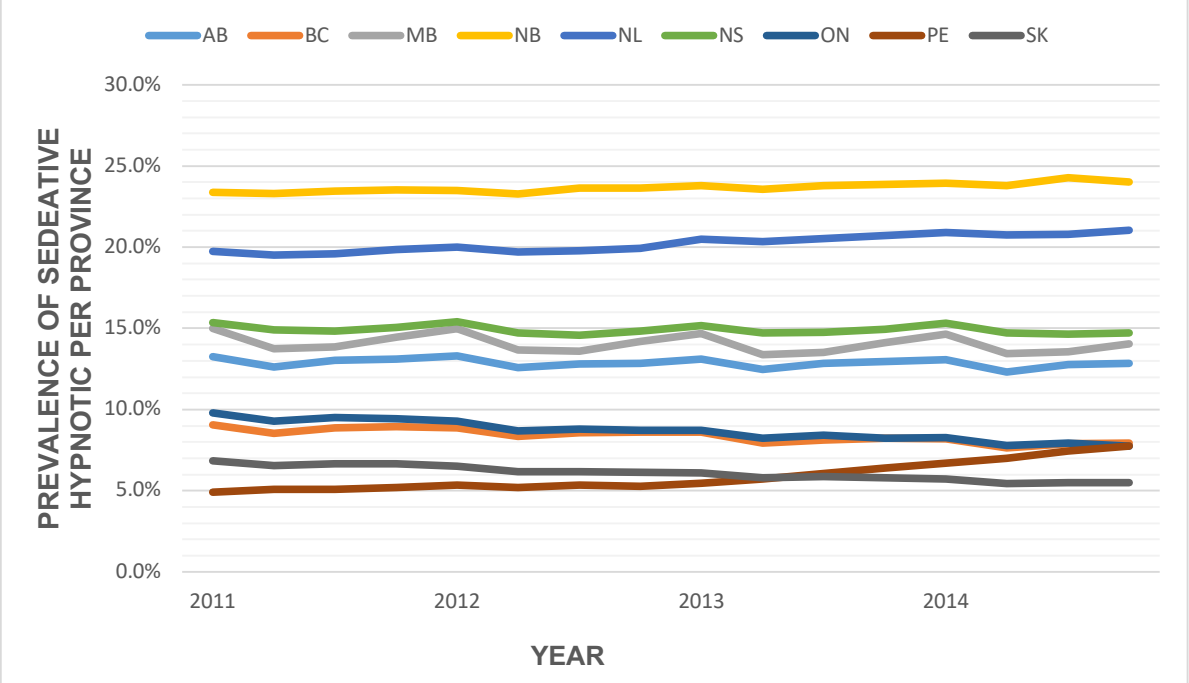
Author, year	Country (medication)	Sample size (setting)	Source of information	Year of follow -up	Prevalence – Any use (age group)	Proportion of long time users (age group)
Cunningham, 2010[117]	Canada (benzodiazepines)	3 934 887 (community)	British Colombia administrative database	2006	37% (70-79) 40% (80+)	56.8% (70-79) 62.5% (80+)
Voyer, 2010[114]	Canada (benzodiazepines)	2 785 (community)	Descriptive study (face to face interviews)	2006	25.4% (65+)	-
Nordfjaern, 2012[118]	Norway (sedative-hypnotics)	58 967 (community)	Nord-Trøndelag Health study	2004-2008	40% (65+)	75% (65+)
Olfson, 2015[101]	United-States (Benzodiazepines)	219 799 647 (all settings)	National electronic medical data	2007-2015	8.7% (65-80)	31.4% (65-80)
Steinman, 2017[109]	Israel (Sedative-hypnotics)	56 808 (all settings)	National electronic medical data	2013-2015	32% (65+) 49% (85+)	59% (65+) 72% (85+)
Turner, 2017[119]	Canada (Sedative-hypnotics)	2 665 (community)	Population survey self-report	2016	16% (65-79) 21.5% (80+)	-
Kimura, 2017[120]	Japan (Sedative-hypnotics)	822 (hospital)	Prospective cohort – pharmacist assessment	2015-2016	37.6% (65+)	-

These snapshots are by no means an all-encompassing picture of sedative-hypnotic use by older adults across the world, however, they clearly illustrate that endemic levels of sedative-hypnotic use exist among older adults in developed countries. Rates of sedative-hypnotic use in older adults remain high and long-term use is most prevalent, particularly among adults aged 85 years and older.

In Canada, the Canadian Institute for Health Information estimates the rate of use of benzodiazepines (including Z-hypnotics) in older adults to be 30.8% in long-term care facilities and 15.1% in the community setting.[2] Rates of chronic use (as defined by >90 days continuous use) of sedative-hypnotics among seniors living in community settings

vary greatly depending on the province, with rates as low as 5.5% in Saskatchewan to upwards of 24% in New-Brunswick[97]. Figure 2 below shows the prevalence of chronic use of benzodiazepines and Z-hypnotics by community-dwelling older adults per province from 2011-2014 [97]. Despite guidelines recommending against long-term use[18] and large-scale efforts from large organizations such as Choosing Wisely Canada to raise awareness and curb unnecessary benzodiazepine use[121], there is no clear trend toward the reduction of the use of these medications in older adults[97]. Estimates from Quebec are not included in the Canadian Institute for Health Information report, however recent studies show that point prevalence rates hover around 20-25% in Quebec[114 122].

Figure 2: *Prevalence of benzodiazepines and Z-hypnotics use in Canadian community dwelling older adults per province from 2011-2014*[97]



3.2.3 Predictors of chronic or long-term use

In order to understand what drives benzodiazepine use, many studies have evaluated usage patterns and predictors of use. Observational register-based studies are considered the best source of data to investigate real-world medicine use[123-125] as administrative data have high external and internal validity[126 127] and make it possible to

conduct reliable individual-level analyses of drug use.[123] [128] There is a lack of consistency in the definitions of chronic or long-term[106] [129], however, most studies define long-term use as 6 months of use during a year.[106] [129] [130] Predictors of long-term use can be divided into three separate categories: characteristics related to individual users, characteristics related to benzodiazepine treatment and characteristics related to prescribers.

Table 6 below presents a summary of predictors associated with long-term use of sedative-hypnotics. The most common patient predictor of long-term use is older age, with 36 of 37 studies finding a positive association.[104] Long-term use is estimated to be 1.6 (95%CI 1.56-1.64) times more likely in adults aged 65-74 and 2.26 (95%CI 2.21-2.31) times more likely in adults aged 75+ when compared to those aged 45-64.[117] Of the eighteen studies that looked at the association of comorbidities with long-term benzodiazepine use, all found the two to be related. [117] The magnitude of association ranged from an OR as low as 1.0, (95% CI, 1.0-1.1) for a Charlson index of 1,[131] and up to OR= 3.61, (95%CI 1.21-4.69) for individuals with at least two confirmed DSM-IV diagnostic categories[129]. Specifically, long-term benzodiazepine use was most commonly related to various psychiatric conditions such as schizophrenia, mood disorders, depression, insomnia and anxiety[117] Gender has also been associated with long-term benzodiazepine use, with most studies showing that women are on average about 33% (OR=1.33, 95%CI 1.32-1.35)[117] more likely than men to use benzodiazepines in both the short and long-term.[117] [132] [133] Other patient characteristics such as lower socio-economic status[117] [131] [134-138] and recent hospitalization[133] [139] [140] are potential predictors of use, however more research is needed to address disparities in various studies.

One drug characteristic suggested to be most strongly associated with long-term use is a low dose of the drug, a trend that while difficult to quantify due to the various definitions, has been observed in 17 different studies.[131] [135] [140-148] Prior use of sedative-hypnotics has also been associated with current long-term use with previous benzodiazepine use being mildly associated with long-term use in individuals with low

previous exposure (< 30 defined daily doses → OR=1.39, 95%CI 1.11-1.76) and very strongly associated in those with previous heavy exposure (>120 defined daily doses → OR=29.78, 95%CI 21.76-40.74)[111] compared to those having never used benzodiazepines.[111 137 142 146 148 149] Among prescriber predictors, a high number of prescribers has been linked to long-term use with patients with more than one prescriber being more than twice as likely to use benzodiazepines for more than three months[141] (OR= 2.21, 95%CI 1.28-3.80).[111 131 141 150-152] The total amount of drug prescribed was also found to be significantly associated with long-term use with patients receiving their prescription from physicians, with the highest rates of benzodiazepine prescription being 1.23 times more likely to become long-terms users (OR= 1.23, 95%CI 1.14-1.32)[144] than those receiving their prescription from an average prescriber.[108 141 144 146 148 153 154] Some preliminary data also indicates that physicians with long-wait times and less frequent access to their patients are more likely to prescribe long-term-use of sedative-hypnotics, however, more research is needed in order to quantify the impact of this effect.[132 144]

Table 6: *Predictors of long-term sedative-hypnotic use*

Predictor	Ratio of studies showing a positive association: all studies reporting the predictor variable	Strength of association*
Individual user characteristics		
Higher age	36/37	Very strong
Female gender	11/17	Strong
Comorbidities	18/18	Very strong
Socioeconomic status (low income)	5/8	Mixed
Hospitalization	2/3	Mixed
Benzodiazepine treatment characteristics		
Use of low and steady dosages	17/20	Strong
High volume of initial prescription	6/8	Strong
Previous benzodiazepine use	4/6	Strong
Prescriber characteristics		
High number of prescribers	6/8	Strong

Long waiting-list	2/2	To be confirmed

* Strength of association is a critical assessment based on the quality, uniformity and amplitude of the observed effect

3.3 Harms associated with sedative-hypnotic use

Large meta-analyses suggest that the number needed to harm for sedative-hypnotic use when compared to placebo is 6 (95%CI; 4.7-7.1) while the number needed to treat is 13 (95%CI; 6.7-62.9).[155 156] This means that for every 13 individuals taking a sedative-hypnotic we can expect one of them to see an improvement in sleep quality, two of them to experience adverse events and the remaining 10 to neither benefit nor be harmed. A strong causal connection between the use of sedative-hypnotics and incident cognitive impairment, falls, fractures and motor vehicle accidents has been established[18]. Additionally, a growing body of evidence points to a moderate causal association with dementia.[157] There is an emerging debate supporting the role of sedative-hypnotics in drug overdoses, infection, cancer, respiratory disease exacerbation and pancreatitis.[158 159]

3.3.1 Cognitive impairment

The use of benzodiazepines as well as non-benzodiazepine drugs is no longer recommended in older adults due to a five-fold increased risk of cognitive impairment.[98 155 160-162] A systematic review of 13 studies revealed moderate-to-large weighted effect sizes across all cognitive domains in long-term benzodiazepine users compared to non-users[163]. Additionally, while patients seem to improve across all cognitive domains following discontinuation, the negative cognitive impact of these drugs on all cognitive domains except sensory processing appears to persist after discontinuation as performance remains below the normal[156]. This suggests that while long-term users may see some cognitive improvement following withdrawal, there may be permanent deficits or deficits that take longer than 6 months to recover[156]. Recent longitudinal studies confirm that sedative-hypnotic users have poorer cognitive performance than non-users, but did not find any evidence that the rate of cognitive decline was greater than in the general population of older adults. [164 165]. We cannot rule out alternative

hypotheses such as the fact that the two main indications for benzodiazepine use (anxiety and insomnia) could be associated with early beta amyloid lesions,[166 167] which could indicate that benzodiazepine use might be associated with poorer cognitive function rather than being the cause.[122] This possibility raises doubt about the validity of this association and also potentially explains why lower than normal performance persists after discontinuation. While the use of benzodiazepines is associated with poorer cognitive performance, it remains unclear whether the drug-related cognitive impairment is permanent or temporary, and whether there are long-term consequences.

3.3.2 Dementia

Despite multiple studies on the link between benzodiazepine use and dementia in older adults, a definitive causal association remains uncertain. Out of the seventeen studies identified and presented in table 7, twelve report an increased risk of dementia in sedative-hypnotics' users[122 168-178], two report mixed results[165 175] and three report no association.[179-181] A recent meta-analysis on 10 of these studies determined that the odds of dementia were 78% higher in older adults who used benzodiazepines than those who did not (OR 1.78; 95%CI 1.33-2.38).[182] One of these studies by Billioti de Gage et al. was able to demonstrate a 51% increased risk for Alzheimer's disease when comparing individuals who had any use of benzodiazepines to those who had never been exposed[122]. This further increased to an 84% increased risk in individuals exposed for 6-months or longer (OR-1.85 95% CI, 1.62-2.08%).[122] Emerging evidence suggests that zolpidem is also associated with dementia, with one study showing a 33% increased risk with any exposure (OR=1.33, 95% CI 1.24–1.41) and a significant dose–response effect for patients with cumulative exposure doses in the higher range of 170 and 819mg/year (OR: 1.65, 95% CI 1.08–2.51).[176] In sub-analyses that included only studies with the highest quality of evidence [122 157 168 170 171 174], and controlled for protopathic bias (when the initiation of the drug occurs in response to a symptom of the disease under study) the strength of association between dementia and benzodiazepines ranged from 1.24 to 2.30[157] Two of the recent studies that found an association argue that the association is due to the prodromal phase, a period of time where patients are issued benzodiazepines to treat prodromal symptoms of early

dementia such as anxiety or insomnia[180 181], and that accounting for this phase nullifies the association. However, one of these studies used first-time use of acetylcholinesterase inhibitors to determine presence of dementia and may not be as reliable[181]. While most studies did not or could not account or stratify the results by indication, as such, it is impossible to determine whether indication acts as an effect modifier in the associations between the use of benzodiazepines and dementia. As with cognitive impairment, we also cannot rule out alternative hypotheses such as the fact that the two main indications for benzodiazepine use (anxiety and insomnia) could be associated with early beta amyloid lesions,[166 167] which could indicate that benzodiazepine use might be an early marker of a condition associated with an increased risk of dementia rather than the cause.[122] Although the evidence points to a relationship between benzodiazepine use and dementia, observational studies cannot yet clarify whether the observed epidemiologic association is a causal effect or the result of unmeasured confounding, leaving us to conclude that more research is required.

3.3.3 Falls & Fractures

Over 30% of older adults experience a fall every year, with rates peaking at 50% in adults over the age of 80.[183] While the etiology of falls is multifactorial[184], benzodiazepines have long been believed to play a significant role in the incidence of falls among older adults.[185] This increased risk of falls and fractures is arguably the most important hazard associated with the use of benzodiazepines and z-drugs in the older population.[18]

Systematic reviews and meta-analyses document an overall risk of benzodiazepine-induced falls of OR 1.57 (95% CI 1.43-1.72).[185 186] Table 8 lists all prospective inquiries seeking to quantify the relationship between benzodiazepines and the risk of falls. A total of nine prospective studies, including one randomized trial, have all found a significant association between benzodiazepine use and falls in adults aged 65 years and older, with odds ratios ranging between 1.20 and 2.83.[187-197] Notable among these

Table 7: *Summary of the evidence on the association between sedative-hypnotics and dementia*

Study/ medications studied	Population n (age) [indication]	Study type (duration)	Dementia measurement	Association between use and dementia (odds ratio or hazard ratio and 95% confidence interval) *	Direction of association
Kungshomen study, Sweden. (Fastbom et al., 1998)[179] Benzodiazepines only	242 (≥75 years) [Any indication]	Cohort (3 years)	Dementia all type, (DSM-III-R criteria), Alzheimer's disease (DSM-III-R criteria), Vascular dementia (Hachinski's scale)	- 3-year benzodiazepine use versus < 3-year use: non-adjusted aOR = 0.40	Inverse association
PAQUID study, France. (Lagnaoui et al., 2002)[168] All sedative-hypnotics	3 777 (≥ 65 years) [Any indication]	Nested case-control study (8 years)	Dementia all type (DSM-III-R criteria)	- Benzodiazepine vs non-users: aOR = 1.7 (95% CI 1.2 - 2.4) - Benzodiazepine or Z-drug vs non-users: aOR = 1.0 (95% CI 0.6 - 1.6) - Former use versus non-users: aOR = 2.3 (95% CI 1.2 - 4.5)	Supports association
Canadian study of Health and Aging, Quebec. (Lagnaoui et al., 2009)[169] Benzodiazepines only	510 women (≥ 65 years) [Any indication]	Nested case-control study (5 years)	Dementia all type (ICD-9 code)	- Current benzodiazepine use versus non-use: aOR = 1.0 (95% CI 0.5 - 2.0) - Former use versus non-use: aOR = 1.5 (95% CI 0.6 - 3.4)	Supports association
National Health Insurance Research database study, Taiwan. (Wu et al., 2009)[170] Benzodiazepines	5 400 (≥ 45 years) [Any indication]	Nested case-control study (8 years)	Dementia all type (ICD-9 code)	- Benzodiazepine vs non-users ○ 90 - 180 days versus < 90 days: aOR = 1.38 (95% CI 1.03 - 1.83) ○ 180 days versus < 90 days: aOR = 1.45 (95% CI 1.18 - 1.79) ○ > 6 months versus <6 months' use: aOR = 1.34 (95% CI 1.09 - 1.64)	Supports association

only					
National Health Insurance Research database study, Taiwan. (Wu et al., 2011)[171] Benzodiazepines only	25 140 (≥ 45 years) [Any indication]	Nested case-control study (11 years)	Dementia all type (ICD-9 code)	- Current use (no discontinuation) versus non-use: aOR = 2.71 (95% CI 2.46 - 2.99) - Dementia risk for former users was reduced as a function of the time since discontinuation: o <1 month aOR = 2.40 (95% CI 1.98–2.92) o 3–6 months aOR = 1.49 (95% CI 1.28–1.74) o 1–2 years aOR = 1.23 (95% CI 1.09–1.40) o >3 years aOR = 1.08 (95% CI 0.98–1.20)	Supports association
Caerphilly prospective study, South Wales. (Gallacher et al., 2012)[172] Benzodiazepines only	1 134 (≥ 45 years) [Any indication]	Prospective cohort (22 years)	Dementia all type, (DSM-IV criteria), Alzheimer's disease (DSM-IV criteria), Vascular dementia (Hachinski's scale)	- All dementia - ever use versus never use: aOR = 2.94 (1.16 - 7.46) - Non-vascular dementia - ever use versus never use: aOR = 3.59 (1.04 - 12.36)	Supports association
PAQUID study, France. (Billioti de Gage et al., 2012)[174] All sedative-hypnotics	1 063 (≥ 65 years) [Any indication]	Prospective cohort (15 years)	Dementia all type (DSM-III-R criteria)	- Benzodiazepine or Z-drug vs non-users: HR = 1.60 (95% CI 1.08 - 2.38)	Supports association
PAQUID study, France. (Billioti de Gage	2 277 (≥ 65 years) [Any	Nested case-control study (20 years)	Dementia all type (DSM-III-R criteria)	- Ever use versus non-use: aOR = 1.55 (95% CI 1.24 - 1.95) - Recent initiation versus non-use:	Supports association

et al., 2012)[174] All sedative-hypnotics	indication]			aOR = 1.48 (95% CI 0.83 - 2.63) - Past initiation versus non-use: aOR = 1.56 (95% CI 1.23 - 1.98)	
National Health Insurance Research data-base study, Taiwan. (Chen et al., 2012)[173] Benzodiazepines only	34 258 (≥ 50 years) [Insomnia]	Retrospective cohort (3 years)	Dementia excluding vascular type (ICD-9 codes)	- Hypnotic BZD + Insomnia vs no hypnotic use + no dementia - All sample: HR = 2.34 (95% CI 1.92 - 2.85) ○ 50-65 years: HR = 5.22 (95% CI 2.62 - 10.41) ○ > 65 years: HR = 2.33 (95% CI 1.90 - 2.88)	Supports association
RAMQ (Regie de l'Assurance Maladie du Québec), Quebec. (Billioti de Gage et al., 2014)[122] Benzodiazepines only	8 980 (≥ 66 years) [Any indication]	Case-control study (10 years)	Alzheimer's disease (ICD-9 codes)	- Ever use versus non-use: aOR = 1.51 (95% CI 1.36 - 1.69) - association increased with exposure density and drug half-life: ○ aOR = (1.32 (95% CI 1.01 to 1.74) for 91-180 prescribed daily doses ○ aOR = 1.84 (95% CI 1.62 to 2.08) for >180 prescribed daily doses) ○ aOR = (95% CI 1.43 (1.27 to 1.61) for short acting drugs ○ aOR = 1.70 (95% CI 1.46 to 1.98) for long acting drugs	Supports association
National Health Insurance Research data-base study, Taiwan. (Shih et al., 2015)[176]	25 218 (≥ 65 years) [Insomnia]	Nested case-control study (4 years)	Dementia all type (ICD-9 code)	- Ever use versus non-use: aOR = 1.33 (95% CI 1.24 - 1.41) - Risk increased with exposure ○ <170 mg Zolpidem/year aOR = 1.18 (95% CI 1.1 - 1.28) ○ 170-819 mg Zolpidem/year aOR = 1.50 (95% CI 1.36 - 1.65)	Supports association

Z-drugs only				○ >820 mg Zolpidem/year aOR = 1.52 (95% CI 1.38 - 1.68)	
UK-based Clinical Practice Research Datalink, United Kingdom. (Imfeld et al., 2015)[180] All sedative-hypnotics	26 459 (≥ 65 years) [Any indication]	Case-control study (15 years)	Dementia all type (Read code)	- Ever use versus non-use: aOR = 0.95 (95% CI .90 – 1.00) - Use <1 year before diagnosis: aOR = 2.20 (95% CI 1.91 - 2.53) - Use >2 -3 years before diagnosis: aOR = 0.99 (95% CI 1.84 – 1.17) - Ever use versus non-use (Z-drugs): aOR = 1.08 (95% CI .95 – 1.23)	No association when accounting for prodromal phase
Three-City Study, France. (Shash et al., 2016)[175] Benzodiazepines only	8 240 (≥ 65 years) [Any indication]	Prospective cohort study (8 years)	Dementia all type (DSM-IV criteria)	- Ever use versus non-use: aHR = 1.10 (95% CI .90 – 1.34) - Ever use versus non-use (long Half-life): aHR = 1.62 (95% CI 1.11 – 2.37) - Ever use versus non-use (short Half-life): aHR = 1.05 (95% CI .85 – 1.30)	No association other than in long half-life benzo-diazepines
Integrated healthcare delivery system, Seattle. (Gray et al., 2016)[165]	3 434 (≥ 65 years) [Any indication]	Prospective cohort study (10 years)	Dementia all type (cognitive abilities screening instrument)	- Ever use versus non-use: ○ 1-30 daily doses: aOR = 1.25 (95% CI 1.03-1.51) ○ 31-120 daily doses: aOR = 1.31 (95% CI 1.00-1.71) ○ >120 daily doses: aOR = 1.07 (95% CI 0.82-1.31)	Supports short-term association but no association in long-term use

German public health insurance data, Germany. (Gomm et al., 2016)[178] Benzodiazepines only	105 725 (≥ 60 years) [Any indication]	Case control study (7 years)	Dementia all type (ICD-10 code)	○ Regular use versus non-use: aOR = 1.21 (95% CI 1.13-1.29)	Supports association
Hong Kong Hospital Authority, Hong Kong. (Chan et al., 2017)[177] Benzodiazepines only	273 (≥ 65 years) [Any indication]	Retrospective Case-Control study (9 years)	Dementia all type (DSM-V criteria)	- Benzodiazepine exposure density >1096 prescribed daily doses vs <1096): aOR = 1.71 (95% CI 1.02-2.89)	Supports association
Helsana Group claims data, Switzerland. (Biétry et al., 2017) [181] Benzodiazepines only	2 876 (≥ 31 years) [Any indication]	Matched case-control study (6 years)	First time use of acetylcholinesterase inhibitors	- Benzodiazepine start prior to diagnosis: ○ 1 year: OR 1.71 (95% CI 1.17-2.99) ○ 3 years: OR 1.19 95% CI .82-1.72) - Adjusted for prodromal phase ○ Short-term (1-9 prescriptions): aOR 0.86 (95% CI 0.71-1.03) ○ Long-term (>30 prescriptions): aOR 0.78 (95% CI 0.53-1.14)	No association when accounting for prodromal phase

*aOR= adjusted OR. Across the studies, adjustments were variably made for age, sex, anxiety, depression, psychotropic drugs, sleep disorders, cognitive function, education, social class, ischemic heart disease, alcohol, hypertension, diabetes, epilepsy, use of platelet inhibitors or oral anticoagulant, hospitalizations, cerebrovascular disorders and/or singleness.

is a five-year study among 23,765 Canadians aged 65 and older by Sylvestre et al. which illustrated not only a significant association between benzodiazepines and falls with odds ratios ranging from 1.23 (95% CI 1.04-1.46) for cumulative clonazepam use to 2.83 (95% CI 1.45-4.34) in flurazepam users after 30 days of exposure. Perhaps the most rigorous support for this relationship arises from the results of a randomized clinical trial on the effect of B-vitamins for the prevention of osteoporotic fractures, which showed that benzodiazepine use was associated with an increased falls risk of HR 1.32 (95 % CI 1.02–1.71).[192] As with dementia, long-acting benzodiazepines have been associated with a higher risk of falls than short-acting benzodiazepines[185 187 190 196], with risk increasing with age[193]. As some of these studies included Z-drugs, the same association with falls applies to non-benzodiazepine sedative use in older adults.[18 98 185] Unfortunately, most studies did not or could not account or stratify the results by indication, as such, it is impossible to determine whether indication act as an effect modifier in the associations between the use of benzodiazepines and falls. The only study which divided participants by indication was a 2002 study by Tängman et al. which revealed that a fall had occurred in 27.5% of participants taking a benzodiazepine for sleep in comparison to only 5.5% in those who took it for anxiety.[194] However, the population in this study consisted of participants with dementia, which limits generalizability and as there was no distinction between nighttime or daytime falls, it is hard to determine if the relationship is exclusively due to the indication. Overall, while the relationship between benzodiazepines and falls seems clear, more research is needed to determine the impact of indication as an effect modifier.

Falls are associated with an increased risk of fractures, the most important being hip fractures.[198-201] Hip fractures incur significant mortality and morbidity, with one-in-three older adults dying within the year following a hip fracture.[202 203] A 2017 meta-analysis of 18 studies confirmed that sedative-hypnotic use is associated with an increased risk of hip fractures (RR = 1.52, 95% confidence interval 1.37-1.68).[198-201 204-218] Risk of hip fracture varied depending on the duration of use. Short-term use was associated with a two-fold increased risk of hip fracture (RR = 2.40, 95% confidence interval 1.88-3.05), surprisingly showing a more potent effect than long-term use (RR =

Table 8: *Summary of the evidence on the association between sedative-hypnotics and falls*

Study	Population (age) [indication]	Study type (duration)	Falls measurement	Association between Benzodiazepine use and falls (association and 95% confidence interval) *	Direction of association
Tennessee nursing homes, USA. (Ray et al., 2000)[190] Benzodiazepines only	2 510 (≥ 65 years) [Any indication]	Prospective cohort study (225 days)	Nursing home incident reports + medical records	- Any benzodiazepine vs non-users: aOR = 1.44 (95% CI 1.33-1.56) o Long half-life benzodiazepines: aOR = 1.73 (95% CI 1.40-2.14) o Short half-life benzodiazepines: aOR = 1.15 (95% CI 0.94-1.40)	Supports association
Silver Network Home Care project, Italy. (Landi et al., 2005)[187] Benzodiazepines only	1 661 (≥ 75 years) [Any indication]	Prospective cohort study (2 years)	MDS-HC assessment	- Any benzodiazepine vs non-users: aOR = 1.36 (95% CI 1.08-1.71) o Long half-life benzodiazepines: aOR = 1.45 (95% CI 1.00-2.19) o Short half-life benzodiazepines: aOR = 1.32 (95% CI 1.02-1.72)	Supports association
PAQUID study, France. (Pariente et al., 2008)[193] All sedative-hypnotics	3 777 (≥ 65 years) [Any indication]	Prospective cohort study (10 years)	Fall-report form	- Benzodiazepine or Z-drug vs non-users: o > 80 years old: aOR = 2.2 (95% CI 1.40-3.40) o Under 80 years old: aOR = 1.3 (95% CI.9-1.19)	Supports association
Projet-pilote prévention des chutes à domicile chez les personnes âgées. Québec. (Leclerc et al.,	937 (≥ 65 years) [Any indication]	Prospective cohort study (~2 years)	Fall-report form	- Any Benzodiazepine vs non-users: aOR= 1.21 (significant at p<0.05)	Supports association

2008)[189] Benzodiazepines only					
Three-City Study, France. (Berdot et al., 2009)[196] Benzodiazepines only	6 343 (≥ 65 years) [Any indication]	Prospective cohort study (4 years)	Fall-report form	- Any Benzodiazepine vs non-users: ○ All benzodiazepines: aOR= 0.99 (95% CI .85-1.16) ○ Long- acting Benzodiazepines: aOR = 1.20 (95% CI 1.00-1.43)	Supports association
Psychogeriatric hospital ward, Sweden. (Tängman et al., 2010)[194] Benzodiazepines only	233 (≥ 60 years + dementia) [Any indication]	Prospective cohort study (2 years)	Fall-report form	- Predisposing factor – no point estimate	Supports association
RAMQ (Regie de l'Assurance Maladie du Québec), Quebec. (Sylveste et al.,2012)[197] Benzodiazepines only	23 765 (≥ 65 years) [Any indication]	Prospective cohort study (5 years)	Fall-related injuries all type (ICD-9 code)	- Benzodiazepine vs non-users: ○ Lorazepam: aHR = 1.40 (95% CI .93-1.43) ○ Alprazolam: aHR = 1.27 (95% CI 1.13-1.42) ○ Clonazepam: aHR = 1.23 (95% CI 1.04-1.46) ○ Flurazepam 30 days: aHR = 2.83 (95% CI 1.45-4.34)	Supports association
Irish Longitudinal study on Ageing, Ireland. (Richardson et al.,2014)[195] Benzodiazepines only	8 175 (≥ 65 years) [Any indication]	Prospective cohort study (2 years)	Falls-related history form	- Benzodiazepine vs non-users: ○ In monotherapy: aRR = 1.32 (95% CI 1.05-1.65) ○ With other drugs: aRR = 1.40 (95% CI 1.04-1.87)	Supports association

B-PROOF study, Netherlands. (Ham et al., 2014)[192] Benzodiazepines only	2 407 (≥ 65 years) [Any indication]	Randomized, double-blind, placebo-controlled trial (2-3 years)	Weekly fall reports	- Benzodiazepine vs non-users: aHR = 1.32 (95% CI 1.02-1.71)	Supports association

*aOR= adjusted OR. Across the studies, adjustments were variably made for age, gender, race, time since admission to facility and since zero time, marital status, diagnosis of dementia, depression, disability, body mass index, ambulatory status, number of activities of daily living with total dependency, incontinence, cognitive impairment, physical restraint use, past falls, use of ; anticonvulsants, antiparkinsonian drugs, antidepressants, antipsychotics, antihypertensive drugs, vasodilators, antihistamines other sedatives, number of medications, foot problems, gait problems, fear of falling, and wandering.

1.20, 95% confidence interval 1.08-1.34).[206] A meta-analysis of six studies of Z-drugs also showed an increased risk of hip fracture (RR = 1.90, 95% confidence interval 1.68-2.13).[188 205 210 211 214 218] Similar to benzodiazepines, short-term use was associated with a two-fold increase in risk (RR = 2.39, 95% confidence interval 1.74-3.29), while episodic use carried an 80% increased risk (RR = 1.80, 95% confidence interval 1.60-2.02).[206] One interpretation for why short-term use more strongly predicts hip fracture incidence is that new users may be unaccustomed to potentiated levels of GABA prior to prescription, so their risk is higher than medium and long-term users.[206]

3.3.4 Motor vehicle accidents

Deficits in non-amnestic cognitive impairments such as attention, concentration, and reaction time impact on driving performance, which underpin the association between sedative-hypnotic use and motor vehicle accidents, described in five separate meta-analyses[219] [220]. A meta-analysis of five on-road experimental studies demonstrated a poorer driving performance of a magnitude of 0.80 (95% CI. 0.35-1.25) standardized mean difference at 5mg diazepam equivalents, rising to 3.07 (95% CI. 0.30-5.83) standardized mean difference at ≥10 mg diazepam equivalents on the standardized deviation of lateral position test.[219] This was confirmed in another meta-analysis of 14 trials which concluded that driving performance diminished significantly with higher doses, longer half-life agents and shorter time from dose to driving.[220] Z-drugs have been found to share a similar effect on the standardized deviation of lateral position test in adults over the age of 55[221], however, these results have not been replicated in younger healthy subjects.[222 223]

In 2013, the U.S. Food and Drug Administration revealed data on sex differences in the association between zolpidem and driving impairment. It was revealed that, as zolpidem is eliminated more slowly in women, and that individuals with high blood levels of zolpidem (50ng/ml) can be impaired even if they feel fully awake, the dose in women should be reduced. Following this announcement, the FDA required manufacturers to provide a sex-specific labeling change which would lower the recommended dose of

zolpidem for women from 10 mg to 5 mg for immediate-release products and from 12.5mg to 6.25 mg in extended-release products.[224]

Studies examining real-life motor vehicle accidents have shown that consumption of benzodiazepines and Z-drugs are associated with a 25% to 2-fold increased risk of motor vehicle accidents.[225-230] Most notable among these is a large longitudinal, nationally representative study amongst 12 387 Canadians which showed that sedative-hypnotics were associated with an increased odds of subsequent motor vehicle accidents of 2.06 (95% CI 1.16, 3.65) independent of medical condition.[228] Z-drugs were also assessed independently from benzodiazepines and were found to increase the incidence rate by 2.3 (95% CI: 2.0-2.7).[230] The data on GABA agonists is summarized in table 9[219 231-234].

Almost all studies included in these systematic were cohort or case-control studies comparing medication users to non-users. Some discrepancies and limitations exist among all the reported studies examining the association between sedative-hypnotics and motor vehicle accidents, however, a consistent trend across multiple countries and datasets points to an overwhelming degree of evidence linking the use of sedative-hypnotics with reduced driving performance and motor vehicle accidents. Future research on the topic should focus on identifying risk factors in order to identify the most “at risk” subpopulations.

3.3.5 Drug overdose

While the risk of fatality from benzodiazepine use alone is unclear[235], concomitant use of GABAergic drugs with other agents that cause central nervous system and respiratory depression, especially opioids, appears to substantially increase mortality risk.[235-238] Multiple studies report that deaths and other severe effects of benzodiazepines are on the rise (see table 10)[100 239-242]. Mortality attributable to benzodiazepine overdoses has increased from 2022 to 8791 deaths in the United-States in 2015, with 75% of overdoses involving opioids.[239] The exact mechanism is unclear, suggesting that current and future research will need to focus on the interaction

Table 9 : *Summary of studies showing an association between sedative-hypnotics and motor vehicle accidents*

Systematic review	Number of studies	Outcome	Results summary	Direction of association
Rapoport et al., 2009[219] Benzodiazepines only	16	Motor vehicle collisions	- Case-control studies pooled odds ratio: 1.61 (95% CI 1.21-2.13) - Cohort studies pooled odds ratio: 1.60 (95% CI 1.29-1.97)	Supports association
Smink et al., 2010[233] Benzodiazepines only	66	Road traffic crashes	- Too divergent to converge results - Increased risk of accident with: o Longer half-life benzodiazepines o Increased dosages o First few weeks of use	Supports association
Dassanayake et al., 2011[232] Benzodiazepines only	21	Road traffic crashes	- Case-control studies pooled odds ratio: 1.59 (95% CI 1.10-2.31) - Cohort studies pooled odds ratio: 1.81 (95% CI 1.35-2.43)	Supports association
Elvik, R., 2013 [234] All sedative-hypnotics	66	Risk of road accidents	- Benzodiazepines fatal accidents studies pooled odds ratio: 2.30 (95% CI 1.59-3.32) - Benzodiazepines injury accident studies pooled odds ratio: 1.17 (95% CI 1.08-1.28) - Benzodiazepines property damage accidents studies pooled odds ratio: 1.35 (95% CI 1.04-1.76)	Supports association
Gjerde et al., 2015[231] All sedative-hypnotics	28	Road traffic crashes	- 25/28 studies with a positive association between car accidents and benzodiazepines/Z-drugs. o Median odds ratio for road traffic crashes was 18	Supports association
Rudisil et al., 2016[243] All sedative-hypnotics	27	Road traffic crashes	- High correlation between benzodiazepines and motor vehicle crashes but no estimate given - 4/5 statistically significant effect for zopiclone with risk ranging from 38% to 200% increase)	Supports association

between GABAergic medications other drugs or co-intoxicants in order to fully understand whether respiratory depression is the causal link between benzodiazepines and drug overdoses.

3.3.6 Infections

GABA agonists have also been linked to an increased risk of infection, purported to be due to effects on immune dysfunction.[244] [245] Of six observational studies on the relationship between benzodiazepine use and infections, four of them have found a significant effect, while the other 2 did not (see table 11)[246-251]. The most recent and largest retrospective study among 804,051 patients reported that current benzodiazepine/zopiclone use resulted in an adjusted hazard ratio of 4.24 (95% CI: 2.27-7.95) for influenza-like related pneumonia and 20.69 (95%CI 15.54-27.54) for influenza-like illness related mortality[246]. The negative association observed in the other two studies can be explained by the higher comorbidity in older adults, which is associated with a higher incidence of pneumonia and mortality, affecting sample size and power in this sub-population.[246] [247] Furthermore, a meta-analysis of FDA randomized clinical trials found that use of Z-drugs was associated with a 24-65% increased risk for infections (depending on the infection type) compared to placebo.[252] Overall, while preliminary evidence points to a causal association, these findings need to be replicated consistently in prospective studies prior to drawing conclusions about an increased risk of infections attributable to sedative-hypnotic use.

3.3.7 Other associated hazards (Cancer, pancreatitis, and respiratory disease exacerbation)

Research has been conducted on the potential association between the use of benzodiazepines and z-drugs with other harms such as pancreatitis, respiratory disease exacerbation, and cancer. A few observational studies on cancer have raised concerns about the link between cancer and sedative-hypnotic use.[253-256] A meta-analysis of 22 observational studies observed a 19% (OR=1.19, 95% CI: 1.16-1.21) increased cancer risk from these medications.[257] However, this field of research has been criticized by a

Table 10: *Summary of the evidence on the association between sedative-hypnotics and drug overdoses*

Study	Population (age)	Study type (duration)	Overdose measurement	Association between Benzodiazepine use and overdoses (association and 95% confidence interval)	Direction of association
UK department of Health, United Kingdom, (Buckley et al., 2004)[242]	United Kingdom population (all ages)	Retrospective cohort study (16 years)	Deaths from drug overdose	- Death from drug overdose: ○ 5.6/million benzodiazepine prescriptions ○ 2.2/million Z-drug prescriptions	Supports association
Nationwide Inpatient Sample, United-States. (Coben et al., 2010)[241]	United-States population (all ages)	Retrospective cohort study (7 years)	Hospitalization for prescription poisoning (ICD-9 code)	- Hospitalizations due to benzodiazepines overdose: ○ 26,321 in 1999 ○ 36,700 in 2006	Supports association
Substance Abuse and Mental Health Services Administration's Drug Abuse Warning Network Emergency Department, United States. (Jones et al., 2015)[240]	United-States population (all ages)	Retrospective cohort study (7 years)	Emergency department visits + deaths from co-overdose (Benzodiazepine + opioids)	- Emergency department visit due to benzodiazepines +opioids: ○ 11/100 000 in 2004 ○ 34.2/100 000 in 2011 - Deaths from co-overdose: ○ .6/100 000 in 2004 ○ 1.7/100 000 in 2011	Supports association
Medical Expenditure Panel Survey, United States. (Bachhuber et al., 2016)[100]	140 million (≥ 18 years)	Retrospective cohort study (17 years)	% filling a prescription, overdose death rate	- % filling a benzodiazepine prescription ○ 4.1% in 1996 ○ 5.6% in 2013 - Benzodiazepine overdose rate ○ .58 (.55-.62)/100 000 adults	Supports association

				in 1996 ○ 3.07 (2.99-3.14)/100 000 adults in 2013	
National Institute on Drug Abuse, United States. (NIH., 2017) [239]	United-States population (all ages)	Government report (13 years)	Deaths	- 4.3-fold increase in total number of deaths ○ 2022 deaths in 2002 ○ 8791 deaths in 2015	Supports association

Table 11: *Summary of the evidence on the association between sedative-hypnotics and infections*

Study	Population (age)	Study type (duration)	Infection ascertainment	Comparison group	Association between sedative-hypnotic use and infections (association and 95% confidence interval)	Direction of association
Veterans Affairs long-term care facility, Pittsburgh. (Vergis et al., 2001)[249] Benzodiazepines only	208 (≥65 years)	Prospective case-control study (2 years)	Pneumonia (conformed by physician + criteria)	Benzodiazepine users vs non-users	- Use of tranquilizers (phenothiazine's or benzodiazepines): o Pneumonia: aOR 2.6 (95% CI 1.2–5.4)	Supports association
Utrecht general practice research network, Netherlands. (Hak et al., 2005)[248] Benzodiazepines only	455 (≥60 years)	Retrospective cohort study (30 days post diagnosis)	Community-acquired lower respiratory tract infections (ICPC-Codes)	Benzodiazepine users vs non-users	- Use of antidepressants or benzodiazepines: aOR 1.89 (95% CI 1.02–3.52)	Supports association
Utrecht general practice research network, Netherlands. (Nadort et al., 2009)[251] Benzodiazepines only	860 (≥60 years)	Retrospective cohort study (30 days post diagnosis)	Lower respiratory tract infections	Benzodiazepine users vs non-users	- Use of antidepressants or benzodiazepines: OR 1.2 (95% CI .7–1.9)	Does not support association

Group Health Institute,Seattle. (Dublin et al., 2011)[250] Benzodiazepines only	3 061 (≥65 years)	Case-control study (3 years)	Pneumonia (ICD-9 code)	Benzodiazepine users vs non-users	- Benzodiazepine use vs non-user: o Pneumonia: aOr= 1.08 (95% CI .80-1.47)	Does not support association
The Health Improvement Network, United Kingdom. (Obiora et al., 2013)[247] Benzodiazepines only	29 697 (all ages)	Nested case-control study (3 years)	Pneumonia and mortality (ICD-9 code)	Benzodiazepine users vs non-users	- Benzodiazepine use vs non-user: o Pneumonia: aOR= 1.54 (95% CI 1.42-1.67 o Short-term mortality: aHR = 1.22 (95% CI 1.06-1.39) o Long-term mortality: aHR = 1.22 (95% CI 1.06-1.39)	Supports association
Clinical Practice Research Datalink, United Kingdom. (Nakafero et al., 2016)[246] All sedative-hypnotics	804 051 (all ages)	Retrospective cohort study (30 days post diagnosis)	Influenza or influenza like illness related pneumonia and mortality	Sedative-hypnotic users vs non-users	- Influenza like illness related pneumonia o Benzodiazepines: aHR = 4.24 (95% CI 2.27-7.95) o Zopiclone: aHR = 1.97 (95% CI .63-6.12) - Influenza like illness related mortality o Benzodiazepines: aHR = 20.69 (95% CI 15.54-27.54) o Zopiclone: aHR = 10.86 (95% CI 6.93-17.02)	Supports association

lack of high quality experimental and epidemiologic evidence to confirm this association as well as concerns about the potential for protopathic bias. Three studies on pancreatitis have flagged an association between benzodiazepines[258], zopiclone[259] and zolpidem[260] and acute episodes of pancreatitis. A 5-fold increased risk of pancreatitis was observed following benzodiazepine overdose (aOR=5.33, 95% CI: 2.26-12.60).[258] Similarly, users of zopiclone thirty days prior to an episode of pancreatitis were more than twice as likely as non-users to have a recorded event (aOR= 2.35, 95% CI: 1.70-3.28)[259]. More research is needed to evaluate and qualify this association before confirming a strong causal connection. The same holds true for new evidence arising from observational studies linking sedative-hypnotic use with the risk of respiratory exacerbations and mortality in patients with chronic obstructive pulmonary disease.[261-265] However once again, due to the design and disparity in methods used, further research is required to establish a clear relationship. With this mounting evidence, the indirect costs of sedative-hypnotic related harms can no longer be ignored. The increased risk of drug-related harms and adverse events associated with sedative-hypnotics lead to a significant burden of healthcare costs[18 266 267].

3.4 Benefits of benzodiazepines and Z-drugs

This chapter will describe the efficacy of benzodiazepines and Z-drugs in older adults for their two main indications of use: insomnia and anxiety.

3.4.1 Insomnia

One of the main indications for the use of sedative-hypnotics is to treat insomnia. Multiple meta-analyses have evaluated the benefits of sedative-hypnotic use in insomnia, all of which have found sedative-hypnotics to show improvements in sleep parameters such as sleep latency, number of awakenings, total sleep time, and sleep quality, when compared to placebo.[155 268] The most recent meta-analysis by Glass et al. from 2005 from participants of all ages pooled the effects of 24 studies involving 2417 participants. Total sleep time increased by 34.2 minutes (95% CI 16.2-52.8) in benzodiazepines users and 25.2 minutes (95% CI 12.8-37.8) in z-drug users compared to placebo.[155] Additionally, the meta-analysis reported a significant decrease in nighttime awakenings (0.63, 95% CI .48-.77), and improvements in sleep quality (0.14

95% CI .05-.23).[155] As our focus is on older adults, Table 12 below presents a summary of all double-blind placebo-controlled studies evaluating the effectiveness of sedative-hypnotics in older adults.

Of the 24 studies comparing sedative-hypnotics to placebo in the treatment of insomnia in older adults, 22 indicate that sedative-hypnotics seem to have a beneficial effect in treating insomnia with reported improvements in sleep quality (effect size 0.14, $p < 0.05$), increased total sleep time (mean 25.2 minutes, $P < 0.001$) and a reduced number of nighttime awakenings (0.63, $P < 0.001$) with sedative use compared with placebo.[155] However, this body of evidence can be very misleading as almost all studies report follow-up times of 14 days or less. Additionally, most studies done have a very small number of participants limiting the robustness of the strength of association. Finally, most studies rely on patient-reported outcomes, rather than objective measures, which can introduce subjective or social desirability bias. Studies suggest that patients may overestimate the potential subjective improvement in sleep with the use of sedative-hypnotics.[4 155 269] Sedative-hypnotic users have been known to attribute to these medications characteristics that extend beyond an ordinary medication[4]. Multiple studies in long-term users show that long-term sedative-hypnotic use is actually associated with a deterioration in sleep quality when compared to non-users.[270-273] So while there seems to be evidence for short-term use of sedative-hypnotics in the treatment of insomnia, there exists little to no evidence to support their long-term use. More research needs to be done to properly quantify the benefits, if any, of sedative-hypnotics in the long-term treatment of insomnia in older adults.

3.4.2 Anxiety disorders

While current guidelines do not recommend benzodiazepines as first-line treatment for anxiety disorders[274], approximately 55-94% of patients with anxiety disorders are treated with benzodiazepines[275]. This most likely stems from the numerous reports supporting the efficacy of benzodiazepines in the treatment of generalized anxiety when compared to placebo.[276-279] Unfortunately, almost all of these studies were conducted in populations which excluded older adults. The only study

***Table 12**: Summary of placebo controlled RCT's on the effectiveness of sedative-hypnotics on insomnia in older adults.*

Study	Population n (age)	Study type (duration)	Treatments	Summary of findings *	Favors benzodiazepines/ Z-drugs
Reeves et al. 1977[280]	41 (>60 years)	Placebo controlled RCT (28 days)	- Triazolam 0.25 mg - Flurazepam 15 mg	Triazolam better than placebo in sleep onset, duration of sleep, nighttime awakenings, and feeling restless($p<0.01$). Flurzepam was better than placebo in onset of sleep and quality of sleep($p<0.05$). Triazolam out performed flurazepam in all measures	Yes.
Goldstein et al. 1978[281]	17 (mean 82 years)	Placebo controlled RCT (4 days)	- Oxazepam 15 mg - Flurazepam 15 mg - Chloral hydrate 500 mg	Only oxazepam was better than placebo in reducing nighttime awakenings ($p<0.01$) and improved quality of sleep($p<0.01$). Flurazepam was better than placebo in decreasing sleep latency (21 mins, $p<0.05$) but showed residual daytime sedative effect.	Yes, however mixed results with flurazepam on efficacy and safety.
Piccione et al. 1980[282]	27 (>60 years)	Placebo controlled crossover RCT - (5 days)	- Triazolam 0.25 or 0.5 mg - Chloral hydrate 250 or 500 mg	Triazolam significantly better than placebo and chloral hydrate in improving quality of sleep($p<0.05$).	Yes.
Fillingim et al. 1981[283]	75 (mean 81 years)	Placebo controlled RCT (4 days)	- Temazepam 30 mg - Flurazepam 30 mg	Both active groups significantly better than placebo in improving quality of sleep ($p<0.01$).	Yes, however flurazepam more likely to cause side-effects
Caldwell et al. 1982[284]	57 (<60 years)	Placebo controlled RCT (5 days)	- Quazepam 15 mg	Significantly greater improvement in sleep than placebo on all sleep questionnaire measures ($p<0.01$).	Yes.

Martinez et al. 1982[285]	60 (<55 years)	Placebo controlled RCT (5 days)	- Quazepam 15 mg	Improved quantity and quality of sleep with Quazepam ($p<0.01$).	Yes.
Elie et al. 1983[286]	30 (<60 years)	Placebo controlled crossover RCT - 7 days washout (28 days)	- Flurazepam 15 mg - Zopiclone 5, 7.5, and 10 mg	Both active groups significantly better than placebo across sleep measures($p<0.01$). Flurazepam and zopiclone 7.5mg equally effective.	Yes
Viukari et al. 1983[287]	37 (mean 74 years)	Placebo controlled RCT (14 days)	- Flunitrazepam 1 mg - Nitrazepam 5 mg	Both benzodiazepines proved to be effective in inducing and maintaining sleep($p<0.05$).	Yes, however both resulted in rebound insomnia.
Vogel et al. 1984[288]	10 (<55 years)	Placebo controlled RCT (7 days)	- Lormetazepam 0.5 mg	Substantial decrease in sleep latency and average increased sleep time of 25 minutes compare to placebo($p<0.05$).	Yes.
Viukari et al. 1984[289]	32 (<60 years)	Placebo controlled crossover RCT - 7 days washout (7 days)	- Brotizolam 0.125 mg - Nitrazepam 2.5 mg	Both drugs deemed more effective than placebo (psychologist assessment + sleep questionnaire)	Yes.
Bayer et al. 1986[290]	89 (<67 years)	Placebo controlled RCT (5 days)	- Loprazolam 0.5 or 1 mg	Significant improvements in both groups for sleep latency, satisfaction with sleep, decreased number of nocturnal awakenings with loprazolam ($p<0.05$). No dose-effect relationship.	Yes, however significant association between loprazolam treatment and side-effects.
Klimm et al. 1987[291]	74 (mean 80 years)	Placebo controlled RCT (7 days)	- Nitrazepam 5 mg - Zopiclone 7.5 mg	Significant improvements in both groups for sleep duration, sleep-onset latency (-18.2 mins, $p<0.04$) and feeling on awakening compared to	Yes, however benefits in nitrazepam offset by side effects.

				placebo(p<0.02).	
Overstall et al. 1987[292]	62 (mean 80 years)	Placebo controlled RCT (7 days)	- Lormetazepam 1 mg - Chlormethiazole 384 mg	Significant improvements in both groups for sleep duration(p<0.02), sleep latency (-1h, p<0.05) and improved quality of sleep compared to placebo(p<0.01).	Yes.
Stewart et al. 1987[293]	17 (<60 years)	Placebo controlled crossover RCT - 72 hours washout (5 days)	- Temazepam 15 - Diphenhydramine 50 mg	Significant improvements in both groups in decreased sleep latency compared to placebo(p<0.05), longer duration of sleep with diphenhydramine versus temazepam (p<0.05).	No, significantly poorer results on neurologic test for temazepam users
Mamelak et al. 1987[294]	36 (<60 years)	Placebo controlled RCT (14 days)	- Brotizolam 0.25 mg - Flurazepam 15 mg	Significant improvements in all groups across all sleep quality indicators (including placebo) (p<0.05). At end of the study only placebo treated group slept significantly longer (rebound insomnia in other groups)	No
Elie et al. 1990[295]	44 (<60 years)	Placebo controlled RCT (21 days)	- Triazolam 0.125 or 0.25 mg - Zopiclone 5 or 7.5 mg	Significant improvements in both groups across all sleep quality indicators. No difference detected between treatment. Constant effectiveness over 3 weeks, no true rebound effect detected.	Yes.
Fairweather et al. 1992[296]	24 (>63 years)	Placebo controlled crossover RCT - 7 days washout (7 days)	- Zolpidem 5 or 10 mg	Zolpidem produced a subjective improvement in sleep compared to placebo.	Yes.
Roger et al. 1993[297]	221 (<58 years)	Placebo controlled RCT	- Triazolam 0.25 mg - Zolpidem 5 to 10	Significant improvements in both groups across all sleep quality	Yes.

		(21 days)	mg	indicators (p<0.05). No difference detected between treatment.	
Leppik et al. 1997[298]	335 (<60 years)	Placebo controlled RCT (28 days)	- Triazolam 0.125 mg - Temazepam 15 mg - Zolpidem 5 mg	Self-reported total sleep duration increased (+1h, p<0.01) and improvements in self-reported sleep latency (-40 mins, p<0.01) across all groups compared to placebo.	Yes, but temazepam and triazolam also shown to cause significantly more side effects.
Roth et al. 1997[299]	335 (<60 years)	Placebo controlled RCT (7 days)	- Quazepam 7.5 to 15 mg	Reduced sleep latency (p<0.02) and wakefulness during sleep (p<0.03). Dose-effect observed.	Yes
Ancoli et al. 1999[300]	549 (>65 years)	Placebo controlled RCT (14 days)	- Zalepon 5 or 10 mg - Zolpidem 5 mg	Zaleplon, 10 mg, and zolpidem, 5 mg, significantly reduced sleep latency during both weeks of the study (-40 mins, p<0.001). Sleep duration increased with zolpidem during weeks 1 and 2 and with zaleplon, 10 mg, (+27 Mins, p<0.05).	Yes.
Morin et al. 1999[301]	78 (mean 65 years)	Placebo controlled RCT (8 weeks + 2 years follow-up)	- Temazepam 7.5 to 30 mg - CBT - Temazepam + CBT	All three active treatments were more effective than placebo (-20 mins sleep latency, +40 mins sleep time, p<0.01). Improvements in sleep favored combination treatment, then CBT, followed by Temazepam alone. Long-term follow-up tended toward null result.	Yes, temazepam shown to be more effective than placebo, but less so than CBT.
Hedner et al. 2000[302]	549 (>60 years)	Placebo controlled RCT (14 days)	- Zalepon 5 or 10 mg	Zaleplon significantly reduced subjective sleep latency during both weeks of the study with both 5- and 10-mg doses (-10 &-13 mins, p<0.001). Subjective sleep quality	Yes, however the was rebound insomnia following discontinuation in the 10mg group.

				was improved for significantly more patients treated with zaleplon 10 mg compared to placebo ($p<0.05$).	
Glass et al. 2008[303]	20 (≥70 years)	Placebo controlled cross-over RCT (14 Days)	- Temazepam 15 mg	Improved sleep quality (mean score, 3.3 +/- 0.9 vs 2.9 +/- 0.8; P = 0.03), total sleep time (6.9 +/- 1.0 hours vs 6.3 +/-1.3 hours; P = 0.02), sleep-onset latency (25 +/- 22 minutes vs 37 +/- 25 minutes; P = 0.03) and number of awakenings (1.5 +/- 1.3 vs 2.0 +/- 1.2; P < 0.001)	Yes, temazepam shown to be more effective than placebo but mitigated by increased risk of falls

* In order to simplify interpretation of study results and render them comparable due to the high heterogeneity of methods used and outcome measures reported blanket statements are sometimes provided in lieu of exact results. Point estimates are however reported when studies used more straightforward measures of sleep.

specifically comparing benzodiazepines to placebo or other treatments in older adults is a 1982 study by Koepke et al. which was able to demonstrate significant improvements in both the Hamilton anxiety scale and the physician target symptom scale when comparing oxazepam 30 and 60 mg to placebo.[304]

While their efficacy in treating anxiety disorders is not in dispute, their efficacy and tolerability in comparison to anti-depressants is a more hotly debated topic.[279] In recent years, there has been a progressive change in the prescribing pattern of physicians from benzodiazepines to newer antidepressants to treat anxiety disorders in older adults.[305-307] The main reason for therapeutic substitution to the newer antidepressants is not based on a direct comparison between their effectiveness but rather on the risks of benzodiazepines as seen in chapter 2.3.[308] Table 13 presents the efficacy and tolerability of benzodiazepines in comparison to antidepressants in the treatment of anxiety disorders.

The studies in Table 11 show overall mixed effects and do not consistently measure or report adverse event rates. Furthermore, many of the studies are relatively old and only compared tricyclic antidepressants and paroxetine to benzodiazepines. The newer selective serotonin reuptake inhibitor antidepressant and atypical antidepressants have never been compared head-to-head with the classic sedative-hypnotics. A major consideration to take into account here is that few of these studies performed sub-analyses among older adults, which is extremely relevant when evaluating a medication's risk/benefit ratio, as we will see in the next chapter. [3]

3.5 Summary

The story of benzodiazepines remains complex. The drugs were introduced on the market at a time when society was looking for a panacea to combat anxiety, depression, and insomnia, and were originally touted as a miracle drug. Individuals, and women especially, who were in their 30's and 40's during the 1970's, are currently

Table 13: *Efficacy and tolerability of benzodiazepines in comparison to antidepressants in the treatment of anxiety disorders.*

Study	Population n (age)	Study type (duration)	Treatments	Summary of findings	Favors benzodiazepines/Z-drugs
Draper and Daly,1983[309]	25 (18-60)	Double-blind RCT (6 weeks)	- Alprazolam 0.5 mg - Amitriptyline 25 mg	No significant difference in response on the Hamilton depression scale or in terms of drop out and adverse events.	No significant difference between treatments
Allsopp et al.,1984[310]	50 (18-65)	Double-blind RCT (12 weeks)	- Diazepam 10-30 mg - Clomipramine 25-150 mg	Significantly better results on the social phobia/agoraphobia inventory, adverse events rate for clomipramine when compared to diazepam ($p<0.05$).	No, antidepressants favorable in terms of efficacy and safety
Kahn et al., 1986[311]	242 (18-70)	Double-blind placebo controlled cross-over RCT – 2-week washout (8 weeks)	- Diazepam 30-55 mg - Imipramine 70-135 mg - Placebo	While both better than the placebo, imipramine showed significantly better results on the Hamilton depression + anxiety scales($p<0.05$), Hopkins symptoms checklist ($p<0.05$), adverse events rate ($p<0.05$) when compared to diazepam.	No, antidepressants favorable in terms of efficacy and safety
Rizley et al.,1986[312]	44 (18-60)	Double-blind RCT (12 weeks)	- Alprazolam 1.5 -2.8 mg - Imipramine - 70-132.5 mg	Significantly better results on the Hamilton depression + anxiety scales, Hopkins symptoms checklist for alprazolam when compared to the imipramine ($p<0.05$). However, significantly higher rate of adverse event in the alprazolam group ($p<0.05$).	Yes, higher efficacy than antidepressant but with a less favorable safety profile
Hoehn-Saric et al., 1988[313]	60 (23-60)	Double-blind RCT (6 weeks)	- Alprazolam 0.5-6 mg - Imipramine	Alprazolam more effective in attenuating somatic symptoms, and imipramine was more effective in attenuating psychic	Yes, benzodiazepine's effects seem favorable in the treatment of

			25-200 mg	symptoms($p<0.05$). However, significantly higher rate of adverse event in the alprazolam group($p<0.05$).	generalized anxiety but with a less favorable safety profile
Tyrer et al.,1988[314]	210 (17-76)	Placebo controlled RCT (6 weeks)	- Diazepam 5mg - Dothiepin 25 mg - Placebo - CBT - Self-help	All groups showed significant improvements on the Montgomery-Asberg depression rating scale ($p=0.046$) and the comprehensive psychopatho-logical rating scale ($p=0.023$). CBT, self-help and dothiepin significantly outperformed diazepam($p=0.03$).	No, antidepressants, CBT and self-help were more favorable in terms of efficacy
Gelernter et al., 1991[315]	65 (35.6 ± 9.6)	Placebo controlled RCT (12 weeks)	- Alprazolam 6,3mg - Phenelzine 90mg - Pacebo - CBT	All groups showed significant improvements on the social avoidance and distress scale, social phobia subscale when compared to placebo($p<0.001$). However, there were no significant differences between groups.	No significant difference between treatments
Rickels et al.,1993[316]	230 (39 ± 12).	Placebo controlled RCT (8 weeks)	- Diazepam 26 mg - Imipramine 143 mg - Trazodone 225 mg - Placebo	All groups showed significant improvements on the Hamilton depression + anxiety scales when compared to placebo($p<0.01$). However, there were no significant differences between groups except in terms of diazepam users experiencing less adverse effects than the antidepressant groups ($p<0.05$).	No significant difference between treatments but with a less favorable safety profile for antidepressants
Möller et al., 2001[317]	307 (48)	Double-blind placebo controlled cross-over RCT – 1-week washout	- Alprazolam 2 mg - Opipramol 200 mg - Placebo	All groups showed significant improvements on the Hamilton depression($p<0.001$) + anxiety scales($p<0.02$) and SCL-90($p<0.01$) when compared to placebo. However, there were no significant differences between groups.	No significant difference between treatments

		(4 weeks)			
Hackett et al.,2003[318]	540 (44)	Double-blind placebo controlled RCT (8 weeks)	- Diazepam 15 mg - Venlafaxine 75 or 150 mg - Placebo	All groups showed significant improvements on the Hamilton anxiety scale and clinical global impression-severity when compared to placebo($p<0.05$). However, there were no significant differences between groups.	No significant difference between treatments
Feltner et al.,2009[319]	169 (36)	Double-blind placebo controlled RCT	- Lorazepam 4.5 mg - Paroxetine 20 mg - Placebo	All groups showed significant improvements on the Hamilton anxiety scale($p<0.001$) and daily assessment of symptoms-anxiety when compared to placebo($p<0.05$). However, there were no significant differences between groups.	No significant difference between treatments
Nardi et al., 2011[320]	120 (34.8 ± 8.8)	Open-label RCT (8 weeks)	- Clonazepam 2 mg - Paroxetine 40 mg	Significantly better results on the number of panic attacks (0.1 vs 0.5, $p<0.01$) and clinical global impression improvement scale (CGI-I: 1.6 vs 2.9, $p=0.04$) and adverse events rate for clonazepam when compared to paroxetine (73 vs 95%; $p=0.001$).	Yes, clonazepam favorable in terms of efficacy and safety

octogenarians with almost fifty years of believing that benzodiazepines are safe and effective therapy. Objective data, showing minimal benefits of benzodiazepines in the face of mounting harms, do not seem to be making a dent in users' psychological and emotional dependence on sedative-hypnotics. Physicians do not have other drugs at their disposal with which to treat insomnia, and so prescriptions continue to be dispensed with increasing frequency to older adults in Canada. This alarming situation is the backdrop against which the notions of inappropriate prescribing and deprescribing have entered professional vernacular.

Chapter 4 – Deprescribing Benzodiazepines

This final literature review chapter provides an overview of deprescribing and how it can be applied as a solution to reducing benzodiazepine use in older adults. We first define deprescribing and weigh the overall benefits and harms of this approach. The key stakeholders in the deprescribing process are discussed, as well as known barriers to deprescribing. The remainder of the chapter will specifically address deprescribing benzodiazepines. The effectiveness of different deprescribing interventions for consumers of benzodiazepines will be described. We will conclude by exploring the role of the patient as the driver for deprescribing, which is the main premise to be tested in the two cluster randomized trials in this thesis.

4.1 Deprescribing

4.1.1 Defining deprescribing

The term 'Deprescribing' was first employed and defined in a 2003 Australian hospital pharmacy journal in an article titled: "Deprescribing: achieving better health outcomes for older people through reducing medications". The article outlined the main principles of deprescribing as: 1) reviewing all current medications, 2) identifying medications to be ceased, substituted or reduced, 3) planning a deprescribing regimen in partnership with the patient and 4) frequently reviewing and supporting the patient. [321] Since then, there have been almost 400 articles focused on deprescribing, and at least 37 different variations on the definition of the term deprescribing.[322] In 2015, Reeve et al. conducted a systematic review of emerging definitions for the term deprescribing and proposed the following definition based on their findings: "*Deprescribing is the process of withdrawal of an inappropriate medication, supervised by a healthcare professional with the goal of managing polypharmacy and improving outcomes*."[322] While very useful, this definition fails to capture the importance of the patient's involvement in the deprescribing process. For this reason, we prefer the recent definition by Scott et al. which describes deprescribing as "*the systematic process of identifying and discontinuing drugs in instances in which existing or potential harms outweigh existing or potential benefits within the context of an individual patient's care goals, current level*

of functioning, life expectancy, values, and preferences."[323] as this definition more accurately captures the multi-faceted concept that is deprescribing.

4.1.2 Benefits and harms of deprescribing

The primary goal of deprescribing is to lower the risks and improve the outcomes associated with those risks. The process of deprescribing can also lead to potential harms for patients, so it is important to explore the actual benefits and harms associated with deprescribing. Some benefits and harms remain theoretical, while others have been proven in real life research studies. Deprescribing envelops many types of interventions, and not all studies report on health outcomes associated with deprescribing, so it is actually quite difficult to systematically evaluate the potential benefits and harms associated with deprescribing. This next section summarizes what is known from the literature on the benefits and harms of deprescribing.

One systematic review included 116 studies and explored the effect of deprescribing in older adults on mortality and health outcomes.[324] The result of ten randomized studies that looked at mortality outcomes showed a non-significant decrease in mortality (OR=0.82, 95%CI 0.61–1.11). However sub-group analyses indicated that mortality was significantly reduced when patient-specific interventions were applied (OR= 0.62, 95%CI 0.43–0.88) in comparison to general educational programs that demonstrated no change in mortality (OR=1.21, 95% CI 0.86–1.69). Patient-specific interventions consisted of interventions where investigators reviewed each patient's medication list and identified targeted medications to deprescribe on an individual basis, and subsequently implemented an intervention to deprescribe these specific medications. Educational interventions were defined as interventions where non-specific educational sessions were provided to health care professionals to broadly modify prescribing behaviours.[325] Deprescribing was not associated with a significant increase in adverse drug events nor did it significantly change cognitive function.[326] As data are sparse and methods vary greatly, this systematic review was not able to find any significant effects of deprescribing on adverse drug withdrawal effects, quality of life, falls or disease recurrence.[324]

For specific medication classes, deprescribing improves outcomes in some cases with benefits varying depending on the type of medication discontinued.[327] For example, the discontinuation of benzodiazepines has been associated with an improvement in cognitive and psychomotor abilities.[327] Withdrawing non-steroidal anti-inflammatory medications yields improvements in blood pressure.[328] However, discontinuing a medication may also lead to a return of symptoms. Results from a systematic review indicate occasional recurrence of symptoms, but that restarting the medication quickly resolves this issue when it occurs.[327] Recurrence of symptoms occurs most commonly with medications such as diuretics or antihypertensives[327]. The need to re-start diuretic treatment occurs in 24-48% of cases in various studies due to the re-emergence of cardiovascular symptoms.[329-332] Similarly, 64% of antihypertensive users required re-prescription of their antihypertensive following cessation in order to meet their blood pressure targets.[333] [334] Withdrawal of medications may also cause a psychological withdrawal reaction.[335] [336] However, this can generally be prevented, or at least minimized by tapering doses during a prolonged discontinuation regimen.[335] Tapering refers to the gradual discontinuation or reduction of a therapeutic dose of a particular drug required by a patient over a prolonged period of time. Tapering is done in order to minimize withdrawal effects so that users can more successfully come off the drug.

Theoretically, deprescribing should lead to a reduction in the harms associated with polypharmacy, but data are lacking. What we know is that deprescribing interventions result in fewer medications being used and a lower prevalence of inappropriate prescriptions in the elderly, however, the long-term effects on adverse drug reactions, hospitalizations, and quality of life have not been rigorously studied.[337] [338] [6] [26] It has also been hypothesized that deprescribing could lead to cost savings. An Australian study estimated that reducing one medication per patient per year would result in $463 million saved each year.[339] Similarly, a study in the USA estimated that the healthcare expenditure associated with the use of inappropriate medications was $7.2 billion per year.[48] By simplifying drug regimens, deprescribing may also lead to

overall improvements in medication adherence[340] and improve patient satisfaction with their medication use.[341] [342] The clinical effects on the pharmacodynamics, pharmacokinetics, and drug-drug interactions with remaining medications is difficult to tease out and remains unclear.[343]

4.2 Approaches to deprescribing

This section explores current approaches to deprescribing. A 5-step deprescribing process has been proposed. Current interventional approaches to deprescribing and their relative effectiveness will be reviewed.

4.2.1 The deprescribing process

Many authors have proposed stepwise models for deprescribing, with varying degrees of complexity.[321] [323] [335] [344-349] Perhaps unsurprisingly, there seems to be a consensus forming to return to Woodward's[321] initial 5-step model of the deprescribing process, first described in 2003.[323] [344] [345] An updated version of this 5-step process is detailed below and presented in figure 3. This updated version is based on Woodward's original model and is complemented by the current body of literature on the subject.

Step 1: Comprehensive medication review

Obtaining a complete medication history from the patient is fundamental for any medication-optimizing intervention.[346] [350] Comprehensive medication review is, therefore, the very first step of the deprescribing process. This review aims to collect a complete list of medications taken regularly, occasionally or even "as required" and includes all prescription and non-prescription medication as well as any herbal medicines or any type of supplements. For each medication, the following information should be sought[346] [351] [352]: formulation, dose, frequency, duration of use, indication, medication allergies/intolerances and previous adverse drug events. If possible, adherence should also be measured.[344] This is critical as it is estimated that up to 96% of general practitioner and hospital medication lists contain at least one error, 24-59% of which may lead to harm[353] [354]. The medication review should be done in collaboration with physicians, nurses, pharmacists, patients and their family members, to obtain

multiple sources of information.[344] Patients should be made aware of the reasoning and intent behind the medication review and should be actively engaged in the process at this point.[345]

Step 2: Risk assessment and identifying potentially inappropriate medications

This step is by far the most important and the most complex step in the deprescribing process. One version of a conceptual framework proposed for deprescribing dedicates eight of its ten steps to address this part of the process.[346] As previously described in Chapter 2, identifying potentially inappropriate medications requires an assessment to determine that the medication incurs more potential harm than good. This can be very hard to quantify for individuals as many factors require consideration in this evaluation.[24 355] Risk can be assessed using drug factors, such as the overall number of drugs, use of "high risk" medications and toxicity.[24 26 323 356 357] Patient factors are also important such as being over 80, cognitive impairment, multiple comorbidities, substance abuse, multiple prescribers and non-adherence.[24 26 323 356 357] Risk should be discussed as a function of the patient's care priorities in order to anticipate and avoid some of the barriers to deprescribing.[341] The discussion should focus on treatment values, preferences, beliefs, as well as goals of care and, should identify which medications are important to the patient and which ones might not be.[344] Following this risk assessment comes a need to identify potentially inappropriate prescriptions. As discussed in Chapter 2, there exists a multitude of tools such as implicit and explicit criteria[358] to assist physicians in identifying drugs to avoid in the elderly. Regardless of the method used, identifying potentially inappropriate medications deemed suitable for deprescribing will always require clinical knowledge and judgment as well as patient input and time.[18 33 37] Physicians should prioritize identifying medications without an appropriate indication, drugs that contribute to prescribing cascades, those causing adverse drug effects, and those with a high risk of future harm.[344] Sometimes this evaluation is tricky, as the data and considerations for each individual patient are not always black and white.[45 359 360]

Step 3: Determining and prioritizing which medications can be ceased

After identifying all potential candidates for deprescribing, healthcare providers must then assess whether a medication can be stopped. In certain circumstances, despite being inappropriate, it may not be suitable to cease a medication immediately.[361] [362] Deciding which medication(s) should be stopped should always be done collaboratively with the patient using shared-decision making.[344] In cases where more than one medication is to be withdrawn, it is best to operate sequentially in order to facilitate the process and minimize potential risks.[321] [335] [347] [363] [364] This step-wise process not only enables proper follow-up and course correction but helps patients to understand and actively participate in the process. When multiple medications can be discontinued, it may not always be clear how to proceed as patient and prescriber goals may differ. In these situations, patients should voice their preferences using shared decision making and weigh these three pragmatic criteria: (1) which drugs have the most harms and least benefits, (2) which medications are easiest to discontinue and (3) which medications is the patient most willing to stop? The suggested approach recommends ranking drugs from high harm/low benefit to low harm/ high benefit and to proceed in that order.[323]

Step 4: Planning and implementing medication withdrawal

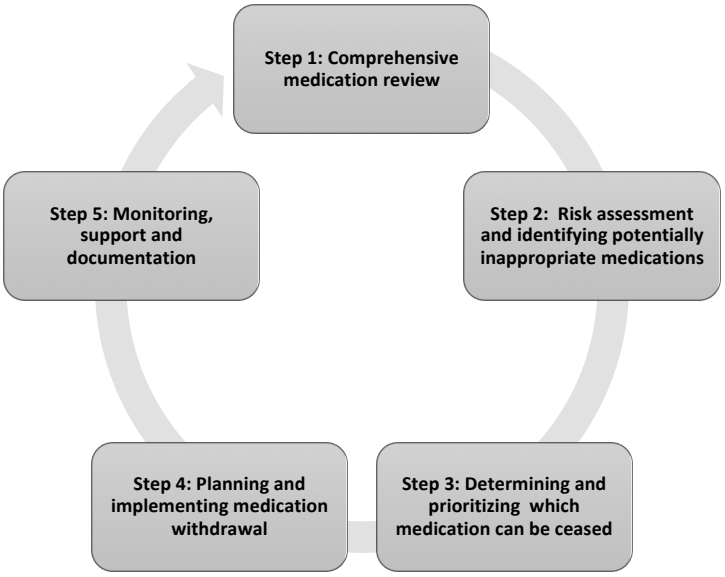
Once the medication to be discontinued has been identified and agreed upon by both the patient and the prescriber, the next step is to plan the tapering or withdrawal protocol. An appropriate drug discontinuation action plan should be discussed with all patients. Abrupt cessation is not recommended with certain medications as it can cause withdrawal symptoms, either physical, psychological or both [335]. It is generally recommended to taper the medication rather than to stop it abruptly even for medications that do not require tapering, in order to prevent or manage withdrawal symptoms or symptom recurrence.[336] [365] Patients report being more comfortable with deprescribing when it is implemented gradually rather than abruptly.[366] Alternate drug or non-drug therapies should be proposed for symptom recurrence should it occur so that patients can self-initiate treatment if required.[341] Slow tapering may also allow

prescribers to find the minimally effective dose should complete cessation be unfeasible, reducing the overall exposure and risks in each patient.[323]

Step 5: Monitoring, support, and documentation

Once initiated, monitoring the deprescribing process is critical to success.[346 367] Monitoring involves tracking adverse drug withdrawal reactions, symptom recurrence, reversal of drug-drug and/or drug-disease interactions and even benefits such as the resolution of adverse drug effects.[344] Support, while tied to monitoring, is distinct and highly valued by patients during the deprescribing process.[368] Support consists of anything supplemental to the monitoring process and which assists patient throughout the process such as providing education on lifestyle choices, advice on coping strategies or even referral to counseling services.[369 370] Finally, the last step of the deprescribing process is documentation. It is critical to document the reasons for, process and outcome of the deprescribing process and to share the documentation with other relevant health professionals. This last step aims to prevent/minimize re-initiation of the therapy as well as potential medication errors.[371 372] Unfortunately, while providing monitoring, support and documentation have been shown to be crucial to the long-term success of the deprescribing process, there exists little to no evidence on the best methods for rolling out these actions.[327]

Figure 3: *Proposed 5-step deprescribing process*



4.2.2 Deprescribing interventions

There exist a number of systematic reviews that critically appraise interventions to reduce inappropriate prescribing in older adults and to optimize medication management for older adults.[6 7 373-375] The systematic review by Kaur et al. included 24 studies, the Cochrane review included 12, the Yver et al. review included 36 studies and the Tja et al review included 26 studies. I also conducted a manual search of the literature for updates and new studies. Various types of interventions were assessed including educational interventions to physicians, online medication reviews, in-hospital geriatrician or pharmacist consultation, multifaceted pharmaceutical care, and computerized support systems. In this case, multifaceted pharmaceutical care consisted of a panel of varying expertise (nurse, pharmacist, geriatrician, etc.), who review, discuss and implement changes based on consensus. Computerized support systems consisted of computer based alert systems where physicians or pharmacists receive warnings based on pre-defined criteria of potential inappropriateness. The conclusions from the reviews were similar: computerized decision support and multifaceted pharmaceutical care are effective in reducing inappropriate prescriptions. Interventions testing an electronic prescribing system, with on-demand or computer-triggered alerts and drug decision support to the prescribers significantly decreased the number of new potentially inappropriate agents by 18% (relative rate .82, 95%CI .69-.98)[376], but did not trigger discontinuation of pre-existing prescriptions.[376-379] A new generation of computerized drug alerts to physicians that provides patient-specific risk estimates of drug-related falls was successful in modifying prescriptions in 25% of cases.[380] Unfortunately, physicians tended to ignore over 90% of alerts because the benefit was judged greater than the risk, or because the drug-drug or disease-drug interaction were considered clinically unimportant.[376-378] Consultation and screening by a geriatrician or specialized hospital-pharmacist have also been shown to be effective in reducing inappropriate prescriptions, but are labor-intensive and inaccessible to many community-dwelling patients.[6 7 381] Passive interventions such as mailing evidence-based educational bulletins to physicians do not change inappropriate prescribing practices.[382] Direct to patient approaches consist of any educational approach which use the bottom-up philosophy to target patients directly to motivate them to act as a

catalyst in the deprescribing process. Direct to patient educational approaches have also shown promising results as these can achieve very interesting discontinuation rates while being relatively labor-light and easy to implement.[383 384]

The most compelling results from medication discontinuation studies involve medication review by a pharmacist followed by direct communication to the physician.[6 7 326 379 382 385] One obstacle is reaching the primary care physician in the ambulatory care setting. Pharmacists only succeed in reaching physicians by phone 56% of the time. When contacted, 15% of physicians agree to switch patients to a more appropriate therapeutic agent, and 9% consider a change in the future.[379] The decision varies depending on the type of prescription[379].

4.3 Stakeholders involved in deprescribing

The patient-physician-pharmacist triad is a critical element of the deprescribing process. This triad is supported by supporting actors such as caregivers, families, friends and nurse practitioners. While their role is critical as stakeholders involved in deprescribing, this thesis will mostly focus on the three primary actors in the deprescribing process. Health-care systems and government can also provide structural and policy support to deprescribing.

4.3.1 The patient-physician-pharmacist triad

The patient-physician-pharmacist triad is central to both appropriate and inappropriate prescribing and deprescribing processes, illustrated in figure 4.

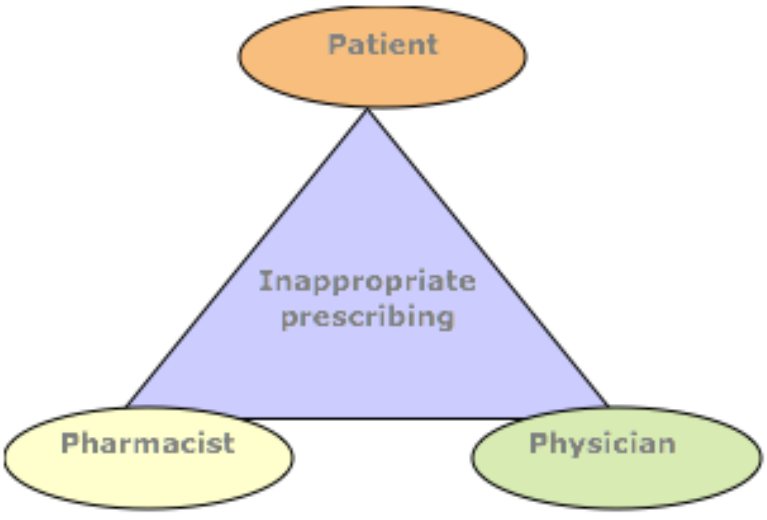


Figure 4: *Patient-physician-pharmacist triad*

Role and importance of the physician

Physicians are trained to provide leadership in developing and supervising patient health care plans, and as such are in charge of prescribing medications when necessary. An increasing prevalence of chronic diseases and patient multi-morbidities has put a significant burden on physicians, who now need to consider deprescribing in the context of complicated drug regimens.[9] Physicians should intuitively lead the deprescribing process, and seem to generally be in favor of deprescribing, with 66% believing the process can be beneficial for the patient.[386] However physicians experience a multitude of challenges when faced with deprescribing (explored later in this chapter) and have even described deprescribing as "swimming against the tide".[387] This is reflected in the many barriers expressed by physicians when attempting deprescribing processes with the patient[388] and may explain why interventions aimed at physicians to reduce inappropriate prescriptions have yielded disappointing results.[376-379 389] Despite this, the impact and role of the physician in the deprescribing process is critical to the success of deprescribing interventions[345 390 391] Physicians are often the first to detect issues triggering the need to deprescribe, and should ideally be the ones to initiate a shared-decision making process by engaging and collaborating with pharmacists and patients in the deprescribing process.[392]

Role and importance of the pharmacist

Traditionally, pharmacists' roles have been limited to preparing, managing and dispensing medication to patients.[393] With growing recognition that healthcare demands are now exceeding physician's capabilities to respond, pharmacists are stepping up to rightly share some of the physician's burden of optimizing medical management.[393 394] This has led to a change in the scope of pharmacy practice in the past few years, with pharmacists now able to provide more services than ever across Canada.[394] For example, depending on the province, pharmacists in Canada can provide such services as renewing/extending prescriptions, changing dosages or formulations, making therapeutic substitutions, emitting prescriptions for specific pre-defined conditions and even initiating prescription drug therapy in some cases.[394] As an expert in medication use, the pharmacist can and should play a collaborative role in the deprescribing

process. Their expertise can be employed in the context of independent/collaborative medication reviews.[395] Their expertise and availability can also be used to address many of the prescriber barriers to deprescribing[395] (which will be addressed later in this chapter). Pharmacists have access to centralized information on all prescriptions taken by a patient assuming they only visit one pharmacy unlike physicians who may only have access to a partial profile when prescribing. Finally, pharmacists have a key role to play as an intermediary/mediator between the patient and the physician in the shared decision-making process around deprescribing[395]

Role and importance of the patient

At the end of the day, the only person ultimately in control of which prescriptions are filled, which medications are consumed, how they are taken is the patient.[396] Patients, therefore, have an inherent right to be involved in the deprescribing process in accordance with the ethical principle of autonomy[397] and surveys have shown that the vast majority of patients wish to do so.[398] Involving patients in the medical decision-making processes is associated with improves outcomes, such as increases in patient satisfaction, medication adherence, quality of life and health outcomes.[399-401] Patients are best positioned as a source of knowledge for determining whether deprescribing is appropriate, as patients (and their families) alone know their full medical history, medications/supplements taken, personal values, beliefs and treatment goals.[325 402-404] Finally, involving the patient in the deprescribing process is required in order to preserve the physician-patient relationship.[405] Patient-mediated approaches seem to be the most effective when it comes to deprescribing.[390]

Role and importance of Caregivers

As previously mentioned, supporting individuals such as caregivers, families, friends and nurse practitioners also play an important role in the deprescribing process. A recent systematic review of nine articles on the effectiveness of caregiver-centered interventions has shown the benefits of these approaches on patient outcomes.[406] In fact, these studies demonstrated the positive effect on indicators such as patient's functional status, burden, depression symptom and self-care ability to name a few.[406]

While not the main focus of this thesis, it is important to note the key role these stakeholders may have on the deprescribing process.

4.3.2 System level deprescribing

Despite not being directly involved in the prescribing/deprescribing triad, policy-level approaches have been implemented in various parts of the world to curb the use of specific medications such as benzodiazepines. Examples of such interventions include the exclusion of benzodiazepines from Medicare Part D in the United-States[407] and the discontinuation of benzodiazepine reimbursement in the Netherlands[408], both intended to control chronic benzodiazepine use and associated costs. In Denmark, complete to partial restrictions were imposed driving license renewals for older benzodiazepine users, depending on the half-life of the benzodiazepine taken[409] in order to reduce the rate of benzodiazepine-related motor vehicle accidents.[409] All three studies reported small to modest improvements in the rate of benzodiazepine use. Sadly, many patients ended up switching to z-drugs, which are also inappropriate.[407-409] It is highly likely that policy interventions achieve very modest results in curbing benzodiazepine use because this class of medication is generic and therefore cheap. This is in sharp contrast with new drugs, where policy is effective in curbing inappropriate use due to costs. Policy interventions are slow to implement and may lead to unintended consequences, creating other health-related challenges.[97 410] While not directly discussed in this thesis, we recognize that higher-level policy approaches could complement patient-level interventions and may be required if a widespread impact is to be achieved.

4.4 Barriers and enablers to deprescribing

Considering the complexity of the deprescribing process, it stands to reason that patient and primary care physician engagement is critical to the success of the deprescribing process.[411] While their role in deprescribing is not as well established, pharmacists' level of engagement and role in the deprescribing process is emerging in the literature as well. This section reviews perceived barriers and enablers to deprescribing from the patient, prescriber and pharmacist perspectives and discusses

additional barriers specific to benzodiazepine deprescribing. By identifying and taking into consideration these barriers and enablers to deprescribing we hoped to gain a better understanding of the challenges and opportunities in the deprescribing process. This in turn allowed us to design an intervention which took into account several of these factors in order to increase our chances of achieving a positive outcome.

4.4.1 Physician perspective

As the prescriber, the physician is the front line health care professional targeted by most deprescribing interventions.[6 7 373-375] A recent systematic review by Anderson et al.[388] of 21 studies exploring prescriber's perspectives on which factors influence their deprescribing behavior for inappropriate prescriptions provides great insight on this topic. Thematic synthesis following the meta-analysis was able to narrow key findings into four categories: feasibility, self-efficacy, inertia, and awareness. In this case, awareness refers to the level of insight a prescriber has into the appropriateness of his/her prescribing. A table summarizing the barriers and enablers to deprescribing from the prescribers' perspective can be found in table 14.

Prescriber barriers

Prescriber barriers that fall under the category of feasibility capture all factors external to the prescriber that affect the probability and ease of deprescribing. Feasibility refers to factors, external to the prescriber, which determine the ease or likelihood of change. The first barrier is patient resistance to change, described in 13 studies.[5 350 370 412-421]. Patients may have discrepant goals to those of the prescriber, may poorly accept alternatives, or may report circumstances that are not propitious to deprescribing. The second barrier, identified in 12 studies, is a lack of tools or resources to properly carry out the deprescribing process.[5 61 370 413 417 419-425] Physicians specifically report limited time and too much effort required from physicians.[5 61 370 413 419-425] Physicians also criticize a limited availability of effective alternatives[5 370 417 424 425]and appropriate reimbursement for deprescribing.[5 370] Health beliefs and culture were also found to be a barrier to deprescribing in six of the studies, since the common culture is to prescribe more and more medications,[414 425 426] and there is a perception that some

patients require prescriptions to validate their illness.[416 417 423] Difficulties stopping prescriptions written by other physicians and specialists, which may be interpreted as a lack of respect for other prescriber's autonomy or hierarchy, and work practices that do not include reviewing patients' medication profile prior to renewal[415 417 419 423 425-427] are additional feasibility barriers.

Self-efficacy is the second impediment for physicians to deprescribe. Self-efficacy refers to factors that influence a prescriber's confidence and belief in their ability to deprescribe. Deficits in knowledge or skills for deprescribing, [350 413-416 421-423 427] such as difficulties assessing the benefit/risk ratio for certain patients, recognizing adverse events or establishing clear-cut diagnoses/indications for certain medicines serve as obstacles. Missing clinical information also makes it challenging for practitioners to make the best medication decisions for their patients[350 413 416 419 421 422 424 426 428], whether due to inadequate information transfer during transitions in care, inaccessible medical records, failure of the patient to disclose relevant information or any other cause. External pressure to follow guidelines despite the complexities of clinical practice[350 413 414 418 419], lack of evidence to support said guidelines[350 413 422] and pressure from other staff to keep certain prescriptions active in order to facilitate institutionalized routines in long-term or acute care, are other influences that impact on physicians' self-efficacy to deprescribe[417 425].

Inertia refers to the failure to act despite being aware of the need for deprescribing and constitutes an additional barrier to practice change. Fifteen studies in the meta-analysis identified fear of the unknown and the uncertainty of triggering negative consequences as factors underlying this inertia. [5 61 350 412-419 421 423 425-427] Potential negative consequences for the prescriber include the possibility of litigation, symptom relapse in the patient, and increased workload for the healthcare team. The belief that drugs work with few side effects ("if it ain't broke don't fix it)[5 415 417 418 423 424 427 429], the belief that prescribing meets the needs of patients and staff[5 370 416-418 423 424 429], the belief that deprescribing is difficult and potentially futile,[5 350 370 417 419 423 425 426 430] and the belief that deprescribing is a low priority issue all feed into the syndrome of inertia[5]

[416] [418] [421] [427]. Finally, lack of insight emerged as an important barrier under the awareness category and occurred when prescribers lacked awareness of the inappropriateness of their own prescribing habits. This barrier was observed rather than reported and consisted of either poor insight about drug appropriateness[419] [421] [426] or holding beliefs discrepant from the consensus ratings about which medications are inappropriate[5] [350] [418] [423] [424].

Prescriber enablers

When patients are motivated and positively receptive to change, it makes it more feasible for the prescriber to deprescribe. [370] [419] [422] Patients with a poor prognosis during end-of-life care are also more apt to want to stop their medicaitons[421]. The presence of resources and access to support services,[350] [370] [419] [424] and the possibility of prescriber reimbursement,[5] allows the deprescribing process to flow more smoothly. Work practices that offer opportunities to conduct medication reviews[350] [412] [416] [418] [420] [421] are also conducive to the deprescribing process, as are regulatory approaches such as raising the prescription threshold[418] [427] or monitoring[423], although the latter are seen as unwelcome by prescribers. Self-efficacy for deprescribing is enhanced when prescribers have good skills and attitudes towards deprescribing, specifically when prescribers feel comfortable deviating from guidelines[422] [427] and have confidence in their overall work experience and training[413] [421] [427]. When evidence-based information/decision support is available, prescribers have an easier time gauging the benefits and harms of deprescribing.[350] [413] [414] [420] Similarly, greater dialogue with patients facilitates shared-decision making[350] [412] [413] [418] [419] as does information-sharing and support from specialists[416] [418] [421] [424]. Inertia is overcome when there is fear about the risks of continuing a drug [418], when prescribers hold positive attitudes towards deprescribing[350] and when the prevailing belief is that deprescribing has benefits[370] [420] [430]. Other enablers include taking ownership of deprescribing[412] [416] [418], and the use of audit and feedback to raise awareness among physicians of inappropriate prescription patterns.[419] [421] [426]

Table 14: *Barriers and enablers to deprescribing from the prescribers' perspective*

Construct	**Studies reporting the construct as barrier**	**Barrier sub-themes within each construct (number of studies with sub-theme)**	**Studies reporting the construct as enabler**	**Enabler sub-themes within each construct (number of studies with sub-theme)**
Feasibility	20 5 61 350 370 412-427	– Patient (13) – Resources (12) – Work Practices (7) – Medical culture (7) – Health beliefs and culture (6)	12 5 350 370 412 416 418-423 427	– Patient (4) – Resources (5) – Work Practices (6) – Regulatory (3)
Self-efficacy	14 350 413 414 416-419 421 422 424-426 428	– Skills/knowledge (9) – Influencers (10) – Incomplete clinical picture (9)	12 350 412-414 416 418-422 424 427	– Skills/attitude (5) – Information/decision support (9)
Inertia	20 5 61 350 370 412-419 421 423-427 429	– Fear of unknown/negative consequences (15) – Drug effective with few side-effects (9) – Prescribing meets need (8) – Deprescribing is difficult/futile (9) – Deprescribing is a lower priority (5)	7 370 412 416 418 420 430	– Prescriber beliefs/attitude (5) – Prescriber behavior (3)
Awareness	8 5 350 418 419 421 423 424 426	– Poor insight (3) – Discrepant beliefs and practice (5)	3 419 421 426	– Audit/feedback system (3)

Overall findings

Overall, the meta-analysis and thematic synthesis of prescriber barriers and enablers to deprescribing highlight the importance of interdependent factors in prescribers' behavior. In comparison to the concept of medication continuity or prescription renewal, which are relatively passive events, deprescribing requires an active decision in order to change the status-quo. In addition to the prescriber's internal willingness and ability to deprescribe, there are also external factors that play an influential role. Interventions targeting physicians need to address these barriers and enablers to deprescribing.

4.4.2 Patient perspective

Although almost all traditional approaches to deprescribing have focused on the primary care provider,[6 7 373-375] there has recently been an increased interest in the patient's role in the deprescribing process.[341 345] Patients are now recognized as critical players in the successful outcome of deprescribing processes.[431] This has led to a keen interest in determining which factors influence a patient's decision to cease a medication.[341] A recent systematic review of 21 studies on the topic by Reeve et al.[341] provides great insights into what is currently known on this topic. Four categories of barriers and four categories of enablers were identified, with a few outlying themes. Table 15 summarizes the barriers and enablers to deprescribing from the patient's perspective.

Patient barriers

The most commonly reported construct, reported in 17 studies[4 366 370 430 432-444], is that of fear. This includes specific concerns such as fearing the return of symptoms, fear of withdrawal effects, fear of worsening the condition treated by the medication. Other non-specific fears and psychological issues related to the cessation of a medication are patients' beliefs of being unable to cope without their medication[445] or new problems arising when the medication is ceased[444]. Disagreement with the physician's perspective that a medication is inappropriate is another common barrier to deprescribing, observed in 15 studies[4 366 370 432 434-440 442-444 446]. Patients may weigh the

perceived necessity for the medication, or the benefit derived from taking the medication as higher than the risks. The lack of confidence in alternative treatments (both pharmacological[434] or non-pharacological[4]), feeling empowered by the medication,[432 446] requiring a medication to validate their condition, and mistrust of the recommendation to stop the medication are other sub-themes that emerge as barriers [436]. External influences also play a role and were described in 14 studies[4 366 370 432 434-436 439-441 443 444 446 447]. Having had a previous bad experience with stopping a medication, and pressure from people surrounding the patient such as their physician, their family or their friend to continue the medication are important barriers to deprescribing. Many patients report feeling pressure to take a medication, being actively discouraged not to cease a medication, and even taking a medication to "please" someone else. The final barrier reported by patients was the process itself, more specifically, difficulties in the deprescribing process, identified in eight studies.[366 370 436-439 443 444] The main sub-theme that emerged was a general lack of time and support offered to patients by physicians, which they considered necessary during and after deprescribing occured[437]. Certain patients reported receiving conflicting information about the deprescribing process. In addition to these four main themes, a few other potential barriers were identified including pragmatic reasons, such as a lack of alternatives[432], taking the medication out of habit[444] and not wanting to change because of old age.[4]

Patient enablers

The most common construct, reported in 18 studies, which enabled deprescribing from the patient's perspective was the perception that there was an appropriate reason to stop the medication. [366 430 432-448] The main sub-themes observed in this category of enablers were the occurrence of side effects, and the overall belief that the medication was not helping anyway. More specifically, the experience or fear of side effects enabled patients to stop their medication. The same could be said of patients who no longer recognized the need for the medication or had lost confidence in its ability to provide benefit. Other sub-themes included having a choice of alternative treatments, fear of addiction (mostly to psychoactive drugs[366 442 444 445]) as well as mistrust of the original prescriber.[432 441] Patients who disliked taking their medication

were also more apt to deprescribe – this theme emerged in 17 studies.[366 370 430 432 433 436-441 443-448] Patients perceived many inconveniences associated with taking medications such as cost and pill burden and liked the psychological benefits of ceasing, which consisted of patients wanting a more controlled and normal life,[430 436 440] free of medication. Some patients also reported that there was stigma linked to the use of medications. [366 432 436] Nine studies highlighted that when the process of deprescribing was viewed favorably, patients saw this as an enabler to deprescribing.[366 434 436 437 439-441 443 444] Patients reported in these studies that support from their physicians, and reassurance that there was always an option to restart their medication should they need to, helped them throughout the deprescribing process. Additionally, the offer of support from other sources, as well as the removal of external factors (such as the root cause of anxiety in a benzodiazepine user[430]) also helped with the process. As with the barriers, a positive influence towards deprescribing acted as an enabler.[4 366 370 432 434 442 447 448] Positive influences consisted of physicians, family, or friends having a positive attitude towards cessation, having a good relationship with the prescriber, and reading in the media (i.e. public approval) to discontinue their medication [447 448]. Some patients reported concerns about the compatibility of different medications and potential interactions,[432] and a lack of concern about the consequences of stopping a medication.[441]

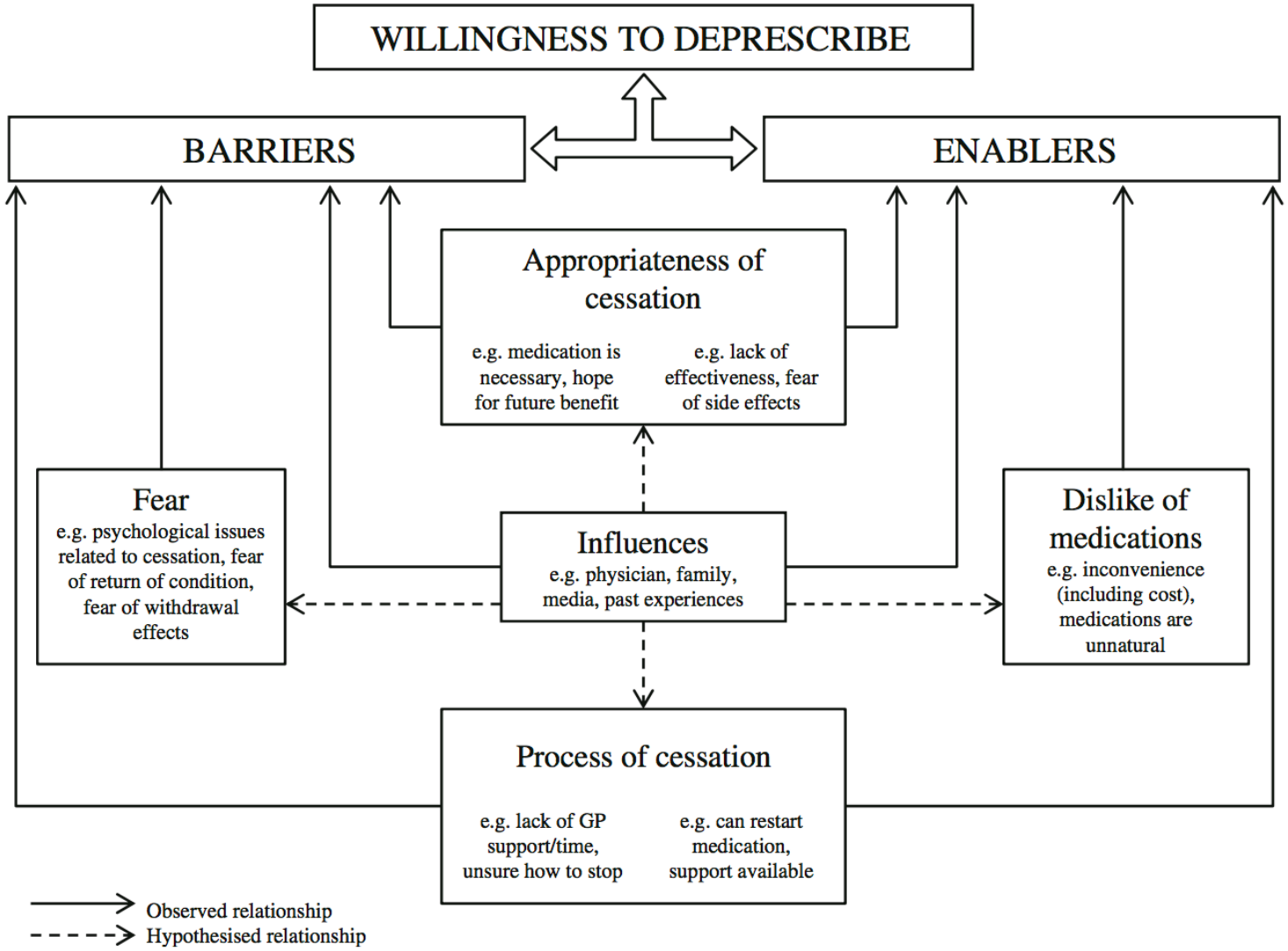
Patient's willingness to deprescribe

Reeve et al. present a framework for gauging a patient's overall willingness to deprescribe (Figure 5).[341] Deprescribing is influenced by a multitude of competing factors and individuals. While not a complete list of factors affecting deprescribing, this model can help inform future deprescribing research aimed at patients. The realist evaluation conducted during my thesis was partially based on lessons learned from the current body of literature and aimed to better understand the deprescribing process from the patient's perspective in the hopes of providing better guidelines for patient-centered deprescribing research.[449]

Table 15: *Barriers and enablers to deprescribing from the patients' perspective*

Construct	**Studies reporting the construct as a barrier**	**Sub-themes within each construct (number of studies with sub-theme)**	**Studies reporting the construct as an enabler**	**Sub-themes within each construct (number of studies with sub-theme)**
Fear (barrier) / Dislike(enabler)	17 4 366 370 430 432-444	– Fear of returning condition (11) – Non-specific fears (12) – Fear of withdrawal effects (4)	17 366 370 430 432 433 436-441 443-448	– Psychological benefit of cessing (9) – Inconvenience (9) – Medications are unnatural (3) – Stigma (2)
Appropriateness	15 4 366 370 432 434-440 442-444 446	– Non-specific fears (11) – Empowerment (4) – Lack of suitable alternatives (3) – Acceptance of condition/ medication (2) – Mistrust of the recommendation to cease (2)	18 366 430 432-448	– Experiencing side effects (10) – Fear of side effects (7) – Medication not necessary (7) – Fear of dependence (4) – Mistrust of original prescriber (2) – Alternative treatment (2)
Influences	14 4 366 370 432 434-436 439-441 443 444 446 447	– Influenced by care provider/family/friends (8) – Previous bad experience deprescribing (8)	8 4 366 370 432 434 442 447 448	– Positive physician (6) – Media/new information about the medication (2)
Process	8 366 370 436-439 443 444	– Lack of primary care physician support/time (6) – Lack of/conflicting information (4) – Lack of ongoing support (2)	9 366 434 436 437 439-441 443 444	– Support from physician (5) – Knowing they could restart the medication (5) – Other support (2) – Removal of external factors (1)
Other	6 4 366 432 435 438 444	– Pragmatic considerations (4) – Habit (1) – Old age (1)	2 432 441	– Medication compatibility/ interactions (1) – Lack of concern for potential consequences (1)

Figure 5: *Overview of patients' willingness to deprescribe from Reeve et al. (2013)*[341]



4.4.3 Pharmacist perspective

Pharmacists are playing a more significant role in managing patients' health,[394] but as yet there is little research on pharmacists' barriers and enablers in the deprescribing process.[395] We will explore what literature is currently available on the topic and hypothesize about plausible barriers and enablers.

Pharmacist Barriers

We expect that pharmacist barriers to deprescribing will at least partially mirror those of physicians. Lack of awareness of inappropriate prescriptions is one example. A survey conducted among Quebec pharmacists reported that less than 50% of pharmacists were aware of the prevalence of polypharmacy or inappropriate prescriptions in the geriatric population.[450] Additionally, only 41% of pharmacists acknowledged being familiar with the Beers criteria.[450] This lack of awareness presents the first, and potentially, the most important barrier to deprescribing from pharmacists' point of view. Pharmacist's general lack of awareness may contribute to a general inertia or fear about upsetting patient-physician relationships or increasing physicians' workload. Regarding self-efficacy, we expect that the same challenges for physicians will be observed for pharmacists. Barriers such as access to patient's information may be amplified if pharmacists do not have access to patient's electronic medical records. Finally, as with physicians, we expect pharmacists may have difficulties with patients accepting change/alternatives. [5 350 370 412-421] There also exists a body of literature detailing difficulties in patient-pharmacist communication due to issues of health literacy.[451] Prescriber barriers such as lack of time/resources, health beliefs, and prevailing medical culture may be present for pharmacists.

Pharmacist Enablers

Pharmacist enablers to deprescribing revolve around their ability to address prescriber and patient barriers.[395] Pharmacists' greater level of access to the patient because of monthly prescription renewals, in comparison to infrequent visits by patients to their physician, provides pharmacists with an opportunity to more reflectively engage in discussions and recommendations about medication safety.[395] This, however, is

conditional upon pharmacists having high-quality information about the patient's medications and health conditions.[395] Pharmacists embedded in primary care practice settings are more effective at making recommendations that are adopted by physicians, than pharmacists who work in community pharmacies.[452] Pharmacists may also directly influence and support patients during the deprescribing process.[341] As patient's beliefs and opinions about medications change over time in response to various factors,[453] the pharmacist is in a key position to identify the optimal time, strategy and patient considerations to optimize the deprescribing process.[454] Once the deprescribing process has been established and set in place, the pharmacist can play a critical role in supporting the patient by addressing any of their fears and concerns along the way.[341]

4.4.4 Barriers specific to deprescribing benzodiazepines

Benzodiazepines are one of the most difficult drug classes to deprescribe due to dependence issues, reticence to discontinue therapy and the presence of withdrawal symptoms, issues similar to those observed in stopping addictive substances such as tobacco[455] or alcohol[456]. Qualitative research with chronic benzodiazepine users reveals a psychological dependence on these medications, with consumers attributing qualities to the medication that enable them to cope with daily life, i.e., affording control over daily stress, promoting sleep and tranquility, and even prolonging life.[4] Most patients deny or minimize side effects. Several express subtle reluctance to outright refusal for tapering them. Others claim that they would be left to suffer without these medications.[4] Interviews with physicians confirm these findings.[5 415 428] Although the family doctor's main concern is to help the patient, he/she often feels overwhelmed by patients' psychosocial problems and reports difficulty dealing with the patient's suffering without prescribing medication.[415 428] Physicians do not view the use of benzodiazepines as being problematic because patients rarely complain of side effects, drug-seeking or escalating dose behavior suggestive of addiction.[5 457] Physicians are also skeptical about non-pharmacologic approaches to insomnia and anxiety.[415 457] Most importantly, physicians wish to avoid having their patients become demanding or difficult if they suggest modifying their prescriptions.[415 457] The good news is that first-time benzodiazepine users' attitudes are generally positive when they are offered

nonpharmacological therapies; the catch is that they do not realize that they should ask for them.[458]

4.5 Current approaches to deprescribing benzodiazepines in older adults

In this section, we summarize all original research evaluating chronic sedative-hypnotic deprescribing interventions in older adults, conducted over the past 20 years. Both randomized and non-randomized studies were reviewed that were reported in English and conducted in populations consisting entirely or almost entirely of older adults aged 65 and older. A total of ten studies were identified. Results are summarized in table 16.

4.5.1 Interventions targeting physicians

Pit et al.[459]

This was a cluster randomized controlled trial with 2 therapeutic arms conducted in Australia and published in 2007. In this study, 20 physicians recruited 849 patients to evaluate the effect of an intervention consisting of physician education combined with patient medication risk assessment, facilitation of medication review and provision of financial incentives, on the quality of medications used in older adults aged >65, compared to usual care. Outcomes observed over the 12-month follow-up were medication use, falls, injuries and quality of life. Authors reported a non-significant reduction in benzodiazepine use at 12 months: odds ratio of 0.51; (95% confidence interval, 0.20–1.30), but showed improvements in falls and injuries as well as no impact on quality of life. Limitations of this study for evaluating the effect of the intervention on benzodiazepine discontinuation include the fact that all drugs – and not just benzodiazepines – were targeted, so sub-analyses of benzodiazepine use are unavailable. Despite solid methodology, this omission greatly limits the pertinence of these results in evaluating physician level interventions to reduce sedative-hypnotic use.

Bourgeois et al.[460]

This was a feasibility study from Belgium published in 2014. In this study, physicians from five eligible Belgian nursing homes were contacted to ask if they were willing to initiate sedative-hypnotic discontinuation in their patients. Of 823 residents identified, 135 were prescribed benzodiazepines or z-drugs long-term. In total, physicians identified 51 residents in which they deemed discontinuation to be feasible, 38 of which agreed to participate in the study. The intervention led to 25/38 (65.8%) participants discontinuing their sedative-hypnotic use, and 7/38 (18.4%) participants reducing their dose at 2 months. At 8 months, one additional participant had successfully discontinued while one had relapsed. The study assessed clinical outcomes through multiple questionnaires and reported no significant difference in withdrawal symptoms by participants and no change in function over the 8 months. Despite impressive success rates, important study considerations greatly limit the validity of the findings. While authors mention that only 28% of the 135 residents were willing to initiate discontinuation, they also excluded all residents taking sedative-hypnotics for anxiety. This greatly limits the external validity and real-world feasibility of the intervention because of selection bias, as only willing/motivated residents and physicians were included. Additionally, the internal validity is greatly impaired by the lack of control group and small sample size.

4.5.2 Pharmacological substitution

Garzon et al. [461]

This was a placebo-controlled, double-blind, crossover randomized controlled trial conducted in Spain and published in 2009. The authors aimed to evaluate the effect of melatonin administration to facilitate discontinuation of regular hypnotic drugs. The authors conducted an 18-week, randomized controlled crossover trial of melatonin vs. placebo where 14 participants received 2 months of melatonin (5 mg/day) and 2 months of placebo. Of the 14 previous BZD users, nine (64.3%) were able to discontinue drug therapy while on melatonin but not on placebo, one was able to discontinue in both phases (odds ratio of 32.5, 95% CI 3.12-337.83 for discontinuation of benzodiazepine on melatonin vs placebo) and four were not able to discontinue in either phase.

Considerable limitations of this study include the very small sample size as well as the exclusion of chronic benzodiazepine users who take benzodiazepines for indications other than insomnia.

4.5.3 Mixed approaches with tapering

Petrovic et al.[462]

This was a feasibility study conducted in Belgium and published in 1999. Authors aimed to evaluate whether a short-term program consisting of temporary pharmacological substitution and psychological support for withdrawal of benzodiazepines was feasible in hospitalized geriatric patients. The study measured the effect of 1-week replacement therapy prior to withdrawal on BZD abstinence at 1 week in combination with psychological support in 49 participants. The investigators replaced the regular BZD regimen with 1 mg lormetazepam (n = 24) or 50 mg trazodone (n = 25) for a week before complete withdrawal. The discontinuation rate was higher in the trazodone group (80.0%) than the lormetazepam group (75.0%) (odds ratio 1.33 95CI 0.35-5.12), although the difference was not significant. The study found no difference in sleep quality measured with the Groningen Sleep Quality Scale (GSQ) between the two groups. Limitations of these results include selection bias because of the method with which participants were identified and recruited which increased the likelihood of only including motivated and willing participants. Additionally, the participants had ample access to physicians and support staff, which may not feasible on a larger scale.

Petrovic et al. [463]

In 2002 these authors conducted a follow up randomized clinical trial to measure the effect of 1-week replacement therapy prior to benzodiazepine cessation. Forty participants were randomly assigned to 1 mg lormetazepam (n = 20) or placebo (n = 20) groups and were again provided psychological support during the study period. The rate of successful discontinuation was significantly higher in the lormetazepam group than the placebo group (80.0 vs. 50.0%, $p < 0.05$). At the 12-month follow-up, only 46% (12/26) of the participants who had initially stopped their medications were still off of

their benzodiazepine, for an actual discontinuation success rate at one year of 30%. Limitations, which applied to their previous study also applied here.

Baillargeon et al.[464]

This was a non-blinded randomized controlled trial with 2 therapeutic arms conducted in Canada and published in 2003. In this study, participants with chronic insomnia and chronic benzodiazepine use (>3months) were recruited through physician referral and media advertisement. Of 119 eligible subjects, 65 met the study's inclusion criteria. Thirty-five participants were randomized to receive an 8-week combination intervention consisting of cognitive-behavioral therapy and physician supervised benzodiazepine tapering while the other 30 only received the tapering part of the intervention. At 8 weeks, immediately after the intervention, 77% [26/34] of the combination group had discontinued their benzodiazepine use vs 38% [11/29] in the tapering alone group (odds ratio 5.32 95CI 1.79-15.84). At 12 months these rates were 70% [23/33] and 24% [7/29] respectively (odds ratio 7.23 95CI 2.33-22.35). Despite impressive success rates, important study considerations greatly limit the validity of the findings. A few of the main considerations include the fact that participants were limited to chronic insomniacs and a small sample size, which greatly limits the generalizability of the results. Additionally, the study excluded eligible participants who lacked motivation, leaving only motivated individuals in the trial. The fact that only 65 (19%) of the 344 potential participants were included in the study and the resources required for the intervention greatly limit the applicability and feasibility of this approach on a large scale.

Curran et al.[465]

This was a randomized controlled trial with 2 therapeutic arms and a control arm conducted in Ireland and published in 2003. Authors aimed to test the effectiveness of two approaches to benzodiazepine discontinuation; Group A: Immediate 10week tapering protocol or Group B: 12 weeks of usual dose followed by the same tapering protocol. Both groups were provided with psychological support throughout the process. 138 participants agreed to participate in this study, however, 34 participants who did not

wish to withdraw their medication were allocated to the control group (Group C). At 6 months, results showed no difference between groups A and B with an overall discontinuation rate of 83/104 (80.0%). Such remarkable results are most certainly accounted for by the fact that the study only included willing and motivated participants. Additionally, the use of participants in the control group with a self-stated reluctance to taper diminishes the value of the comparator group.

Morin et al. [466]

This was a randomized controlled trial with 3 therapeutic arms conducted in Canada and published in 2004. This study evaluated the effectiveness of a supervised benzodiazepine taper, singly and combined with cognitive behavioural therapy, for benzodiazepine discontinuation in older adults with chronic insomnia. Interventions were spread out over 10 weeks and participants were followed up for 12 months. Of 156 potentially eligible participants, 76 were randomized to the 3 study arms (cognitive behavioral therapy n=24, supervised taper n= 25, combined n=27). At the 12-month follow-up, benzodiazepine discontinuation rates were 33% [8/24], 52 % [13/25] and 59 % [16/27] respectively. The combined approach was non-significantly more effective than cognitive behavioural therapy alone (odds ratio 2.91 95CI .93-9.14) or tapering alone (odds ratio 1.33 95CI .45-4.02). Participants were chronic insomniacs and the sample size was small, which limits the generalizability of the results. Specifically, the cognitive behavioural part of the intervention was tailored for chronic insomniacs. Additionally, while mostly aged over 65, participants were as young as 55 in this study, limiting its applicability to older adults.

Salonoja et al. [384]

This was a randomized controlled trial conducted in Finland and published in 2010. The study aimed to assess the persistence of one-time counseling by a geriatrician to reduce psychotropic drugs when compared to usual care. The intervention consisted of instructions to withdraw, reduce or change psychotropic drugs followed by a 1-h lecture about these drugs and their adverse effects. A total of 528 participants were recruited (259 intervention vs. 269 control). From these, 34

participants in the intervention group and 46 in the control group were taking BZD/Z-drugs at baseline. At the one-year follow –up benzodiazepine use decreased by 12/34 (35%) in intervention group while it increased by 2/46 (4%) in usual care group (p= 0.012). The shortcoming of this study is its small sample size and feasibility issues for scaling up the intervention.

4.5.4 Clinical Pharmacy Model

Roberts et al.[467]

This was a cluster randomized controlled trial conducted in Australia and published in 2001. A clinical pharmacy model is a framework centered around the pharmacist, which describes, defines and sets in place the tools, support and other resources required in order for pharmacists to more efficiently and effectively address an issue in their everyday practice. For example, in this study, they aimed to evaluate whether a year-long clinical pharmacy program involving clinical pharmacist support, education and medication reviews could change drug use, mortality and morbidity in nursing home residents. The study involved 905 residents in 13 intervention nursing homes and 2325 residents in 39 control nursing homes. While not the main objective of the study, the intervention resulted in a reduction of 597 benzodiazepine prescription items/year/1000 residents in comparison to a +278 increase in usual care, for an absolute difference of 875 benzodiazepine prescription items/year/1000 residents (p= 0.024). Additionally, authors reported no significant changes in morbidity indices or survival. Limitations of this study include the fact that while results show a significant change in practice habits, no results are available at the patient level to identify actual discontinuation rates. This greatly limits how results can be interpreted in evaluating the intervention's effect on benzodiazepine discontinuation.

4.5.5 Summary and lessons learned

This review shows that a wide variety of interventions have been employed to deprescribe sedative-hypnotics in older adults. The results suggest that pharmacological approaches with psychological support achieve the best success rates.[461-463] However, this estimate may be biased as all participants across these

studies were willing and motivated individuals. Additionally, most of these studies had very small sample sizes and were not adequately powered. Cognitive behavioural therapy requires extensive resources and provision of this intervention may not be feasible on a large scale. Some physician-centered approaches also showed promise,[460 465] while others did not[459]. However, the two studies showing a significant effect suffered from the same methodological flaws as the non-pharmacological interventions described above. The two studies that investigated mixed supervised tapering protocols and/or cognitive behavioral therapy yielded positive results.[464 466] However, both of these studies focused on older adults with chronic insomnia, which limits their generalizability to the general older adult population by excluding individuals taking sedative-hypnotics to treat anxiety. Additionally, these approaches are also very resource intensive on physicians and may suffer from feasibility issues when scaled-up. Finally, the only patient-directed educational strategy discussed in this review (other than the studies presented in this thesis) achieved a lower success rate.[384] Compared to other interventions, this type of approach potentially reflects real-life practice better and depending on the methods used, may be much easier to implement on a larger scale. One other major concern not addressed in most of these studies is the the long-term effectiveness of interventions on the relapse of benzodiazepine use as a lot of the studies do not have a long enough follow-up period to observe relapse. For example, studies have shown relapse rates as high as 40-50% 12-24 months following successful discontinuation.[148 463 468]

Overall the scope of research on deprescribing sedative-hypnotics in older adults is much narrower than research on medication appropriateness at large. [6 7] Pharmacists have not been involved in deprescribing studies of benzodiazepines in older adults and may be a target for future interventions. In comparison to the body of literature on deprescribing sedative-hypnotics in the general population,[469] the amount of research specific to older adults is very underwhelming and generally of poor quality.

4.6 The patient as a driver of deprescribing

4.6.1 Proof of concept

Many approaches have attempted to deprescribe medications, with the majority targeted at healthcare professionals, despite a significant body of literature on the important role patients play in the deprescribing process. This type of approach embodies the traditional paternalistic model of patient care, consistent with a "top-down" managerial style described in management and organizational development theory.[470] [471](See figure 6) Physicians acquire information about which medications to prescribe or de-prescribe and decide which drug the patient should or should not take. This paternalistic/top-down model represents the status quo. In 2009, the EMPOWER study[472] attempted to challenge the status quo by offering a new approach to deprescribing centered around the patient. This new modus operandi drew on theories of self-management and collaborative doctor-patient partnerships and is illustrated as a "bottom-up" change strategy in figure 6. [470] [471]

Figure 6: *Top-down Vs Bottom-up approaches*

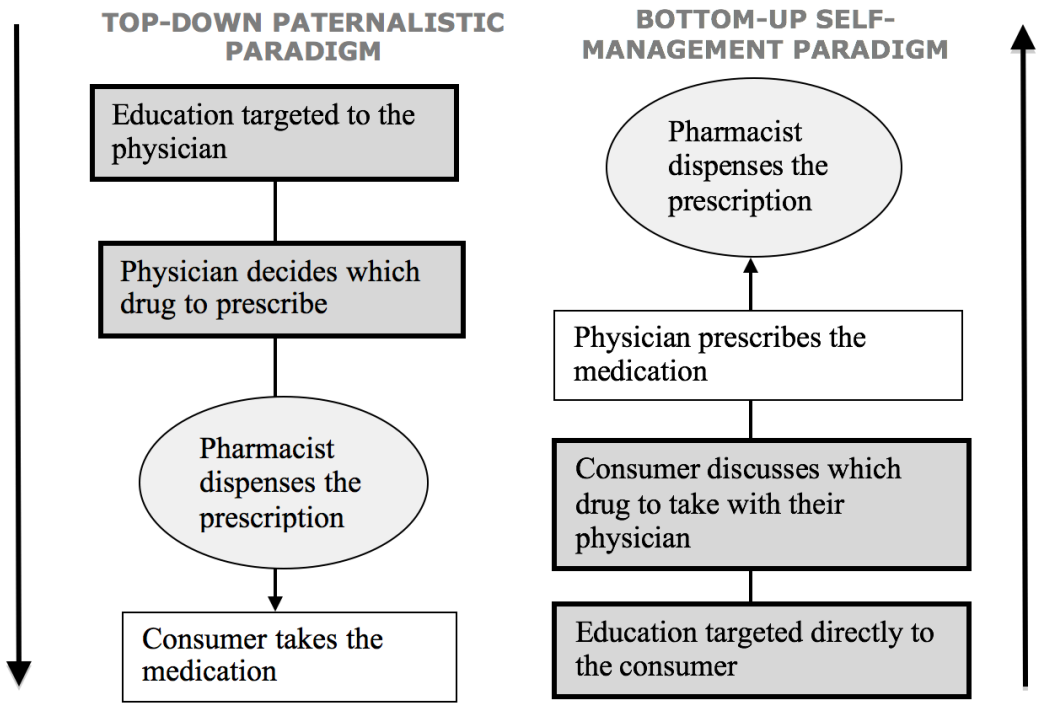


Table 16: *Summary of current approaches to deprescribing benzodiazepines in older adults*

Author, year, country, study	Setting	Intervention/ control	Number of participants Mean (SD) age	Follow-up duration	Study results: Effect of intervention on withdrawal	Clinical outcomes
Petrovic et al., 1999, Belgium, feasibility withdrawal study	Hospital	Temporary substitution with 1 week of 1 mg lormetazepam vs. 1 week of 50 mg trazodone Psychological support was provided as well	56 (7refused;24 lormatezapem/ 25 trazodone) 80.9 years	6 weeks	Discontinuation rate: lormetazepam 18/24 (75.0%) vs. trazodone 20/25 (80.0%) ($p > 0.05$)	No significant difference in the Groningen Sleep Quality score between groups
Roberts et al., 2001, Australia, Cluster RCT	Nursing homes	Introduction of a clinical pharmacy model (Clinical pharmacist support + education + medication reviews) vs usual care	3230 residents (905 residents in intervention nursing homes vs 2325 residents in usual care homes) ~98% of residents aged 60+, ~91 > 70	22 months	Change in number of benzodiazepine prescription items/year/1000 residents: -597 in the intervention group vs +278 in usual care, absolute difference of 875 benzodiazepine prescription items/year/1000 residents	No significant changes in morbidity indices or survival.

Petrovic et al., 2002, Belgium, double-blinded, placebo controlled RCT	Hospital	Temporary substitution with 1 week of 1 mg lormetazepam vs. 1 week of placebo, followed by complete withdrawal Psychological support was provided if participants faced any problems	40 (20 lormetazepam/ 20 placebo) 81.5 years	12 months	Discontinuation rate at 1 month: lormetazepam 16/20 (80%) vs. placebo 10/20 (50%) ($p < 0.05$) At 1-year follow-up: lormetazepam 8/20 (40%) vs. placebo 4/20 (20%)	Higher proportion of placebo group (40%) to lormetazepam group (25%) reported worsening sleep on the Pittsburgh Sleep Quality Index(PSQI) ($p < 0.001$). Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ): no difference between groups at 1 month ($p > 0.05$)
Curran et al., 2003, Ireland, RCT	Community	Patients allocated to group A (BZD dose tapering from week 1); group B (given usual BZD dose for 12 weeks and then taper); group C (continued using BZD)	138; 104 agreed to participate in the withdrawal study and 34 chose to participate but not withdraw; these were allocated to group C Age range 65–93 (mean 77+/-6.9)	6 months	Overall discontinuation rate 83/104 (80.0%) No difference between groups A and B	No difference in sleep between groups Withdrawal group had higher medical outcomes study short form-36 scores and higher social functioning at 24 weeks ($p < 0.05$)

		All groups received psychological support				
Baillargeon et al., 2003, Canada, RCT	Community	Patients allocated to group A (8-week, physician supervised, BZD dose tapering + 8 weeks cognitive behavioral therapy); group B (BZD dose tapering only)	65 (35 subjects in the combined treatment group and 30 in the tapering only group) 67.4 years	12 months	Discontinuation rates: At 8 weeks 77% [26/34] v. 38% [11/29] At 12 Months 70% [23/33] v. 24% [7/29]	Not measured
Morin et al., 2004, Canada, RCT	Community	Patients allocated to group A (10-week, physician supervised, BZD dose tapering); Group B (10-weeks cognitive behavioral therapy); or group C (Combined)	76 (25 subjects on taper only, 24 on cognitive behavioral therapy and 27 on combined treatment) 62.5 years	12 Months	Discontinuation rates: At 12 Months Group A: 33% [8/24] Group B: 52 % [13/25] Group C: 59 % [16/27]	Increased sleep efficiency across all groups No significant Change in Benzodiazepine Withdrawal Symptom Questionnaire

Pit et al., 2007, Australia, Cluster RCT	Community	Physicians allocated to intervention group (education, medication risk assessment and feedback) or usual care	849 (452 patients in intervention practices, 397 patients in usual care practices) ≥ 65 years old	12 months	Reduction in benzodiazepine use at 12 months: non-significant odds ratio of 0.51; (95% confidence interval, 0.20–1.30)	Significant change in risk of falls, injury and injuries requiring medical attention No effects on quality of life
Garzon et al., 2009, Spain, placebo controlled, double-blind, crossover RCT	Community	5 mg melatonin substitution for 2 months, followed by 2 months of placebo, vice versa	14 regular users of BZD 74.7 years	2 months	9/14 (64.3%) were able to discontinue BZD during melatonin substitution, 1/14 (7.1%) discontinued during both phases and 4/14 (28.5%) were not able to discontinue	Northside Hospital Sleep Medicine Institute test, Geriatric Depression Scale and Goldberg Anxiety Scale scores improved with melatonin vs. baseline and vs. placebo ($p < 0.025$ for all)
Salonoja et al., 2010, Finland, RCT	Community	Medication review by a geriatrician plus patient education with gradual tapering	528 (259 intervention vs. 269 control) 34 participants in the intervention group and 46 in the control group were taking	12 months	BZD use decreased by 12/34 (35%) in intervention group vs. increased by 2/46 (4%) in usual care group ($p = 0.012$)	Not measured

		vs. usual care	BZD/Z-drugs at baseline Mean (SD) age intervention group 72.8 (5.6) years[b] Mean (SD) age control group 72.9 (5.9) years			
Bourgeois et al., 2014, Belgium, feasibility study	Nursing home	GP's willingness to initiate BZD discontinuation with tapering recommendation	Of 135 residents, GPs indicated that discontinuation was feasible in 51 residents Of 51 residents that GPs agreed, 13 residents refused leaving 38 residents	8 months	At 2 months: 25/38 (65.8%) discontinued BZD/Z-drug, 7/38 (18.4%) reduced dose, 6/38 (15.8%) relapsed At 8 months: 66% completely discontinued BZD/Z-drugs	No significant Change in Benzodiazepine Withdrawal Symptom Questionnaire No change in Activities of Daily Living scores over 8 months. Those who relapsed did not have reduced sleep, but did have reduced quality of life

In the bottom-up approach, the patient drives prescription decisions from information gathered on the internet, through friends, or via an accredited academic source (as in the EMPOWER study). The patient-centered approach ultimately aims to inform and empower patients, enabling them to act as a catalyst or to help in the reduction of all forms of inappropriate prescribing. To our knowledge, no published study to date had targeted the patient as a driver of safer prescribing practices before EMPOWER. Since then, there has been a significant increase in patient-centered deprescribing research with new questionnaires[342 473] and patient-centered processes being developed[345].

4.6.2 Patient-centered care and shared-decision making

Although there is no common definition to define patient-centered care, there exists agreement that it revolves around three core concepts: (1) patient participation and involvement, (2) the relationship between the patient and the healthcare professional, and (3) the context where care is delivered.[474 475] Patient-centered care has already been shown to improve patient satisfaction, quality of life, adherence and overall health outcomes.[399-401] Shared-decision making is a process that is fundamental to patient-centered care and refers to the process of educating patients on the benefits, risks, and alternatives of a treatment followed by patient engagement in a dialogue with their healthcare provider to come to a medical decision where both parties have a say.[392] It has two main components: patients' decision support and patients' decision aids. Patients' decision support refers to a systematic, theory-based clinical strategy for helping those individuals who wish to engage with their health care providers in making these kinds of preference-sensitive choices while patients' decision aids are standardized evidence-based tools which facilitate the process of patients' decision support.[476] Research has shown that physicians recognize the need for shared-decision making when considering the cessation of a medication[350 477]. Additionally, research suggests that the majority of patients wish to be involved in medical decision-making processes, even if the final decisions are taken by their physicians.[398 399] While there has been criticism around the barriers to scaling up the shared decision process,

evidence suggests that these concerns are mostly myths and that this approach can be implemented on a large scale.[478]

4.6.3 Are patients ready to act?

A major question was whether real-life community-dwelling older adults were interested and ready to get involved in the deprescribing process. The idea to develop knowledge transfer programs aimed at consumers to reduce inappropriate prescribing first emerged from the WOW "*What Older women Want*" study. In this study, 5000 women aged 55-95 from across Canada were surveyed and ranked medication side effects highest among their top health concerns.[22] Over two-thousand same-aged men admitted to similar fears of adverse drug events in 2008 during the follow-up Men's Health Study.[21] With 88% of women and 63% of men primed to the issue of medication risk, it seemed logical to target this audience for knowledge transfer interventions on how to take control and reduce drug-related risk. While this guided what would then become the EMPOWER study[472] in order to have a practical evaluation of whether patients were ready to become catalysts in the deprescribing process, other researchers aimed to gain a better theoretical understanding of patients attitudes towards the deprescribing processes.[473]

Reeve at al. developed a questionnaire in order to capture patients' views and beliefs regarding cessation of medications.[473] Early results of this questionnaire from a sub-sample of 100 Australian older adults in ambulatory care indicated that 92% (95%CI 86.7-97.3) of patients would be willing to stop a medication if their doctor said it was possible to do so.[342] [472] This was accompanied by 68% (95%CI 58.9-77.1) of participants having an active desire to reduce the number of medications they were taking and 65% (95%CI 55.7-74.4) who felt they were taking a large number of medications.[342] These results were recently confirmed in community-dwelling older adults from Quebec with 71.9% (95%CI 63.3-78.3) of patients willing to stop a medication if their doctor recommended it, 50.8% (95%CI 42.3-59.7) of patients wishing to reduce their number of medications and 51.2% (95%CI 41.6-60.0) who felt they were taking a large number of medications.[479] Between-country differences could be

explained by the number of drugs consumed - 10 per day in the Australian sample and 6 per day in the Canadian sample - as this variable is associated with the outcomes.[479] It should be noted that hypothetical willingness to deprescribe may not translate into a genuine willingness to deprescribe in real-life practical situations.[480 481]

4.6.4 Patient empowerment for deprescribing benzodiazepines

Despite our belief that patients were ready to get involved in the deprescribing process, we felt that empowerment triggers would be necessary to motivate patients to action. Patient empowerment is a process designed to facilitate self-directed behavior change by increasing one's ability to think critically and act autonomously.[482] The World Health Organization describes empowerment as “a process through which people gain greater control over decisions and actions affecting their health”[483]. The empowerment approach is designed to help patients choose personally meaningful, realistic goals. To maximize the chance of success, patients must be internally motivated rather than externally motivated. Patient empowerment was deemed critical to the success of the trials in this thesis due to the physical and psychological dependence that occurs with benzodiazepines, which can interfere with the discontinuation process.[5 415 428] With this in mind, various elements and theories were integrated into the intervention to facilitate patient empowerment.[484] The main hypothesis driving the research in this thesis was that participants who acquired new information and changed their beliefs regarding benzodiazepines would benefit most from the tools provided and that the support offered might act as a cue to action to initiate deprescribing.

4.7 Summary

This chapter defined the concept of deprescribing and illustrated just how complex the process can be, with multiple stakeholders and other factors having an important influence on outcomes. Several deprescribing interventions have been tested to reduce polypharmacy and inappropriate prescriptions, however, most of them targeted care providers rather than patients. Few interventions to reduce benzodiazepine use in older adults were rolled out outside of the supervised hospital or

clinic setting, and no approach tested patient-directed education to community-dwelling seniors. The concept of a patient-centered intervention to deprescribe benzodiazepines and the importance of shared-decision making have strong appeal in theory but require rigorous testing. The rest of this thesis describes our approach to developing and evaluating patient-centered interventions for community-dwelling seniors to deprescribe benzodiazepines and how we overcame barriers to deprescribing by embedding solutions within the intervention mechanisms.

Gaps in the existing literature

With this in mind, it becomes clear that there are important gaps in the literature on deprescribing benzodiazepines in older adults. First, there is very little quality evidence on the effectiveness of interventions to deprescribe benzodiazepine in community-dwelling older adults. Most current studies on the topic are underpowered, often flawed methodologically (short follow-up times, use of motivated individuals, etc.) or are not done in the community-dwelling population. Secondly, there is currently little to no practical research into bottom-up approaches, empowerment approaches such as patient-centered care to deprescribing in contrast to a vast body of literature on the effectiveness on top-down approaches. Thirdly, very little is known about the deprescribing process from the patient's perspective with most of the literature one again favoring the prescriber's perspective. Finally, similarly to patients, there is an important gap in the literature on the potential role and impact of pharmacists in the deprescribing process in comparison to the literature on the role and impact of physicians. This thesis will therefore aim to contribute to the body of literature by providing insights into these topics.

Chapter 5 – Objectives

The overarching objective of this thesis was to conceive and evaluate novel approaches to deprescribing benzodiazepines in community-dwelling older adults. My thesis is divided into three separate projects. In the first project, the EMPOWER trial, I compare the effect of a direct-to-consumer educational intervention against usual care on benzodiazepine therapy discontinuation among community-dwelling older adults. In the second project consisted, I conduct a realist evaluation using the quantitative and qualitative results of the EMPOWER trial to better understand the deprescribing process from the participants' perspectives, in order to inform my third project: the D-PRESCRIBE intervention. The development of the D-PRESCRIBE intervention addresses the contextual barrier of the lack of provider support to patients in whom the EMPOWER brochure triggered a motivation to deprescribe. In the D-PRESCRIBE trial, I added an evidence-based pharmaceutical opinion to be simultaneously delivered alongside the direct-to-consumer intervention. The goal of D-PRESCRIBE was to evaluate the effectiveness of a pharmacist-initiated educational knowledge transfer intervention to both patients and prescribers on the discontinuation of inappropriate prescriptions among community-based older adults, compared to the delivery of the EMPOWER brochure to patients alone.

5.1 Specific objectives - Project 1: The EMPOWER randomized trial

5.1.1 Article 1: A drug education tool developed for older adults changes knowledge, beliefs and risk perceptions about inappropriate benzodiazepine prescriptions in the elderly

The primary objective of the first article of this thesis was to **develop and test an educational tool for deprescribing inappropriate benzodiazepine use in older adults**. *We hypothesized that the educational tool would elicit cognitive dissonance resulting in improvements in patient knowledge, beliefs, and perceived medication risk. This would then lead to greater motivation for initiating discussions about drug discontinuation with a doctor or pharmacist and greater self-efficacy for tapering*

benzodiazepine use. In order to achieve this, we tested whether cognitive dissonance was achieved through knowledge acquisition and belief modification, thereby providing proof of concept for how the intervention might work.

More precisely, objectives of the first article were to: 1) Evaluate participants' change in knowledge, beliefs and risk perception around the use of benzodiazepines in older adults after reading the intervention, 2) Evaluate the frequency of occurrence of cognitive dissonance, 3) Compare changes in self-efficacy for discontinuing benzodiazepines post-intervention and 4) Evaluate correlates and anticipated health behaviors associated with increased risk perception associated with benzodiazepine use.

5.1.2 Article 2: Reduction of inappropriate benzodiazepine prescriptions among older adults through direct patient education: the EMPOWER cluster randomized trial.

The primary objective of the second article of this thesis was **to test the effectiveness of direct patient education about drug harms on benzodiazepine therapy discontinuation among community-dwelling adults 65 years and older with chronic use of benzodiazepine therapy compared to usual care at six months.** *We hypothesized that directly empowering chronic users with knowledge about risks, suggestions for lower-risk therapeutic options, and self-efficacy for implementing tapering protocols would result in a minimal 20% difference in benzodiazepine therapy discontinuation when compared to usual care.* In order to accomplish this, we conducted a pragmatic cluster randomized controlled trial comparing the impact of the intervention on benzodiazepine use compared to usual care.

Secondary objectives of this article were to: 1) assess rates of dose reduction in addition to complete cessation, 2) conduct a process evaluation of subsequent events after receipt of the intervention and 3) evaluate risk differences for discontinuation of an inappropriate medication by subgroups of interest.

5.1.3 Article 3: Use of the EMPOWER brochure to deprescribe sedative-hypnotic drugs in older adults with mild cognitive impairment.

The primary objective of the third article of this thesis was to **examine whether cognitive status affected the comprehension and success rates of the EMPOWER patient-centered educational approach to the deprescribing of benzodiazepines.** *We hypothesized that as sedative-hypnotic use is associated with cognitive impairment and that individuals with mild cognitive impairment may demonstrate significant impairments in their ability to understand, reason and participate in health-related decisions, their response to the intervention may differ from individuals with normal cognition.* Overall, we sought to determine whether patients with mild cognitive impairment retained the capacity to understand educational material related to drug harms and whether this population responded differently to the EMPOWER intervention. In order to accomplish this, we conducted a sub-analysis of participants based on their cognitive status and evaluated differences in benzodiazepine discontinuation and other key factors.

5.2 Specific objectives - Project 2: The realist evaluation

5.2.1 Article 4: A realist evaluation of patients' decisions to deprescribe in the EMPOWER trial

The primary objective of the third article of this thesis was to **conduct a realist evaluation to reveal how the EMPOWER intervention might generate different outcomes in different circumstances, and how mechanisms work in particular contexts, by enabling or motivating participants to make different choices during the deprescribing process**. *We hypothesized the mechanisms embedded within the EMPOWER intervention would work differently under a range of contexts, and that different factors would influence deprescribing decisions among individuals who successfully deprescribed benzodiazepines versus those who did not attempt or failed to deprescribe.*

More specifically, the objectives of the fourth article in this thesis were to test the following mechanisms: whether the EMPOWER intervention (1) triggered patients' motivation to deprescribe by increasing knowledge and concern about benzodiazepines; (2) augmented patients' capacity and self-efficacy to taper benzodiazepines and (3) created opportunities for the patient to discuss and receive support from a healthcare provider to engage in the deprescribing process. We identified in which contexts these mechanisms led to successful or failed deprescribing outcomes.

5.3 Specific objectives - Project 3: The D-PRESCRIBE randomized trial

5.3.1 Article 5: Development of an evidence-based pharmaceutical opinion for deprescribing

The primary objective of the fifth article of this thesis **was to develop a prototype for pharmaceutical opinions that would effectively convey information about drug harms and potential solutions, with the aim of increasing interprofessional knowledge and communication around deprescribing**. *We hypothesized that an evidence-based pharmaceutical opinion could incorporate information that would overcome the barriers to deprescribing observed during the course of the EMPOWER trial.* In order to accomplish this, a prototype was developed based on information in the literature and adapted based on feedback received from both physicians and pharmacists.

5.3.2 Article 6: Comparison of Interventions to Reduce Sedative-Hypnotic Prescriptions Among Older Adults in the Outpatient Setting: the EMPOWER vs. D-PRESCRIBE Pragmatic Cluster Randomized Trials

The primary objective of the sixth article was **to evaluate the comparative effectiveness of the D-PRESCRIBE intervention compared to the EMPOWER intervention alone**. *We hypothesized that a pharmacist-initiated educational knowledge transfer intervention to both consumers and prescribers would result in a minimal 12.5% increase in benzodiazepine therapy discontinuation compared to the*

EMPOWER study. In order to accomplish this, we conducted a pragmatic cluster randomized clinical trial comparing the impact of the D-PRESCRIBE intervention on benzodiazepine discontinuation compared to usual care followed by a comparison using the EMPOWER study as a historical control group.

More specifically, in the sixth article, we aimed to evaluate: 1) the benefit of simultaneously educating physicians and consumers on benzodiazepine discontinuation among community-dwelling older adults, compared to usual care; and 2) the value added by a pharmaceutical opinion delivered to the prescriber at the same time that the EMPOWER brochure is given to consumers, on discontinuation of benzodiazepine therapy. Secondary objectives were: 1) to assess rates of dose reduction in addition to complete cessation and 2) to conduct a process evaluation of subsequent events after receipt of the intervention.

Chapter 6 – Methods

This chapter provides a detailed description of the methods used for each of the three thesis projects. First, I will review the methodology used for the two cluster randomized deprescribing trials. A protocol for each trial was published in the peer review literature. Both protocols are included in this chapter, along with additional explanatory details. Both trials were also registered at Clinicaltrials.gov (https://clinicaltrials.gov/show/NCT01148186 & https://clinicaltrials.gov/ct2/show/NCT02053194). In the second section of this chapter, I will delve into an explanation of realist methodology, which uses a structured combination of qualitative and quantitative methods to understand if and how an intervention works for specific people under specific contexts.

6.1 Cluster randomized trials

This thesis reports the results of both the EMPOWER (Eliminating Medications Through Patient OWnership of End Results) and D-PRESCRIBE trials (Developing Pharmacist-led Research to Educate and Sensitize Community Residents to the Inappropriate Prescriptions Burden in the Elderly). Both of these trials were pragmatic cluster randomized controlled clinical trials that aimed to evaluate the impact of an educational intervention to reduce chronic use of benzodiazepines in community-dwelling older adults. Both trials adhered to the latest version of the Consolidated Standards of Reporting Trials (CONSORT) statement for cluster randomized trials.[485] In addition to including both published protocols, this chapter expands on some of the methodological challenges we confronted during the design and conduct of the 2 trials, and how these were resolved during the course of my thesis work. Specifically, complementary information on various aspects of the trials is provided, including our decision-making process for complexities related to design logistics and study flow, ethical issues, data measurement challenges and the choice of statistical models used in both trials. Of note, the D-PRESCRIBE trial included 3 additional drug classes other than benzodiazepines and Z-drugs, but assessment and review of these drug classes are not included as part of this thesis.

6.1.1 EMPOWER protocol

An educational intervention to reduce the use of potentially inappropriate medications among older adults (EMPOWER study): protocol for a cluster randomized trial

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Key words: Patient education, benzodiazepine use, inappropriate prescription, older adult health, cognition disorders, drug therapy, polypharmacy

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TRIAL REGISTRATION: clinicaltrials.gov Identifier: NCT01148186. URL: https://clinicaltrials.gov/show/NCT01148186

Abstract:

Background: Currently, far too many older adults consume inappropriate prescriptions, which increase the risk of adverse drug reactions and unnecessary hospitalizations. A health education program directly informing patients of prescription risks may promote inappropriate prescription discontinuation in chronic benzodiazepine users.

Methods/Design: This is a cluster randomized controlled trial using a two-arm parallel-design. A total of 250 older chronic benzodiazepine users recruited from community pharmacies in the greater Montreal area will be studied with informed consent. A participating pharmacy with recruited participants represents a cluster, the unit of randomization. For every four pharmacies recruited, a simple 2:2 randomization is used to allocate clusters into intervention and control arms. Participants will be followed for 1 year. Within the intervention clusters, participants will receive a novel educational intervention detailing risks and safe alternatives to their current potentially inappropriate medication, while the control group will be wait-listed for the intervention for 6 months and receive usual care during that time period. The primary outcome is the rate of change in benzodiazepine use at 6 months. Secondary outcomes are changes in risk perception, self-efficacy for discontinuing benzodiazepines, and activation of patients initiating discussions with their physician or pharmacist about safer prescribing practices. An intention-to-treat analysis will be followed.

The rate of change of benzodiazepine use will be compared between intervention and control groups at the individual level at the 6-month follow-up. Risk differences between the control and experimental groups will be calculated, and the robust variance estimator will be used to estimate the associated 95% confidence interval (CI). As a sensitivity analysis (and/or if any confounders are unbalanced between the groups), we will estimate the risk difference for the intervention via a marginal model estimated via generalized estimating equations with an exchangeable correlation structure.

Discussion: Targeting consumers directly as catalysts for engaging physicians and pharmacists in collaborative discontinuation of benzodiazepine drugs is a novel

approach to reduce inappropriate prescriptions. By directly empowering chronic users with knowledge about risks, we hope to imitate the success of individually targeted anti-smoking campaigns.

Trial registration: ClinicalTrials.gov identifier: NCT01148186

Background

Appropriate and safe prescribing for older adults is rendered difficult by the increased risk of side effects, drug-drug interactions, and adverse events, due to associated comorbidities and high prevalence polypharmacy in this population [1,2]. Prescriptions are considered inappropriate when potential risks outweigh potential benefits, and safer therapeutic alternatives exist that have similar or superior efficacy [3-5]. Avoiding the use of inappropriate and high-risk drugs is an important, simple and effective strategy for reducing medication-related problems and adverse drug events in older adults [5]. The Beers Criteria for Potentially Inappropriate Medication Use in Older Adults identifies, grades and qualifies potentially inappropriate medications. The criteria were developed by a panel of geriatric pharmacy experts who applied a modified Delphi method to a systematic review of all medications and graded the evidence to reach a consensus on a recommended list of drugs to avoid in older people [5-7].

Currently, far too many older adults are taking inappropriate prescriptions, which further increases the risk of adverse drug reactions and unnecessary hospitalizations [5,8-11]. Inappropriate prescribing has been estimated to occur in 12 to 40% of community-dwelling non-hospitalized older adults aged over 60 years, depending on the criteria used and the country studied [3,5,9-14]. A conservative estimate of the incremental healthcare expenditures related to inappropriate prescribing among community-dwelling older adults is $7.2 billion in the United States [12].

Benzodiazepines represent one of the most prevalent inappropriate prescriptions, consumed by 19% of older adults (range 10 to 42%) [15]. The new Beers list, released in 2012, recommends that all short- and long-acting benzodiazepine sedative-hypnotic drugs used for the treatment of anxiety and insomnia should be

avoided in older adults, due to an excessive risk of delirium, falls, fractures and motor vehicle accidents [5,16-19]. Benzodiazepines have also been shown to increase the risk of amnestic and non-amnestic cognitive impairment and may lead to incident dementia [20,21].

Previous research has attempted to define the best strategy to inform and educate relevant parties, to try and implement safer prescribing practices, and to eliminate benzodiazepine use. The problem is that chronic benzodiazepine users develop a psychological dependence to benzodiazepines, and both physicians and consumers have difficulty implementing tapering protocols [22]. Many patients deny or minimize side effects, or express reluctance to risk suffering without these medications [22]. For these reasons, physicians are hesitant about insisting on benzodiazepine discontinuation for fear of upsetting the doctor-patient relationship or because they believe that the patient tolerates the medication with minimal side effects [23].

Interventions to reduce benzodiazepine use in older people have been tested [24-47]. Several approaches have yielded insignificant results; other approaches, such as physician-targeted online drug audits, didactic educational activities and letters from physicians advising on risks associated with benzodiazepine use, have resulted in discontinuation rates ranging from 16 to 25% [43-47]. Despite achieving mild success in benzodiazepine discontinuation, these approaches are rarely feasible on a large scale and can be linked to extensive fees.

Targeting consumers directly as catalysts for engaging physicians and pharmacists in collaborative discontinuation of benzodiazepine drugs is a novel approach to reduce inappropriate prescriptions that has never been tested. Studies have shown that collaborative efforts to taper benzodiazepine use do not result in an increased workload for family physicians [48]. This type of approach could empower patients to participate in medication safety, diminish physician workload and do so at lower costs than current approaches in changing medical practice.

The aim of the current cluster randomized controlled trial is to determine the effectiveness of an educational tool directed at older adults on subsequent cessation of benzodiazepine use.

Methods/Design

Trial design

Study objectives

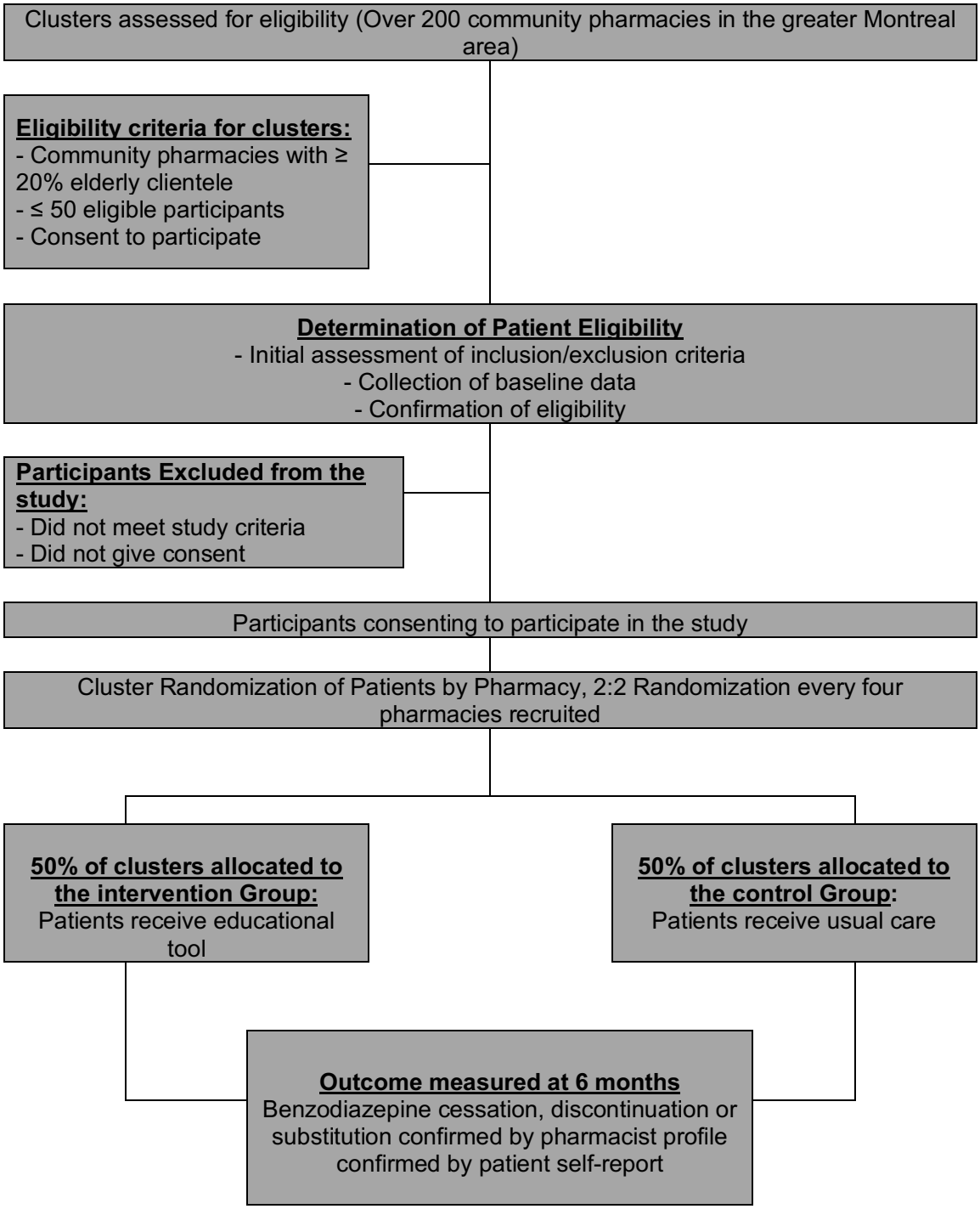
The primary objective of the EMPOWER trial is to evaluate the effectiveness of a new knowledge transfer tool on a community-based sample of chronic benzodiazepine users, as measured by the rate of benzodiazepine discontinuation at 6 months with 1-year follow-up, to determine whether change rates are sustained over the long-term. The acronym EMPOWER stands for “Eliminating Medications through Patient OWnership of End Results”.

Secondary objectives are to determine whether receipt of a knowledge transfer tool by chronic benzodiazepine users changes risk perceptions and self-efficacy for discontinuing benzodiazepines, and leads patients to initiate discussions about safer prescribing practices with their physician or pharmacist.

Design

This is a cluster randomized controlled trial. The rationale for choosing a cluster design is to prevent contamination across the intervention and control arms by individual clients served by the same pharmacy. The cluster and unit of randomization is the community pharmacy. There are two arms in this parallel randomized controlled trial: the educational intervention arm and the control arm. A 50:50 ratio of participants will be used in each study arm. Figure 1 illustrates the study flow.

Figure 1. Study flow chart.



Study site: clusters and characteristics

The study is being conducted in the greater Montreal area in Quebec, Canada. Collaboration with a drugstore chain was established, and all pharmacies within a 3-hour driving radius (approximately 200 km) of Montreal were identified and listed. Pharmacies were listed in random order by a computer-generated program, contacted sequentially and screened for eligibility criteria. Clusters consist of community pharmacies with ≥20% older adults. In order to prevent small or empty clusters, pharmacies with ≤50 eligible participants following the initial screening process are not recruited to the trial.

Study population

The study population comprises chronic benzodiazepine users aged 65 years and older.

Eligibility criteria for individual patients to enroll in the study

Selection of participants will be according to the following inclusion and exclusion criteria.

Inclusion criteria

1. Men and women aged 65 years and older.
2. With at least five active prescriptions (polypharmacy).
3. Of which one is an active benzodiazepine prescription that has been dispensed for at least 3 consecutive months prior to screening, based on pharmacy records.
4. Patients who are willing to participate in the study.

Exclusion criteria

1. A diagnosis of severe mental illness or dementia ascertained by the presence of an active prescription for any antipsychotic medication, and/or a cholinesterase inhibitor or memantine in the preceding 3 months.

2. Unable to communicate in French and/or English.
3. Evidence of significant cognitive impairment (score under 21 on the Montreal Cognitive Assessment (MoCA) [49]).
4. Patients living in a long-term care facility.

Ethical approval

The study protocol was approved on 26 July 2009 by the Research Ethics Board of the Centre de Recherche de l'Institut Universitaire de Gériatrie de Montreal, Canada (ClinicalTrials.gov identifier: NCT01148186).

Enrollment

Enrollment in the trial is conducted in collaboration with a regional pharmacy chain. A letter from the vice-president of the chain was sent to all affiliated pharmacies inviting pharmacists to participate in the trial by recruiting eligible clients served by their medication dispensing units. Company headquarters then identified a list of all chain drugstores within a 3-hour driving radius of the research center and sent a list to the research team. This list was sorted in random order by a computer-generated program and pharmacies are contacted systematically to ascertain their interest in participating in the study. Pharmacies interested in participating are supplied with a list of eligible participants identified from the company's centralized electronic database by a preset inclusion/exclusion filter that applies all inclusion and most exclusion criteria. Any pharmacy found to have less than 50 potential candidates is excluded from the project to avoid small or empty clusters. Otherwise, pharmacies are enrolled in the study and proceed with participant recruitment.

Recruitment of participants and application of eligibility criteria

Recruitment of participants occurs through a three-step screening process. First, pharmacy clients are filtered by the company's centralized computer system using preset eligibility criteria for age and medication use. Second, participating pharmacists receive a list of eligible clients with a matching set of personalized name and address

labels from company headquarters through internal mail, and are asked to review the list to exclude patients with undetected dementia or those living in care facilities. Using the final list of potential participants, pharmacists tally the numbers and contact the research team to request an appropriate number of English and French study invitational materials intended for mailed distribution to participants.

Invitational materials consist of a headquarters pre-approved invitation letter personalized on behalf of the pharmacist and an accompanying brochure describing a study on 'better drug management'. The flyer invites participants to contact either their pharmacist directly or the study coordinator by phone if they have any questions or are interested in participating in the study. Letters and invitations are put in envelopes by the pharmacy personnel, affixed with the address labels provided by company headquarters and mailed to all eligible participants.

One week after sending out the invitations, the pharmacist notes all replies spontaneously received from potential participants indicating their willingness or refusal to participate in the study. The pharmacist then calls the remaining candidates to ascertain their interest in participating in the study and, if so, to obtain permission to give their names and phone numbers to the study coordinator. According to protocol, a maximum of three phone calls and voice messages must be attempted over a 2-week time period in order to reach participants, after which time potential participants are declared not interested. All affirmative responses are recorded by the pharmacist, and the names and phone numbers of interested clients are transferred to the research staff at the end of the 3-week period following the invitation mail-out to participants.

The study coordinator then contacts all potential participants referred by the pharmacists (with the client's permission) and arranges an appointment at the person's residence to complete the third screening stage: signed consent if eligible and collection of baseline data. During the home visit, a research assistant reviews the medication currently taken by the patient, queries the medical history and administers the MoCA. Signed consent to participate in the study is then obtained from individuals who meet

the study criteria after baseline cognitive and health status screening. All baseline data are collected from the questionnaires indicated in Table 1 under T0 at this time.

Table 1. Overview of data collection and measurements in both trial arms

	Baseline	**Follow-up post-intervention**			
Visit number	T0	T1	T2	T3	T4
Time	1-7 months pre-intervention	7 days	6 weeks	6 months	1 year
Inclusion and exclusion criteria	X				
Socio-demographic characteristics	X				
SMAF questionnaire	X				
GHS questionnaire	X				
MoCA	X				
Rey 15-Item Memory Test	X				
GAI	X		X	X	X
Depression PHQ-9	X[a]		X	X	X
Insomnia questionnaire	X[a]		X	X	X
Medication use characteristics	X				
Benzodiazepine tapering questionnaire		X	X	X	X
Medication knowledge questionnaire	X	X			
BMQ-Specific	X	X			
Self-efficacy scale	X	X			
Intervention related questionnaire		X	X	X	
Intervention appreciation questionnaire				X	

[a]Only administered if related outcome present. BMQ-Specific, Beliefs about Medicines Questionnaire - Specific segment; GAI, Geriatric Anxiety Inventory; GHS, general health status; MoCA, Montreal Cognitive Assessment; PHQ, Patient Health Questionnaire; SMAF, functional autonomy measurement system.

Randomization

Randomization

A statistician, blinded to pharmacy and cluster size, generates a random allocation sequence using computer-generated random digit numbers. For every four pharmacies recruited, a simple 2:2 randomization is used to allocate the four clusters into intervention and control groups. Towards the end of recruitment, randomization might be skewed to favor the least populated study arm to allow the desired 50:50 allocation ratio.

Concealment of allocation

Prior to random allocation into either arm of the study, informed consent, agreement to enroll in the study and ascertainment of eligibility will all be obtained from the pharmacists and their clients. Up until the point of randomization, neither the research assistant, the cluster representative (the pharmacist), nor the client will know the allocation of the clusters. After randomization, only the research assistant will be aware of treatment allocation. Pharmacists and participants will not be informed, and will remain unaware of the fact that there is another group in the study; nor will they be informed of the procedures for the other arm. Participants' link to the project will be the pharmacist, but participants of the same pharmacy will not normally be in contact with each other. Randomization is performed in clusters to prevent bias in case this happens. Therefore, all participants from the same pharmacy will be randomized as a single cluster, thereby receiving the same treatment and remaining blinded to treatment allocation.

Blinding

As the intervention is educational in nature, blinding of the intervention is impossible. However, to preserve a certain level of blinding and to protect sources of bias, the following measures are taken.

For participants, blinding is achieved by presenting the project to participants as a project on optimizing medication management. Consenting participants understand that their medication profiles will be transmitted to the research team within the following months and that they will receive a customized letter at some point during the year which may contain recommendations for change, which they can then decide to take to their physician or pharmacist for discussion.

For pharmacists, blinding is achieved by presenting the same study timeline. Pharmacists are aware that their clients will receive an intervention at some point during the following year and remain blinded to group allocation throughout the course of the study. Pharmacists also remain blinded to other participating pharmacies. Since pharmacies are randomized as clusters, they are located in distinct geographic locations and generally have no reason to interact with one another.

Thus, blinding pertains to both the individual and cluster level.

The educational intervention

The educational intervention consists of a seven-page letter-size paper brochure developed specifically for this trial. The language for the intervention is set at a grade six reading level and written in 14-point font to facilitate accessibility of the material. The brochure is mailed to the intervention group within 1 week of group allocation. The control/wait-list group receives the educational tool 6 months later. As the intervention is sent individually to participants and participants within each cluster are unknown to one another, the intervention only pertains to the individual participant. (see appendix 2)

Theory and development of the intervention

The tool aims to promote active learning by using constructivist learning theory principles, incorporated during the development of the intervention. Constructivist learning theory activates users to create new knowledge in order to make sense out of the presented material. The goal of this approach is to allow the learner to interact with the academic material, fostering their own selecting, organizing and information

integrating processes [50]. Many other learning theories were integrated in the different parts of the intervention, such as cognitive dissonance, social comparison, peer champion theories and self-assessment theory. Cognitive dissonance theory confronts two inconsistent cognitions held simultaneously by the same individual. This process aims to create an aversive motivational state in the individual who will then seek to alter one of these perceptions to remove the pressure caused by this conflict [51]. The tool also includes elements of social comparison and peer champion theories [52]. Social comparison consists of comparing oneself to others in order to evaluate or enhance personal aspects [53]. Thus, the evaluation of the ability or inability to accomplish a certain action depends on a proxy performer's success. The efficacy of social comparison depends on whether the comparer assimilates or contrasts him/herself to others [52]. Thus, aspects such as previous agreement with the peer's views and comparability with the peer champion are paramount for the comparison to work [53]. A self-assessment component was also introduced to promote insight about potential misinformation or beliefs held about benzodiazepine use [54,55]. A common idea in models of risk perception is that risk is perceived from two dimensions: knowledge of and beliefs. Information about the risks associated with benzodiazepine use was therefore in incorporated into the tool. It has also been shown that pre-existing beliefs frequently supersede information transfer about risks [56]. In order to understand the drivers and consequences of risk perception the behavior motivation hypothesis was used. This hypothesis, which is endorsed by most models of health behavior, describes the determinants of risk perception and their effects on behavior change [57]. It is important to note that perception of risk has been shown to be positively related to preventive health behavior in conditions where expectations of success in dealing with the risk are acceptable and when recommendations for preventive behavior are presented as effective [58].

The textual content of the intervention was based on guidelines concerning the use of benzodiazepines in older people as well as a systematic review of the evidence. The initial content of the tool was drafted by a geriatrician and graduate student, and then validated by a panel of colleagues with expertise in geriatric pharmacy. Following

validation, a health librarian reviewed the content to ensure that the wording met standards for patient literacy. The tool was initially developed in English then backward-forward translated into French.

Components of the intervention

The cover page of the brochure has an image of a pillbox filled with several medications titled 'You May Be At Risk', followed by 'You are currently taking (name of benzodiazepine)'. Brochures are customized according to each patient's medication profile. The first page of the intervention lists four true or false questions regarding the safety, side effects, withdrawal symptoms and alternatives to the use of the benzodiazepines, and is entitled 'Test Your Knowledge'. The second page contains the correct answers as well as an explanation for each statement. The goal is to create cognitive dissonance and challenge the patient's beliefs for each incorrect answer by incorporating elements of constructivist learning theory into the answers. The third page incorporates a self-assessment component as well as educational facts on potential inappropriate use, side effects, drug-drug interactions and information about physiological changes that occur with age that affect drug metabolism. Suggestions for equally or more effective therapeutic substitutes, as well as evidence-based risks associated with benzodiazepine use in older people, are presented on the fourth and fifth pages. The sixth page highlights one woman's success story in weaning herself off benzodiazepines. The last page outlines a simple 21-week tapering program that can be adapted to the patient's medication use. For contrast and visual enhancement, visual tools such as color shading and several pictures of older adults and medication are used throughout the tool. In order to make sure the intervention is used appropriately, the words 'Please Consult your Doctor or Pharmacist Before Stopping Any Medication' appear as a warning in large lettering on four different occasions throughout the tool.

Acceptability of the intervention

To determine the readability and comprehension of the information, the tool was field-tested in six focus groups of older adults (n = 60). Based on the focus group

feedback, elements of the tool, such as the wording, ordering of the material and the visual presentation were changed in an iterative process until acceptability was reached.

Study arms

Participants allocated to the experimental group receive the written educational program via mail immediately following randomization. Telephone follows-ups are conducted 1 week, 1 month, 6 months and 1 year post-intervention, and last 5 to 10 minutes. Participants in the control 'wait-list' group are monitored during the first 6 months following randomization and then receive the same intervention as the experimental group.

Study outcomes

Outcomes are measured at all study follow-up points. At baseline, questionnaires are completed at the participants' homes during an interview with the research coordinator. Follow-up is by telephone interview with the same coordinator. Self-reported socio-demographic variables, health status variables and prescription details are collected at baseline.

Primary outcomes

Prescription change rate at 6 months

The primary outcome of the study is cessation of benzodiazepines in the 6 months following receipt of the intervention, ascertained by pharmacy renewal profiles and confirmed by patient self-report. A 1-year follow-up will be undertaken to determine whether change rates are sustained over the long-term. The definition of discontinuation will be an absence of any benzodiazepine prescription renewal at the time of the 6-month follow-up. Dose reductions will also be measured and will be defined as ≥50% reductions in the renewal profile for at least 3 consecutive months beginning at the time of the 6-month follow-up. The discontinuation/dose reduction rate among participants in

the experimental arm will be compared to the discontinuation/dose reduction rate among participants in the control arm. In this way, we will be able to determine the absolute rate of discontinuation attributable to the intervention. This outcome measure pertains to the individual level.

The 6-month period and 1-year follow-up were chosen because although there is no agreement on the time frame of change, the trans-theoretical model supposes that, typically, once people start thinking about changing their behavior, decision and planning of the action is usually done within the following 6 months. Maintenance of the new behavior begins after 6 months of being in the active stage of changing and continues for at least 6 months [59]. Pharmacy profiles, supplied monthly by fax to the research center by the pharmacist, were chosen to measure prescription change rates because of the high amount of information they contain. Pharmaceutical profiles vary in the information they contain between pharmacies of the same chain depending on the owners. However, vital information to determine change rates, such as the date of renewal, the dose and the quantity of the prescription are always listed. Using this objective measure allows comparison and validation of patient reported outcomes, and thus more accurately and objectively determines the effect of the intervention.

Secondary outcomes

Change in risk perception

Change in perception of risk associated with benzodiazepine use will be evaluated through a self-reported measure, along with change in knowledge and change in beliefs. The self-reported measure will consist of participants answering whether they perceived the same, increased or no risk from consumption of their benzodiazepine medication after having read the brochure, and will be collected 1 week post-intervention. Change in knowledge will be measured by comparing the pre- and post-intervention (T1) answers from the four true or false questions in the 'Test Your Knowledge' section of the questionnaire. The first statement targets safety of long-term benzodiazepine and reads, '(Example: Valium®) … is a mild tranquilizer that is safe

when taken for long periods of time'. The second statement focuses on side effects and is phrased, 'The dose of Valium® that I am taking causes no side effects'. The third statement, focusing on withdrawal, is worded, 'Without Valium® I will be unable to sleep or will experience unwanted anxiety', and the fourth, on alternative treatment options, states, 'Valium® is the best available option to treat my symptoms'. Change in beliefs is measured by comparing the pre- and post-intervention (T1) total scores on the Specific section of the Beliefs about Medicines Questionnaire (BMQ-Specific) adapted for benzodiazepines [60,61]. Statements remained identical to the originals with the exception that the word 'medicines' was replaced by 'benzodiazepine' in each statement. The beliefs in medications questionnaire is a validated measure used to assess cognitive representations of medications [60,61]. These outcome measures pertain to the individual level.

Change in risk perception was chosen as a secondary outcome in order to reflect the behavior motivation hypothesis described earlier. As patient-reported outcomes are not always objective, two additional and more objective outcomes were chosen to evaluate risk perception: change in knowledge and change in beliefs about benzodiazepines. This was done because a common idea in models of risk perception states that risk is perceived from two dimensions: knowledge of and beliefs about that risk, as mentioned earlier. The rationale for choosing the score for the knowledge questionnaire was that it allows a quantification of the knowledge transfer aspects of the intervention. The rationale for choosing the BMQ-Specific instrument to measure beliefs relates to its ability to isolate and score participants' beliefs about a specific medication; both in terms of the dangers and concerns participants have regarding their prescription (Specific-Concerns), and the necessity they attribute to this same prescription (Specific-Necessity). The BMQ-Specific consists of two 5-item factors belonging to each sub-score. Participants indicate their degree of agreement with each statement on a 5-point Likert scale (1 = strongly disagree to 5 = strongly agree). Both scales are then summed into their respective scores (5 to 25 scale) with higher scores indicating stronger beliefs in that concept. A necessity-concerns differential can also be derived from these scales by subtracting the concern sub-score from the necessity sub-score. This differential can

be considered as the cost benefit analysis for each patient, where costs (concerns) are weighed against perceived benefits (necessity beliefs) [60,61].

Change in self-efficacy

The second secondary outcome measure will be change in self-efficacy. Self-efficacy will be measured pre- and post-intervention (T1) with the medication reduction self-efficacy scale, a scale that was developed and tested in the context of previous benzodiazepine tapering studies [62]. Participants will indicate their level of confidence for achieving a pre-determined medication reduction goal on a scale of 0 to 100 (0 = not at all confident to 100 = extremely confident), which is based on Bandura's original guidelines for the development of task-specific self-efficacy scales. Post-intervention, participants will also be asked to rate on this same scale their level of confidence about eventually discontinuing using the tapering program provided. This outcome measure pertains to the individual level. The rationale is that self-efficacy gives a clear indication of a patient's belief about their capability to discontinue benzodiazepines and may be a potential predictor of benzodiazepine discontinuation.

Initiation of discussion with a physician or pharmacist about the decision to taper benzodiazepines

The third secondary outcome will be the potential of the intervention to activate participants to discuss safer prescribing options with their physician or pharmacist. At T1 to T3 participants will be asked to indicate: if they had spoken to friends and/or family about the intervention, and if they had spoken to or intended to discuss medication discontinuation with either their physician or pharmacist. Reactions and results of these behaviors will be noted. These intentions are considered as measures of self-initiated medication risk reduction behaviors. This outcome measure pertains to the individual level.

The intervention was designed to target consumers directly as catalysts for engaging physicians and pharmacists in collaborative discontinuation of their benzodiazepine drugs or other inappropriate medications. Observing this outcome will

allow us to determine the intervention's potential for engaging participants in collaborative medication management. Furthermore, it will also allow us to identify at which point the intervention failed, and whether psychological dependence on the part of consumers or obstructive behavior on the part of the physicians or pharmacists was the cause of the intervention's failure.

Sample size

The main question driving the sample size for this study is whether chronic inappropriate medication users who receive the knowledge transfer tool are more likely to discontinue use at 6-month follow-up compared to users who do not receive the intervention. A systematic review was undertaken to identify similar studies and compare discontinuation rates for benzodiazepine drugs. Inclusion criteria were: rigorous randomized controlled trial methodology, inclusion of adults aged 65 years and older, community setting, a non-imposed intervention, and interventions that targeted inappropriate benzodiazepine prescriptions and included a prescription discontinuation measure. Eight studies met the inclusion criteria and were used in the sample size calculation estimates. Many other studies were identified that presented very different estimates, however these varied greatly in setting, population or measure and were irrelevant to the current study.

We expect our intervention to achieve a rate of discontinuation that is at least as great as that achieved in previous studies by medication review by pharmacist and contact with physician (range 19 to 24%, mean 22%) [29,43,63] or by simple discontinuation letters (range 13 to 20%, mean 16%) [47,64-67]. However, it is possible that individuals who do not receive the intervention may have rates of discontinuation as high as 6% for inappropriate prescriptions (range 2 to 6%, mean 4%) [29,43,47,64-66]. Our study will therefore be powered to detect a minimal 20% increase in inappropriate medication discontinuation due to use of the intervention and an absolute minimal rate of discontinuation of 25%. Based on an alpha of 0.05 and 80% power to detect a 20% difference, 58 participants are needed for each group. To detect greater differences, a lower sample size is needed. However, due to the cluster design of this study,

adjustments need to be made to account for both clustering and for the effect of the coefficient of variation of the cluster size [68]. Based on current recruitment data (16 clusters, cluster sizes 6 to 27), the coefficient of variation was established at 0.527 using the minimum/maximum cluster size estimation method [68] and estimated intra-cluster correlation set at 0.05. After computing the coefficient by which to multiply our sample size to account for these factors we obtained 1.79 [69]. Current loss to follow-up in the study (in the first 185 recruited participants) was established at 9%. Therefore 114.2 (58 x 1.79 x 1.10 = 114.2) participants will be needed for each group. A sample of 250 individuals will be recruited.

Analysis plan

Data will be analyzed using an intention-to-treat approach. Descriptive statistics (means, proportions) will first be calculated to assess the balance between the groups on important confounders, such as age, sex, health status, baseline beliefs about medications and benzodiazepine use. In order to answer the main research question driving this study - whether an educational intervention targeting consumers directly as catalysts for engaging physicians and pharmacists in collaborative discontinuation achieves an inappropriate prescription discontinuation rate of at least 20% compared to usual care - we will use a marginal model estimated via generalized estimating equations (GEE) with a binary outcome and an identity link, with an exchangeable correlation structure to account for correlation between participants in the same cluster [69]. Risk differences between the control and experimental groups will be calculated and the robust variance estimator will be used to estimate the associated 95% confidence interval (CI) and *P* value [70]. As a sensitivity analysis (and/or if any confounders are unbalanced between the groups), we will estimate the risk difference for the intervention via a marginal model estimated via GEE with an exchangeable correlation structure. The robust variance estimator will again be used. In secondary analyses, we will calculate risk differences in subgroups of interest (for example, very older people, women, baseline beliefs about medication and degree of polypharmacy). The analysis will be carried out at both the cluster and individual levels.

In order to determine whether the patient intervention altered beliefs about the necessity-concern ratio, knowledge or risk perception for the inappropriate prescriptions, as well as self-efficacy, paired t-tests will be used to evaluate change scores pre- and post-intervention. The potential of the intervention to engage participants in preventive health behaviors will be evaluated via chi-square tests comparing intervention and control groups. These analyses will be carried out at the individual level.

Discussion

To date there is no effective or sustainable approach to reduce benzodiazepine use in older adults [24-42]. Previous research on strategies to reduce benzodiazepine consumption has applied paternalistic approaches to patient care, similar to the 'top-down' managerial approach described in management and organizational development theory [71,72]. An example of this approach is when physicians acquire warning letters from study investigators and send these letters to patients asking them to schedule an office visit to discuss benzodiazepine discontinuation. Our educational intervention draws on theories of self-management and collaborative doctor-patient partnerships, and provides a means to test a 'bottom-up' change strategy [71,72]. In the bottom-up model, patients drive prescription decisions from information gathered on the Internet, through friends or via an accredited academic body. To our knowledge, no published study to date has targeted the patient as a driver of safer prescribing practices. By directly empowering chronic users with knowledge about risks, suggestions for lower-risk therapeutic options and self-efficacy for implementing tapering protocols, we hope to imitate the success of individually targeted anti-smoking campaigns [73].

To maintain the generalizability of the findings from our study, exclusion criteria have been kept to a minimum. In order to fulfill recruitment needs, no limits on cluster size were imposed to pharmacies meeting the cluster eligibility criteria. Since some pharmacies identified over 200 potential participants, while others barely covered the 50 potential candidate minimum to qualify as a cluster, cluster sizes are expected to vary. However, this was considered both in the sample size calculations and analyses.

The study has been designed as a pragmatic trial that takes place in the real-world setting. The intervention is theoretically-based and incorporates a practical and contemporary learning and psychological approach to help participants overcome hard-to-achieve lifestyle modifications. Thus, we expect that implementing an educational intervention trial in a practical setting will yield both internally and externally valid evidence for reducing inappropriate benzodiazepine use, by directly targeting and activating community-dwelling older adults in a previously unexplored approach.

Trial status

The trial is currently recruiting participants and was approximately 80% complete at time of publication.

Abbreviations

BMQ-Specific: Beliefs about Medicines Questionnaire - Specific segment; CI: confidence interval; GAI: Geriatric Anxiety Inventory; GEE: generalized estimating equations; GHS: general health status; MoCA: Montreal Cognitive Assessment; PHQ: Patient Health Questionnaire; SMAF: functional autonomy measurement system.

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6.1.2 D-PRESCRIBE protocol

A consumer-targeted, pharmacist-led, educational intervention to reduce inappropriate medication use in community older adults (D-PRESCRIBE trial): study protocol for a cluster randomized controlled trial

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TRIAL REGISTRATION: clinicaltrials.gov Identifier: NCT02053194. URL: https://clinicaltrials.gov/ct2/show/NCT02053194

Abstract:

Background: Medication safety for older persons represents an ongoing challenge. Inappropriate prescriptions – those with a high risk of evidence-based harm – persist in up to 25% of seniors, and account for a significant proportion of avoidable emergency department visits. This project is the sequel to the EMPOWER study, in which a novel consumer-targeted written knowledge transfer tool aimed at empowering older adults to act as drivers of benzodiazepine de-prescription resulted in a 27% reduction of inappropriate benzodiazepine use at 6-month follow-up (NNT=4). Failure to discontinue in the EMPOWER study was attributable to re-emerging symptoms among participants, prescribing inertia, and lack of knowledge and skills for substituting alternate therapy among physicians and pharmacists. To maximize de-prescription of inappropriate therapy, educational medication-risk reduction initiatives should be tested that simultaneously include patients, physicians, and pharmacists. The objective of this trial is to: 1) test the beneficial effect of a new de-prescribing paradigm enlisting pharmacists to transfer knowledge to both patients and prescribers in a two-pronged approach to reduce inappropriate prescriptions, compared to usual care and 2) Evaluate the transferability of the EMPOWER study concept to other classes of inappropriate prescriptions.

Methods: We intend to conduct a 3-year pragmatic cluster randomized parallel-group controlled trial to test the effect of the new de-prescribing intervention compared to usual care for reducing 4 classes of inappropriate prescriptions from the 2012 Beers criteria among 450 community-dwelling older adults with polypharmacy. Inappropriate prescriptions will include benzodiazepines, sulfonylurea hypoglycemic agents, 1st generation antihistamines and non-steroidal anti-inflammatory drugs. The study population is community-dwelling older adults recruited from community pharmacies in Quebec. The intervention was developed based on a systematic review of the evidence for each medication. Participants in the experimental group will receive the written educational program following randomization and have their pharmacist send their physicians an evidence-based pharmaceutical opinion to recommend de-prescription and be followed for a year. The control group will be wait-listed for 6 months.

Discussion: System change to effectively reduce medication risk among community-dwelling seniors requires a coordinated approach targeting physicians, pharmacists, and patients. This trial will test the feasibility and effectiveness of a tripartite approach to de-prescribing.

Trial registration: Registered via ClinicalTrials.gov on January 31st 2014, identifier: NCT02053194.

Background:

Older adults rank concerns about medication side effects highest on their list of health priorities, with 89% of those with chronic conditions willing to attempt cessation of one of their medications if deemed appropriate by a physician. [1-3] Seniors have good reason to be concerned: as life expectancy improves and older adults live longer with chronic conditions, they are also more likely to consume multiple medications. [4, 5] Polypharmacy is a risk factor for adverse drug events including drug-drug interactions, emergency department visits due to therapeutic competition, hospitalization and death.6-8. Some medications confer greater risk than others, and are termed inappropriate when their risks outweigh the benefits, and when safer therapeutic alternatives exist that have similar or superior efficacy. [9-11]

Despite the development of guidelines identifying inappropriate medications among older adults such as the BEERs criteria [9], inappropriate prescriptions persist in up to 25% of community-dwelling non-hospitalized older adults aged 65+, depending on the criteria used and the country studied. [10, 12] Interventions aimed at physicians and pharmacists for reducing inappropriate medication use include medication reviews and software alerts [13, 14] In a previous study [15], we developed and tested a consumer-targeted written knowledge transfer tool aimed at empowering older adults to act as drivers of safer prescribing practices. This resulted in a 27% discontinuation rate in the intervention group independent of patient factors [15] and thus EMPOWER provided

proof of concept that directly targeting consumers as drivers of safer prescriptions can be effective for reducing medication risk.

Several challenges and opportunities became apparent in the EMPOWER study. Patients stated in 33% of cases that physicians were reluctant to change their prescription. Second, we realized that if the de-prescribing process were to become sustainable over the long-term, the new paradigm would have to be entrenched within the pharmaceutical sector and involve the prescriber, the patient and the pharmacist.

A tripartite approach to de-prescribing is supported by a recent systematic review on the barriers of deprescribing, which suggests that the decision to stop a medication by an individual is influenced by multiple competing barriers and enablers. [16] In this review, a total of four enablers and barriers to de-prescribing were identified. Enablers consisted of agreement with appropriateness of cessation, positive influences such as support from the pharmacist and/or physician, dislike of medication as well as the presence of a clear cessation process. Barriers to cessation consisted of fear of cessation, negative influences such as discouragement from the pharmacist and/or physician, disagreement over the appropriateness of cessation, as well as the absence of a clear cessation process. Using this knowledge as well as our own findings from the EMPOWER study, which also demonstrated barriers to cessation such as prescribing inertia and a lack of knowledge and skills for substituting alternate therapy, we developed the current approach to the patient deprescribing process. This trial aims to address these barriers and to test the beneficial effect of enlisting pharmacists to transfer knowledge on inappropriate prescriptions simultaneously to both patients and prescribers.

Methods/Design:

Trial design

Study objectives

The primary objective of the trial is to evaluate the effectiveness of a pharmacist-initiated educational knowledge transfer intervention to both patients and prescribers on

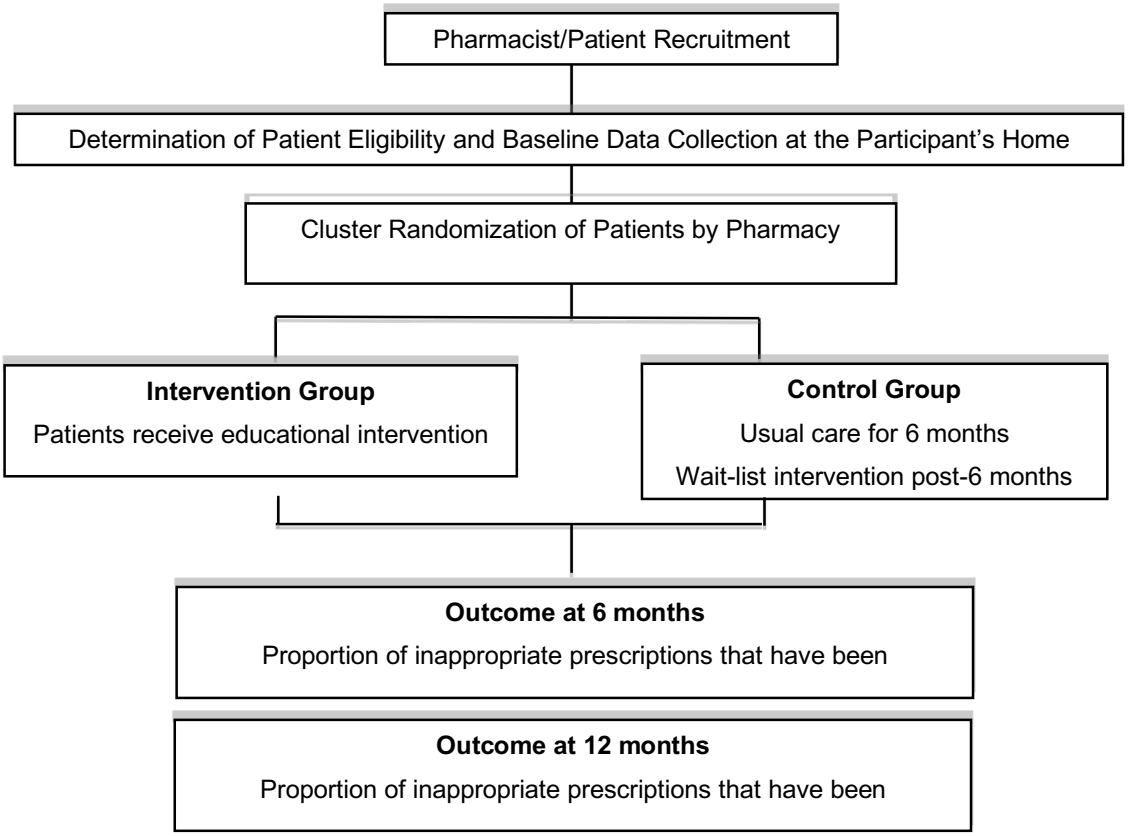
the discontinuation of inappropriate prescriptions on a community-based sample of chronic inappropriate prescription users as measured by the rate of targeted medication discontinuation at 6-months, with 1-year follow-up to determine whether change rates are sustained over the long-term. The acronym D-PRESCRIBE stands for “Developing Pharmacist-led Research to Educate and Sensitize Community Residents to the Inappropriate prescription Burden in the Elderly”.

Secondary objectives of the study include: evaluating the added benefit of implicating physicians and pharmacists in a patient-targeted educational intervention on the discontinuation of inappropriate prescriptions in comparison to the EMPOWER [15, 17] study, where patients alone were targeted; to test the transferability of this novel approach to inappropriate prescription discontinuation explored in the EMPOWER study to other classes of inappropriate medications; to better understand the mechanisms by which the educational tool affects participants’ risk perception, knowledge and beliefs with respect to inappropriate prescription use; to evaluate the impact of evidence-based pharmaceutical opinions on physicians’ perception of the prescription as inappropriate; and to document response rates and the overall feasibility of using pharmaceutical opinions as a clinical tool to catalyze physicians to deprescribe inappropriate prescriptions.

Design:

This is a pragmatic, cluster randomized, parallel controlled trial. A cluster design was chosen to prevent contamination across the intervention and control arms by individual clients served by the same pharmacy. The cluster and unit of randomization consists of each community pharmacy. There are 2 arms in this parallel-randomized controlled trial for each of the 4 medication categories targeted: the educational intervention arm and the control arm. A 50:50 ratio (intervention: control) of participants will be used in each medication class arm. Figure 1 illustrates the flowchart.

Figure 1: Study flow



Study site: Clusters and characteristics

The study is being conducted in the greater Montreal area in Quebec, Canada. Collaboration was established with the pharmacies of three local drugstore chains within a 2-hour driving radius (~100km) of Montreal. Pharmacies are randomly ordered via a computer-generated program, and subsequently invited to participate in the trial in that order. Clusters consisted of community pharmacies who are able to track medication dispensing, who have a ≥ 20% elderly clientele, and who consent to participate in the project.

Study population

The study population comprises chronic users of the 4 targeted classes of inappropriate prescriptions among community-dwelling older adults recruited from community pharmacies in Quebec.

Men and women 65 years of age and older with chronic consumption (> 3-month claims) of one of 4 target inappropriate prescriptions classes are eligible for participation in this trial. The choice of these 4 medication classes was based on moderate to high-quality evidence and the strength of the recommendations presented in the 2012 Updated Beers Guidelines for Inappropriate Prescriptions, [9] as well as their frequency of use in the general population. [18-20] There is a strong recommendation for avoiding the four classes of prescription medications chosen in this trial (see Table 1) with moderate to strong evidence backing these recommendations. [9]

Table 1: Target medication classes

Medication class	Rationale

All benzodiazepines as well as non-benzodiazepine hypnotics.	• Associated with:
	  ○ A five-fold increased risk of cognitive events [21-24],
	  ○ A 30% to two-fold increased risk of falls [25-27], a 50% increased risk of hip fractures [27-31], and
	  ○ A 25% to 2-fold increased risk of motor vehicle accidents. [32-34]
	  ○ Increased risk of Alzheimer's disease by up to 80%. [35]
	• Similar evidence of harm exists for non-benzodiazepine hypnotics. [9]
	• Hypnotics are associated with a greater than threefold increased risk of death even when prescribed <18 pills/year [36]

Anticholinergic agents including first-generation antihistamines (as single agents or as part of combination products)	• Can cause cognitive impairment [24]
	• Have been associated with an increased risk of [37-42]:
	  ○ Confusion,
	  ○ Dry mouth,
	  ○ Constipation,
	  ○ Functional decline.

Long-acting sulfonylurea oral hypoglycemic agents chlorpropamide or glyburide used for the	• Estimated to be responsible for 11% of emergency hospitalizations for adverse drug events in older adults. [43] • Glyburide is associated with a 52% greater risk of experiencing at least one episode of hypoglycemia compared

treatment of diabetes	with other secretagogues and with 83% greater risk compared with other sulfonylureas. [44, 45] • Chlorpropramide has potential to cause SIADH (syndrome of inappropriate antidiuretic hormone secretion). [46] • Glyburide was a new addition to the Beers list in 2012. [9, 47]
Chronic non–COX-selective nonsteroidal anti-inflammatory drug (NSAIDs).	• Increased risk of gastro-intestinal) bleeding/peptic ulcer disease in older adults. • Ulcers, bleeding, or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3–6 months, and in about 2%–4% of patients treated for 1 year with trends continuing with longer duration of use. [48-50] • Use of misoprostol or a proton pump inhibitor reduces this risk, it does not eliminate it.

* A full list of medication associated with these drug classes is presented in Appendix 1

Patients with a diagnosis of severe mental illness or dementia ascertained by the presence of an active prescription for any antipsychotic medication and/or a cholinesterase inhibitor or memantine in the preceding three months, those unable to communicate in French and/or English as well as patients showing evidence of significant cognitive impairment (a baseline screening score < 24 on the Mini-Mental State Exam [MMSE] [51]) are excluded. Additionally, patients in assisted-living facilities will be excluded from the study population.

Ethical approval

The study protocol was approved by the Research Ethics Board of the Centre de Recherche de l'Institut Universitaire de gériatrie de Montreal Canada on September 17th, 2013 (ClinicalTrials.gov identifier: NCT02053194)

Enrollment

Enrollment in the trial was conducted in collaboration with three regional pharmacy chains. Company headquarters provided the research team with a list of all

chain drugstores with an appropriate version of the pharmacy software within a 100-km radius of the research center. Following this, a high-ranking company representative of each of the three banners circulated an announcement to all pharmacist owners to participate in the project. Following these announcements, pharmacy lists were randomized and then each one contacted systematically in that order to assess interest in participation. Pharmacies interested in participating then met in person with a research coordinator to sign a collaboration engagement, thus confirming their participation in the trial.

Recruitment of participants and application of eligibility criteria

Participants will be recruited to the trial in a systematic fashion. Participating pharmacists will approve the extraction from the pharmacy software of a comprehensive list of all clients meeting eligibility criteria for the study, divided according to the 4 targeted drug classes, and listed in random order by drug class. An extraction algorithm was developed and validated to reflect the inclusion and exclusion criteria of participants for the study, and applied across all participating pharmacies. The pharmacist then systematically and sequentially phones each client from each of the 4 drug classes to invite them to be contacted by the research team for more information about participating in a study on safe medication management, to a maximum of seven consenting participants per drug class or until no more names remain on the lists. The pharmacist records all responses and transfers the names and phone numbers of those who responded affirmatively to the research staff. Research assistants then contact all potential participants referred by the pharmacists (with the client's permission), re-explains the details to confirm interest in participation and then arrange an appointment at the participant's residence or at the research center (based on patient preference) to complete the third screening stage: signed consent if eligible and collection of baseline data. During this visit, a research assistant reviews the medication currently taken by the patient, queries the medical history and assesses cognitive function. Signed informed consent to participate in the study is then obtained from individuals who meet the study criteria after baseline cognitive and health status screening. This procedure is followed until 3 clients from each drug class have been recruited per pharmacy, or until

such time as there are no more eligible clients at that pharmacy or clusters have been filled. Participants taking one or more of the targeted drug classes will be randomly assigned to only one group and receive the intervention for a single drug class only.

Randomization

Randomization/Concealment of allocation

Randomization will be by pharmacy cluster after recruitment procedures are complete for the cluster. Randomization will be done in blocks using a 1:1 ratio every time two an even number of pharmacies and their patients complete enrolment and baseline data collection. Allocation of the intervention by a third party will be blinded, via a computer-generated random digits generated by a research assistant not involved in participant recruitment, as will data analysis and ascertainment of the outcome. The trial is nonetheless considered open-label because both the research assistant who delivers the interventions and the study participants and pharmacists who receive the educational materials will be aware that the intervention is being delivered.

Blinding

As the intervention is educational in nature, blinding of the intervention is impossible. However, to preserve a certain level of blinding and to protect against sources of bias, the following measures are taken. For participants, blinding is achieved by presenting the project to participants as a project on optimizing medication management. Consenting participants understand that their medication profiles will be transmitted to the research team within the following months and that they will receive a customized letter at some point during the year which may contain recommendations for change, which they can then decide to take to their physician or pharmacist for discussion. For pharmacists, blinding is achieved by presenting the same study timeline. Pharmacists are aware that their clients will receive an intervention at some point during the following year and remain blinded to group allocation throughout the course of the study. Pharmacists also remain blinded to other participating pharmacies. Since pharmacies are randomized as clusters, they are located in distinct geographic

locations and generally have no reason to interact with one another. Thus, blinding pertains to both the individual and cluster level.

Intervention

The intervention is multifaceted, consisting of the delivery of educational materials about inappropriate prescriptions to both patients and their prescribers by the pharmacist. The pharmacist will deliver in person or by mailing the educational material to the patient in the form of a written educational brochure that was developed and tested during the EMPOWER study [15]. All educational material will be customized to the type of inappropriate prescription being consumed by the patient. All materials have already been developed and tested for acceptability [17]. Pharmacists will also provide a letter to their clients explaining why they are receiving an intervention, and a pamphlet inviting them to schedule a consultation. The pharmacist will deliver the educational material to the physician in the form of a faxed pharmaceutical opinion 2 weeks after having delivered the intervention to patients. The research team will provide the pharmacist with the customized educational materials for their patients, and examples of evidence-based pharmaceutical opinions that could be sent to the patient's physician depending on the type of inappropriate medication consumed. The evidence-based pharmaceutical opinions were developed by the research team, reviewed by experts, field-tested among a cohort of physicians as well as a team of pharmacists, and adapted until consensus was reached on the content and format for the final versions. The evidence-based opinions refer to the Beers criteria and other literature detailing the risk of harm associated with use of each targeted drug class for older adults, and include suggestions for safer therapeutic alternatives. The pharmacist is allowed flexibility in their choice of whether to use the pharmaceutical opinions provided by the research team, adapt it to their needs, draft their own pharmaceutical opinion for the physicians or not send out any opinion at all. All study materials are distributed to each participating pharmacist assigned to the intervention group immediately after randomization.

The comparator for this study will be usual care during the six-month time period post-randomization. Usual care is a common comparator for a pragmatic trial, since it captures a wide, realistic range of alternate practice scenarios [52]. After enrolment, all pharmacists will be informed that the project materials will be delivered "sometime over the next year." We will explain to the pharmacists that delays with various study procedures may take 3-6 months and that the recruitment process for the study is long. We will request that no action be taken by the pharmacist other than usual care until such time as the study materials are delivered to them. The control group pharmacists will be given all the educational materials at the end of their 6-month wait period post-randomization.

Study Follow up:

Study follow-ups include 2 telephone calls 1 week and 6 weeks post-randomization, and a single in-person interview at six months post-intervention. Telephone interviews last from 5 to 10 minutes while the final in-person interview may take up to 30 minutes.

Outcomes

Prescription discontinuation rates at 6 months

The primary outcome for the trial is discontinuation of any of the targeted inappropriate prescriptions. The time period for ascertainment of the outcome is 6-months post-intervention. The 6-month time period was selected according to data obtained in the EMPOWER study and is consistent with the transtheoretical model of change which predicts that once people start thinking about changing their behavior, they usually make a decision and implement their plan of action within 6 months. [53] A follow up at one year will be obtained to monitor long-term changes and to assess whether discontinuation persists.

Outcomes will be measured from the administrative database used for public drug claims reimbursement for both the intervention and control groups. This database includes all prescriptions filled at the pharmacy as well payment claims to pharmacists

for all services rendered, such as the delivery of pharmaceutical opinions to physicians. Prescription data contain information on all dispensed prescriptions including drug name, dispensation date, dosage, drug form, duration and quantity of the drug dispensed, as well as the license number of the physician who wrote the prescription. Discontinuation of an inappropriate prescription will be defined as the lack of a claims renewal for that medication during a minimum of three or more consecutive months (with no subsequent renewals) as well as the absence of initiation of another inappropriate prescription of the same class.

Secondary outcomes:

Medical Research Council guidance for complex intervention studies recommends that process evaluations be conducted within the trial to assess the fidelity and quality of implementation of the intervention, to clarify causal mechanisms, and to identify contextual factors associated with variation in outcomes. [54] We therefore intend to track the sequence of events stemming from the delivery of the knowledge transfer tools to each pharmacist in the intervention group. The following parameters will be measured:

- *Delivery of the educational brochures to the patients* by their pharmacists,
- *Prevalence, timing and type of pharmaceutical opinion*s sent by the pharmacists to the patients' primary care providers
- *Effect of the patient knowledge transfer tool* on patients' beliefs about the use of their inappropriate medications and their intent to discuss cessation with their doctor or pharmacist
- *Effect of the pharmaceutical opinion on the prescriber's behavior.*
- *Patient-physician encounters to discuss inappropriate prescriptions.*
- *Patient self-Efficacy & improvement in self-efficacy in ability to change medication.*

Table 2 illustrates the time points for measurement of each outcome during the study.

Table 2. *Overview of data collection and measurements in both trial arms*

	Baseline	Follow up		
Visit number	T0	T1	T2	T3
Time	Day 0	7 days post	6-weeks post	6-months post
Inclusion & exclusion criteria	X			
Sociodemographic characteristics	X			
SF-12	X			X
VES-13	X			X
MMSE	X			
PATD	X			X
Blood glucose monitoring		X[c]	X[c]	X[c]
Medication use characteristics	X			
Benzodiazepine Tapering Questionnaire		X[a,b]	X[a,b]	X[a,b]
DTSQs		X[c]		X[c]
Medication risk assessment	X	X		
BMQ-Specific	X	X		
Patient Self-Efficacy Scale	X	X		X
Intervention related questionnaire		X	X	X
Intervention Appreciation Questionnaire				X

[a]: Only administered if in Benzodiazepine group

[b]: Only administered if Benzodiazepine tapering had begun

[c]: Only administered if in Sulfonylurea group

PATD: Patients Attitude Towards Deprescribing Questionnaire [55]

VES-13: Vulnerable Elders Survey [56]

DTSQs: Diabetes Treatment Satisfaction Questionnaire [57]

SF-12: 12-Item Short Form Survey to measure health status and health related quality of life [58]

MMSE: Mini-Mental State Exam [59]

BMQ-Specific: Beliefs about Medicines Questionnaire - Specific segment [60]

Sample size

The main question driving the sample size is whether the delivery of a knowledge transfer intervention by pharmacists to consumers of inappropriate prescriptions and their prescribers is more likely to result in discontinuation of inappropriate prescription over a 6-month time period compared to usual care. We hypothesize that our

intervention will achieve a rate of discontinuation that is at least as great as that achieved in previous studies by medication review by a pharmacist and contact with a physician (maximum rate 27% in EMPOWER [15]) compared to usual care (maximum rate of discontinuation 6%). [13, 14, 18, 61-65] These figures were derived from published studies in the elderly conducted in the community setting with a non-imposed intervention targeting inappropriate prescriptions, and included a prescription discontinuation measure. We therefore intend to power our study to detect a minimal 20% increase in any inappropriate medication discontinuation over usual care, and an absolute minimal rate of discontinuation of 25%, which would compare to EMPOWER. We are also interested in conducting sub-group analyses by drug class as the four drug classes we have chosen have different indications and may have different rates of discontinuation due to the intervention. Our calculations also account for the cluster design, with adjustments made for both clustering and for the effect of the cluster size. [66] We assume that the intracluster correlation coefficient (ICC) will be similar to the ICC observed in the EMPOWER study (0.008). [67] Based on pilot work from EMPOWER [17], we have chosen the minimal number of participants per drug class (n=3) in order to augment the likelihood that each consenting pharmacy will achieve the required number of participants. Limiting the number of participants per pharmacy and per drug class should also lower design effects when compared to the Empower study where clusters varied from 2 to 27 participants per pharmacy. [66] With an estimated ICC of 0.05 (worst-case scenario) for the 3 participants recruited per drug class, we would require 17 pharmacies per group (51 participants per arm) to be able to estimate a 20% absolute discontinuation rate difference between trial arm by drug class with 80% power and alpha 0.05. [67] To detect greater differences, a lower sample size is needed. Thus, we would have ample power for the overall comparison. Based on preliminary recruitment rates for the D-Prescribe trial during a run-in period, we have observed that only 1 out of every 10 pharmacies who participate are able to recruit the desired number of participants with a participant range per pharmacy of 3-12 and a mean of 6 participants per pharmacy. This may be because smaller pharmacy chains are eligible for inclusion, compared to the Empower trial. Based on our previous research we assume that 10% of participants will withdraw or be lost to follow-up. We

have therefore inflated our sample size to 450 participants (112 per medication class) from an estimated 75 pharmacies. Additionally, to compare the added benefit of the pharmaceutical opinion in comparison to the educational material alone, we chose to recruit an additional 3 participants from the benzodiazepine group. This was powered to detect a minimal 12.5% difference between participants in this study and the EMPOWER study and accounted for the previously mentioned sample size considerations.

Analysis

To determine whether randomization was effective, descriptive statistics (means, proportions) will be calculated to assess the balance between the groups on important confounders such as age, sex, health status, baseline beliefs about medications and the degree of polypharmacy. The primary analysis will focus on answering the main research question driving this study - whether the intervention results in an increased discontinuation rate of inappropriate prescriptions of at least 20% compared to usual care. We will use a marginal model estimated via generalized estimating equations (GEE) with a binary outcome and an identity link, with an exchangeable correlation structure to account for correlation between participants in the same cluster. Participants will be analyzed as randomized (i.e. intention to treat). Risk differences between the control and experimental groups will be calculated and the robust variance estimator will be used to estimate the associated 95% confidence interval and p-value. [68] If any confounders (age, sex, degree of polypharmacy or health status) are unbalanced between the groups, we will estimate the unadjusted and adjusted odds ratios for the intervention via a marginal model estimated via GEE with an exchangeable correlation structure. The robust variance estimator will again be used. All analyses described above will be repeated for each drug class during sub-analysis. As a sensitivity analysis, we will compare results obtained with the GEE to other procedures that account for clustering such as generalized linear mixed models.

The fidelity and quality of implementation of the intervention by the pharmacists will be assessed by rates of delivery of the educational materials to the participants and

their primary care providers. The types of pharmaceutical opinions delivered and the patients' and physicians' responses to receipt of the knowledge transfer tools will be reported as proportions, along with 95% confidence intervals, and will be stratified by type of prescription. In order to determine whether the patient intervention altered beliefs about the necessity-concern ratio for the inappropriate prescriptions, linear mixed models will be used to evaluate change-scores pre-and post-intervention for each medication class with the pharmacist as a random effect. To better understand the explanatory mechanisms driving the success or failure of the intervention, we will track the sequence of events following randomization for each patient in the intervention group. The chronological order of billings for pharmaceutical opinions, prescription changes, and patient visits to the physician for each participant and each type of prescription will be ascertained. These will be compared to the dates and content of the response cards returned by the physicians and the patients' reports of what transpired during any discussions with health providers about their medication. Analysis of these temporal "pathways" will provide valuable insight into how and why the de-prescribing process occurred or did not occur for each participant.

Discussion:

The EMPOWER study demonstrated that direct-to-consumer education is effective at eliciting shared decision making around the overuse of medications that increase the risk of harm in older adults. Our hope here is to demonstrate the added value of using pharmacists as a bidirectional conduit of evidence-based knowledge to patients and physicians to drive the reduction of inappropriate prescriptions. In various countries, legislative and regulatory changes have led to a wider scope of pharmacist practice for substituting or discontinuing certain medications. [63] Data from randomized trials indicate that patients benefit from increased pharmacist involvement in their care. [69]

The patient-centered process developed for this study aims to reinforce known enablers and address barriers to medication cessation. By providing the patient with evidence-based information in the educational brochures we expect to increase

patient's endorsement of appropriate cessation, increase their dislike of the medication, reduce the fear of re-emerging symptoms, and equip them with the skills to safely taper. Patient empowerment is a key mechanism for increasing patient responsibility in shared decision-making with health care providers. [70] Use of an evidence-based pharmaceutical opinion aims to catalyze and support pharmacists and physicians by providing them with the appropriate tools and information to positively influence and encourage patients to initiate de-prescribing. Only forty-one percent of community pharmacists admit familiarity with the Beers criteria of drugs to avoid in the elderly. [71] As such, the evidence-based pharmaceutical opinion serves a dual purpose in educating both pharmacists and physicians about the latest pharmacogeriatric recommendations. This tripartite educational approach to pharmacists, physicians and patients is intended to achieve synergistic impact.

Strengths:

Strengths of the study include but are not limited to its pragmatic design, which will allow the observed process to reflect real world practice as accurately as possible. Systematic recruitment of participants via community pharmacies, blinding of the study hypothesis from participants, physicians, pharmacists, and evaluators as well as objective assessment of drug discontinuation rates from pharmacy prescription renewal profiles will increase the trial's internal validity. Comparison with EMPOWER and other studies will allow us to examine the synergic effects of our intervention compared to direct-to-consumer and direct-to- prescriber interventions alone. Additionally, a comparison of discontinuation rates for the 4 different drug classes may allow us to identify different barriers and/or enablers that need to be addressed for different medication indications.

Limitations:

Limiting the list of inappropriate medications to 4 drug classes only will restrict the study's potential generalizability to all inappropriate prescription. Contamination between the experimental and control groups is possible, but we expect it to be minimal. Pharmacists will be informed that the intervention will be staggered over the course of a

year and they should follow usual care until receipt of the study materials. Physicians may end up with patients in both the control and experimental arms of the study, but this is unlikely as pharmacies generally serve a specific geographic area and patients will be recruited throughout Quebec. The physician will not be contacted directly because of the potential to influence the outcome of the intervention during the study period and/or to interfere with the pharmacist-doctor relationship. Information on what occurs during the physician-patient encounter will therefore be limited.

Trial status

The trial is currently recruiting participants and is approximately 60% complete at the time of publication.

List of Abbreviations:

- MMSE: Mini-Mental State-Exam
- ICC: Intracluster correlation coefficient
- GEE: generalized estimating equations

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Appendix 1:

Benzodiazepines	First generation Antihistamines	Long Acting Sulfonylurea	Non–COX-selective NSAIDs
Alprazolam	Hydroxyzine	Chlorpropamide	Aspirin(>325mg/day)
Estazolam	Promethazine	Glyburide	Diclofenac
Lorazepam	Brompheniramine		Diflunisal
Oxazepam	Carbinoxamine		Fenoprofen
Temazepam	Chlorpheniramine		Etodolac
Triazolam	Clemastine		Ibuprofen
Clorazepate	Cyproheptadine		Ketoprofen
Chlordiazepoxide	Dexbrompheniramine		Meclofenamate
Chlordiazepoxide-amitriptyline	Dichlorphenamide		Mefenamic acid
Clidinium-chlordiazepoxide	Diphenhydramine (oral)		Meloxicam
Clonazepam	Doxylamine		Naproxen
Diazepam	Tripprolidine		Oxaprozin
Flurazepam			Piroxicam
Quazepam			Sulindac
Eszopiclone			Tolmetin
Zolpidem			
Zaleplon			

6.1.3 Choice of trial design for the EMPOWER and D-PRESCRIBE trials

We opted for a pragmatic cluster-randomized random controlled design for each trial. The main rationale for choosing a cluster design is to prevent contamination across the intervention and control arms, should individual clients served by the same pharmacy know each other and interact, or should pharmacists working in the same pharmacy be assigned to different groups and influence each other[486]. In health services research, individual randomization usually results in the same health professional providing care for patients in both the control and intervention group, leading to unmasking of treatment allocation and a high probability of contamination if two patients are assigned different treatments by the randomization scheme. Cluster randomization allows health professionals to provide the same care to all of their patients in a given study and avoids potential "new practice contamination" between groups[487]. In the EMPOWER trial, there were 2 arms: those who immediately received the EMPOWER intervention and those who received usual care for the first 6 months. The control comparator for the EMPOWER intervention is usual care, with the new intervention delivered to the controls after the 6-month wait-list period is over and the primary outcome has been ascertained.

When designing the D-PRESCRIBE trial, we deliberated whether we should replicate the 2-arm parallel nature of the EMPOWER trial, or whether we should use a factorial design. A factorial design would have enabled a 4-prong comparison between the EMPOWER intervention alone, the pharmaceutical opinion intervention alone, the two interventions together, and usual care. This factorial design option would have allowed us to more easily and effectively demonstrate the relative effectiveness of each component of the intervention as well as to quantify any synergistic effect.[488] However, one of the objectives of the D-PRESCRIBE trial was to test whether the proof of concept provided by the EMPOWER trial was applicable to other inappropriate medication classes besides benzodiazepines. Our analyses suggested that both the sample size and logistics would have been insurmountable using a factorial design for 4 different medication classes. For reasons of efficiency and because we already had the EMPOWER data to use as a historical control for the benzodiazepines, we opted for

simplicity and financial viability over potential advantages in design robustness that a factorial design would have provided. However, we decided to increase the sample size of the sedative-hypnotic sub-population of the D-PRESCRIBE trial to match the EMPOWER sample size one-to-one (n=300). This would allow a historical comparison between the two trials, permitting us to detect a significant added benefit on deprescribing of 12.5% (50% greater than EMPOWER alone) in favour of the D-PRESCRIBE intervention, with 80% power and 95% confidence.

6.1.4 Study Flow

This section describes the study flow for the two cluster randomized trials in this thesis and expands on the information available in the articles above.

EMPOWER

From March 2010 to February 2013, 165 community pharmacies in the greater Montreal area were solicited for participation in the EMPOWER trial. The list of targeted pharmacies consisted of all Jean Coutu chain pharmacies that were within two hundred kilometers of the research center. Pharmacies were deemed eligible if at least 20 percent of their clientele were aged sixty-five years or older and if at least fifty potentially eligible patients could be identified. In total, 111 pharmacies were contacted and thirty pharmacies meeting eligibility criteria consented to recruit for the project. The main reasons for non-participation were lack of interest in research (n=63), competing priorities (n=30), lack of personnel to recruit (n=16) and an insufficient number of eligible clients (n=2).

Pharmacies who agreed to participate received a list of all potentially eligible clients from Jean Coutu's centralized database of all clients. The list was produced using a pre-set algorithm based on the trial inclusion and exclusion criteria. Participating pharmacists would then receive a list of eligible clients with a matching set of personalized name and address labels from company headquarters through internal mail, and were asked to review the list to exclude patients with undetected dementia or those living in long-term care facilities. Pharmacies then contacted the remaining list of

clients meeting the study requirements to determine whether each client would be interested in being contacted by the research team to find out more about the trial. The pharmacist then forwarded a list of clients who wished to be contacted by the research coordinator, who phoned each client to set up a home interview. During the home interview, potentially eligible participants were screened to rule out cognitive impairment, a baseline assessment was conducted and signed consent was obtained. Once this procedure was completed for every potentially eligible participant, the pharmacy would be closed for recruitment and ready for randomization. For every four pharmacies having finished recruitment, a simple 2:2 randomization was used to allocate the four clusters into intervention and control groups. An independent statistician, blinded to pharmacy and cluster size, oversaw randomization by generating a random allocation sequence using computer-generated random digit numbers to determine group assignment. In total, thirty eligible community pharmacies representing 2716 potentially eligible participants resulted in 400 participants being assessed for eligibility. In total, 303 participants were randomized with 15 pharmacies assigned to each study arms (n=148 in the intervention group and n=155 in the control group).

Once randomized, pharmacies would either receive the intervention or be wait-listed for 6 months and then receive the exact same intervention depending on group allocation. The EMPOWER brochures were then sent out by mail from the pharmacy to their participants. The research team contacted participants by phone one week after receipt of the intervention to confirm receipt of the intervention and to collect T1 questionnaires. Participants who had not received the intervention received an appropriate follow-up from the research team to ensure they got the brochure. Additionally, participants having not read the intervention yet were invited to do so and contacted shortly after to collect T1 data. Additional follow-ups were done by phone at six weeks and six months for T2 and T3 data collection. Drug dispensing data were sent to the research team by the Jean Coutu headquarters once a pharmacy had completed all of its study follow-ups. Patient data was collected using standard forms, de-nominalized, entered into the database and identified by a unique code for each participant.

D-PRESCRIBE

From January 2014 to November 2016, 91 community pharmacies in the greater Montreal area were solicited for participation in the D-PRESCRIBE trial. The list of targeted pharmacies consisted of all pharmacies who were part of the Pharmaprix, Uniprix and Brunet chains, and that were within one hundred kilometers of the research center. We did not include Jean-Coutu pharmacies in order to avoid contamination. Pharmacies were deemed eligible if at least 20 percent of their clientele were aged sixty-five years or older. In total, seventy pharmacies were recruited to the trial. The main reasons for non-participation were lack of interest in research (n=16) and an insufficient number of eligible clients (n=5).

At study onset, each pharmacy chain advised its pharmacists of our collaboration and circulated an announcement to all pharmacist owners encouraging them to participate in the trial. Following these announcements, pharmacy lists were randomized and then each one contacted systematically in that order to assess interest in participating. Pharmacies interested in participating then met in person with a research coordinator to sign an individualized collaboration agreement, thus confirming their participation in the trial. Pharmacies who agreed to participate completed a baseline questionnaire and then received a comprehensive list of all clients meeting eligibility criteria for the study, divided according to the four targeted drug classes, and listed in random order by drug class from Telus, who administers the pharmacy chains' reimbursement software. This extraction was done using an algorithm that was developed and validated to reflect the inclusion and exclusion criteria of participants for the study and applied across all participating pharmacies. Pharmacists were asked to review the list to exclude clients with undetected dementia or those living in long-term care facilities. Pharmacies then systematically contacted the remaining clients to determine whether they would be interested in being contacted by the research team. A list of up to seven names was sent to the research center where potentially eligible and interested participants would receive additional information by phone from a research assistant. Consent and enrolment followed the same procedure as for the EMPOWER trial. For every two pharmacies having finished recruitment, a simple 1:1 randomization

was used to allocate the two clusters into intervention and control groups. An independent statistician, blinded to pharmacy and cluster size, oversaw randomization by generating a random allocation sequence using computer-generated random digit numbers to determine group assignment. Towards the end of the trial, the randomisation was changed to 2:1 in favour of the control group to adjust group imbalances. In total, we recruited 91 community pharmacies, seventy of which actively participated in the project, resulting in 943 participants being assessed for eligibility. This resulted in 543 participants who were randomized with 34 pharmacies assigned to the intervention arm (n=261) and 36 pharmacies assigned to the control group (n=242).

Once randomized, pharmacies would either receive the intervention or be wait-listed for 6 months and then receive the exact same intervention depending on group allocation. Once ready to receive the intervention, pharmacies would be contacted by the research center to set up an appointment with a coordinator to receive study material and answer a questionnaire. The research team provided the pharmacist with the customized educational materials for their patients, and examples of evidence-based pharmaceutical opinions that could be sent to the patient's physician depending on the type of inappropriate medication consumed. Pharmacists were then charged with delivering the educational brochure to their patients either by hand when they came in the pharmacy or by mail. The educational material to the physician in the form of a faxed pharmaceutical opinion was sent, at the pharmacists' discretion, approximately two weeks after having delivered the intervention to patients. Meanwhile, the research team contacted participants by phone one week after receipt of the intervention to confirm receipt of the intervention and to collect T1 questionnaires. The research team also followed-up with the pharmacist if participants had not received the intervention in order to ensure they would receive it. Additionally, participants having not read the intervention yet were invited to do so and contacted shortly after to collect T1 data. An additional follow-up was done by phone at six weeks for T2 data collection. At six months' post-intervention participants were visited by the research team in order to collect T3 data. Pharmacist were also visited once more to collect in-pharmacy patient notes, copies of pharmaceutical opinions sent, and to administer a follow-up

questionnaire. Pharmaceutical profiles were sent to the research team by Telus once a pharmacy had completed all of its study follow-ups. Due to the pragmatic nature of the trial, the research team had no way of knowing if the pharmaceutical opinion was sent to the prescriber exactly as intended, in a modified version, or not at all, until trial completion and review of the pharmacists' notes. The research team did not have clearance to contact any of the prescribers directly. Patient and pharmacist data was collected using standard forms, de-nominalized, entered into the database and identified by a unique code for each participant/pharmacy. Collaboration agreements and consent forms were kept separate and not identified by participants'/pharmacies' unique identifier in order to preserve anonymity.

6.1.5 Statistical Analysis

Additional details of the statistical analyses are provided here. In both trials, in order to determine whether randomization was effective, descriptive statistics (means, proportions) were calculated to assess the balance between the groups on important confounders such as age, sex, health status, baseline beliefs about medications and the degree of polypharmacy. Details for all descriptive analyses can be found within each published manuscript. The more complex analyses conducted in the context of this thesis, while also described in each respective manuscript, are explored in greater detail below.

Generalized estimating equations

In both trials, the primary analysis focused on answering the main research question driving this study - whether the intervention resulted in an increased discontinuation rate of benzodiazepines compared to usual care. However, the statistical analysis of cluster randomized trials has an additional level of complexity due to participants from the same cluster sharing similarities[489-492]. Notably, participants who belong to the same pharmacy are more likely to receive similar care and may be similar in other characteristics such as socioeconomic status or geographic neighbourhood distribution. For this reason, participants from the same cluster are not fully

independent, and special considerations are required when analyzing results from cluster-randomized trials[487].

Similarities between participants in a cluster are measured by the intra-cluster correlation coefficient (ICC)[490 492 493]. The ICC consists of the inter-cluster variance divided by the sum of the intra-cluster variance and inter-cluster variance and thus is always between zero and one[490 494]. The more the intra-cluster variation leans toward the null, the closer the ICC value will be to one. An ICC of one indicates that all individuals have an identical response and that there is thus a strong correlation between the responses in a cluster. At the opposite end, if the intra-cluster variance is superior to the inter-cluster variance the ICC value will lean towards zero. An ICC of exactly 0 indicates that there is absolutely no correlation between the individual responses observed in a cluster and as such individuals can be considered completely independent[489 490]. A high ICC needs to be considered in the analyses[487 490].

Estimating the ICC is critical in determining the sample size needed to account for the increased variance, as a bigger sample of individuals will be required to attain the same statistical power[490]. For both studies, we assumed that the intracluster correlation (ICC) would vary between 0.02 and 0.2 in our sample, based on previous cluster-based studies reported in the literature from physician and pharmacy practices looking at the intent to change health behaviors.[495 496] For example, Thompson et al. report an ICC of 0.01 for the intent to quit smoking and an ICC of 0.2 to reduce drinking within 61 physician practices.[495] Based on this, we aimed for a conservative ICC estimate of 0.05 in our sample size calculation in order to ensure we would not underestimate the necessary sample size.

We selected generalized estimating equations (GEE) for the statistical analysis of the primary outcome of benzodiazepine discontinuation in both trials, as GEE can account for the correlated nature of cluster-randomized clinical trials[497]. More specifically, we used a marginal model estimated via GEE with a binary outcome and an identity link, with an exchangeable correlation structure to account for correlation

between participants in the same cluster. GEE's were run with participants as randomized (i.e. intention to treat) for EMPOWER and D-PRESCRIBE, as well as per protocol for D-PRESCRIBE. Risk differences between the control and experimental groups were calculated and the robust variance estimator was used to estimate the associated 95% confidence interval and p-value.[492] If any confounders (age, sex, degree of polypharmacy or health status) were unbalanced between the groups, we estimated the unadjusted and adjusted odds ratios for the intervention via a marginal model estimated via GEE with an exchangeable correlation structure. The robust variance estimator would be used in such as situation. As a sensitivity analysis, we compared results obtained with the GEE to other procedures that account for clustering such as the adjusted chi-squared, ratio estimator and parametric modeling approaches.

A number of statistical approaches permit consideration of the clustering effect for binary outcomes in individual-level analyses in randomized trials.[498] These methods include the adjusted chi-square approach, the ratio estimator approach, parametric modeling and generalized estimating equations.[499] We opted to use the generalized estimating equations approach over all of the other ones because it is the only approach that does not need the specification of an underlying distribution for the sample observation in order to provide a valid estimate.[499] Additionally, this approach can readily be extended to adjust for a combination of cluster and individual-level covariates, which yields consistent and asymptomatically normally distributed estimators or regression coefficients.[499]

Both the EMPOWER and D-PRESCRIBE studies were powered at 80% (2-sided test α level of .05) to detect a minimal 20% difference in benzodiazepine discontinuation due to the use of the intervention[6 7 107 379 380 500-502]. Based on study results of 30 clusters representing 303 participants, we calculated a coefficient of variation [k] of 0.62, an intracluster correlation (ICC) of 0.008 and an average cluster size of 10.1, which resulted in a maximum design effect of 1.03. A minimal sample size per group of 60 individuals was therefore required to achieve the desired power[490].

6.1.6 Additional considerations

Challenges in recruiting frail older adults to clinical trials

There are numerous challenges to recruiting community-dwelling older adults to clinical trials.[503-508] These challenges include access issues due to reduced mobility, the reachability of potential participants through traditional media, the need to screen for cognitive impairment prior to obtaining informed consent (otherwise it is not "informed" consent if there is a lack of comprehension), disinterest and fears/concerns about participation.[503 504] Traditional media is unlikely to be as effective for recruitment in this population due to several barriers due to various impairments (physical, hearing loss, technological).[503] However it is estimated that radio/television cost 1850$ per randomized participant compared to more traditional approaches like brochure/letters or newspaper advertisements at 453$ and 478$ respectively per participant randomized.[509] In order to address most of these concerns, we chose to use an approach where participants were first contacted directly by their pharmacists to assess initial interest, and we also provided an in-home assessment interview so participants did not have to travel to the research center for their evaluation. The staff would read the study consent form with the participant in the familiar setting of their home and take the necessary time to ensure participants were properly informed/ answer any questions or concerns they may have about the project before obtaining signed consent. We also only contacted potential participants after they provided their names to their pharmacists to allow us to contact them. This established a certain level of trust based on their relationship with their pharmacist. Participants were identified using an algorithm, which was run by the main pharmacy chain office and not by the local pharmacy, allowing us to keep the pharmacist blinded to the exact purpose of the study. While recruitment could have also been achieved through physicians, either at an individual physician level or at a clinic level, the potential for cross-contamination and difficulties in keeping the physicians blinded to our inclusion/exclusion criteria was simply too great compared to recruiting through pharmacies. Finally, in order to make the trial as pragmatic as possible, we kept the inclusion and exclusion criteria to a minimum in order to have a

maximally representative and as externally generalizable sample of community-dwelling older adults as possible.

Questionnaire and material development

Full details of the questionnaires that were administered at each time point are listed in each published protocol. However notable changes between the two projects included the addition of two questionnaires in the D-PRESCRIBE trial: the Patients' Attitude Towards Deprescribing questionnaire to more accurately predict attitudinal determinants of deprescribing, and the SF-12, a generic health-related quality of life outcome measure, in order to quantify overall changes in health status. The Patients' Attitude Towards Deprescribing (PATD) is a 15-item (~5-7 minutes) questionnaire, which aims to capture the views and beliefs of patients regarding cessation of medications.[473] The PATD was determined to be valid through piloting, expert review and gamma rank correlation with other previously validated beliefs about medicines questionnaires, with reliability test-retesting concordance of 71.3 % (95 % confidence interval, 64.1–78.5 %). [473] The SF-12 was added as health status may play an important role in patient's decisions to stop benzodiazepines, and measurement of this dimension could contribute to understanding study outcomes. The SF-12 is a short-form of the SF-36 Health Survey. It was designed to be broad-ranging but brief enough for practical use in large-scale surveys and yet still reproduce the physical and mental scores of the SF-36.[510] When compared with the SF-36, intra-class reliability correlations were 0.75 for the SF-12 version, compared with 0.81 for the full SF-36. The correlation between the two scales was 0.94. Additionally, the SF-12 has been used extensively in healthcare research to measure health-related quality of life and health status in the elderly, and for which normative data is available to ascertain the representativeness of the population included in the trial.[511 512]

The second major change between the two trials was the development and addition of pharmaceutical opinions. This topic is covered in detail in section 8.1, and was published as a separate peer-reviewed paper, so will not be discussed here in order to avoid repetition.

Ethical considerations

In both manuscripts, we mention that “Pharmacists and participants will not be informed and will remain unaware of the fact that there is another group in the study; nor will they be informed of the procedures for the other arm.” This was feasible because we presented the study to both participants and pharmacists as a medication safety study where we would review pharmaceutical profiles of participants and that they would possibly be contacted in the following 12 months if we had educational material concerning one of their medications. This timeframe allowed us to use a wait-list group for 6 months without any ethical issues as all participants would eventually receive the intervention within the specified time-frame. In reality, participants were pre-identified using an algorithm in collaboration with the pharmacy chain, allowing us not to reveal the specific targeted medications to the pharmacists until delivery of the intervention.

Cluster number considerations

In EMPOWER, no limit was set on the number of participants that could be recruited in a single pharmacy. As such, the number of clusters was simply determined by when the study reached its recruitment objective or approximately 300 participants. In D-PRESCRIBE, as there were more than one class of medication we conducted a sample size calculation with varying ICC and number of participants per pharmacy in order to determine our best option for both the main and sub-analysis. This gave us the table presented below, which allowed us to choose an ideal scenario of 3 participants recruited from each pharmacy (double for benzodiazepines). Despite this, final number of pharmacies recruited was once again based on meeting recruitment objectives.

SUBGROUP ANALYSIS							MAIN ANALYSIS						
		Number of subjects per drug class							Number of subjects per pharmacy				
Power	ICC	3	4	5	6		Power	ICC	9	12	15	18
80	0.02	19	14	12	10		90	0.02	9	8	6	6
80	0.05	20	15	13	11		90	0.05	11	9	8	8
80	0.1	21	17	15	13		90	0.1	14	13	12	11
80	0.2	25	21	19	18		90	0.2	20	19	18	17

Patient Centeredness

With patient-centeredness becoming a cornerstone of interventions designed to optimize the benefit-risk of medications, in addition to being a stakeholder in the interventions itself, there are benefits to involving patients in other components of the project (e.g., design of the intervention, dissemination of findings, etc.). In our case, we involved patients in the development and validation of the EMPOWER brochure. As detailed in the EMPOWER protocol, before the intervention was ever used, we conducted 6 focus groups at the geriatrics institute and gradually changed the intervention based on the feedback from these group until it reached its final form which was deemed acceptable in the last focus groups. In fact, one of the major aspects of the intervention, the tapering protocol consisting of images of pills, was in fact a byproduct of these focus groups and seems to be one of the most appreciated features of the brochure, with the tapering schedule now being implemented in the AssystRx software after we were contacted by heads of pharmacy chains to use it on a larger scale. Finally, while not part of this thesis, we have also in fact benefitted from involving patients in the dissemination of findings. Dr. Tannenbaum's team (myself included) have organized and participated in deprescribing fairs where we invite the general public as well as influencers and practitioners to come and learn about deprescribing. One of the sessions sometimes consists of "D-Prescribing" champions (those who stopped their medication during the study) to come and talk about their deprescribing experience and how it may have affected their life.

Outcome ascertainment

Outcome ascertainment was arguably the most challenging aspect of my thesis. Outcome ascertainment required accurate information from each participant's pharmacy dispensing file. Pharmaceutical profiles were obtained for each participant retroactively starting three months prior to enrolment, and for three months post-trial completion. For the intervention group, this required 12 consecutive months of data collection. If a patient died, we carried the last data point forward in intent-to-treat analyses. However, if a participant changed pharmacies, and the new pharmacy was not included in the trial, we had to contact the new pharmacy in order to obtain follow-up dispensing data.

Our trials had a zero-tolerance level for missing data, which we succeeded in achieving with much time and effort. The dispensing profiles for each patient were used to ascertain dose reduction and discontinuation of benzodiazepines, as well as to assess substitutions. For data analysis purposes, each benzodiazepine dose was converted to a benzodiazepine equivalent dose in lorazepam equivalents (see published protocols above) with the baseline being established as the average daily dose for the months preceding study entry. All patients were coded as one of the following: 0 = no change, 1 = cessation without substitution, 2 = ≥25% dose reduction, 3 = cessation with appropriate substitution, 4 = <25% increased dose, 5 = Cessation of at least one of multiple benzodiazepines, 6 = Cessation with inappropriate substitution. This was then recoded to obtain a dichotomous outcome: success (1 or 3 or 5) or failure. All patients coded with a two were considered a partial success. As there is no generalizable definition for a significant reduction in benzodiazepine dose (as any use is considered inappropriate) we had to make a clinical call determining that a 25% reduction would be clinically significant. Two investigators blindly and independently coded each participant's profile, with differences being resolved via arbitration by a third independent investigator. We also asked participants to self-report whether they discontinued their benzodiazepine. To our surprise, in many cases, the self-reported data did not match our objective ascertainment derived from the pharmaceutical profiles. As self-report data are often subject to recall or social desirability bias (e.g. in order to please, participants report having stopped benzodiazepines when in fact they continued to fill their prescriptions), we opted to use dispensing data as the gold standard, rather than the self-reported outcomes.

6.1.7 Design strengths and limitations

Design strengths

As the design of both trials is very similar, we will first discuss the general strengths of each trial design and then the specific strengths of each trial.

The first major strength of these two trials is the use of cluster randomization. Cluster randomization is frequently used in the evaluation of health services[491]. While in

conventional clinical trials the unit of randomization is the patient, in cluster randomized trials the randomization unit is a cluster made up of health professionals and patients. When evaluating health services, using individual randomization would make it difficult for the health professionals involved to provide different care to their different patients and could lead to contamination between the study arms. As such, cluster randomization provides an easy solution which allows health professionals in a study to provide the same care to all of their patients and avoid the potential contamination between study groups in the evaluation of new practices[487]. In the case of both the EMPOWER and D-PRESCRIBE trials, pharmacists were unaware of the inappropriate medication(s) being targeted by the study until they received the educational material to be handed out to patients and physicians. If randomization had been individualized, the usual care group may have been contaminated by the knowledge acquired by the pharmacist during receipt of the intervention materials (i.e. the pharmacist could start behaving differently towards the wait-list control group), thereby diluting the intervention effect. Additionally, individual randomization would make it unethical for pharmacists to intervene in some cases and not in others once the potential issue with their patient's medications had been identified. For these reasons, clusters of health professionals (pharmacists at a community pharmacy), rather than individual participants were allocated to one of the study groups (Intervention or usual care).

The second major strength was the use of randomization, using a wait-list control group, which maximizes the internal validity of the trials. Randomization allows, on average, to obtain comparable groups for known and unknown confounding factors[513]. In both trials, this allowed us to recruit similar groups of pharmacists willing to collaborate in establishing collaborative educational approaches with their patients. This design also allowed us to use usual care as a comparator to the interventions to evaluate the effectiveness of the intervention and the magnitude of the changes observed. The use of usual care permits consideration of normal practice, the effect of time (to evaluate spontaneous discontinuation rates) as well as secular trends in professional practice over time (for example, changes in treatment guidelines).

The third major strength of the trial design was its pragmatic nature, thus maximizing generalizability and external validity. Typically, trials can fall into two broad categories: pragmatic and explanatory. Pragmatic trials are designed to evaluate the effectiveness of interventions in real-life routine practice conditions, whereas explanatory (or efficacy) trials aim to test whether an intervention works under optimal situations. Pragmatic trials produce results that can be generalized and extrapolated to real-world practice settings.[514] We deliberately ensured that exclusion criteria were kept to a minimum, recruited pharmacists and participants in a systematic fashion, allowed for flexibility in the fidelity of sending out the pharmaceutical opinions by the pharmacists, blinded pharmacists and participants to the study hypothesis and intervention until enrolment, randomization and baseline assessment was complete, and used the pharmacy as the unit of randomization to prevent contamination. In some cluster randomized trials, recruitment of participants occurs after randomization of the clusters, augmenting the chances of selection bias[515-518]. Knowledge of group allocation could easily influence pharmacists to recruit a certain type of participant over others. Depending on how pharmacists would potentially bias the recruitment, over-estimation or under-estimation of the study effect could occur. For example, should pharmacists in the intervention arm decide to only approach clients who they know will be compliant or receptive to getting off a medication, the effect would be over-estimated. Similarly, if these same pharmacists chose more problematic patients knowing they would receive additional support from the research center in comparison to usual care, under-estimation of the effect could occur. In our case, we were able to limit selection bias by identifying all participants within a cluster before randomizing the cluster[515] as well as blinding both participants and pharmacists up until delivery of the intervention. The study was branded as a study on the “safe management of medications in older adults” to both parties. Pharmacists were unaware of the exact study criteria until receipt of the intervention as eligible patients were identified using an algorithm. Neither participants nor pharmacists had any advance expectation that would receive educational materials about benzodiazepines. We also told everyone that they would be contacted “sometime in the next year since it took time to go through all their files.” We received ethics approval to refrain from disclosing the 6-month randomization component of the trial to

both pharmacists and participants since both the intervention and control arms would receive the identical intervention within one year of randomization.

There were a few additional strengths to both trials. These included the objective and blind assessment of drug discontinuation rates from pharmacy prescription renewal profiles by two independent reviewers, which increases internal validity. Additionally, pre-emptive considerations to the sample-size due to the cluster design and potentially high rate of attribution of older adults allowed for sufficient power to be achieved if recruitment goals were met. Finally, both trials exclusively targeted adults over 65, a unique group usually underrepresented in randomized clinical trial community settings.

Strengths specific to D-PRESCRIBE

Specific strengths to D-PRESCRIBE include the change in the way we recruited participants by limiting the number of participants recruited per pharmacy to three per medication class. This limits cluster size, which in turn reduces the potential impact of the cluster design by making it more likely that observations are independent from one another. Additionally, the similarity in methods with the EMPOWER trial permit an efficient historical comparison to be achieved when comparing both interventions and avoiding the use of a more laborious and time-consuming factorial design to evaluate the added value of the pharmaceutical opinion over the EMPOWER intervention alone.

Design limitations

Despite their many advantages, cluster-randomized trials are not without limitations. Indeed, they are more prone to the introduction of certain types of biases when compared to simple randomized controlled trials[515 519-521]. Pragmatic trials have a higher risk of selection, attrition, confusion and information biases.

Attrition bias is a type of selection bias which occurs when one or more clusters is lost during the course of a cluster trial.[518 519] A reduction in the number of clusters may diminish the trial's statistical power[490 522]. In order to prevent and mitigate this type of bias, a number of strategies were put in place. We recruited pharmacies and signed

collaborative agreements with the owner of each pharmacy, not with specific pharmacists who worked there. In this way, when pharmacists took vacations, time off, or quit, the replacement pharmacists would be alerted to the collaborative agreement and ensure continuity of the project. Similarly, should a pharmacy owner change, continuity would be ensured by the staff and consent sought from the new owner. Only a change in ownership and subsequent withdrawal of consent could end a pharmacy's participation in the study, however, should this ensue, the research team would ensure proper follow up of participants. Fortunately, this particular scenario did not occur, due to our relationship with the Jean Coutu, Pharmaprix, Uniprix and Brunet directors in Quebec. The introduction of an attrition bias is also possible if certain clusters do not recruit any participants. In this case, even if the recruited pharmacies had similar characteristics at the beginning of the study, they may differ from the actual participating pharmacies.

Confounding bias occurs in cluster trials when only a small number of clusters are randomized. Randomization is usually more effective in countering this bias when a large number of clusters and individuals are randomly assigned to their study group [515]. This type of bias can contribute to an over-estimation or under-estimation of the effect of the intervention.

Differential information bias can occur when researchers and/or participants are aware of group allocation, and it can lead to an over-estimation or under-estimation of the effect of the intervention.[523] For example, if an investigator were un-blinded to group allocation, they might code the outcome in favour of discontinuation in unclear cases. In our projects, investigators remained blinded to group allocation at all times, including during outcome assessment. Additionally, the effectiveness of the intervention was assessed using objective variables and independently assessed by multiple reviewers blinded to group assignment. All of which contributed to preventing this type of bias.

The simple fact that participants and pharmacists were part of a trial can lead to a change in practice habits due to behaviors being monitored in the context of the study.

This is referred to as the Hawthorne effect and this effect can be described as any result, positive or negative, which cannot be attributed to experimental factors, but rather to the psychological effect on research subjects being included in a research project and monitored[524]. In our case, the Hawthorne effect might translate into participants being aware that they are in a medication safety trial, then pro-actively going through all their medications to see which ones they can discontinue. The Hawthorne effect usually explains high rates of outcomes in the control group, in our case this would-be discontinuation of benzodiazepines in the control group. Our analyses revealed that most discontinuations in the control group occurred shortly after the first study visit, so were likely due to sensitization following the interview. As the discontinuation rate of benzodiazepines in the control arm was approximately 5% in both trials, the potential dilution of effect attributable to the intervention is gauged to be minimal.

Although contamination between groups in any trial is always a possibility, we expect it was minimal in our trials. Pharmacists were informed that the intervention would be staggered over the course of a year and they should follow usual care until receipt of the study materials. Physicians could end up with patients in both the control and experimental arms of the study, but this is unlikely as pharmacies generally serve a specific geographic area and patients were recruited from a large geographic radius around Montreal. Physicians were not contacted at any point by the research team due to the potential to influence the outcome of the intervention during the study period and/or to not interfere with the pharmacist-doctor relationship.

EMPOWER specific limitations

Limitations specific to the EMPOWER trial include the relatively brief 6-month time frame for outcome reporting. Longer follow-up times could potentially reveal relapse rates or higher discontinuation rates as several participants who achieved dose reductions were still following the tapering protocol at study end-point. Secondly, only patients with polypharmacy, as defined by the long-term use of five or more medications were included, which limits the generalizability of results to this sub-group. Even though

there is still no consensus on the cut-off number of medications used to define polypharmacy[525], evidence from recent studies supports the definition of "five or more medications" for identifying community based older people at risk of harm from polypharmacy.[381 526 527]28-30 As such, this criterion was initially chosen as older adults with polypharmacy are at greater risk of adverse drug event and may have benefited more from the intervention. Additionally, recruitment rates for pharmacies (18%) and individual participants (11%) were low and excluded potential participants with cognitive impairment. As such it is possible that our study population contained more motivated pharmacists and clients and over-estimated the effectiveness of the intervention. Blinding of both pharmacists and participants to the primary outcome of the study mitigates against this, but still compromises external validity. While cluster size varied immensely across clusters (from 2 to 22 participants per pharmacy), and the number of clusters (n=30) in the EMPOWER trial is modest, this is not expected to have caused any issues as the study ended up being statistically overpowered, and we detected a very low ICC of 0.008. Appropriate analytic techniques were implemented to account for this in the outcome analyses. Finally, subgroup analyses may have been underpowered to detect differences.

D-PRESCRIBE specific limitations

As the thesis pertains only to the sedative-hypnotic branch of the D-PRESCRIBE trial, the limitations mentioned here are limited to this sub-group of the study. The main concerns specific to the D-PRESCRIBE project in addition to repeating some of the limitations for EMPOWER mentioned above lies in the flexibility given to pharmacists with the pharmaceutical opinion aspect of the intervention. As pharmacists are allowed flexibility on whether or not to send the opinion and whether or not they wish to modify it will reduce the adherence rate to our study protocol and complicate and lower the power of analyses done on the effect of this component.

6.1.8 Ethical considerations

Both trials were approved by the Research Ethics Board of the Centre de Recherche de l'Institut Universitaire de Gériatrie de Montréal, Canada on July 26th 2009

and September 17th 2013 respectively (Appendix 4). All participants signed informed consent and were informed that they were free to withdraw at any time.

6.2 Methods used to conduct a Realist Evaluation

This next section describes the methods that we used to conduct a realist evaluation alongside the EMPOWER trial. The goal of the realist evaluation was to gain a better understanding of the benzodiazepine deprescribing process from the participants' perspective. Chapter 7 includes the manuscript that was published describing the methods and results of this realist evaluation, however, this section is meant to provide additional methodological details that could not be included in the manuscript due to word count limitations

6.2.1 Why a realist evaluation? - "Black Box" VS "White box" evaluation

In traditional research, investigators attempt to provide an estimate of program effectiveness through the assessment of one or more outcomes, often established *a priori* [528-530]. This is often referred to as the "black box" evaluation, which is practical in examining the efficacy of interventions under controlled conditions where a relatively small number of carefully selected outcomes are assessed based on the anticipated effects of a limited number of variables while controlling for the effects of identified confounders[531]. However, in the real world, this over-simplified model of assessment provides little information about the effectiveness of complex interventions within uncontrolled, context-rich settings and may be insufficient to inform future implementation efforts [530 532 533]. Theory-based or theory-driven approaches provide an alternative to black box evaluations that examine not only outcomes but also the possible causes and contextual factors associated with change[534]. Theory-driven evaluation may be defined as any approach or strategy that integrates the use of theory in the conceptualization, design, conduct, interpretation, and application of evaluation[535]. It aims to not only generate insight with regard to program effectiveness but to also explain possible underlying causal mechanisms based on postulated associations between program inputs, mediating factors and program outputs.[535] As

theory-driven evaluations, such as realist evaluations, are intended to reveal the inner mechanisms by which an intervention works, they have been referred to as “white box” evaluations, aimed at transparently clarifying which specific components of a complex intervention work for specific individuals in specific circumstances.[528 533 535 536]

6.2.2 What is a realist evaluation?

Pawson and Tilley describe realist evaluation (RE) as an explanation-driven, generic approach to evaluation grounded in scientific realism[528]. Scientific realism aims to examine regular patterns that exist within reality and offers a more comprehensive understanding of these patterns by providing in-depth explanations through the exploration of generative causal mechanisms, which are sensitive to contextual factors[534 536]. RE is not a method or a technical procedure; rather it is a logic of inquiry that attempts to answer the question, “What works, for whom, in what circumstances? and why?.” RE is accomplished through the identification and examination of underlying generative mechanisms (M) associated with the intervention or program, the conditions or contexts (C) under which the mechanisms operate, and the pattern of outcomes (O) produced. Program or intervention mechanisms are not viewed as equivalent to program components; rather, they are an attempt to represent how program resources are received, interpreted and acted upon by the participant to produce an outcome or pattern of outcomes. This, Pawson and Tilley suggest, may be expressed as linked C-M-O configurations (or C+M=O). They also specify that the evaluation should a) have an explanatory focus, b) investigate linked configurations of context(s), mechanism(s) and outcome(s), and c) use multiple, mixed methods of data collection to do so[528].

The realist evaluation cycle consists of 4 phases. In phase one, initial program theories to be tested are formulated based on all relevant data. From there, potential C-M-O configurations can be developed. Phase 2 consists of data collection. Appropriate methods should be used to properly assess initial C-M-O configurations and it is also important to note that a pragmatic and mixed method approach is strongly recommended. Phase 3 consists of data analysis and hypothesis testing on the initial C-M-O configurations. Finally, in phase 4, proposed C-M-O’s are refined based on results

achieved. It is not expected that the end result of a realist evaluation will represent a complete explanation of all possible patterns of outcomes associated with the program or intervention studied, or even that the refined C-M-O configurations will provide generalizable representations of what works, for whom and in what circumstances. Instead, it is suggested that RE operates at a middle range, using concepts and data that lie between the description and hypotheses of day-to-day implementation and a universal "theory". It is anticipated that the mid-range theories produced through the process of program specification or C-M-O refinement may contribute to further cycles of inquiry and, therefore, to ongoing theoretical development[528].

6.2.3 Our realist evaluation

The following section describes how we chose to conduct our realist evaluation.

Design

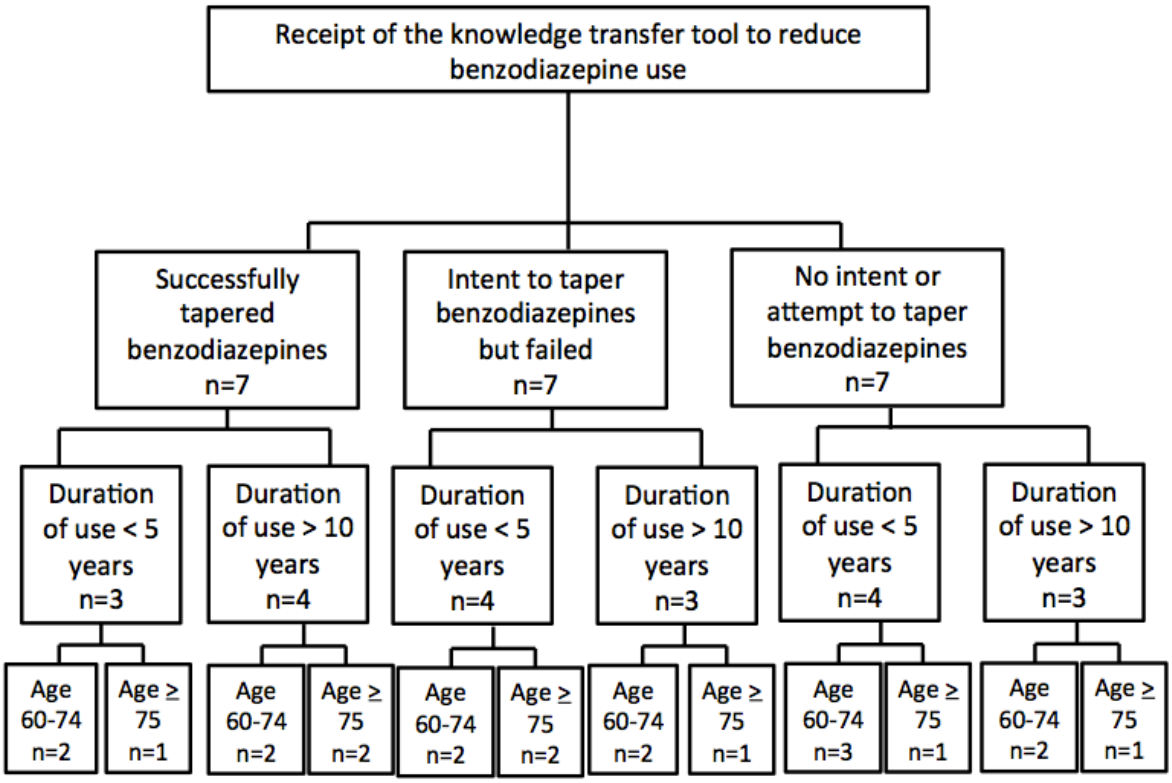
A sequential explanatory mixed methods study design (quantitative → qualitative) was used.[537] This method is a two phase design where the quantitative data is collected first followed by qualitative data collection. The purpose is to use the qualitative results to further explain and interpret the findings from the quantitative phase.[537] The rationale for using a mixed methods design was 1) to draw upon the strengths of quantitative research to measure differences in participants who succeeded or failed to initiate benzodiazepine tapering and/or discontinuation, and 2) to perform in-depth qualitative interviews to better understand the context and experiences of each participant and the role these played in each participant's lived experience of the deprescribing process.[538]

Participants and contrast sampling

Participants were recruited to the qualitative study from among 85 individuals who had completed the trial at the time in-depth interviews were conducted. We used a contrast-based sampling strategy, triaging individuals according to trial outcome, age, sex and duration of benzodiazepine use, as these are known predictors of benzodiazepine dependence. Recruiting individuals who chose not to taper their benzodiazepines was more difficult than recruiting those who succeeded in tapering,

however, we continued recruitment until thematic saturation was achieved (7 individuals per group). The diversity of the patient profiles (sex, duration of benzodiazepine administration, and age) was respected during recruitment. The total number of the participants was 21 (mean age 75, age range 68-87), see figure 7.

Figure 7: *Contrast sample design – Diagram of patients recruited for patient in-depth qualitative interviews.*



Formulation of initial program theories and Contexts-Mechanisms-Outcomes configurations

For this study, we began the process of theory formulation with a synthesis of the relevant literature. This first stage involved the identification of concepts, program theories, and potential frameworks. This included, but was not limited to such themes as health outcome prioritization in older adults, predictors of medication cessation and benzodiazepine cessation in particular, patient-centered/behavioral theories, attitudes

towards deprescribing, and patient enablers/barriers to deprescribing.[341 539-542] Using this information, we developed the initial conceptual framework, theories and working propositions, which would then be refined through data analysis and interpretation.

Context was defined as all the factors in a patients' environment during receipt of the intervention and during the deprescribing process. The outcome was defined as whether or not the deprescribing intervention was successful. The specific mechanisms that we tested were whether the EMPOWER brochure: (1) triggered older adults' motivation to deprescribe by increasing knowledge and concern about benzodiazepines; (2) built capacity to taper by augmenting self-efficacy; and (3) drove opportunities to receive support from a healthcare provider to deprescribe. The program theories embedded in the EMPOWER intervention are based on Mitchie et al's behavior change wheel[543], targeting motivation, capacity and opportunity. Mitchie et al. define motivation as the mental process that energizes and directs behaviors. Capability refers to the psychological and physical capacity of the individual to engage in the behavior. Opportunity refers to the external factors that permit or promote a behavior to happen and include both the physical and social environment of the individual. Table 17 links the program theories and mechanisms to the corresponding intervention components.

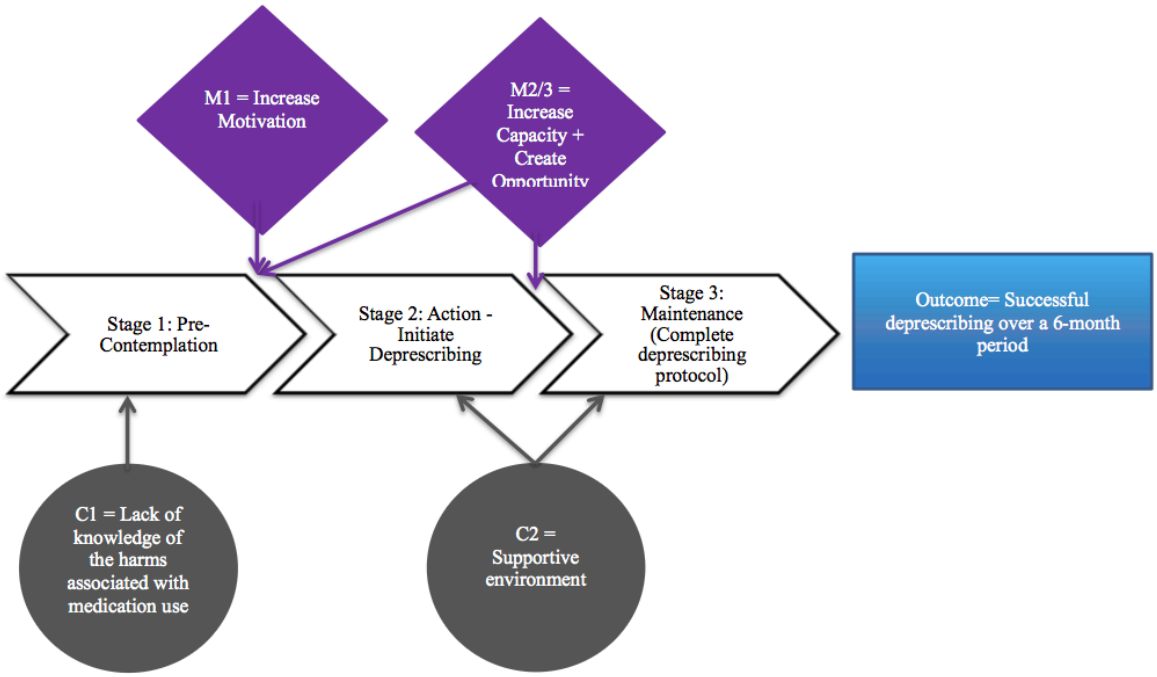
Table 17: *Links between program theories and mechanisms to the corresponding intervention components.*

Program Theory/Mechanism	**Components of the EMPOWER brochure**		
Increase motivation to deprescribe by changing knowledge and beliefs	Messaging on the front page "You May be at Risk" to raise awareness of the harms of benzodiazepines	Interactive knowledge test with 4 true/false questions and answers about the harms of benzodiazepines,	Information about changes in drug metabolism with age that can lead to a higher risk of side effects, meant to change beliefs and elicit concern about

		aimed at increasing knowledge	the safety of the medication in older adults
Increase capacity to taper by augmenting self-efficacy	A list of alternative non-pharmacological approaches to sleep and anxiety that patients can use as substitutes	An inspirational story using social comparison and peer championing to increase self-efficacy for tapering	Provision of an easy-to-use visual 16-20 week tapering tool showing when to take a whole, half or quarter pill, and when to skip the dose completely
Drive opportunities to discuss and initiate deprescribing with a healthcare provider	Instruction to "Please consult your doctor or pharmacist before stopping any medication" in a large red box	Logos on the brochure provide source credibility for the patient to initiate conversations	The printed format of the 8-page brochure makes it an effective knowledge transfer piece to take and show to a healthcare provider

This in turn led to the development of our initial deprescribing Context-Mechanism-Outcome configuration as illustrated in Figure 8.

***Figure 8**: Initial deprescribing Context-Mechanism-Outcome configuration*



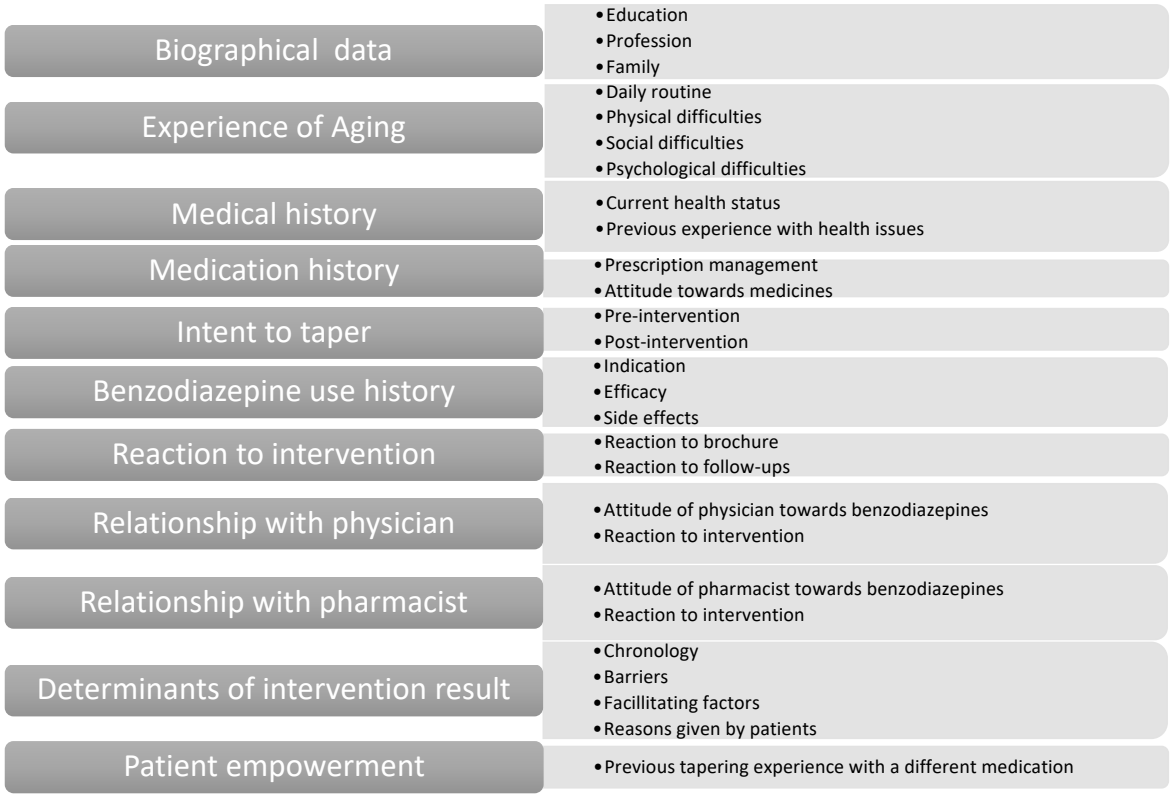
Qualitative data

Quantitative data were obtained via semi-structured interviews conducted at participants' homes in order to explore the perceptions, motivations, and experiences of participants in relation to receipt of the educational intervention about benzodiazepines. Interviews lasted approximately one hour, were recorded with consent and professionally transcribed verbatim. The interviews were based on a discussion guide (see appendix 5), the major themes of which included the following: attitude to medication in general, benzodiazepine prescription history, relation with the doctor and with the pharmacist, initial reaction to the intervention, decision to try to taper benzodiazepine, other actors involved in the decision–making process (doctor, pharmacist) and their reaction to the intervention, experience with the tapering process and the patient's perception of involvement in sharing responsibility about medication safety.

Analysis of qualitative data

The primary method of qualitative data analysis was thematic content analysis.[544] Discourses were contrasted according to the subject types developed from the strategic variables. Interviews were coded using Dedoose software, which allows for rapid segmenting of information and rebuilding of the corpus around various themes. The themes were derived from the data using an inductive approach supported by quotes. Initially, two researchers independently read the transcripts and field notes, then collaboratively developed first-order codes (open and near data), which were subsequently verified by double coding (see Figure 9). Furthermore, after the next rereading, the second order thematic coding was done which directed us towards building concepts. These concepts were regularly reviewed and discussed with the entire research team.

Figure 9: *First and second order coding of interviews*



Quantitative Data

Quantitative data was collected using participants from the EMPOWER study. Full details are presented in the methods section of article 7.4, so we will avoid repeating them here. Briefly, information about participants' knowledge, beliefs risk perception, self-efficacy and outreach to a health professional were measured and reported using the appropriate statistical methods.

Combining the datasets using mixed methods

We combined quantitative and qualitative results in an iterative fashion through a triangulation protocol for integrating data in mixed methods studies using a convergence coding matrix,[545] as described by Farmer et al.[546] We employed two types of triangulation a) multiple investigators, whereby the triangulation protocol was independently applied by two researchers and b) methodological, where the results were compared between the two methods of data collection. First, the content of both files was reviewed to identify key themes that emerged from each data set to create a unified list of themes to compare. These themes form the rows of the convergence coding matrix used to summarize similarities and differences between the two sets of data. Findings were then compared with respect to the meaning and prominence of the themes in order to apply the convergence coding scheme, which codes each theme as being in agreement, partial agreement, silence or dissonance between the two datasets.[546] Meaning of the themes was assessed by congruence in thematic content between the quantitative and qualitative data, while prominence was assessed based on the quantitative frequency of endorsement of each theme among participants in both datasets. Results of the convergence coding were compared for completeness across data sources, and level of agreement across researchers. Differences were discussed and adjudicated by an independent third investigator. [546] See table 18.

Table 18: *Convergence coding matrix for factors leading to success or failure of the intervention*

Theme	**Convergence Code: Theme meaning and prominence**			
	Agreement †	Partial agreement †	Silence†	Dissonance †
Decision to taper benzodiazepines:				
Positive factors:				
Encouragement by a health professional	X			
Previous support from physicians/ positive attitude towards discontinuation			X	
Lack of psychological attachment to the drug	X			
Preventive perspective on active and healthy aging			X	
Perception of increased risk	X			
Stable health status			X	
Certainty and confidence about tapering	X			
Provision of an easy-to-use tapering tool	X			
Negative factors				
Previous discouragement from physicians / Negative attitude of physician towards discontinuation	X			
Unquestioning belief in their physician				X
Lack of perception of personal risk	X			
Poor health status		X		
Reliance on medication for coping/everyday function	X			
Quality of life focus during end-of life			X	

Success in tapering benzodiazepines:	Agreement †	Partial agreement †	Silence†	Dissonance †
Positive factors:				
Supportive pharmacist or physician				X
Negative factors:				
Discouragement from a physician	X			
Loss of confidence to complete the tapering process			X	
Intolerance to recurrence of symptoms	X			

† Agreement: full agreement between the sets of results on both elements of comparison, Partial agreement: partial agreement between the sets of results on elements of comparison, Silence: Theme mentioned in one set of results but absent from the other, Dissonance: disagreement between the sets of results on both elements of comparison.

Formulation of the refined program theories and Contexts-Mechanisms-Outcomes configuration

Following, triangulation, we adjusted our initial model to better fit what we observed. This final model is described in the manuscript in chapter 7.4, where the final results of our realist evaluation are presented.

6.2.4 Additional considerations

Evolution over time for how to conduct a realist evaluation

Realist evaluation, being a relatively new methodology, is still developing standardized procedures and methods of operation. Almost 20 years after its initial development by Pawson & Tilley in 1997[547], new articles continue to appear such as "What's in a mechanism? Development of a key concept in realist evaluation"[548] by Dalkin et al., in an attempt to clarify and standardize one of the key concepts behind realist evaluations. Outcomes are easily differentiated from contexts and mechanisms. However, deciding whether aspects of implementing the intervention contribute

contextually or mechanistically to the overall explanatory effort is more complex [533] [534] [549] Realist evaluation experts suggest that "*Intervention resources are introduced in a context, in a way that enhances a change in reasoning. This alters the behavior of participants, which leads to outcomes.*" [548] During the course of my thesis, a change in scientific thinking in the field started to take place, which is leading to a re-formulation of the initial C+M =O configuration to the newer M (resources) + C → M(reasoning) = O for realist evaluation methods. It is now postulated that resources and reasoning are mutually constitutive of a mechanism. By explicitly disaggregating them into these concepts, it can help operationalize the difference between a mechanism and a context.[548] However, as I conducted the analyses for my thesis prior to this change in dogma, we decided to publish the mixed-methods paper based on our initial C+M= O configuration.

Lack of clear reporting guidelines

Similarly, when I began this project, there was a complete absence of reporting guidelines for realist evaluations. The result was a very heterogeneous quality of reporting of results of realist evaluations in the literature during the years when I started writing up my findings. Authors simply putting their own spin on manuscript organization and the level of information provided, which made it very hard to compare various realist evaluations. We, therefore, struggled with the format for reporting my work, since no previous publications had ever addressed the topic of deprescribing from a realist perspective. Fortunately, the first RAMESES (Realist And Meta-narrative Evidence Syntheses: Evolving Standards) guidelines finally appeared in 2014[550] and were officially updated in late 2017.[551] As such, publication of our realist evaluation manuscript in Chapter 7 follows the RAMESES guidelines for realist evaluation, and are of the highest reporting quality possible.[552]

6.2.5 Strength and limitations

Design strengths

The first major strength is the use of mixed methods. Quantitative studies measure baseline data and detail the impact of the intervention on the patient in terms

of effectiveness and outcomes of intervention strategies. However, quantitative analysis is rarely able to capture the contextual factors that affect the participant's journey from receipt of the intervention to potentially initiating a change in behavior. Qualitative studies, on the other hand, can describe the intervention processes from the point of view of the person and provide a better understanding of patients' preferences, needs and resultant interpersonal interactions subsequent to the receipt of the intervention. A limitation of qualitative research, on the other hand, is its inability to capture essential parameters required to describe the process at a group or population level. Our use of mixed methods combines two different and complementary analytical frameworks, which we believe strengthens the process evaluation of the intervention and the reasons underpinning the outcomes of the EMPOWER trial. This mixed-methods approach enabled us to explore the breadth, depth, and complexity of the patient's experience of deprescribing from a social, behavioral and health perspective, allowing stronger inferences about the various contexts affecting patients' decisions than could be achieved through a quantitative or qualitative lens alone.[553] This method not only allowed us to strengthen the conclusions that could be observed in both data sets but also allowed us to develop new research questions for further investigation.

The second major strength of this project is the use of the realist evaluation itself. The realist evaluation method employs a theory-driven approach, which examines not only the outcome, but also the possible causes and contextual factors associated with change, which is exactly what we want to know when evaluating the implementation of complex behavioral interventions.[534] Realist evaluation aims to not only generate insight about the program's effectiveness, but also explain possible underlying causal mechanisms based on the proposed mechanisms embedded in the intervention.[535] Understanding patterns of behavior through the lens of generative causal mechanisms that are affected by contextual and social influences is key.[534 536 554 555] We believe the realist evaluation was the ideal method to address our objective of exploring the decisional processes of older adults after receipt of the EMPOWER deprescribing intervention.

Design limitations

There are acknowledged weaknesses associated with the use of qualitative methods.[556] Qualitative research is a very time-consuming process which requires skilled interviewers to carry out data collection as well as skilled analysts to perform a very labor-intensive analysis process.[557] Due to the nature of this method, it is possible for important issues to be overlooked by researchers despite researchers' best intentions.[556] In qualitative research, inquiry is generally open-ended, therefore participants have more control over the data collected as their personal experience and knowledge influence the observations and conclusions.[558] This may result in researchers' interpretations being limited and potentially incomplete, depending on who was interviewed and whether a complete saturation of experiences was obtained. When used alone, qualitative methods sometimes result in data that cannot be verified objectively against the population whole. In our study, we addressed some of these limitations through a combined use of quantitative and qualitative methods.

The main limitation to the realist evaluation design is its relatively narrow scope in the face of all possible mechanisms and contexts that affect deprescribing from the patient's perspective for different medication classes. It is almost certain that other mechanisms and contexts trigger motivation to deprescribe beyond what is described and what we were able to capture with our interview questions in this realist evaluation of benzodiazepines. For example, one could argue that other mechanisms exist for deprescribing other drug classes that we did not test in this study. One untested mechanism is the provision of information about the lack of drug benefits for certain agents in specific populations, such as statins to reduce cholesterol levels in palliative care patients with limited life expectancy. [356] [559] Realist evaluations rarely provide a complete explanation of all possible patterns of outcomes associated with the program or intervention studied. Instead, realist evaluation operates at a middle range, using concepts and data that lie between the description and hypotheses of day-to-day implementation and a universal theory. It is therefore anticipated that the mid-range theories produced in our refined CMO configuration will contribute to further cycles of

inquiry and ongoing theoretical development about the patient's experience of deprescribing.[528]

6.3 Conclusion

Conducting community-based clinical trials and mixed methods studies present formidable methodological challenges. Decisions must be taken that balance feasibility and scientific rigor. The choices we made targeted maximal external and internal validity and aimed to achieve results that are accurate and precise, and that best represent the observed data. The new C-M-O configuration generated by the realist evaluation remains hypothetical but provides a new line of inquiry for the next study. The next chapter includes four published manuscripts, reporting the results from the EMPOWER trial as well as the realist evaluation associated with the project. Chapter eight comprises two manuscripts, which describe results from the D-PRESCRIBE study. The first manuscript explains how the pharmaceutical opinions were developed, and the second compares the effectiveness of the D-PRESCRIBE intervention to its predecessor EMPOWER.

Chapter 7 – EMPOWER Results

7.1 A drug education tool developed for older adults changes knowledge, beliefs and risk perceptions about inappropriate benzodiazepine prescriptions in the elderly.

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ABSTRACT

Objective: To develop and test an educational tool for older adults that increases risk perception about benzodiazepines through knowledge acquisition and change in beliefs.

Methods: A written educational tool was mailed to 144 benzodiazepine consumers aged ≥ 65 years recruited from community pharmacies. Knowledge and beliefs about inappropriate prescriptions were queried prior to and 1-week after the intervention. Primary outcome was a change in risk perception. Explanatory variables were a change in knowledge and beliefs about medications. Self-efficacy for tapering and intent to discuss discontinuation were also measured.

Results: Post-intervention, 65 (45.1%) participants perceived increased risk. Increased risk perceptions were explained by better knowledge acquisition (mean change score 0.9, 95% CI (0.5, 1.3)), and a change in beliefs (BMQ differential mean change score -5.03, 95% CI (-6.4, -3.6), suggesting elicitation of cognitive dissonance. Self-efficacy for tapering, (mean change score 31.2, 95% CI (17.9, 44.6), and intent to discuss discontinuation of benzodiazepine with a doctor (83.1% vs 44.3%, $p<0.001$) were higher among participants who perceived increased risk.

Conclusion: Risk perception surrounding inappropriate prescriptions can be altered through direct delivery of an educational tool to aging consumers.

Practice implications: Patients should be targeted directly with information to catalyze discontinuation of inappropriate prescriptions.

1. Background:

Medication safety in the elderly population represents a unique challenge. Older adults are at increased risk of drugs side effects, drug-drug interactions and adverse events due to age-related changes and associated disease [1,2]. The 2012 updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults, lists all drugs-to-avoid in the elderly to reduce the risk of drug-related adverse events [3,4]. All benzodiazepine sedative-hypnotic drugs used for the treatment of anxiety and insomnia feature on this list due to an excessive risk of delirium, falls, fractures and motor vehicle accident [5].

With every update to the Beers criteria, significant efforts are made to inform and educate relevant parties to try and implement safer prescribing practices. We sought to develop an educational intervention to inform consumers directly about the risk of benzodiazepine drugs. We chose benzodiazepine drugs because qualitative research suggests that chronic users develop a psychological dependence to benzodiazepines, attributing them qualities that extend beyond their ordinary capacity [6]. Most consumers deny or minimize side effects while expressing subtle reluctance to outright refusal for being left suffering without these medications [6]. For these reasons physicians often express reticence for insisting on benzodiazepine discontinuation for fear of upsetting the doctor-patient relationship or because they believe that the patient tolerates the medication with minimal side effects [7].

The objective of this study was to develop and test an educational tool targeted directly to older consumers on the risks associated with benzodiazepine use in the geriatric population. By applying constructivist learning theory to the development of the educational intervention, we aimed to evaluate the potential of this tool for increasing the patient's risk perception by eliciting cognitive dissonance through knowledge acquisition and belief alteration. We hypothesized that improvements in patient knowledge, beliefs and perceived medication risk would lead to greater motivation for initiating discussions about drug discontinuation with a doctor or pharmacist and greater self-efficacy for tapering benzodiazepine use.

2. Methods

A quasi-experimental study was conducted among a cohort of chronic benzodiazepine users aged 65 years and older in Montreal, Canada. Participants were randomized to immediately receive an educational intervention to reduce inappropriate prescriptions or to a six-month wait-list group. The current analysis presents interim results on short-term changes in risk perceptions about benzodiazepines due to the intervention. The study was approved by the Institut Universitaire de Gériatrie de Montréal Ethics Committee in Montreal, Quebec, Canada.

2.1 Participants

The study population included community-dwelling men and women aged 65 years and older, consuming at least five prescription medications including a benzodiazepine dispensed for at least three consecutive months. Exclusion criteria were a diagnosis of severe mental illness or dementia ascertained by the presence of an active prescription for any antipsychotic medication and/or a cholinesterase inhibitor or memantine. Participants unable to communicate in French and/or English or showing evidence of significant cognitive impairment (score under 21 [8] on the MOCA (Montreal Cognitive Assessment)) were also excluded.

2.1.2 Recruitment

Participants were recruited from community pharmacies in the greater Montreal area. Pharmacists identified eligible patients from their databases and invited them to enroll in the study through personalized mailed invitations, referring them to the study coordinator. A telephone follow-up from the pharmacist (or delegate) aimed to ascertain interest in the study from eligible participants who had not spontaneously contacted the coordinator. An appointment was made with the study coordinator at participant's residence for those who provided permission to be contacted for the study. Signed consent was obtained from individuals who met study criteria after baseline cognitive and health status screening.

2.2 The Educational Intervention

2.2.1 Theory and development of the intervention

Social cognitive theory, which consists of health promotion through social cognitive means, guided the development of the intervention [9]. The specific learning model that was applied was constructivist learning. Constructivist learning theory aims to promote active learning through creation of knowledge that seeks to make sense out of the material presented. The goal of this approach is to create an environment where the learner can interact with academic material, fostering their own selecting, organizing and information integrating processes [10]. Such theories have already proven successful in other health promotion interventions such as in educational materials for smoking cessation [11].

A critical component of constructivist learning theory is elicitation of cognitive dissonance [12]. Cognitive dissonance occurs when a person's preconceived notions about the self and the world clash with new knowledge acquisition; the discrepancy that is evoked results in a state of tension known as cognitive dissonance [12]. Our educational intervention for reducing benzodiazepine was developed to create cognitive dissonance by soliciting an aversive motivational state in recipients by confronting two inconsistent cognitions on benzodiazepine use. The theory holds that as the experience of dissonance is unpleasant, the individual will be motivated to remove the pressure caused by this conflict by altering one of these perceptions to achieve consonance [12]. For instance, if an individual previously believed that benzodiazepines were safe, the threatening content of the tool challenges this belief by providing information that benzodiazepines incur several harmful risks, thus putting into question whether consumption should be continued [13,14] We also incorporated social comparison theory into the content of the intervention to reassure participants about their newfound uncertainty regarding benzodiazepine use. Social comparison states that: "people evaluate their opinions and abilities by comparison respectively with the opinions and abilities of others" [15]. It thus consists of comparing oneself with others in order to evaluate or to enhance some aspects of the self [16]. Here, the evaluation of the ability or inability to do a specific action relies on the success of a proxy performer. The

efficacy of this theory depends on whether the comparer assimilates or contrasts him/herself to others [17]. Comparability with a peer champion's narrative and previous agreement with the peer's views are important factors for the comparison to work [16]. A self-assessment component was also introduced, which aimed to promote insight about potential misinformation or beliefs held about benzodiazepine use by providing feedback on incorrect assumptions [18,19].

Textual content of the intervention was based on a systematic review of the evidence as well as guidelines concerning the use of benzodiazepines in the elderly. A geriatrician and graduate student drafted the initial content of the tool, which was then validated by a panel of colleagues with expertise in geriatric pharmacy and reviewed by a health librarian to ensure that the wording met standards for patient literacy at the Grade 6 level. The tool was developed in English, and backward and forward translated into French.

2.2.2 Components of the intervention

The cover page of the brochure states "You May Be At Risk" with a picture of a pillbox with several medications in it, followed by "You are currently taking (name of the patient's benzodiazepine)". The first page of the intervention is entitled "Test Your Knowledge" and consists of four true or false questions on the use of the benzodiazepines. The second page lists the correct answers. Elements of constructivist learning theory are incorporated into the answers to create cognitive dissonance and challenge the patient's beliefs for each incorrect answer. The third page incorporates self-assessment and education about potential inappropriate use, side effects, drug-drug interactions and information about physiologic changes that occur with age that affect drug metabolism. The fourth and fifth pages present evidence-based risks associated with benzodiazepine use in the elderly and suggestions for equally or more effective therapeutic substitutes. The sixth page describes a case scenario highlighting one woman's success at weaning herself off benzodiazepines. The last page outlines a simple 21-week tapering program. The reader is encouraged on four occasions and is

warned in large, red lettering to “Please Consult your Doctor or Pharmacist Before Stopping Any Medication.”

2.2.3 Acceptability of the intervention

The tool was field-tested with a convenience sample of older adults to determine the readability and comprehension of the information. Six focus-groups (n=60 adults) were conducted. Based on the focus group discussions, the wording, ordering of the material and visual presentation of the intervention was changed in an iterative process until acceptability was reached. The final educational intervention consisted of a seven-page letter-size paper brochure written in 14-point font. The educational tool was mailed to the study participants within six months of the initial assessment.

2.3 Study outcomes

2.3.1 Primary outcomes

The primary outcome was a self-reported change in perception of risk associated with benzodiazepine use one-week post-intervention. Participants were asked whether they perceived the same, increased, or no risk from consumption of their benzodiazepine following the intervention. A common idea in models of risk perception is that risk is perceived from two dimensions: the first being knowledge about the risk, and the second, beliefs about that risk [20]. To explain changes in perception of risk we therefore measured changes in knowledge and beliefs about medications as a mechanism through which cognitive dissonance could occur.

Change in knowledge was measured by comparing the pre-intervention and post-intervention answers from the four-item true or false questions listed in the “Test Your Knowledge” section of the questionnaire. The first statement on the safety of long-term benzodiazepine was “(Example: Ativan®) is a mild tranquilizer that is safe when taken for long periods of time”. The second statement focused on side effects and was worded, “The dose of Ativan® that I am taking causes no side effects.” The third statement on withdrawal was phrased, “Without Ativan® I will be unable to sleep or will

experience unwanted anxiety," and the fourth statement on alternative treatment options reads: "Ativan® is the best available option to treat my symptoms".

Change in beliefs was measured by comparing the pre- and post-intervention total scores on the specific section of the beliefs about medicines questionnaire (BMQ-Specific) adapted for benzodiazepines [21,22]. The rationale for choosing the BMQ-Specific instrument to measure beliefs relates to its ability to isolate and score participants' beliefs (second dimension of risk perception) about a specific medication, both in terms of the necessity of taking their prescription (Specific-Necessity) and the dangers of this same prescription, such as long-term toxicity, side-effects and dependence (Specific-Concerns). The BMQ-specific consists of two five-items factors belonging to each sub-score. Participants indicate their degree of agreement with each statement on a 5 point Likert scale (where 1=strongly disagree through 5=strongly agree). Scores are then summed into their respective sub-category (5-25 scale) with higher scores indicating stronger beliefs. A necessity-concerns differential can also be calculated by subtracting the concern sub-score from the necessity sub-score. This differential can be thought of as the cost-benefit analysis for each patient, where costs (concerns) are weighed against perceived benefits (necessity beliefs) [21,22]. A negative change in BMQ-differential score thus indicates a greater perception of risk.

2.3.2 Secondary outcomes

Two secondary outcomes were selected to measure anticipated behaviors potentially resulting from a change in risk perception: self-efficacy for tapering benzodiazepines and the intent to discuss benzodiazepine discontinuation with a doctor or pharmacist. The behavior motivation hypothesis was used to understand the drivers and consequences of risk perception. This hypothesis describes the determinants of risk perception and their effects on behavior change and is endorsed by most models of health behavior [23]. Perception of risk has been shown to be positively related to preventive health behavior when expectations of success in dealing with the risk are acceptable, and when recommendations for preventive behavior are presented as effective [24]. Self-efficacy for tapering benzodiazepines was measured pre- and post-

intervention on the Medication Reduction Self-efficacy scale, which allows the respondent to rate on a scale of 0 to 100 their degree of confidence for tapering and discontinuing benzodiazepines [25].

In order to measure anticipated behavior as a function of the participant's willingness to empower themselves in health-related decisions following the intervention, participants were asked to indicate (yes/no) post-intervention: if they had spoken to friends and family about the intervention, and if they had spoken to or intended to discuss medication discontinuation with their doctor and/or pharmacist. These intentions were considered as a preliminary measure of preventive health behavior. Finally, initial reaction to the questionnaire and whether they had read it more than once was also collected.

Outcomes were measured at baseline and one week following receipt of the intervention. At baseline, questionnaires were completed at the participants' homes during an interview with the research coordinator. Follow up was by telephone interview with the same coordinator. Self-reported socio-demographic variables, health status variables and prescription details were collected at baseline.

2.4 Statistical analysis

Participant characteristics were summarized using means with standard deviations for continuous data and percentages for categorical data. The number of participants reporting increased risk perceptions one week after the intervention was reported as a proportion of all participants. To examine potential differences in the baseline characteristics of participants who perceived increased risk versus those who did not, group comparisons were conducted. There were few missing baseline data (n=0-5 per variable), which were replaced by the mean group value.

To determine whether a change in knowledge or beliefs explained changes in risk perception as a result of receiving the educational intervention, changes in knowledge and beliefs from pre- to post-intervention were computed for each individual,

as well as within and between groups of individuals who reported increased risk perceptions versus those who did not. Correct knowledge pre- and post-intervention was reported as the proportion of individuals endorsing the correct answer for each question. A sub-analysis among participants with potential for change, denoted by CAIA, or Change in the Answer from an Incorrect Answer, was also conducted to determine change in knowledge among participants who initially answered a question incorrectly, but subsequently changed to the correct answer at 1-week follow-up. Participants with correct answers at both time-points were thus excluded from the CAIA measure, as there was no potential for cognitive dissonance. An overall score for knowledge was computed as the sum of correct answers (0-4 range). A change in belief was measured by comparing the BMQ-specific-necessity score, specific-concern score and necessity-concern differentials both within and between the increased risk and no increased risk group. Participants who had evidence of both a change in knowledge and a change in beliefs were denoted as having experienced cognitive dissonance.

Self-efficacy scores for discontinuing benzodiazepines were compared both within and between RISK groups from baseline to post-intervention, as were responses to the query about self-efficacy for tapering benzodiazepines. Participants with missing data for any of the BMQ-specific variables (n=3) or the self-efficacy variables (n=7-8) were withdrawn from these analyses. In order to determine the increased likelihood of anticipated preventive behaviors according to risk perception, the odds of endorsing a behavior were regressed against risk perception using univariate logistic regression. Missing data were replaced by a negative answer for the latter analyses,

A chi-square test was used when comparing groups while McNemar's test was used to examine changes within groups from baseline to post-intervention for categorical variables. Independent T-tests were used to compare groups while paired T-tests were used to examine changes within groups from baseline to post-intervention for continuous variables. The statistical significance for all analyses was set at $p<0.05$ and trend at $p<0.10$ (two-sided tests). SPSS Version 20.0 (SPSS Inc. Chicago, IL, USA) was used for all analyses.

3. Results

3.1 Recruitment

Participants were recruited from 12 pharmacies. The response rate to the mailed invitation to enroll in the study among eligible participants identified by their pharmacists was 15%. A total of 144 participants who received the educational intervention are included in this analysis.

3.2 Baseline Characteristics

Table 1 shows demographic, general health status and prescription-related characteristics of the entire cohort at baseline. Participants were mostly female (73%), had an average age of 75, and the majority (83%) had no formal college or university education. Half of all participants had previously attempted benzodiazepine discontinuation, 25% of whom had successfully weaned off the drug at some point.

3.3 Change in Risk Perceptions

Post-intervention, 45.1% (n=65) of participants reported increased perceived risk from consumption of benzodiazepines. There were no statistical differences in baseline characteristics between individuals perceiving an increased risk (RISK) and those with no perceptions of increased risk (NO RISK), except for a trend showing a shorter duration of benzodiazepine use among the RISK group ($p= 0.08$) (Table 1).

3.4 Change in knowledge

Knowledge about benzodiazepines was similar between groups at baseline. Changes in knowledge both within and between risk groups are described in **Table 2**. Eighty percent (52/65) of participants in the RISK group changed an answer from incorrect to correct on at least one knowledge question from pre- to post-intervention compared to only 41% (33/79) in the NORISK group. The RISK group demonstrated a significantly higher proportion of correct answers post-intervention on the safety, side effects and alternatives questions compared to the NORISK group ($p<0.001$). Only participants in the RISK group who had the potential for knowledge acquisition showed a statistically significant increase on the overall knowledge score (mean change score

1.77 SD (1.3)). The change in overall score was significantly greater among these individuals in the RISK group post-intervention compared to the NORISK group (mean change score 0.91 95% CI (.5, 1.3)).

3.5 Changes in Beliefs

Beliefs about benzodiazepines were similar between groups at baseline. **Table 3** shows changes in beliefs about the necessity, perceived negative consequences, and risk-benefit ratio of benzodiazepine use. Eighty-three percent (54/65) of participants in the RISK group had an improved BMQ-differential score (negative change) from baseline to follow-up, indicating increased risk perception, compared to 27% (31/79) of participants in the NORISK group. The RISK group showed statistically significant group differences across all three of these BMQ outcomes ($p<0.001$) while no significant group changes were detected in the NO RISK group. Post-intervention, the RISK group reported significantly lower scores on the necessity subscale (mean change score -1.31, 95% CI (-2.3, -.4)), significantly higher scores on the concerns subscale (mean change score 3.72, 95% CI (2.9, 4.5)) and a statistically greater necessity-concerns differential (mean change score -5.03, 95% CI (-6.4, -3.6)), compared to the NO RISK group.

3.6 Frequency of cognitive dissonance

According to an operational definition of cognitive dissonance predicated upon a change in knowledge and a change in beliefs about benzodiazepine consumption due to receipt of the intervention, 44/65 (68%) of participants in the RISK group and 19/79 (24%) of participants in the NORISK group experienced cognitive dissonance. The experience of cognitive dissonance was associated with a six-fold higher likelihood of patients reporting increased risk perception about their benzodiazepine prescription (OR= 6.61 95%CI (3.2, 13.8)).

3.7 Change in self-efficacy for tapering benzodiazepines

The RISK group reported significantly greater improvements in self-efficacy for discontinuing benzodiazepines following the intervention (mean change score 31.24

95% CI (17.9, 44.6)) compared to the NORISK group. The added benefit of the tapering protocol on self-efficacy scores for discontinuing benzodiazepines within the RISK group was 6.05, 95% CI (3.0, 9.1). No statistically significant differences in self–efficacy were found in the NO RISK group.

3.8 Change in health behaviors aimed at discontinuing benzodiazepine use

Figure 1 shows correlates and anticipated behaviors associated with an increased risk perception post-intervention. The RISK group reported a significantly higher likelihood of reading the tool more than once (OR= 8.34 95%CI (3.9, 17.9)), intention to discuss the intervention with family and friends (OR= 2.65 95%CI (1.3, 5.5)), and intention to discuss discontinuation with a physician (OR= 6.17 95%CI (2.8, 13.5)), or pharmacist (OR= 6.29 95%CI (2.8, 14.3)), compared to the NORISK group.

4. Discussion and conclusion

Findings from this study indicate that a personalized patient-targeted benzodiazepine educational intervention delivered directly to the individual consumer via written material was effective in changing medication risk perceptions in 45% of older chronic users. Heightened risk perception was explained by significant changes in knowledge and beliefs about benzodiazepines due to receipt of the tool. Our study suggests that participants in whom the intervention elicited changes in knowledge and beliefs may have experienced cognitive dissonance as the mechanism underlying increased risk perception. Participants with increased risk perception reported greater self-efficacy for tapering benzodiazepines and marked intent to engage in preventive health behaviors by discussing medication safety with a health professional.

The participants in this study are representative of other older chronic benzodiazepine users reported in previous studies, with a mean age of 77 years and a 10-year average duration of benzodiazepine use [6,26-27]. Neither age nor duration of use were significant predictors of the ability to perceive increased risk, suggesting that our intervention is effective in a wide range of individuals regardless of entrenched habits or beliefs. To our knowledge, this study is the first to demonstrate a positive

effect of targeting older adults directly about medication appropriateness, thereby bypassing health professionals and engaging patients as drivers of change to catalyze physicians and/or pharmacists in a collaborative effort to reduce medication-related risk.

4.1.1 Mechanisms underlying the change in risk perception

The educational intervention developed in the current study aimed to change risk perception by creating cognitive dissonance through self-assessment, new knowledge provision, and social comparison. We hypothesized that a change in knowledge and beliefs would create cognitive dissonance, thus leading to a change in risk perception. Unfortunately, our study was not designed to ascertain cognitive dissonance directly. By operationalizing cognitive dissonance as a change in both knowledge and beliefs, we were able to show that individuals who experienced cognitive dissonance were six times more likely to report increased risk, thus supporting the application of constructivist learning theory. Interestingly, the intervention was only effective in changing risk perceptions in 45% of participants. This may be explained by the fact that many benzodiazepine users are psychologically dependent on their medication. This psychological dependence likely creates compelling opposition to new learning and denial of risk, possibly explaining the lack of significance across all components of the tool for the 55% of participants who reported no increase in risk perception. Our findings are consistent with another study on medication discontinuation where the majority of participants tended to reject the first suggestion of discontinuation [6], as well as with studies on breast cancer risk by Alexander et al. where only 50% of participants changed risk perceptions when presented with an educational intervention [28].

Baseline knowledge was similar across all participants, with the greatest knowledge change occurring in participants who perceived increased risk. Participants who correctly answered the knowledge questions post-intervention were eight times more likely to reread the tool (OR=8.34, 95%CI (3.9, 17.9)) than those who perceived no increased risk suggesting that rereading the intervention may be associated with better learning.

4.1.2 Preventive health behavior

Our results also showed a significant difference between groups on self-reported intent to discuss medication discontinuation with a family member, pharmacist or physician. These measures signify readiness to engage in preventive health behaviors. Whether or not these intentions translate into action remains to be determined.

4.1.3 Strengths and limitations

The major strength of this study was systematic measurement of knowledge, beliefs and risk perceptions. Missing data was imputed to reflect a worst-case scenario, and at best underestimated the impact of the intervention. Few validated instruments exist to reliably measure benzodiazepine-related knowledge, beliefs and behaviors. Although the BMQ-Specific questionnaire has been previously tested, the benzodiazepine-related knowledge questions were not. Similarly, risk perception was measured with a single self-reported item and not a full instrument, and the elicitation of cognitive dissonance was assumed rather than measured directly. Finally, this study was conducted in community pharmacies and thus is not generalizable to frailer patients living in health care facilities or long-term care.

4.2 Conclusion

In conclusion, a home-based educational program consisting of a document mailed to participants demonstrated significant effects on medication knowledge, beliefs and risk perception in a cohort of older benzodiazepine users. By changing knowledge and increasing perceived risk, consumer-targeted drug information elicited a desire among many older adults to discuss medication safety with their health care providers. The results of an ongoing randomized trial will demonstrate whether these changes wrought by the educational intervention are sufficient to result in discontinuation of inappropriate prescriptions.

4.3 Practice Implications

The aging consumer may be an under-utilized catalyst of change for reducing potentially inappropriate prescriptions.

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Table 1
Descriptive demographic and health status characteristics at baseline. Values are Mean, standard deviation (SD) or number (%).

Characteristics	All (N=144)	RISK † (N=65)	NO RISK † (N=79)	*p*-value
Female, n (%)	105 (73%)	47 (72%)	58 (73%)	0.88
Age (years), Mean (SD)	74.9 (6.5)	75.3 (6.1)	74.6 (6.8)	0.52
College or University education, n (%)	25 (17%)	11 (17%)	14 (18%)	0.90
Living alone, n (%)	69 (48%)	29 (45%)	40 (51%)	0.47
MOCA#, Mean (SD)	25.4 (2.4)	25.4 (2.4)	25.4 (2.5)	0.94
General Health Status (fair to bad), n (%)	43 (30%)	19 (29%)	24 (30%)	0.88
Comorbidities, Mean (SD)	7.0 (2.5)	6.8 (2.3)	7.1 (2.6)	0.62
Indication for taking Benzodiazepines, n (%)				
- Insomnia	94 (65%)	42 (65%)	52 (66%)	0.88
- Anxiety	64 (44%)	27 (42%)	37 (47%)	0.52
Duration of benzodiazepine use (years), Mean (SD)	10.5 (8.2)	9.2 (7.8)	11.6 (8.4)	0.08
Previous attempts at cessation, n (%)	80 (56%)	32 (49%)	48 (61%)	0.24
Successful attempts, n (%)	20 (25%)	5 (16%)	15 (31%)	0.11

† RISK: Perceived an increased risk vs NO RISK: Perceived no risk or same risk as pre-intervention.
#MOCA: The Montreal Cognitive Assessment (scale 0-30)

Independent sample t-test for continuous variables, chi square for categorical variables.

* Level of significance, $p<0.05$.

Table 2

Effect of the educational tool on Knowledge. Values are number (%), mean or standard deviation (SD).

Variables	Within groups at one week						Between groups at week 1			
Questions	Group	Baseline	*p*-value (between groups)	Post-intervention	CAIA[#], n (%)	*p*-value (CAIA[#])	Difference (%)	*p*-value	Difference in CAIA[#] (%)	*p*-value (CAIA[#])
1 - Safety, n (% With correct answer)	RISK[†](n=65)	23 (35.4%)		56 (86.2%)*	33/42 (78.6%)*	<0.001				
	NO RISK[†](n=79)	26 (32.9%)	.75	41 (51.9%)*	24/62 (38.7%)*	0.014	34.3*	<0.001	39.9*	<0.001
2 - Side-effects, n (% With correct answer)	RISK[†](n=65)	4 (6.2%)		28 (43.1%)*	26/63 (41.3%)*	<0.001				
	NO RISK[†](n=79)	3 (3.8%)	.51[$]	10 (12.7%)*	8/77 (10.4%)*	0.039	30.4*	<0.001	30.5*	<0.001
3 - Withdrawal, n (% With correct answer)	RISK[†](n=65)	13 (20.0%)		32 (49.2%)*	21/55 (38.2%)*	<0.001				
	NO RISK[†](n=79)	18 (22.8%)	.69	29 (36.7%)*	18/68 (26.5%)*	0.043	11.6	0.13	11.7	0.17
4 - Alternatives, n (% With correct answer)	RISK[†](n=65)	7 (10.8%)		41 (63.1%)*	35/60 (58.3%)*	<0.001				
	NO RISK[†](n=79)	15 (19.0%)	.17	27 (34.2%)*	18/70 (25.7%)*	0.023	29.8*	<0.001	32.6*	<0.001
Test score	Group	Baseline	*p*-value (between groups)	Post-intervention	CAIA[#], Mean (SD)	*p*-value (CAIA[#])	Difference (95% CI)	*p*-value	CAIA[#] (95% CI)	*p*-value (CAIA[#])
Overall (/4), Mean (SD)	RISK[†](n=65)	0.72 (0.9)		2.42 (1.3)	1.77 (.1.3) *	<0.001				
	NO RISK[†](n=79)	0.79 (0.9)	.69	1.35 (1.3)	0.86 (1.10)	0.682	1.06 (.6, 1.5) *	<0.001	0.91 (.5, 1.3) *	<0.001

[†] RISK: Perceived an increased risk vs NO RISK: Perceived no risk or same as pre-intervention
[#]CAIA: Change among those with an incorrect answer (excludes participants with correct answers at both time-points).
Within groups: Paired t-test for continuous Variables, McNemar's test for categorical variables.
Between groups: Independent sample t-test for continuous variables, chi square for categorical variables.
[$] Wilcoxon non-parametric test.
* Level of significance, p<0.05.

Table 3a
Change in beliefs associated with risk perception post-intervention. Values are mean or standard deviation (SD).

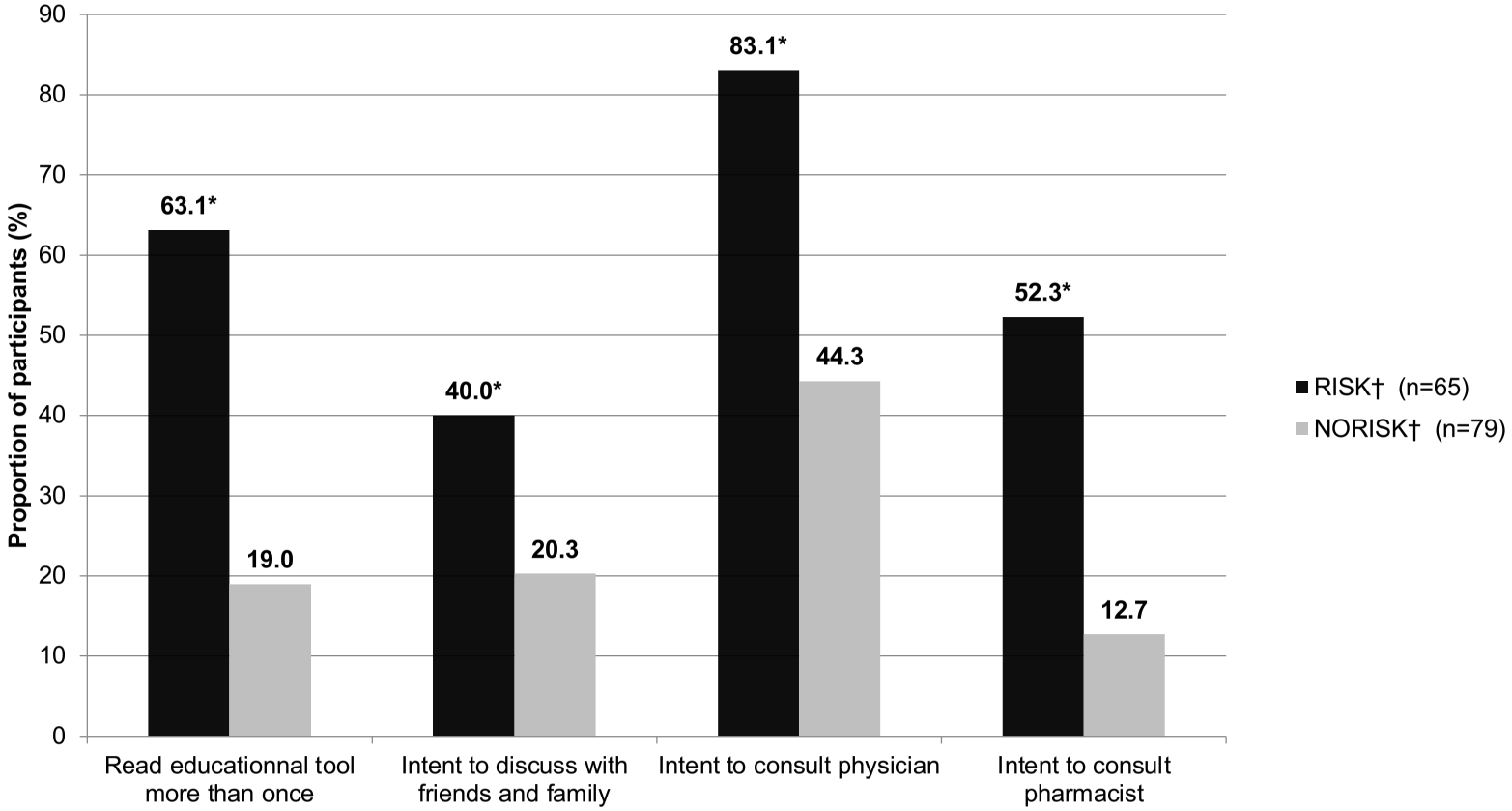
Variables	Within groups at one week					Between groups at week 1	
	Group	Baseline	Post-intervention	Difference (95% CI)	*p*-Value	Difference (95% CI)	*p*-Value
Belief about necessity of the drug[b], Mean (SD)	RISK[a]	14.22 (3.3)	12.60 (2.4)	−1.62 (−2.5, −0.8) *	<0.001	−1.31 (−2.3, −0.4)*	0.007
	NO RISK[a]	13.97 (3.7)	13.91 (3.3)	−0.06 (−0.9, 0.8)	0.883		
Belief about side-effects of the drug[b], Mean (SD)	RISK[a]	13.40 (2.3)	16.14 (2.5)	2.75 (2.0, 3.5) *	<0.001	3.72 (2.9, 4.5)*	<0.001
	NO RISK[a]	12.71 (2.1)	12.42 (2.3)	−0.28 (−0.8, 0.3)	0.296		
Necessity Concern[c] differential, Mean (SD)	RISK[a]	0.83 (4.3)	−3.54 (3.8)	−4.37 (−5.6, −3.1)*	<0.001	−5.03 (−6.4, −3.6)*	<0.001
	NO RISK[a]	1.27 (4.6)	1.49 (4.4)	0.22 (−.9, 1.3)	0.697		
Self-efficacy for discontinuation of drug[d], Mean (SD)	RISK[a]	32.42 (33.4)	68.71 (36.6)	36.29 (24.8, 47.8)*	<0.001	31.24 (17.9, 44.6)*	<0.001
	NO RISK[a]	31.9 (35.1)	37.47 (42.4)	5.56 (−4.5, 15.6)	0.276		

Table 3b
Added impact of tapering tool on self-efficacy for discontinuation post-intervention.

Variables	Group	On their own	With Tapering tool	Added value of tool (95% CI)	*p*-Value	Difference (95% CI)	*p*-Value
Self-efficacy for discontinuation of drug[d], mean (SD)	RISK[a]	68.71 (36.6)	74.80 (32.3)	6.05 (3.0, 9.1)*	<0.001	32.66 (20.1, 45.2)*	<0.001
	NO RISK[a]	40.68 (42.4)	42.09 (41.6)	1.42 (−1.7, 4.5)	0.368		

Within groups: paired *t*-test, between groups: independent sample *t*-test.
[a] RISK: perceived an increased risk vs NO RISK: perceived no risk or same as pre-intervention.
[b] Specific-necessity and concern scales range from 5 to 25, higher scores indicating more agreement with the concept.
[c] "Benefit-risk ratio", necessity – concern scale, ranges from −20 to 20.
[d] Scaled from 0 to 100.
* Level of significance, $p < 0.05$ [28].

Figure 1.
Correlates and anticipated behaviors associated with risk perception.



7.2 Reduction of Inappropriate Benzodiazepine Prescriptions Among Older Adults Through Direct Patient Education: The EMPOWER Cluster Randomized Trial

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TRIAL REGISTRATION: clinicaltrials.gov Identifier: NCT01148186. URL: https://clinicaltrials.gov/show/NCT01148186

Abstract

Importance: The American Board of Internal Medicine Foundation Choosing Wisely Campaign recommends against the use of benzodiazepine drugs for adults 65 years and older. The effect of direct patient education to catalyze collaborative care for reducing inappropriate prescriptions remains unknown.

Objective: To compare the effect of a direct-to-consumer educational intervention against usual care on benzodiazepine therapy discontinuation in community-dwelling older adults.

Design, Setting, and Participants: Cluster randomized trial (EMPOWER [Eliminating Medications Through Patient Ownership of End Results] study [2010-2012, 6-month follow-up]). Community pharmacies were randomly allocated to the intervention or control arm in non-stratified, blocked groups of 4. Participants (303 long-term users of benzodiazepine medication aged 65-95 years, recruited from 30 community pharmacies) were screened and enrolled prior to randomization: 15 pharmacies randomized to the educational intervention included 148 participants and 15 pharmacies randomized to the "wait list" control included 155 participants. Participants, physicians, pharmacists, and evaluators were blinded to outcome assessment.

Interventions: The active arm received a deprescribing patient empowerment intervention describing the risks of benzodiazepine use and a stepwise tapering protocol. The control arm received usual care.

Main Outcomes and Measures: Benzodiazepine therapy discontinuation at 6 months after randomization, ascertained by pharmacy medication renewal profiles.

Results: A total of 261 participants (86%) completed the 6-month follow-up. Of the recipients in the intervention group, 62% initiated conversation about benzodiazepine therapy cessation with a physician and/or pharmacist. At 6 months, 27% of the intervention group had discontinued benzodiazepine use compared with 5% of the control group (risk difference, 23% [95% CI, 14%-32%]; intracluster correlation, 0.008;

number needed to treat, 4). Dose reduction occurred in an additional 11% (95% CI, 6%-16%). In multivariate sub-analyses, age greater than 80 years, sex, duration of use, indication for use, dose, previous attempt to taper, and concomitant polypharmacy (10 drugs or more per day) did not have a significant interaction effect with benzodiazepine therapy discontinuation.

Conclusions and Relevance: Direct-to-consumer education effectively elicits shared decision making around the overuse of medications that increase the risk of harm in older adults.

Trial Registration: clinicaltrials.gov Identifier: NCT01148186

Background

The US Patient Protection and Affordable Health Care Act encourages greater use of shared decision making in health care through provision of evidence-based information that apprises patients of the risks and benefits of different treatments.[1] Based on the concepts of patient-centered medicine and patient preferences, consumer education is a core tenet of promoting collaborative self-management for cost containment and health improvement.[2,3] However, the effect of involving patients in the decision to curtail medical treatments and resources is viewed by some as expecting too much.[4]

In 2012, the American Board of Internal Medicine (ABIM) Foundation launched its Choosing Wisely campaign to help physicians and patients select which interventions should be discontinued to reduce the overuse of medical resources that increase the risk of harm.[5] As part of this campaign, the American Geriatrics Society advised physicians and patients to refrain from using benzodiazepines as first-line treatment for insomnia in older adults.[6] The decision to target benzodiazepines derives from the potential for benzodiazepines to elicit cognitive deficits and increase the risk of falls and hip fractures.[7-10] Benzodiazepines comprise 20% to 25% of inappropriate prescriptions in the elderly,[11,12] with a reported prevalence of use ranging from 5% to 32% in community-dwelling older adults.[13-15] Although physicians recognize the risks associated with benzodiazepines, almost 50% continue to renew prescriptions, citing patient dependence and benefit as justification for their actions.[16-19]

The effect of direct-to-consumer patient education and empowerment to reduce benzodiazepine prescriptions has not yet been fully examined.[20] Direct-to-consumer advertising of prescription drugs by the pharmaceutical industry has clearly been shown to influence patient demand for medicines.[21] However, there is concern that inconsistent enforcement of the US Food and Drug Administration (FDA) requirement to provide consumers with a balanced presentation of risks and benefits in the drug information package, and the lack of subsequent revision to include data on drug harms from postmarketing pharmacoepidemiological research, has led to inappropriate

overuse of some prescription drugs.[21,22] Educational interventions aimed at achieving patient empowerment around medication overtreatment has potential to catalyze shared decision making to deprescribe. Patient empowerment is a process that aims to “help people gain control, which includes people taking the initiative, solving problems, and making decisions, and can be applied to different settings in health and social care and self-management.” [23]

The objective of the EMPOWER (Eliminating Medications Through Patient Ownership of End Results) cluster randomized trial was to test the effectiveness of direct patient education about drug harms on benzodiazepine therapy discontinuation among community-dwelling adults 65 years and older receiving long-term benzodiazepine therapy. Secondary objectives were to assess rates of dose reduction in addition to complete cessation and to conduct a process evaluation of subsequent events after receipt of the intervention. Cluster randomization served to prevent contamination between participants in the same pharmacy.

Methods

Design, Setting, and Participants

A 2-arm, parallel-group, pragmatic cluster randomized clinical trial was conducted in Quebec, Canada. The trial protocol has been published. [24] The Research Ethics Board of the Centre de Recherche de l’Institut Universitaire de Gériatrie de Montreal approved the study protocol on July 26, 2009. All patients signed an informed consent form prior to the screening interview. Recruitment occurred between July 2010 and November 2012.

The study included 30 community pharmacies (cluster units) in the greater Montreal area. Eligibility criteria for clusters included local community pharmacies with 20% or more of their clientele consisting of older adults and a minimum of 50 eligible participants. A full list of pharmacies within 200 km of the research center was obtained through collaboration with the pharmacy chain’s headquarters. This list was

randomized, and pharmacies were systematically contacted by the research team to assess interest in participating.

The sampling frame for individual participants was a list of all adults 65 years and older receiving long-term benzodiazepine therapy from each participating pharmacy, provided to pharmacists by the central database system of the pharmacy chain. Eligibility criteria for individual participants included a minimum of 5 active prescriptions, one being an active benzodiazepine prescription (short, medium, or long acting) dispensed for at least 3 consecutive months prior to screening. Participants with polypharmacy (>5 medications) were recruited to extend the generalizability of the findings from this trial to the typical elderly benzodiazepine user with multi-morbidity and associated polypharmacy. Exclusion criteria included a diagnosis of severe mental illness or dementia, an active prescription for any antipsychotic medication and/or a cholinesterase inhibitor or memantine in the preceding 3 months, and residence in a long-term care facility. All clients meeting study criteria received a recruitment mailing followed by telephone call invitations from their pharmacists. Patients who expressed interest in participating in the study were directed to the study team and screened for eligibility via in-home interviews with a research assistant. Clients who were unreachable after 3 attempts were not re-contacted. During the in-home interview, patients with evidence of cognitive impairment, defined by a screening score less than 21 on the Montreal Cognitive Assessment, were excluded. [25] Baseline demographic data and information on the indication for and duration of benzodiazepine use, as well as any previous attempts at discontinuation, were collected. Health status was determined (excellent, very good, good, fair, or poor). The presence of an anxiety disorder was ascertained by a score of 9 or higher on the Geriatric Anxiety Inventory. [26]

Intervention

The patient empowerment intervention consisted of an 8-page booklet based on social constructivist learning and self-efficacy theory, and its development and testing have been previously detailed.[24] The intervention comprises a self-assessment

component about the risks of benzodiazepine use, presentation of the evidence for benzodiazepine-induced harms, knowledge statements designed to create cognitive dissonance about the safety of benzodiazepine use, education about drug interactions, peer champion stories intended to augment self-efficacy, suggestions for equally or more effective therapeutic substitutes for insomnia and/or anxiety, and stepwise tapering recommendations.[24] Tapering recommendations consist of a visual 21-week tapering protocol showing a picture-based diminishing schedule of full-pill, half-pill, and quarter-pill consumption. The visual schematic for the deprescribing protocol was proposed by consumers during the development and usability testing of the intervention to enable application to any benzodiazepine, regardless of dose. The intervention asks participants to discuss the deprescribing recommendations with their physician and/or pharmacist. The information is included in a letter-size paper handbook, with the language set at a sixth-grade reading level and written in 14-point font to facilitate accessibility to the material. The intervention was personalized according to the participant's pharmacy profile to include the name of the specific benzodiazepine the participants was taking. The intervention was mailed to the intervention group within 1 week of group allocation while the usual care (wait list) group received the educational tool 6 months following group allocation. A full version of the intervention is available in the eAppendix in the Supplement.

Outcomes

The primary outcome was complete cessation of benzodiazepine use in the 6 months following randomization. Cessation was defined as an absence of any benzodiazepine prescription renewal at the time of the 6-month follow-up that was sustained for 3 consecutive months or more, in the absence of substitution to another benzodiazepine. This was ascertained via pharmacy renewal profiles, which contained information on drugs purchased, dates of purchase, dose, and quantity served. Dose reduction was defined as a 25% or greater dose reduction compared with baseline sustained for 3 consecutive months or more. A baseline average daily dose per month was established using pharmaceutical profiles for the 6 months before randomization. Dose reduction was then calculated by comparing patients' average daily dose per

month at 6 months after randomization compared with baseline. All doses were converted to lorazepam equivalents. To ensure an accurate representation of the pharmaceutical profiles, a list of pharmacies visited by participants was collected at baseline. At follow-up, patients were queried whether they switched pharmacies. A complete follow-up with the pharmacy in use at the 6-month follow-up was completed for all study participants. One investigator (P.M.) and 1 research nurse, blinded to group allocation, independently assessed outcomes according to a prespecified protocol. Agreement was obtained in 94% of cases, with differences adjudicated by a third investigator (C.T.).

Process Evaluation

After the primary end point had been ascertained using the pharmacy renewal profiles and in order to understand the events that occurred after receipt of the intervention, a 6-month semi-structured interview was conducted by telephone with participants in the intervention group. Interviews lasted approximately 30 minutes. Participants were queried whether they had discussed the possibility of tapering their benzodiazepine medication with a physician, pharmacist, or both (yes/no); what was decided during these discussions (open ended); whether tapering was attempted (yes/no); if any difficulties were encountered during the tapering process (open ended); reasons why any attempts failed (open ended); justification of why participants felt they did not want to discontinue their benzodiazepine medication (open ended); and satisfaction about learning about the risks of benzodiazepine use (yes/no).

Randomization and Allocation Concealment

A 1:1 allocation ratio was assigned by an independent statistician using non-stratified blocked randomization for groups of 4 pharmacies using computer-generated random digits. The study was described as a “medication safety study for older adults” without mention of benzodiazepines in particular; thus, participants remained blinded to the intervention at the time of enrollment. Group allocation was concealed from both the

pharmacists and their clients by telling them that the intervention would be delivered to the clients at some point during the next year.

Sample Size

The study was powered at 80% (2-sided test α level of .05) to detect a minimal 20% difference in benzodiazepine therapy discontinuation due to the use of the intervention. [19, 27-33] On the basis of the study results, we calculated a coefficient of variation (kappa) of 0.62, an intracluster correlation (ICC) of 0.008, and a median cluster size of 10.1, which resulted in a maximum design effect of 1.03. A minimal sample size per group of 60 individuals was therefore required. [34]

Statistical Methods

Differences in baseline characteristics between groups were compared. To assess the primary outcome, we estimated the unadjusted risk difference (prevalence of the outcome) and 95% confidence intervals via generalized estimating equations (GEEs) using the participant as the unit of analysis, the pharmacy as the cluster, an exchangeable correlation coefficient to account for clustering effects of participants within each pharmacy, and discontinuation as a dichotomous outcome, assessed for each participant at 6 months after randomization. Both intent-to-treat (ITT) and per-protocol analyses were performed. Participants who were lost to follow-up were designated as having neither discontinued nor reduced the dose of benzodiazepines in ITT analyses. Generalized estimating equations with an identity link and an exchangeable correlation structure were used to account for possible correlation between individuals in the same cluster.[35] The number needed to treat was calculated as the inverse of the difference in absolute event rates between the experimental and control groups.[36] In secondary analyses, to control for possible confounding effects between groups, multiple logistic regression models were used, with age (<80 years vs ≥80 years), sex, education (high school or less vs college or university), health status (fair and poor vs other), benzodiazepine use for insomnia (yes/no), anxiety disorder detected with the Geriatric Anxiety Inventory (yes/no), benzodiazepine dose (<0.8-mg/d

lorazepam equivalent vs ≥0.8 mg/d),[37] previous attempt at tapering (yes/no), duration of benzodiazepine use (<5 years or ≥5 years), and number of medications (<10 per day vs ≥10 per day) included in the model. To determine whether any of the aforementioned-listed characteristics differentially impacted on cessation rates, analyses were performed to estimate risk differences for each of the subgroups using interaction terms in the GEE model under ITT and per-protocol conditions. Proportions of participants reporting having discussed discontinuation with a physician or pharmacist were calculated. Responses to the open-ended questions about failure to initiate discontinuation or abandonment of the tapering protocol were analyzed by content analysis according to emergent themes. All statistical analyses were run using RStudio 0.97.310.0, R-3.0.2, with statistics subpackage for GEE (Rstudio Inc), an integrated development environment for R.

Results

Study Participants and Follow-up

A total of 165 community pharmacies were consecutively contacted over a 2-year period. Of these, 30 pharmacies (18%) consented. The most common reasons for nonparticipation in the project included lack of interest in participating in a research project (n = 63 [38%]), competing priorities (n = 30 [27%]), inability to reach the pharmacy owner to obtain consent (n = 24 [15%]), and inadequate personnel to aid recruitment (n = 16 [10%]) (Figure 1). The centralized electronic pharmacy records database identified 2716 potentially eligible clients in the participating pharmacies who were 65 years and older and who regularly renewed benzodiazepine prescriptions. Approximately 1 in 6 spoke with their pharmacist and agreed to meet with the research team. Four hundred clients were screened for eligibility, and 75% agreed to participate and were eligible to enroll in the trial. In total, 30 clusters and 303 eligible participants were randomized. Figure 1 depicts the study flow of the clusters and the participants for the trial. The median (range) number of participants per cluster was 10 (2-27).

Of the 303 participants randomized, 261 were available for 6-month follow-up (86%). There was no difference in the baseline characteristics of participants who

withdrew or were lost to follow-up between or within trial arms. The mean (SD) age of the participants at baseline was 75 (6.3) years, 69% were women, and one-quarter (24%) had earned a college degree. The most common self-reported indications for taking a benzodiazepine were insomnia (60%) and/or anxiety (48%). Participants used benzodiazepines for mean duration of 10 years and had an average daily dose consumption of 1.3-mg equivalents of lorazepam (Table 1).

Outcomes

In ITT analyses, complete cessation was achieved in 40 of 148 participants (27%) compared with 7 of 155 controls (5%) (prevalence difference, 23%; 95% CI, 14%-32%) (Table 2). There was a crude 8-fold higher likelihood of achieving discontinuation among those who received the intervention compared with controls (odds ratio, 8.1; 95% CI, 3.5-18.5) and an adjusted odds ratio of 8.3 (95% CI, 3.3-20.9) when all baseline characteristics were accounted for. Figure 2 illustrates the risk differences for discontinuation of benzodiazepines in subgroups of participants by treatment allocation using ITT analysis. No significant interactions were observed between the intervention assignment and participant characteristics, suggesting that the effect of the intervention was robust across variable predisposing characteristics. An additional 11% (95% CI, 6%-16%) of individuals who received the intervention achieved dose reductions. The number needed to treat for any discontinuation or dose reduction was 3.7 in ITT analyses (Table 2). Per-protocol analysis yielded similar results.

Patient Empowerment and Process Evaluation

Six-month telephone follow-up interviews with all participants in the intervention group who completed the trial (n = 123) revealed that 62% initiated discussions about benzodiazepine therapy discontinuation with their physician and/or pharmacist, and 58% attempted discontinuation (Table 3). The majority (72%) of participants desiring discontinuation opted to follow the tapering protocol provided. Others required a customized tapering protocol because more than 1 benzodiazepine was being used or because the type of benzodiazepine pills or capsules could not easily be halved or

quartered and substitution was required to appropriately taper. Of the 71 participants who attempted cessation, 38 (54%) were successful; 16 (22%) achieved dose reduction, of which one-third was continuing the tapering process; and 17 (24%) failed. Withdrawal symptoms such as rebound insomnia or anxiety occurred in 42% of participants attempting to taper. No major adverse effects requiring hospitalization were reported. Of the 40 participants, 5 (13%) who discontinued benzodiazepine therapy received substitutions with trazodone (3 cases), paroxetine (1 case), or amitriptyline (1 case). In 7 individuals who attempted to taper, complete discontinuation was discouraged by their health professional. Among the 52 recipients who elected not to taper, discouragement by their physician or pharmacist was the most common reason provided (n = 17 [33%]), followed by fear of withdrawal symptoms (n = 13 [25%]), lack of concern about taking benzodiazepines (n = 12 [23%]), and difficult life circumstances (n = 6 [12%]). Several participants reported that their physician discouraged use of the tapering protocol because of a perceived absence of adverse effects from their benzodiazepine use. Of the 123 participants, 120 (98%) acknowledged satisfaction with receiving medication risk information.

Discussion

Delivery of an empowerment intervention to engage older adults in discussing the harms of benzodiazepine use with their physician and/or pharmacist yielded a benzodiazepine discontinuation rate of 27% compared with 5% in the control group 6 months after the intervention. An additional 11% of recipients achieved dose reductions. The effect of the intervention was robust across age, indication, dose, and duration of benzodiazepine use.

Strengths and Weaknesses of the Study

Strengths of this study include systematic recruitment of participants via community pharmacies; blinding of the study hypothesis from participants, physicians, pharmacists, and evaluators; and objective assessment of drug discontinuation rates from pharmacy prescription renewal profiles. Compared with previous studies, this trial

exclusively targeted seniors older than 65 years, examined patient empowerment as a means of initiating shared decision making around potentially harmful medication, and addressed the issue from the patient's rather than the physician's perspective. [19, 27-29,38,39] One limitation is the 6-month time frame for outcome reporting. Longer follow-up times could reveal relapse rates or higher discontinuation rates as several participants who achieved dose reductions were still following the tapering protocol at study end point. Recruitment rates for pharmacies (18%) and individual participants (11%) were low and excluded potential participants with cognitive impairment. Despite this, selection bias is unlikely because neither pharmacists nor participants were aware of the primary outcome of the study other than it being a medication safety study for older adults. Pharmacies were recruited systematically across socioeconomic and geographic living areas around Montreal, and although data on participant income could not be collected, no differences between groups were observed on other variables that correlate with poverty in the senior population such as female sex, educational status, and polypharmacy. [40,41] Subgroup analyses may have been underpowered to detect differences. Cursory content analysis of the events that followed receipt of the intervention may have been limited by patient recall and the nonintimate nature of the 6-month follow-up.

The process of shared decision making around benzodiazepine therapy discontinuation and physicians' motivations for counseling against benzodiazepine therapy discontinuation could not be evaluated because there was no direct contact with physicians during the trial.

Relevance of the Findings and Implications for Clinicians

Our findings suggest that direct-to-consumer education successfully leads to discussions with physicians and/or pharmacists to stop unnecessary or harmful medication. Discontinuation or dose reduction of benzodiazepines occurred in more than one-third of the participants who received the empowerment intervention. The Beers criteria for inappropriate use of medications provide guidance for 53 drugs to be avoided in the elderly. [10] This trial only addressed deprescription of benzodiazepine

medication, which arguably may be one of the most difficult classes of medication to withdraw because of psychological and physical dependence. [15,42]

Previous studies have examined the effect of other types of brief interventions by physicians on patient discontinuation of benzodiazepine use, as well as pharmacist-initiated communication with general practitioners to deprescribe potentially inappropriate medication.[31,43,44] Sending a letter of advice from family physicians to patients achieved a discontinuation rate of 24% at 6 months, but the effect size was reported as much lower because 12% of participants in the control group also achieved discontinuation.[28] Our use of a cluster randomized design with prerandomization enrolment of participants may help explain the larger effect seen in the present study. Furthermore, the added value of directly educating the patient, in the absence of initial physician involvement, likely promotes patient buy-in for discontinuation at an early stage and allows the patient to act as a catalyst for initiating discussions about medication management, which is a more effective approach than the traditional paternalistic approach to patient care.[23] The booklet used for this trial, which directly delivers information on drug harms to patients, could be distributed in the nonresearch environment in pharmacies or on the Internet in conjunction with other community education initiatives such as the American Geriatrics Society website (http://www.healthinaging.org), thus achieving widespread reach.

Three issues arise for future consideration. First, participants reported that their physician discouraged discontinuation of benzodiazepines in several cases. Many physicians continued to perceive the benefits of benzodiazepines as outweighing their risks. [19] Second, benzodiazepines were sometimes substituted with equally harmful sedative medication. A similar phenomenon was found to occur in US nursing home residents when coverage for benzodiazepine medications was interrupted during implementation of the Medicare Part D reimbursement policy in 2006. [45] Continuing medical education to physicians about the harms of all sedative-hypnotic medication may eventually overcome this obstacle. Third, pharmacists were solicited less often than physicians to discuss benzodiazepine therapy discontinuation. With the expanding scope of pharmacists' practice and an increasing emphasis on interprofessional models

of care, community pharmacists may be underutilized players to participate in efforts to reduce costly and unnecessary medical treatments. [46]

Conclusions

Supplying older adults with evidence-based information that allows them to question medication overtreatment appears safe and effective and is consistent with the priorities expressed by the ABIM Choosing Wisely campaign. Without a direct-to-patient educational component, promotional efforts for deprescription to physicians may fail or have a smaller impact. In an era of multi-morbidity, polypharmacy, and costly therapeutic competition, direct-to-consumer education is emerging as a promising strategy to stem potential overtreatment and reduce the risk of drug harms. The value of the patient as a catalyst for driving decisions to optimize health care utilization should not be underestimated.

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Table 1: Participant characteristics at baseline

Variable	Intervention n=148	Control n=155
Age in years (mean ± SD, range)	75.0 ± 6.5 (65-91)	74.6 ± 6.2 (65-95)
Female (%)	70.3	68.4
College or university education (%)	21.6	25.8
Lives alone (%)	46.6	54.8
Self-reported fair/poor health	35.8	34.8
Montreal cognitive assessment score (mean ± SD, range)	25.4 ± 2.4 (21-30)	25.4 ± 2.5 (21-30)
Self-reported indication for benzodiazepine use (%)		
Insomnia	60.8	60.0
Anxiety	45.9	49.0
Pain	2.7	3.2
Other	6.8	6.5
Anxiety disorder (%)*	32.4	30.3
Mean benzodiazepine dose in mg of lorazepam equivalents/day (mean ± SD, range)	1.2 ± 0.8 (0-4.8)	1.3 ± 0.8 (0-4)
Benzodiazepine type (%)**		
Short acting	29.1	24.5
Intermediate acting	66.2	72.9
Long acting	4.7	2.6
Duration of benzodiazepine use (mean number of years ± SD, range)	9.6± 8.7 (0.3-48)	11.2 ± 8.3 (0.5-40)
Previously attempted cessation (%)	45.2	49.4
Number of medications/day	9.9 ± 3.9 6(4-24)	9.9 ± 3.4 (4-21)

*Score of ≥ 9 on the Geriatric Anxiety Index

** Short-acting benzodiazepines: oxazepam and alprazolam.

Intermediate-acting benzodiazepines: lorazepam, bromazepam, clonazepam and temazepam,

Long-acting benzodiazepines: flurazepam and diazepam.

Table 2: Prevalence, risk difference and odds ratios for discontinuation and discontinuation plus dose reduction of benzodiazepines at 6-month follow-up

	Outcome n (%)	Risk difference (95% CI)*	Number-needed-to-treat	Crude OR (95% CI)	Adjusted OR ** (95% CI)
Discontinuation of benzodiazepines					
Intention to treat analysis					
Intervention (n=148)	40 (27.0)	0.23		8.05	8.33
Usual Care (n= 155)	7 (4.5)	(0.14-0.32)	4.35	(3.51-18.47)	(3.32-20.93)
Intracluster correlation		0.008		0.008	0.01
Per protocol analysis					
Intervention (n=123)	38 (30.9)	0.26	3.85	8.53	8.10
Usual Care (n= 138)	7 (5.1)	(0.16-0.36)		(3.69-19.76)	(3.34-19.66)
Intracluster correlation		0.007		0.007	0.005
Discontinuation plus dose reduction of benzodiazepines					
Intention to treat analysis					
Intervention (n=148)	56 (37.8)	0.27		5.05	5.49
Usual Care (n= 155)	17 (11.0)	(0.18-0.37)	3.70	(2.66-9.59)	(2.78-10.84)
Intracluster correlation		0.006		0.006	0.01
Per protocol analysis					
Intervention (n=123)	54 (43.9)	0.34	2.94	6.33	6.73
Usual Care (n= 138)	16 (11.6)	(0.22-0.45)		(3.10-12.92)	(3.12-14.55)
Intracluster correlation		0.03		0.03	0.02

*95% CI's were calculated using robust standard errors
**Adjusted for age, sex, education, health status, indication of benzodiazepine use for insomnia, anxiety disorder, benzodiazepine dose, previous attempt at tapering, duration of benzodiazepine use and number of medications.

Table 3: Effect of the empowerment intervention on self-reported participant empowerment

	All **n=123** n (%)	**Discontinuation of benzodiazepines** **n= 38** n (%)	**Discontinuation or dose reduction** **n= 54** n (%)
Discussion with a health professional after receipt of the intervention			
Physician only	44 (35.8)	14 (36.8)	20 (37.0)
Pharmacist only	5 (4.0)	2 (5.3)	2 (3.7)
Both	27 (21.9)	13 (34.2)	18 (33.3)
Neither	47 (38.2)	9 (23.6)	14 (25.9)
Attempt to discontinue			
Yes, using the tapering protocol in the brochure	51 (41.4)	26 (68.4)	32(59.3)
Yes, using a customized protocol from a physician or pharmacist	18 (14.6)	10 (26.3)	14 (25.9)
Yes, method not stated	2 (1.6)	2 (5.3)	2 (3.7)
No	52 (42.3)	0	6 (11.1)
Patient satisfaction with receipt of the intervention			
Appreciated receiving medication risk information	120 (97.5)	38 (100)	54 (100)

Figure 1: Trial flow

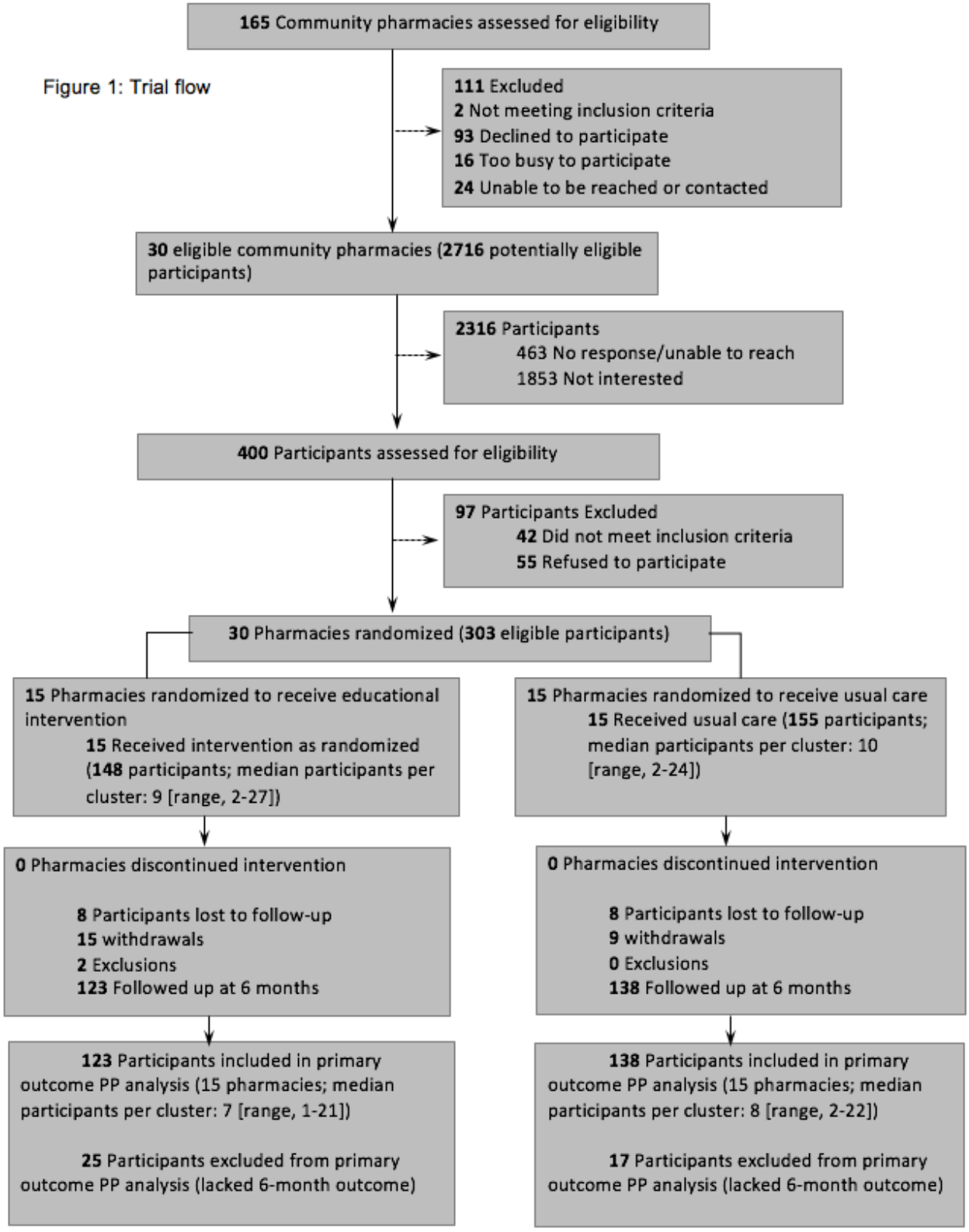
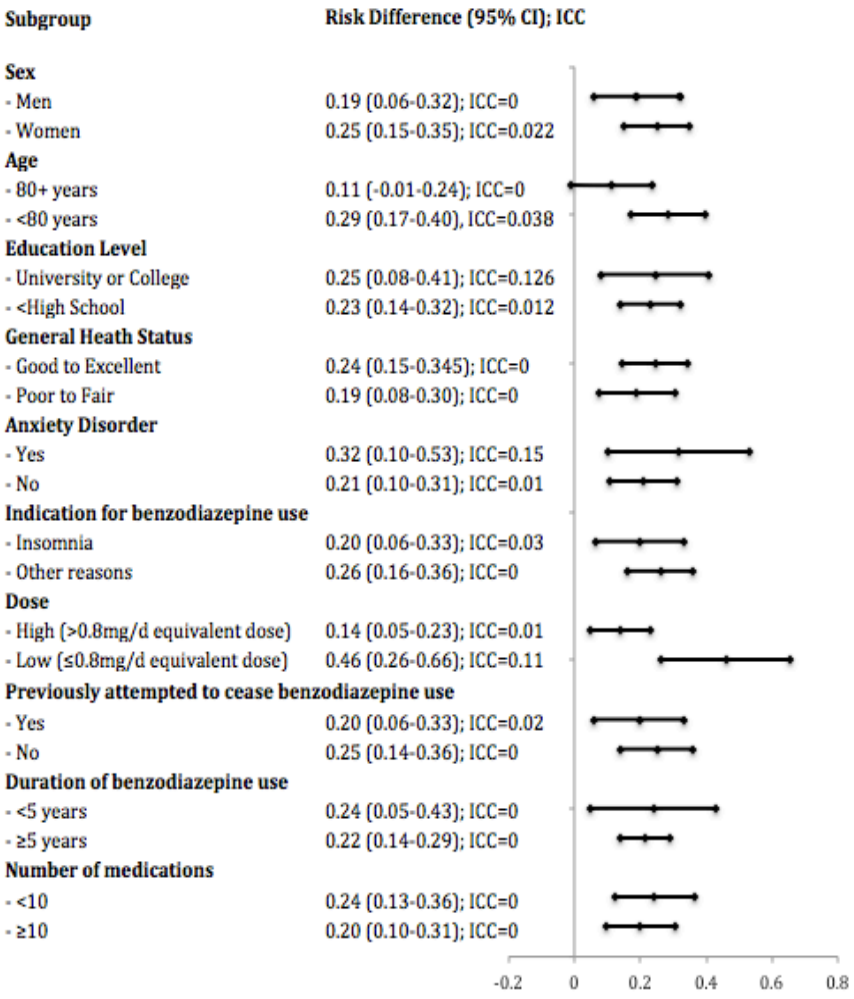


Figure 2. Forest plot of risk differences with 95% confidence intervals for discontinuation due to the intervention within subgroups of interest



7.3 Use of the EMPOWER brochure to deprescribe sedative-hypnotic drugs in older adults with mild cognitive impairment.

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TRIAL REGISTRATION: clinicaltrials.gov Identifier: NCT01148186. URL: https://clinicaltrials.gov/show/NCT01148186

ABSTRACT:

Background: Evidence-based mailed educational brochures about the harms of sedative-hypnotic use lead to discontinuation of chronic benzodiazepine use in older adults. It remains unknown whether patients with mild cognitive impairment (MCI) are able to understand the information in the EMPOWER brochures, and whether they achieve similar rates of benzodiazepine discontinuation.

Methods: Post-hoc analysis of the EMPOWER randomized, double-blind, wait-list controlled trial that assessed the effect of a direct-to-consumer educational intervention on benzodiazepine discontinuation. 303 community-dwelling chronic users of benzodiazepine medication aged 65-95 years were recruited from general community pharmacies in the original trial, 261 (86%) of which completed the trial extension phase. All participants of the control arm received the EMPOWER brochure during the trial extension. Normal cognition (n = 139) or MCI (n = 122) was determined during baseline cognitive testing using the Montreal Cognitive Assessment questionnaire. Changes in knowledge pre- and post-intervention were assessed with a knowledge questionnaire and changes in beliefs were calculated using the Beliefs about Medicines Questionnaire. Logistic regression was used to compare knowledge gained, change in beliefs and benzodiazepine cessation rates between participants with and without MCI.

Results: Complete discontinuation of benzodiazepines was achieved in 39 (32.0% [24.4,40.7]) participants with MCI and in 53 (38.1% [30.5,46.4]) with normal cognition (adjusted OR 0.79, 95% CI [0.45-1.38]). Compared to individuals with normal cognition, MCI had no effect on the acquisition of new knowledge, change in beliefs about benzodiazepines or elicitation of cognitive dissonance.

Conclusions: The EMPOWER brochure is effective for reducing benzodiazepines in community-dwelling older adults with mild cognitive impairment.

Key words: Patient education, Benzodiazepines, Inappropriate prescription, Deprescribing, Discontinuation

Background:

Sedative-hypnotic use is associated with cognitive impairment, and may contribute to mild neurocognitive disorders in older adults.[1-3] For this reason, both long and short-acting benzodiazepines are listed in the 2015 Beers criteria of medications to avoid in older adults.[3,5] A mild neurocognitive disorder is defined in the DSM-5 as a noticeable decrement in cognitive function beyond that of normal aging, which requires individuals to engage in compensatory strategies to maintain independence.[4] The term is meant to replace the previously used diagnosis of mild cognitive impairment (MCI). Over 1-in-5 community dwelling older adults have MCI at any given time, although the exact prevalence is difficult to estimate due to the variability in the criteria used, the source of subjects, the fluctuating nature of the condition and the reference standards. [4-6] Individuals with MCI may demonstrate significant impairments in their ability to understand, reason and participate in health-related decisions. [7] Longitudinal data suggest that medical decision-making capacity in patients with MCI tends to decline over time. [8]

The majority of long-term benzodiazepine users aged 65 years of age and older report not being concerned about side effects, mainly because they have never been alerted to the risks. [9] However, when provided with evidence-based information about harm in the form of a mailed educational brochure, 27% of chronic users discontinued benzodiazepines within 6 months in the EMPOWER trial. [10] It remains unknown whether patients with MCI retain capacity to understand the material in the brochure, and whether they respond equally well to the educational intervention. The objective of this report is to examine whether cognitive status affected the comprehension and success rates of the EMPOWER patient-centered educational approach to the deprescribing of benzodiazepines.

DESIGN & METHODS:

Study Population:

Participants in the EMPOWER trial were adults aged 65 years and older with polypharmacy (≥ 5 medications), taking at least one chronic benzodiazepine prescription (≥ 3 months). Participants with self-reported epilepsy, a diagnosis of established dementia, or a mental health disorder requiring treatment with antipsychotic medication, were deemed ineligible. In order to exclude patients with undiagnosed dementia from the study, the Montreal Cognitive Assessment (MoCA) was administered at an in-home baseline screening interview. The MoCA was chosen due to its high sensitivity and specificity for distinguishing normal individuals from those with MCI. [11] Participants with a MoCA score of 26 and over were qualified as having normal cognition, while those with scores of 21 to 25 were classified as having mild cognitive impairment (MCI). [11] Participants with scores under 21 were excluded in order to eliminate all potential cases of dementia. [11] In the original EMPOWER trial, participants randomized to the control group were wait-listed to receive the EMPOWER brochure at the end of the 6-month study period. In an extension to the trial, participants in the control arm were followed for an additional 6 months after study completion in order to evaluate their response to the EMPOWER brochure. This paper analyses all EMPOWER participants (from the intervention and control arm) having received the EMPOWER brochure and having completed the post-intervention EMPOWER assessment by 1-year (n=261). [10]

Intervention:

The EMPOWER brochure consists of an 8-page paper-based benzodiazepine deprescribing tool embedded with program theories which participants received by mail. Development of the intervention has previously been described in detail. [10,12] A generic version of the EMPOWER tool is available at http://www.criugm.qc.ca/fichier/pdf/BENZOeng.pdf . The deprescribing tool was individualized with the name of the participant's benzodiazepine on the front page. It included true and false questions about the harms of benzodiazepines, a short paragraph describing changes in drug metabolism with age, suggestions for alternate non-drug therapies for anxiety and

insomnia, a peer champion story, and a standard 21-week tapering protocol showing a picture-based diminishing schedule of full-pill, half-pill, and quarter-pill consumption. The pictogram was proposed by consumers during the development of the intervention and allows participants to apply the benzodiazepine tapering protocol regardless of the type or dose of sedative-hypnotic consumed.

Data Collection:

Baseline data, including demographic characteristics and prescription details were recorded during the initial in-person interview. Follow-up data was collected by phone one week, 6 weeks and 6 months after each participant received the EMPOWER brochure by mail. Benzodiazepine cessation or dose reduction was ascertained using pharmacy renewal profiles, which contained information on drugs purchased, dates of purchase, dose, and quantity served. Cessation was defined as an absence of any benzodiazepine prescription renewal, sustained for a minimum of three months during the follow-up period. A significant dose reduction consisted of a >25% dose reduction, sustained over a minimum of three months when compared to baseline use. Withdrawal symptoms were measured using the benzodiazepine withdrawal symptom questionnaire 6 weeks and 6 months post-intervention. Participants reporting any withdrawal symptoms at either time point were qualified as having experienced withdrawal symptoms. [13]

Change in Knowledge, Beliefs and Self-Efficacy to Taper Benzodiazepines

In order to evaluate whether MCI participants understood and reacted similarly to the content of the deprescribing intervention, we measured knowledge gained, change in beliefs, improvements in self-efficacy and frequency of outreach to a healthcare professional. Change was calculated by comparing responses on the pre and post-intervention questionnaires. For knowledge, this consisted of scores on four true or false questions. [12] Beliefs about the necessity of taking benzodiazepines versus associated harms were measured by comparing the total scores on the specific section of the beliefs about medicines questionnaire. [14] Change in self-efficacy was evaluated with

the Medication Reduction Self-efficacy scale. [12] Outreach to a healthcare professional was measured by self-report.

Analysis:

Participant characteristics were described using means with standard deviations for continuous data and percentages for categorical data. A chi-square test was used when comparing baseline characteristics of MCI vs non-MCI participants. Univariable logistic regression was used to determine the odds of all reported outcomes comparing participants with normal cognitive function to those with MCI. Multivariate analyses were adjusted for variables that were significantly associated with MCI at baseline, namely living arrangement, education, baseline self-efficacy and anxiety as an indication for therapy (Table 1). The results are reported as proportions with 95% confidence intervals (CI), and odds ratios (OR) with 95% CI, as appropriate. By combining participants who were randomized to the intervention, as well as the wait-list control group who received the brochure during the trial extension, the sample was powered to detect a 15% difference in proportions of individuals with and without MCI who discontinued benzodiazepines, based on an alpha of 0.05 and 80% power. The statistical significance for all analyses was set at $p < 0.05$ (two-sided). SPSS Version 20.0 (SPSS Inc. Chicago, IL, USA) was used for all analyses.

RESULTS:

Participants in the post-hoc analysis consisted of older adults aged 74.4 years (6.3-year standard deviation) (Table 1). Participants were taking an average of 10 different medications and reported a mean of 7 comorbidities, with almost one third classifying their health status as unfavorable. The mean duration of benzodiazepine use was 10.7 years, indicated for insomnia and/or anxiety. Almost half (45.6%) of patients reported a previous attempt to taper their benzodiazepine. One third of the latter (15.7%) succeeded in the attempt, prior to re-initiating the drug at a later date.

One-hundred-and-twenty-two (46.7%) participants were classified as having MCI at baseline. Participants with MCI were less well educated, more likely to live alone,

more likely to be taking their benzodiazepine to treat anxiety, and expressed a lower level of confidence for successful tapering than their counterparts with normal cognitive function. (Table 1)

Complete discontinuation of benzodiazepines was achieved in 92 participants, with 39 (32.0% [30.5,46.4]) meeting MOCA criteria for mild cognitive impairment and 53 (32.0% [24.4,40.7]) having normal cognition (Adjusted OR= 0.79, 95% CI 0.45 to 1.38). An additional 28 participants significantly reduced their benzodiazepine dose during the same time period (12 in the normal group and 16 MCI participants). In total, 65 (46.8% [38.7-55.0]) participants with normal cognition and 55 (45.1% [36.5,53.9] MCI participants achieved dose reduction or complete discontinuation (Adjusted OR= 1.07, 95% CI 0.62 to 1.83) (Table 2).

Compared to participants with normal cognition, those with MCI exhibited the same ability to acquire new knowledge and change their beliefs following the intervention. Self-efficacy to taper and experience of withdrawal symptoms was the same in both groups. Additionally, cognitive status did not affect the participants' decision to partake in a discussion about the intervention with their healthcare provider (Table 2).

DISCUSSION:

Although previous research indicates that individuals with MCI perform significantly worse than controls in multiple aspects of medical decision-making [7,8,15], we did not detect any difference in response to the EMPOWER deprescribing brochure among older adults who met MOCA criteria for MCI. Participants with MCI demonstrated improvements in knowledge and self-efficacy, were able to change their beliefs about benzodiazepines, and initiated discussions about deprescribing with a health care provider. Clinicians should be encouraged to distribute the EMPOWER brochure to their MCI patients in order to engage patients in conversations about deprescribing sedative-hypnotics, leading to shared decision-making despite declining cognitive status.

Strengths and limitations:

This is the first study of its kind to explore the association between MCI and the success rates of a patient-centered educational deprescribing intervention in a community-based clinical trial of older, community-dwelling adults. As the mild neurocognitive disorder diagnosis was not yet developed at the time of the study and the MoCA's usefulness in detecting mild neurocognitive disorder is modest [16], we categorized participants according to the older MCI diagnosis. Our results are only generalizable to patients with mild-to-moderate MCI since we used a MoCA cut-off score of 21, thus excluding the lower spectrum of MCI (19-20), which overlaps with early dementia. Additionally, as we did not re-measure scores on the MOCA at study endpoint, and were unable to ascertain whether cognition improved after discontinuation. The mean lorazepam equivalent dose was only 1.25 mg/day in both groups of participants, which may have facilitated tapering.

Conclusions:

This report illustrates that the EMPOWER brochure can be distributed in community-dwelling older adults with MCI and still work, whether directly through patient comprehension of the material or through the support of caregivers or family. The EMPOWER tool can and should be used in primary care or memory clinics for chronic benzodiazepine users who are candidates for deprescribing sedative-hypnotic medication.

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GRAPHICS:

Table 1: Participant Characteristics at Baseline by Cognitive Status

Characteristics	All (N=261)	MCI (n=122)	Normal cognition (n=139)	p-value
Female, n (%)	187 (71.6)	90 (73.8)	97 (69.8)	.494
Age years, Mean (SD)	74.4 (6.3)	75.3 (6.7)	73.7 (5.8)	.08
Education – college or university degree, n (%)	67 (25.6)	21 (17.2)	46 (33.1)	.003*
Living alone, n (%)	137 (52.4)	75 (61.5)	62 (44.6)	.01*
MOCA†, Mean score (SD)	24.5 (2.4)	23.3 (1.4)	27.4 (1.3)	.000*
General health status (poor or fair), n (%)	88 (32.8)	49 (32.8)	44 (31.7)	.895
Comorbidities, Mean (SD)	7.4 (2.5)	7.2 (2.4)	7.6 (2.7)	.335
Self-reported indication for benzodiazepine:				
Insomnia‡, n (%)	159 (60.9)	73 (59.8)	86 (61.9)	.417
Anxiety‡, n (%)	126 (48.3)	70 (57.4)	56 (40.3)	.006*
Duration of benzodiazepine use (years), Mean (SD)	10.7 (8.8)	10.3 (8.0)	10.9 (9.4)	.548
Previous attempts at cessation, n (%)	119 (45.6)	52 (42.6)	67 (48.2)	.321
Successful attempts, n (%)	41 (15.7)	14 (11.5)	27 (19.4)	.123
Benzodiazepine type®, n (%): Short-acting	70 (26.8)	36 (29.5)	34 (24.5)	.358
Intermediate acting	180 (70.0)	81 (66.4)	99 (71.2)	.400
Long acting	11 (4.2)	5 (4.1)	6 (4.3)	.888
Benzodiazepine Equivalent dose©, Mean (SD)	1.24 (.85)	1.27 (.75)	1.25 (.82)	.571
Number of medications at baseline	9.86 (3.7)	9.72 (3.8)	9.98 (3.6)	.574
Baseline Self-efficacy in tapering benzodiazepine (/100), Mean (SD)	38.05 (35.6)	31.2 (34.8)	44.1 (35.4)	.004*

* Level of significance, $p < 0.05$.

© benzodiazepine dose in mg of lorazepam equivalents/day

† MOCA: The Montreal Cognitive Assessment (scale 0–30)

‡ Based on medical diagnosis but self-reported by patients

® Short-acting = half-life <6 hours, Intermediate acting = half-life 6-20 hours, Long-acting = half-life >20 hours

Table 2: Outcomes of the EMPOWER Intervention by Cognitive Status

Primary Outcome	All (n=261) (n,%)	MCI (n=122) (n,%)	Normal cognition (n=139) (n,%)	Univariable OR (95% CI)	Multivariable OR (95% CI)*
Cessation	92 (35.2)	39 (32.0)	53 (38.1)	0.76 [.46-1.27]	.79 [.45-1.38]
Dose Reduction	28 (10.7)	16 (13.1)	12 (8.6)	1.60 [.72-3.53]	2.04 [.86-4.83]
Cessation + Dose Reduction	120 (45.9)	55 (45.1)	65 (46.8)	.94 [.57-1.52]	1.07 [.62-1.83]
Process Outcomes					
Improvement in knowledge	157 (60.2)	75 (61.5)	82 (59.0)	1.11 [.68-1.82]	1.06 [.62-1.80]
Change in beliefs	147 (56.3)	67 (54.9)	80 (57.6)	.89 [.54-1.47]	.84 [.48-1.43]
Improved self-efficacy for tapering	144 (55.2)	68 (55.7)	76 (54.7)	1.04 [.64-1.70]	.89 [.52-1.54]
Discussed intervention with a physician	102 (39.1)	43 (35.2)	59 (42.6)	.73 [.44-1.22]	.75 [.43- 1.32]
Discussed intervention with a pharmacist	55 (21.1)	26 (21.3)	29 (20.8)	1.02 [.57-1.86]	.89 [.46-1.72]
Experienced withdrawal symptoms during cessation	31 (11.9)	12 (9.8)	19 (13.7)	.69 [.32-1.49]	.60 [.27-1.35]

* analyses adjusted for living arrangement, education, anxiety as an indication for benzodiazepine treatment and baseline self-efficacy

7.4 A realist evaluation of patients' decisions to deprescribe in the EMPOWER trial

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STRUCTURED ABSTRACT:

BACKGROUND AND OBJECTIVES: Successful mechanisms for engaging patients in the deprescribing process remain unknown, but may include: (1) triggering motivation to deprescribe by increasing patients' knowledge and concern about benzodiazepines; (2) building capacity to taper by augmenting self-efficacy; and (3) creating opportunities to discuss and receive support for deprescrbing from a healthcare provider. We tested these mechanisms during the EMPOWER trial, and investigated the contexts that led to positive and negative deprescribing outcomes.

DESIGN: A realist evaluation using a sequential mixed methods approach, conducted alongside the EMPOWER randomized clinical trial

SETTING: Community, Quebec, Canada.

PARTICIPANTS: 261 older chronic benzodiazepine consumers, who received the EMPOWER intervention and had complete 6 month follow up data.

INTERVENTION: Mailed deprescribing brochure on benzodiazepines.

MEASUREMENTS: Motivation (intent to discuss deprescribing; change in knowledge test score; change in beliefs about the risk-benefits of benzodiazepines, measured with the Beliefs about Medicines questionnaire;); Capacity (self-efficacy for tapering) and Opportunity (support from a physician or pharmacist)

RESULTS: The intervention triggered the motivation to deprescribe among 167 (n=64%) participants (mean age 74.6 years $\pm$ 6.3, 72% women), demonstrated by improved knowledge (risk difference, 58.50% [95% CI, 46.98%-67.44%]) and increased concern about taking benzodiazepines (risk difference, 67.67% [95% CI, 57.36%-74.91%]). Those who attempted to taper exhibited increased self-efficacy (risk difference, 56.90% [95% CI, 45.41%-65.77%]). Contexts where the deprescribing

mechanisms failed included lack of support from a health care provider, a focus on short-term quality of life, intolerance to withdrawal symptoms, and perceived poor health.

CONCLUSION: Deprescribing mechanisms that target patient motivation and capacity to deprescribe yield successful outcomes in contexts where healthcare providers are supportive, and patients do not have internal competing desires to remain on drug therapy.

Key words: deprescribing, benzodiazepines, realist evaluation, mechanisms, EMPOWER

ClinicalTrials.gov identifier is NCT01148186

ARTICLE SUMMARY:

STRENGTHS AND LIMITATIONS OF THE STUDY:

- Use of a mixed methods approach enabled us to explore the breadth, depth, and complexity of the patient's experience of deprescribing.
- Use of the realist evaluation allowed us to investigate how the mechanisms underlying deprescribing interventions interact with specific contexts to yield positive or negative outcomes
- This study was conducted alongside a large cluster randomized clinical trial.

INTRODUCTION

Deprescribing refers to the collaborative process of tapering, discontinuing, stopping, or withdrawing medications in order to reduce adverse drug events and improve outcomes. [1-5] Deprescribing has many steps [1,3,6], with one key component being the engagement of patients in shared decision-making. [1,7-15] Research suggests that older adults have conflicted feelings about medications [4,14]: 78% of older adults believe that medications are necessary to improve health, but at the same time, 68% would like to reduce their current medication use, with 92% willing to stop a regular medication if advised to do so by their physician [14]. A better understanding of the mechanisms that trigger patient motivation and capacity to engage in the deprescribing process could reduce the use of potentially inappropriate medications.

The aim of realist evaluation is to reveal how an intervention might generate different outcomes in different circumstances, and how mechanisms work in particular contexts, by enabling or motivating participants to make different choices [16]. Educational strategies to increase patients' knowledge, beliefs, and motivation are hypothesized to influence deliberate action on the part of the patient to curtail the use of a drug [10]. However, what works, for whom, under which circumstances and why, are questions that have never been explored systematically from the patient's point of view. Recent reviews on deprescribing call for a realist evaluation of large deprescribing trials to investigate how the mechanisms underlying deprescribing interventions interact with specific contexts to yield positive or negative outcomes. [17,18] The EMPOWER trial, which demonstrated a number-needed-to-treat of 4 for the effectiveness of mailing a benzodiazepine deprescribing brochure on complete cessation of benzodiazepines at 6 months, provides a timely opportunity to examine which deprescribing mechanisms worked under which circumstances. [12]

The initial theory underpinning the development of the EMPOWER intervention was that most – if not all - older adults are unaware of the age-related harms of taking benzodiazepine anti-anxiety drugs and sleeping pills. Side effects of sedative-hypnotics are well-documented in the literature but rarely talked about in practice as being a

potential cause of memory impairment, falls and fractures [19-24], feared by many older adults [25,26]. Not understanding why medications should be discontinued is a patient barrier to deprescribing [4,27,28]. As most patients are uninformed of the potential risks associated with the use of benzodiazepines, we hypothesized a linear behavior change process whereby providing patients with an interactive educational brochure detailing associated risks, safer alternatives, and steps for tapering, would trigger patients' motivation, capacity and opportunity to initiate the deprescribing process through discussion of medication discontinuation with a healthcare provider.

This paper reports a realist evaluation of the deprescribing process from the patient's perspective. The realist evaluation tests the following mechanisms: (1) whether the EMPOWER intervention triggered patients' motivation to deprescribe by increasing knowledge and concern about benzodiazepines; (2) augmented patients' capacity and self-efficacy to taper benzodiazepines; and (3) created opportunities for the patient to discuss and receive support from a healthcare provider to engage in the deprescribing process. We also determined in which contexts successful and failed deprescribing outcomes occurred.

METHODS

Study design

A realist evaluation was conducted alongside the EMPOWER randomized controlled trial. [12] This report follows RAMESES II guidelines for realist evaluation. [16] The approach was chosen to inform the implementation of future deprescribing initiatives by examining the possible causes and contextual factors associated with change. [28] Realist evaluation is a theory-based, sequential mixed methods approach that seeks to gain a deeper understanding of contexts, mechanisms and outcomes. This is accomplished through the identification and examination of underlying generative mechanisms (M) associated with the intervention or program, the conditions or contexts (C) under which the mechanisms operate, and the pattern of outcomes (O) produced. These may be expressed as linked Contexts-Mechanisms-Outcomes configurations (or C+M=O).[28] In this case, the (C) consists of all internal and external factors that can

influence the deprescribing process, and the (O) refers to whether or not the deprescribing intervention was successful. The mechanisms (M) that we aimed to test were whether the EMPOWER brochure: (1) triggered older adults' motivation to deprescribe by increasing knowledge and concern about benzodiazepines; (2) built capacity to taper by augmenting self-efficacy; and (3) drove opportunities to receive support from a healthcare provider to deprescribe.

The study was approved by the Institut Universitaire de Gériatrie de Montréal Ethics Committee in Montreal, Quebec, Canada.

Environment surrounding the evaluation

The EMPOWER trial "Eliminating Medications through Patient Ownership of End Results" was a pragmatic randomized trial that examined the effectiveness of a direct-to-consumer, written educational brochure mailed directly to patients on subsequent discontinuation of sedative-hypnotic medication.[29] The EMPOWER trial was rolled out between July 2010 and November 2013, with community-dwelling participants randomly recruited via pharmacists located within a 200 km radius of the Montreal urban area in Quebec, Canada. Participants were 303 older, community-dwelling, chronic users of benzodiazepine medication, and agreed to home visits and telephone follow-up interviews by the research team. All benzodiazepine prescriptions for seniors were covered under the publicly financed drug plan in the province of Quebec, excluding the program's deductible (if applicable). Provincial governments covered physician reimbursements for patient visits, and drug dispensing fees for pharmacists, as part of Canada's universal health care program.

The EMPOWER intervention

The 8-page EMPOWER brochure, available at http://www.criugm.qc.ca/fichier/pdf/BENZOeng.pdf, [30] aims to promote active learning by incorporating and using constructivist learning principles. [31] The brochure includes a self-assessment component and presentation of the evidence-based risks associated with benzodiazepine use in an effort to elicit cognitive dissonance.[10] Elements of social

comparison theory [32], through the use of peer champion stories, are also integrated in the intervention. The brochure provides a self-guided tapering schedule, consisting of a visual tapering protocol showing pictures of full pills, halved pills and quartered pills [30].

Evaluation of mechanisms and contexts

The mechanisms embedded in the EMPOWER intervention are based on Mitchie et al's behavior change wheel [33], targeting motivation, capacity and opportunity. Mitchie et al. define motivation as the mental process that energizes and directs behaviors. Capability refers to the psychological and physical capacity of the individual to engage in the behavior. Opportunity refers to the internal and external factors that permit or promote a behavior to happen, and include both the physical and social environment of the individual. Table 1 links the program mechanisms to the corresponding intervention components.

The evaluation of mechanisms and contexts consisted of quantitative data collection and analysis, qualitative data collection and analysis, and triangulation of the quantitative and qualitative results. [34] Data collection was conducted between July 2010 and November 2013 as part of the EMPOWER clinical trial. Analysis, triangulation and refinement of the Context-Mechanism-Outcome configuration took place subsequent to completion of the trial.

Data collection methods

Quantitative data included pre- and 1-week post-intervention information on knowledge about benzodiazepine-related harms, beliefs about the necessity of taking benzodiazepines versus concern about harms, self-efficacy for tapering, and intent to discuss deprescribing with a health care provider. We measured gains in knowledge with the four true or false questions listed in the ''Test Your Knowledge'' section of the questionnaire. [29,30] Correct answers were summed to a maximum of 4 points, and answers were compared prior to and after receiving the intervention. Participants' beliefs about consuming benzodiazepines were measured with the Beliefs about Medicines questionnaire (BMQ-Specific) at both time points. The BMQ-Specific consists

of two validated 5-item sub-scales assessing the respondents' perceptions about the necessity and concerns associated with taking benzodiazepines. [35] Participants indicate their degree of agreement with each statement on a 5 point Likert scale (1=strongly disagree, 5=strongly agree). Scores are summed into their respective sub-category (5-25 point scale) with higher scores indicating stronger beliefs. Risk perception was assessed using a single question 1-week post intervention in which participants were asked whether they perceived the same, increased, or no risk from consumption of their benzodiazepine following the intervention. In order to determine whether the EMPOWER brochure increased capacity to taper by augmenting self-efficacy, we measured self-efficacy for tapering on the Medication Reduction Self-efficacy scale, which allows the respondent to rate on a scale of 0 to 100 their degree of confidence for tapering benzodiazepines.[36] Higher scores indicate greater self-efficacy. Participants were also asked to indicate (yes/no) post intervention if they had spoken to or intended to discuss medication discontinuation with their doctor and/or pharmacist. Health status was assessed at baseline using the first item of the Short-Form-12 Health Survey and dichotomized by categorizing poor to fair responses as poor health. [37]

Qualitative data were collected after the 6-month follow-up, using semi-structured interviews conducted at participants' homes to determine the contexts under which the deprescribing mechanisms succeeded or failed. Twenty-one participants were strategically sampled for the interviews using a contrast sample design, based on cessation of benzodiazepines (yes or no) combined with intent to discuss tapering (yes or no). [38] Interviews lasted approximately one hour, were recorded with consent and professionally transcribed verbatim. The interviews were based on a pre-established discussion guide, the major themes of which included initial reactions to the intervention, reasons underlying the decision to taper, experience with the tapering process, and personal interactions with health care providers (Supplemental File 1).

Analysis

The three mechanisms of increasing motivation, capacity and opportunity were tested using quantitative analysis. Participants with complete follow-up data were

included in the quantitative analysis (n=261, mean age 74.6 ± 6.3, 72% women). Data were described and compared using means with standard deviations and independent t-tests for continuous data, and percentages and Chi-square tests for categorical data, according to each of three outcomes: intent to deprescribe with successful discontinuation, intent to deprescribe with failed discontinuation, and no intent to deprescribe. Individuals who achieved a dose reduction were classified as intent to deprescribe with failed discontinuation. Participant changes in knowledge, in the BMQ necessity and concerns subscales, and in self-efficacy scores for tapering were computed from baseline to post-intervention. Risk differences with 95% confidence intervals were calculated for the proportion of participants in each group who demonstrated increased knowledge, heightened concern about benzodiazepine use, and augmented self-efficacy for tapering. The statistical significance for all analyses was set at $p<0.05$ (two-sided) [39] SPSS Version 21.0 (SPSS Inc. Chicago, IL, USA) was used for all analyses.

Qualitative data from the semi-structured interviews were analyzed using thematic content analysis to explore the contexts under which the program mechanisms led to positive or negative outcomes. [40] Discourses were contrasted according to whether participants discontinued benzodiazepines and/or expressed the intent to discuss discontinuation. Interviews were coded using Dedoose software. Contextual themes were derived from the data and supported by quotes. Initially, two researchers independently read the transcripts and field notes, then collaboratively developed first order codes, which were subsequently verified by double coding. Second order thematic coding was performed for the purpose of building concepts.

Quantitative and qualitative results about context were combined and analyzed in an iterative fashion through use of a triangulation protocol using a convergence coding matrix, [41] as described by Farmer et al. [42] The convergence matrix served to inform which contexts favorably or unfavorably influenced a patient's decision to deprescribe based on agreement, partial agreement, or dissonance between the quantitative and qualitative data. [41,42] Differences were adjudicated via discussion and consensus. [42] The convergence-coding matrix is available from the authors upon request.

RESULTS

Linking mechanisms to outcomes

The mechanism of triggering motivation to deprescribe occurred in 167 of 261 individuals (64%) who received the EMPOWER intervention (Table 2). Participants who expressed an intent to deprescribe post-intervention had improved knowledge (risk difference, 58.50% [95% CI, 46.98%-67.44 %]), lower perceived necessity scores (risk difference, 56.03% [95% CI, 44.63%-64.81%]), increased concern (risk difference, 67.67% [95% CI, 57.36%-74.91%]), and a greater perception of risk about their benzodiazepine medication than those who were not motivated to attempt deprescribing (risk difference, 35.14% [95% CI, 23.06%-45.39%]). Individuals who decided to deprescribe exhibited higher capacity for tapering after receipt of the EMPOWER brochure, with enhanced self-efficacy compared to those in whom the intervention did not trigger motivation (risk difference, 56.90% [95% CI, 45.41%-65.77%]) (Table 2). Approximately half of individuals with augmented motivation and capacity to deprescribe initiated a conversation with their physician, and 25% spoke to a pharmacist about deprescribing. Neither post-intervention self-efficacy scores nor creating the opportunity to discuss deprescribing with a healthcare provider distinguished between positive or negative outcomes among motivated individuals.

Contexts associated with positive deprescribing outcomes

Table 3 shows the results of the qualitative analysis, describing the contexts that enabled the EMPOWER mechanisms to achieve positive deprescribing outcomes. Favorable personal contexts included stable health status, and a positive outlook on aging. Individuals who were not dealing with acute health issues were more receptive to tapering off benzodiazepines, as were individuals who prioritized long life expectancy over the short-term benefits of continued use or the transient discomfort associated with deprescribing benzodiazepines. Individuals who succeeded in tapering had the highest baseline self-efficacy for being able to discontinue (Table 2). External influences associated with successful discontinuation were previous and ongoing support or encouragement from a health care provider (Table 3).

Contexts in which the EMPOWER mechanisms failed

Thirty-six percent of the participants in the trial reported no desire to deprescribe after receipt of the EMPOWER brochure. These individuals showed no gain in knowledge and no increase in perceived risk post-intervention (Table 2). Failure for the EMPOWER intervention to elicit motivation to deprescribe was more likely among individuals who reported poor health (40% vs 28%, 12.28% [95% CI, 0.44 %-24.18 %]). During the qualitative interviews, participants dealing with ongoing health issues expressed a strong reliance on benzodiazepines for everyday coping (Table 4). Other contexts associated with the decision not to attempt deprescribing included previous reassurance by a physician that benzodiazepines were safe or necessary and the belief that the benefits of benzodiazepines outweighed the risks for immediate symptom relief (Table 4). Contexts that led participants to abort the deprescribing process once they showed initial motivation, capacity and opportunity to deprescribe included the lack of support from a healthcare provider, intolerance to withdrawal symptoms, and a sudden loss of confidence to live without sleeping pills were (Table 4).

Refining the context-mechanism-outcome configuration for deprescribing interventions

The initial context-mechanism-outcome configuration that drove the development of the EMPOWER intervention was a simple, linear progression along different stages of readiness to deprescribe, similar to Prochaska & DiClemente's transtheoretical model of change (Figure 1a). [43] We believed that the EMPOWER brochure would trigger motivation and capacity to deprescribe, moving patients from pre-contemplation about deprecribing to action and maintenance, by increasing knowledge about the harms of benzodiazepines, enhancing self-efficacy, and creating opportunities to discuss deprescribing with a healthcare professional. We assumed the healthcare provider would provide a supportive context, encouraging the patient to deprescribe, thereby yielding a positive outcome. This initial configuration oversimplified the stages through which individuals transitioned after receiving the deprescribing intervention. Figure 1b depicts a revised, non-linear context-mechanism-outcome configuration that takes into account the complexity of internal and external contexts on initiating and completing the

deprescribing process from the consumer's perspective. The revised model recognizes that new information influences beliefs and actions only if the information generates a desire strong enough not to be overwhelmed by competing motivations arising from other sources. In many instances, the desire for risk reduction, which was the prime motivator behind the development of the EMPOWER intervention, did not supersede concerns about symptom recurrence, or other psychological and health factors, as well as interpersonal relationships with healthcare providers, which played critical contextual roles in the outcome of the intervention.

DISCUSSION

This realist evaluation tested the mechanisms embedded in the EMPOWER intervention, and showed that motivation and capacity to deprescribe were triggered in 64% of older chronic benzodiazepines consumers, the majority of whom created an opportunity to discuss deprescribing with a healthcare provider. These findings support the theory that provision of new knowledge about medication harms can raise concern and augment patients' self-efficacy to deprescribe. However, the analysis also indicates that human motivation to deprescribe is complex and unstable. A variety of internal and external contexts can interfere with the decision to deprescribe. Internal influences include perceptions about one's health status, long-term health goals, fear of symptom recurrence, and psychological attachment to the drug. The main external influence that blocks consumer-directed deprescribing mechanisms is the lack of support from a health care provider.

Our findings contribute to the literature by illustrating that linear progression along different stages of readiness to deprescribe does not fully explain successful deprescribing from the patient's perspective. This conclusion is consistent with other critiques of the transtheoretical model, which claim that the stages of readiness are arbitrary, that human beings do not make logical and stable plans to change their behavior, and that setbacks can occur along the trajectory of change. [44] Education appears to be necessary but insufficient for many individuals, and new strategies will be needed to trigger deprescribing in prohibitive contexts where the EMPOWER

mechanisms failed. As capacity and motivations change over time, reminders and ongoing discussions about the risks of inappropriate medications may progressively trigger and sustain patients' commitments to engage in the deprescribing process. Some competing factors may wane, such as poor health. Offering cognitive behavioural therapy to patients during the most difficult last quarter period of the tapering protocol may augment self-efficacy for overcoming withdrawal symptoms. [36] Interventions can be directed at health care providers who discourage deprescribing efforts. Continuing medical education to inform health providers about the mounting evidence on the harms of benzodiazepine use may curtail the phenomenon of physicians who continue to promote the use of inappropriate medication. [20,45] Future research directions should also include measurement of cognitive dissonance, which lies at the heart of constructivist learning.[46] Methods to measure cognitive dissonance, defined as a feeling of tension between two sets of competing beliefs and motivations, may shed light on the way in which tensions about deprescribing are played out and drive behavior change [46,47]. As we did not directly ask patients if they felt internal tension, we were unable to record feelings or processes of cognitive dissonance.

Use of a mixed methods approach enabled us to explore the breadth, depth, and complexity of the patient's experience of deprescribing from a social, behavioural and health perspective, allowing stronger inferences about the various contexts affecting patients' decisions than could be achieved through a quantitative or qualitative lens alone. [48] However, other mechanisms and contexts may trigger motivation to deprescribe beyond what is described in this realist evaluation. One untested mechanism is provision of information about the lack of drug benefits in certain populations, such as statins to reduce cholesterol levels in palliative care patients with limited life expectancy. [49,50] Another challenge that we experienced during the conduct of this realist evaluation was differentiating between the mechanisms and contexts associated with deprescribing. [51] For instance, when participants stated that their physician or pharmacist undermined their decision to deprescribe, it was clear this factor changed the reasoning of the participants. However, we were not sure whether this factor should be labeled as a mechanism or a context. Since the mechanism of

action is defined as the “how” behind the generation of outcomes, we initially thought that healthcare provider support was a mechanism that brought about deprescribing. [51] Upon iterative reflection and discussion of the C-M-O configurations, we came to the conclusion that healthcare provider support was actually a context that enabled or hindered the consumer’s motivation, capacity and opportunity to deprescribe, as triggered by the EMPOWER intervention. We drew this conclusion by subscribing to Pawson and Tilley’s initial approach to realist evaluation, which seeks to identify mechanisms at the level of the individual’s human reasoning. [52] Others, such as Dalkin et al. posit that interpersonal relationships between stakeholders are a key factor that influence human reasoning, and argue that mechanisms can also be evaluated through the social lens of human and systems interactions. [51] Deprescribing in particular is a complex social process that involves patients, prescribers and pharmacists, so our analysis may be faulted by some for studying the consumer’s decision-making processes in isolation. For this reason, we chose not to make a table listing discrete C-M-O relationships in this paper, but instead focused on broadly describing and testing the mechanisms embedded in the EMPOWER intervention, and outlining the different personal, interpersonal and external contexts that led to positive or negative outcomes. We created Figures 1a and 1b with difficulty, and some skepticism about whether these complex interactions could be illustrated in simple form. As the field of realist evaluation evolves, new terminology and formats may emerge that better capture a way of graphically illustrating the science of human interactions and behavior change.

In conclusion, this realist evaluation conducted alongside a clinical trial provides important insights about deprescribing from the patient’s perspective, and increases current understanding about the specific mechanisms and contexts that generate positive or negative outcomes when attempting to engage patients in curbing the over- and potentially inappropriate use of medicines.

Figures and Legends:

Figure 1 a: Initial Deprescribing Context-Mechanism-Outcome configuration

Figure 1b: Refined Deprescribing Context-Mechanism-Outcome configuration

Legend:

C = Context (grey circles);

M = Mechanism (purple diamonds);

O = Outcome (blue rectangles)

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TABLES

Table 1: Program mechanisms embedded in EMPOWER intervention

Mechanisms	Components of the EMPOWER brochure		
Increase motivation to deprescribe by changing knowledge and beliefs	Messaging on the front page "You May be at Risk" to raise awareness of the harms of benzodiazepines	Interactive knowledge test with 4 true/false questions and answers about the harms of benzodiazepines, aimed at increasing knowledge	Information about changes in drug metabolism with age that can lead to a higher risk of side effects, meant to change beliefs and elicit concern about the safety of the medication in older adults
Increase capacity to taper by augmenting self-efficacy	A list of alternative non-pharmacological approaches to sleep and anxiety that patients can use as substitutes	An inspirational story using social comparison and peer championing to increase self-efficacy for tapering	Provision of an easy-to-use visual 16-20 week tapering tool showing when to take a whole, half or quarter pill, and when to skip the dose completely
Drive opportunities to discuss and initiate deprescribing with a healthcare provider	Instruction to "Please consult your doctor or pharmacist before stopping any medication" in a large red box	Logos on the brochure provide source credibility for the patient to initiate conversations	The printed format of the 8-page brochure makes it an effective knowledge transfer piece to take and show to a healthcare provider

Table 2: Linking Mechanisms to Outcomes

Mechanisms	Outcomes					
	All (n=261)	Successful deprescribing (n=92)	Intent but failed deprescribing (n=75)	No attempt to deprescribe (n=94)	Successful and failed intent vs no attempt* P-value/ Risk difference (95% CI)	Successful completion vs failed intent to deprescribe P-value/ Risk difference (95% CI)
Increased Motivation						
Change in Knowledge:						
Baseline knowledge (/4), Mean (SD)	.85 (.99)	.97 (1.08)	.87 (.97)	.71 (.90)	.10	.54
Post-intervention knowledge (/4), Mean (SD)	1.92 (1.40)	2.64 (1.23)	2.01 (1.34)	1.13 (1.20)	.00*	.00*
Increase in knowledge post-intervention, n (%)	156 (59.8)	80 (86.9)	55 (73.3)	21 (22.3)	58.5 [47.0-67.4]*	13.6 [1.6-25.9]*
Beliefs about benzodiazepines						
Baseline belief about necessity[a] (/25), Mean score (SD)	13.8 (3.4)	13.0 (.3)	14.3 (.4)	14.1 (.4)	.23	.01*
Post-intervention belief about necessity[a], Mean score (SD)	12.58 (3.32)	11.07 (.30)	12.55 (.32)	14.05 (.35)	.00*	.10
Participants with a decrease in score about necessity post-intervention, n (%)	138 (52.8)	75 (81.5)	47 (62.7)	16 (17.4)	56.0 [44.6-64.8]*	18.9 [5.3-32.0]*
Baseline concern[a], (/25), Mean score (SD)	13.4 (2.7)	13.4 (.3)	14.1 (.3)	12.9 (.3)	.00*	.01*
Post-intervention concern[a], Mean score (SD)	14.42 (3.41)	15.60 (.37)	15.34 (.36)	12.56 (.28)	.00*	.62
Participants with increased concern post-intervention, n (%)	138 (52.8)	70 (76.1)	59 (78.7)	9 (9.7)	67.7 [57.3-74.9]*	-2.6 [-15.0-10.4]
Risk Perception:						
Participants perceiving increased risk post-intervention, n (%)	118 (44.8)	51 (55.4)	45 (60.0)	21 (22.3)	35.1 [23.1%-45.4]*	-4.6 [-19.1-10.4]
Building Capacity						
Self-Efficacy for Tapering						
Baseline self-efficacy (/100), Mean (SD)	37.8 (35.7)	47.3 (34.6)	35.0 (37.4)	31.0 (33.6)	.03*	.02*
Post-intervention increase in self-efficacy score, Mean change (SD)	25.44 (42.78)	35.78 (36.80)	36.03 (44.63)	6.00 (40.93)	.00*	.97
Participants with increased self-efficacy post-intervention, n (%)	145 (55.5)	70 (76.1)	57 (76.0)	18(19.1)	56.9 [45.4-65.8]*	0 [-12.6-13.3]
Creating opportunity						
Outreach to a health care professional:						
Discussed with physician, n (%)	103 (39.5)	42 (45.6)	38 (50.6)	23 (25.0)	23.4 [11.3-34.1]*	-5.0 [-19.8-10.0]
Discussed with pharmacist, n (%)	56 (20.1)	25 (27.1)	22 (28.9)	9 (9.7)	18.6 [8.7-27.1]*	-2.2 [-15.9-11.3]

Independent sample t-test for continuous variables, chi square for categorical variables.

* Level of significance, $p < 0.05$.

‡ As some participants selected more than one condition, total does not equal 100%.

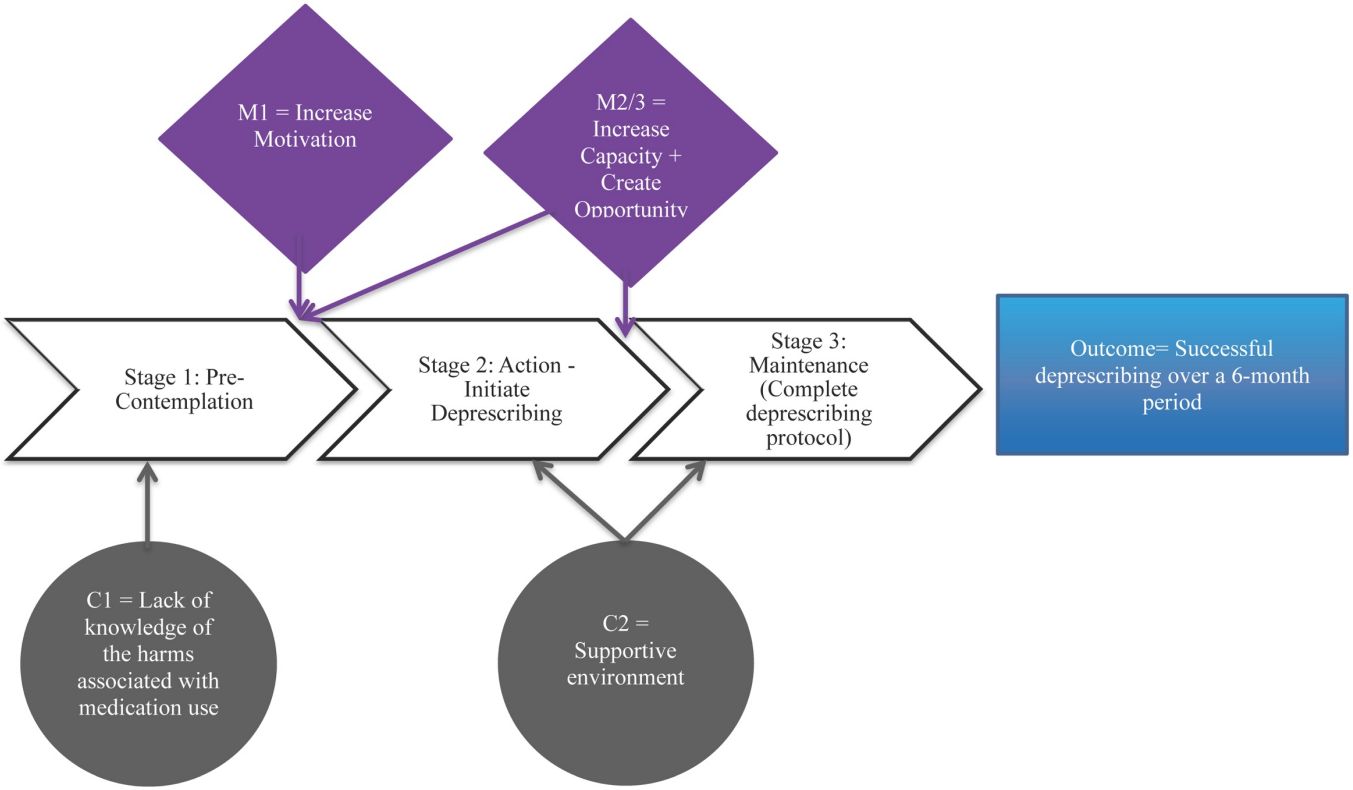
Table 3: Contexts associated with positive outcomes

Contexts	Outcomes			Supporting citation
	Successful deprescribing (n=7)	Failed deprescribing (n=7)	No attempt to deprescribe (n=7)	
Previous support from physician/ positive attitude towards discontinuation	5 (71%)	4 (57%)	1 (14%)	*"He [my doctor] told me the drug was not good for me and that I could experience side effects while taking it."*[72 y.o. man, successful taper]
Stable health status	5 (71%)	4 (57%)	2 (29%)	*"I don't have as much pain as I used to. It's now under control so it was easier for me to stop. Before - no way."* [68 y.o. woman, successful taper]
Certainty and confidence about tapering (post-intervention)	6 (86%)	4 (57%)	1 (14%)	*"I persuaded myself that I needed to get rid of this, no matter what."* [84 y.o. man, successful taper]
Perception of increased risk	6 (86%)	5 (71%)	1 (14%)	*"My physician told me it [the drugs] could cost me my memory. My memory has become very important to me."* [79 y.o. man, successful taper]
Lack of psychological attachment	5 (71%)	3 (43%)	1 (14%)	*"I understood I could stop taking it [after I read the brochure], that it was not an obligation [to take it]."* [72 y.o. woman, successful taper]
Positive outlook on aging	3 (43%)	1 (14%)	0	*"At my age I don't believe in miracles such as being able to sleep for 8, 9 or 10 hours each night. It would be impossible for me, so I content myself with the hours of sleep I get."* [84 y.o. man, successful taper]
Tapering tool provides support	5 (71%)	3 (43%)	0	*"In the past I tried to stop the pill all at once. But using the tapering tool, I understood that it need to be a gradual and not a drastic process."* [84 y.o. man, successful taper]
Supportive health care provider	3 (43%)	2 (29%)	0	*"When I told my doctor I wanted to stop, he said, "no problem, let's do it."* [87 y.o. woman, successful taper]

Table 4: Contexts associated with negative outcomes

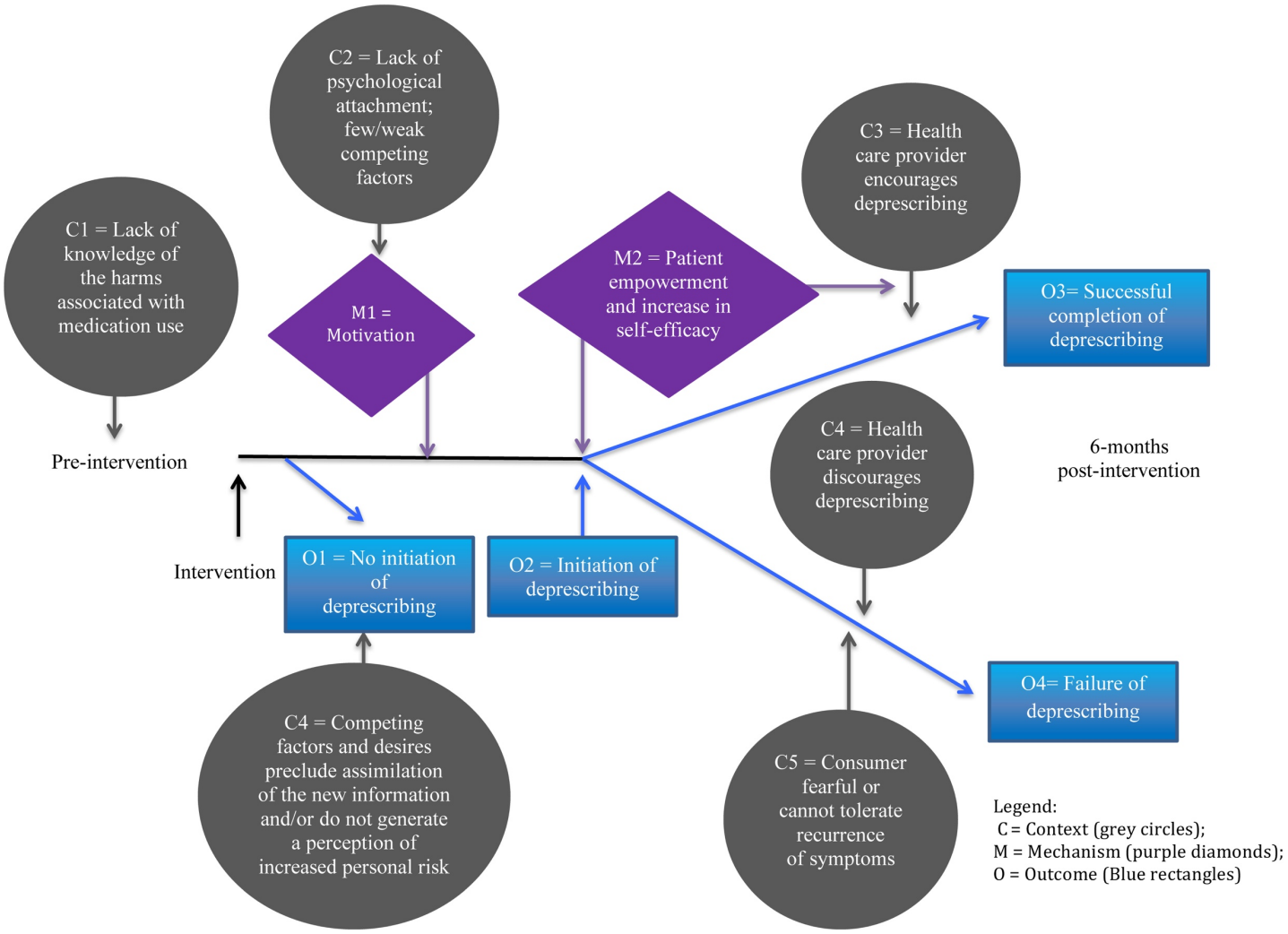
Key theme	Successful deprescribing (n=7)	Failed deprescribing (n=7)	No attempt to deprescribe (n=7)	Supporting citation
Previous discouragement from physician	1 (14%)	1 (14%)	5 (71%)	*"I asked him [my doctor], "Are there any of my medications I could stop?" He told me, "No, we're not taking anything away, you are doing well". I then told him my medication was getting very expensive to which he replied, "You know Mr., life is priceless".* [75 y.o. man, no intent to taper]
Poor health status	0	1 (14%)	4 (57%)	*"If anyone stops my pills, poof, I would die for sure because of my poor health.".* [70 y.o. woman, no intent to taper]
Unquestioning belief in their physician	1 (14%)	1 (14%)	3 (43%)	*"If you take all your pills as prescribed, you'll never have problems in your life […] When my doctor prescribes something for me, I know it's not junk, I know it's good for me. And I don't question it".* [72 y.o. man, no intent to taper]
Lack of perception of personal risk	1 (14%)	2 (29%)	5 (71%)	*"I recall that he [my doctor] told me that in the long-term my benzodiazepine could affect my memory. But my memory is fantastic."* [72 y.o. man, no intent to taper]
Reliance on medication for coping/everyday function	1 (14%)	1 (14%)	4 (57%)	*"Without this medication, I know that my life would be plagued by anxiety, of this I am certain.""* [68 y.o. woman, no intent to taper]
Quality of life focus during end-of life	0	2 (29%)	3 (43%)	*"At my age I don't care about the risks. I don't care if I live to 100 or not."* [85 y.o. woman, failed tapering]
Discouragement from a physician	1 (14%)	3 (43%)	5 (71%)	*"My doctor told me: "At your age, don't worry about it. You've been taking this pill for a while and you are fine. You aren't taking a dangerous dose at all."* [85 y.o. woman, failed tapering]
Intolerance to recurrence of symptoms/withdrawal effects	0	5 (71%)	_	*"When I decreased the dose I started getting headaches. I felt miserable not being able to sleep at night."* [85 y.o. man, failed tapering]
Loss of confidence to complete the tapering process (post-intervention)	0	4 (57%)	4 (57%)	*"I knew that I'd be in trouble without my pills. It's been a long time now. How can I put it in words? If I ran out of pills I'd be in trouble."* [85 y.o. man, failed tapering]

Figure 1a: Initial Deprescribing Context-Mechanism-Outcome configuration



Legend: C = Context (grey circles); M = Mechanism (purple diamonds); O = Outcome (Blue rectangles)

Figure 1b: Refined Deprescribing Context-Mechanism-Outcome configuration



Chapter 8 – D-PRESCRIBE Results

8.1 A prototype for evidence-based pharmaceutical opinions to promote physician-pharmacist communication around deprescribing

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Abstract

Context: Interprofessional communication is an effective mechanism for reducing inappropriate prescriptions among older adults. Physicians' views about which elements are essential for pharmacists to include in an evidence-based pharmaceutical opinion for deprescribing remain unknown.

Objective: To develop a prototype for an evidence-based pharmaceutical opinion that promotes physician-pharmacist communication around deprescribing.

Methods: A standardized template for an evidence-based pharmaceutical opinion was developed with input from a convenience sample of 32 primary care physicians and 61 primary care pharmacists, recruited from conferences and community settings in Montreal, Canada. Participants were asked to comment on the need for clarifying treatment goals, including personalized patient data and biomarkers, highlighting evidence about drug harms, listing the credibility and source of the recommendations, providing therapeutic alternatives and formalizing official documentation of decision-making. The content and format of the prototype underwent revision by community physicians and pharmacists until consensus was reached on a final recommended template.

Results: The majority of physicians (84%-97%) requested that the source of the deprescribing recommendations be cited, that alternative management options be provided, and that the information be tailored to the patient. Sixteen percent of physicians expressed concern about the information in the opinions being too dense. Pharmacists also questioned the length of the opinion and asked that additional space be provided for the physician's response. A statement was added making the opinion a valid prescription upon receipt of a signature from physicians. Compared to a non-standardized opinion, the majority of pharmacists believed the template was easier to use, more evidence-based, more time efficient and more likely to lead to deprescribing.

Conclusion: Physicians and pharmacists endorsed a standardized template that promotes interprofessional communication for deprescribing (available at https://www.deprescribingnetwork.ca/pharmaceutical-opinions). The outcome of the D-Prescribe trial will determine the effectiveness of these evidence-based pharmaceutical opinions on deprescribing processes and outcomes. *Can Pharm J (Ott)* 2018;151:xx-xx.

Knowledge into practice

- Very little information exists on the development and standardization of pharmaceutical opinions in Canada.
- This study describes physicians' and pharmacists' input on the development of a standardized template for evidence-based pharmaceutical opinions aimed at promoting deprescribing.
- Both physicians and pharmacists endorsed the final prototype, which incorporates essential elements to facilitate communication for deprescribing.

Introduction

Each province and territory in Canada takes a different approach to expanding the scope of pharmacists' services. [1] Alberta and British Columbia, among others, permit pharmacists to change drug doses and formulations and make therapeutic substitutions. Pharmacists in Saskatchewan and Nova Scotia, but not British Columbia or Ontario, can additionally prescribe for minor ailments. In Quebec and Ontario, pharmacists can send pharmaceutical opinions to physicians to facilitate communication around the quality use of medicines. [2]

The pharmaceutical opinion program has been around for decades in Quebec,[3] but was only implemented in Ontario in 2011.[4] A pharmaceutical opinion is a document sent from a pharmacist to the prescriber detailing a problem with a patient's pharmacotherapy and recommending a management strategy to address the drug-related problem.[5] Pharmaceutical opinions can cover a broad range of issues, from suboptimal prescribing and potential drug-drug interactions to adverse drug reactions and nonadherence. A study of over 700,000 pharmaceutical opinions indicated that 68% of opinions resulted in a change in prescription. [4]

One of the anticipated goals of the pharmaceutical opinion is to reduce the use of inappropriate prescriptions.1,[5] Prescriptions are deemed inappropriate when their risks outweigh their benefits and when safer therapeutic alternatives exist that have similar or superior efficacy.[6-8] In Canada, inappropriate prescribing is estimated to occur for 42% of women and 31% of men aged 65 years and older, with rates up to 47% among women aged 85 and older.[9] A survey distributed in 2013 to 3927 pharmacists across Québec revealed that fewer than 50% of respondents were aware of the prevalence of polypharmacy, inappropriate prescribing or drug-related hospitalizations in the geriatric population.[10] Furthermore, approximately 50% of Quebec participants in the EMPOWER randomized trial who initiated a conversation about deprescribing benzodiazepines with their pharmacist and/or physician reported that their pharmacist and/or physician discouraged discontinuation.[11] These findings align with other reports that physicians and pharmacists sometimes block attempts at

deprescribing.[12] Based on the 2013 Quebec pharmacist survey, we hypothesized that a lack of evidence-based knowledge about drug harms in older adults could be an impediment to deprescribing. In order to raise awareness of inappropriate prescriptions and to increase receptivity and capacity for deprescribing among physicians and pharmacists, we sought to develop a model for communication using pharmaceutical opinions that would effectively convey information between physicians and pharmacists about drug harms and potential solutions. Standardized clinical documentation exists for pharmacists to draft pharmaceutical opinions in Ontario, [13] but no such guidance is available in Quebec and to our knowledge, none includes referenced evidence-based information about inappropriate prescribing.

Objective

The objective was to develop a prototype for pharmaceutical opinions that would effectively convey information about drug harms and potential solutions, with the aim of increasing interprofessional knowledge and communication around deprescribing.

Methods

Theory behind the development of the prototype for the evidence-based pharmaceutical opinion

The first step towards developing a standardized template for an evidence-based pharmaceutical opinion about inappropriate prescriptions was to explore the barriers and facilitators behind the process of deprescribing from the physicians' perspective. Based on published reports in the literature, physicians identify 3 important predictors of engaging in the deprescribing process: agreement or disagreement with the appropriateness of drug cessation, confidence and skills for implementing a deprescribing protocol, and positive or negative extrinsic pressures to cease medication use.[12] We hypothesized that if the pharmacist transmitted a pharmaceutical opinion that provided solid evidence for the inappropriateness of certain drug classes and clear direction on how to discontinue medications, physicians might be more likely to engage in interprofessional deprescribing efforts.

We also sought to understand the enablers and challenges of using pharmaceutical opinions from the pharmacists' perspective. Pharmacists report several problems with the use of pharmaceutical opinions. Some of these barriers include workflow interruptions, physician resistance, documentation, unclear program criteria and a lack of time.4 Advanced training and access to an automated system facilitate use. [4] We hypothesized that a pre-structured model for a pharmaceutical opinion, designed by physicians and pharmacists, with the information formatted in such a way that compels physicians to adhere to the pharmacist's evidence-based recommendations, might be helpful. This type of opinion should leave no doubt as to the credibility of the information and should greatly reduce the time and documentation required by pharmacists for drafting and sending the opinion. Additionally, this type of pharmaceutical opinion, if based on published consensus guidance for deprescribing inappropriate prescriptions, could eventually be implemented as an automatic alert leading to a pre-filled opinion where only patient details would need to be entered.

With these considerations in mind, we developed an initial prototype for a pharmaceutical opinion partly based on Ontario's standard format [13] with lessons learned from evidence-based trials testing different ways of presenting the relative benefits and harms of competing therapeutic approaches. [14, 15]

Components of the prototype for the evidence-based pharmaceutical opinion

The initial evidence-based pharmaceutical opinion consisted of several elements. To illustrate content, we use the example of the oral sulfonylurea hypoglycemic agent glyburide, used to treat type 2 diabetes.

Personalized patient information and biomarkers

The pharmaceutical opinion contains personalized information including the patient's name, date of birth, drug targeted by the opinion, the indication for the prescription and the rationale behind the pharmaceutical opinion. Relevant clinical and laboratory parameters are added as appropriate. In the case of glyburide, spaces are

provided for the pharmacist to insert information, if available, on the patient's creatinine clearance, recent hypoglycemic episodes, their latest blood glucose and HbA1C.

Credibility and source of the recommendations

This section outlines the source of the consensus guidance or clinical practice guideline that recommends which drugs to avoid or deprescribe in older adults. In the case of medium- to long-acting sulfonylurea drugs, we cited the American Geriatrics Society Beers List rating, with the additional endorsement of clinical practice guidelines released by Diabetes Canada. [16]

Evidence-based information about drug harms

In this section, evidence is cited about specific drug harms, with peer-reviewed references to back up each claim. For glyburide, the opinion stated that glyburide increases the risk of severe hypoglycemia by 50% compared to other sulfonylurea agents [17-19] and that hypoglycemia may worsen physical and cognitive functioning in the frail elderly or in those with cognitive impairment. [20] Furthermore, hypoglycemia increases the risk of fall-related fractures by 70% in older adults and glyburide is not recommended in patients with a creatinine clearance less than 60 mL/min. [6, 16]

Recommended alternatives

Alternative evidence-based pharmacological and nonpharmacological treatment options are listed next to checkboxes that allow prescribers to endorse a given course of action. For instance, Diabetes Canada recommends several safer agents to treat diabetes in the elderly in lieu of glyburide, including metformin and dipeptidyl peptidase-4 inhibitors (DPP4).[16] Starting doses and the schedule of dose escalation are provided. There is also the option to cease glyburide and re-assess the HbA1c at the next follow-up visit. As the DPP4 class of drugs requires restricted access reimbursement for seniors in Quebec, the formulary code and cost are indicated on the opinion. A table on the flipside of the pharmaceutical opinion compares the cost, relative harms and contraindications of each alternative, available formulations and the anticipated reduction in HbA1C.

Age-appropriate treatment goals

Prescribing for older adults needs to consider treatment goals as a function of symptom reduction, long-term health outcomes and avoidance of harm. [21-23] For glyburide, the opinion reminds prescribers that the usual HbA1C target in older adults is less than 7%, that frail older adults can tolerate a target of 7%-8.5% and that the priority in older adults with cognitive impairment is to avoid hypoglycemia <4.0 mmol/L at all times. [16]

Signature

This section allows physicians to sign or initial the pharmaceutical opinion and endorse a given course of action for pharmacists to follow upon receipt of the returned document.

Input and feedback from physicians

The initial prototype for the pharmaceutical opinion was distributed to 60 primary care physicians from diverse geographic settings attending a symposium for continued professional development credits. The course coordinators agreed to let us distribute the prototype and feedback questionnaire in the course package along with other course material. The feedback questionnaire for the prototype consisted of 12 five-point Likert-scale questions on the different elements of the prototype, one multiple choice question on the preferred method of receiving pharmaceutical opinions, 5 open-ended questions and a section for comments. Twelve questions queried physicians' degree of agreement with statements about the usability of the pharmaceutical opinion, such as the tool's appearance, design, layout, quality and content of the information, clarity of the recommendations, appropriateness of the references, relevance to decision-making, feasibility of use in multiple contexts and anticipated impact on prescribing practices. Open-ended questions queried what physicians liked and disliked about the different elements of the prototype and asked for suggestions for improvement. Participation in the feedback session was completely voluntary. Time was used during breaks to fill out the questionnaire. Consent to participate was provided by returning the anonymous

questionnaire at the end of the conference. Thirty-two physicians provided feedback and returned the questionnaires.

Input and feedback from pharmacists

Sixty-one community pharmacists provided input on the prototype for the evidence-based pharmaceutical opinion during participation in the D-PRESCRIBE trial.[24] Briefly, the D-PRESCRIBE trial enrolled a random sample of community pharmacists who dispensed 4 classes of inappropriate prescriptions to adults aged 65 years and older: benzodiazepines and Z-drugs, long-acting sulfonylureas, first-generation antihistamines, and NSAIDs.[6] The initial prototypes were shown to each pharmacist individually during the pre-enrollment phase of the trial and each pharmacist was invited to respond to semi-structured interview questions. The feedback questionnaire for the prototype consisted of 9 five-point Likert-scale statements querying agreement on the prototype's content and usability and 4 open-ended questions on whether the pharmacist would distribute the prototype "as is" or with modifications. The study was approved by the Institut Universitaire de Gériatrie de Montréal on September 17, 2013.

Analysis

Analyses proceeded sequentially. First physicians provided input on the initial template, then pharmacists suggested changes to the physicians' edits in order to optimize usability. The results are presented in aggregate format for the purposes of this report. Specifically, feedback from physicians was analyzed by categorizing endorsement for each of the prototype elements by pre-defining agreement as "strongly agree" or "agree" with the usefulness and desirability of inclusion of each element. Proportions are reported with 95% confidence intervals. The frequency of preferred methods for communicating with pharmacists was calculated. Pharmacists' feedback from the questionnaires was summarized using the same methods as for physicians.

Open-ended questions from physicians and pharmacists were analyzed using thematic content analysis. [25] Responses were categorized using a first order thematic

code developed collaboratively by the 2 researchers. Themes were supported by quotes from at least 2 respondents in the open-ended questions. Themes were used to guide modifications to the template.

Results

Thirty-two physicians and 61 pharmacists provided feedback on the pharmaceutical opinion prototype. Physician responses to the 12 questions on the usability of the pharmaceutical opinion are summarized in Table 1. Overall, there was endorsement of the prototype on all aspects of appearance, layout, design and the quality of the content, with agreement ratings for each item ranging from 84%-97%. Sixteen percent of respondents expressed concern about the length of the opinion and the time required to read it. Twelve percent reported learning no new information. The majority of physicians stated a preference for receiving the pharmaceutical opinion by facsimile (n = 24, 75%), with the remainder requesting contact by phone (n = 9, 28%) or via email (n = 5, 16%).

Pharmacist responses to the 9 questions on the usability of the pharmaceutical opinion are reported in Table 2. Overall, pharmacists endorsed the evidence-based recommendations for the 4 classes of inappropriate prescriptions, with agreement ratings ranging from 93%-98%. When compared to pharmaceutical opinions currently being used in their practice, pharmacists reported that the standardized template was quicker and easier to fill out, was more evidence-based and had a higher probability of leading to prescription change, with agreement rates ranging from 72%-100% for each of these questions. When pharmacists were asked if they would send out the prototype "as is" without changes, 66% indicated that they would for the benzodiazepine prototype, 79% for the first-generation antihistamine prototype, 72% for long-acting sulfonylureas and 69% for the NSAID prototype.

What physicians and pharmacists liked about the deprescribing prototype

The main themes identified included 1) the choice of therapeutic alternatives, 2) clear and concise formatting of the information and 3) documentation of the source and

content of the evidence-based information. Physicians appreciated the fact that multiple alternatives were listed as substitution possibilities and that each option was accompanied by available information on cost, dose, and restricted reimbursement access information. Physicians mentioned that they liked being reminded of the patient's clinical and laboratory parameters, when available, and the principles of treatment goals, as it requires extra time to look up this information from their patient file.

What physicians did not like about the deprescribing prototype

Physicians indicated that: 1) there was insufficient space to provide comments and explanations for their decisions to deprescribe or substitute therapy 2) the information was too dense and 3) the prototype did not allow official authorization for a change in prescription. Leaving space for a physician to sign and write down their license number does not make the opinion an official prescription.

What pharmacists did not like about the deprescribing prototype

Similar to physicians, some pharmacists (n = 12) indicated that too much information was provided in the prototype and that it was too long. The second major concern was disagreement with some of the alternatives presented. Specifically, a few pharmacists (n = 10) were uncomfortable about suggesting alternatives that were not covered by public drug coverage programs, as these options might be unfeasible for some of their patients. Pharmacists also suggested that a statement be added to make the opinion official.

Recommendations for improvement

The main recommendations for improving the design and layout of the prototype were to 1) make the content shorter (1 page if possible) and 2) add space for the physician to write comments and instructions to the pharmacist. With respect to the content, physicians asked that information be provided on how to classify older adults in terms of individual risk (i.e., how to discriminate between frail and non-frail older adults). A few physicians requested information on medication adherence. Both physicians and

pharmacists asked that evidence-based pharmaceutical opinions be developed for other medication classes to assist in decision-making around appropriate prescribing.

Modifications to the deprescribing pharmaceutical opinion

The final, revised versions of pharmaceutical opinions for sedative-hypnotics, first-generation antihistamines, and oral sulfonylurea agents are available online at https://www.deprescribingnetwork.ca/pharmaceutical-opinions. A box for comments was inserted. We also added the following statement for physicians to sign: "I certify that this prescription is an original prescription, that the identified pharmacist is the intended sole recipient and that this original prescription will not be re-used," in order to make the prescription official in Quebec. All critical information including the signature and comment box was placed on the first page. The flipside includes additional information only, making the pharmaceutical opinion functional as a 1-page document.

Discussion

The purpose of the evidence-based pharmaceutical opinion is to educate and empower pharmacists and physicians with the same information in order to promote interprofessional collaboration around deprescribing inappropriate drugs for older adults. Obtaining physicians' and pharmacists' input on the content and format of the evidence-based pharmaceutical opinion led to the development of a standardized template that resonated with both professions' needs. Major issues around knowledge-sharing and licensing to deprescribe were addressed, which may serve to overcome barriers to interprofessional collaboration. [26]

Physicians endorsed the majority of items in the initial prototype, however, there was still variability in preference about the length and content of the standardized template. The diversity in responses likely represents the heterogeneous composition of our convenience sample of respondents. Physicians who provided feedback were from different geographic locations in Quebec. The pharmacists we surveyed also reflect a convenience sample of community pharmacists who agreed to meet with the research team during enrolment in the subsequent D-PRESCRIBE trial, aimed at testing the

effectiveness of the deprescribing opinion on medication discontinuation in older adults. [24] Interestingly, 3 pharmacists were surprised by the amount of information on the first page of the pharmaceutical opinion. These 3 pharmacists reported learning in school that “physicians wanted very short opinions, not more than a sentence or 2.” A small group of physicians (n = 3) confirmed that shorter opinions were preferred in their comments on our survey, however, most physicians appreciated the detailed information provided by the evidence-based clinical practice guidelines and consensus statements. Another source of variability was the choice of recommended alternatives. Some pharmacists endorsed the options that were provided, others disagreed or requested that additional alternatives be added to the list of options. Individual practice patterns are well recognized in the literature, indicated by differences in physicians’ and pharmacists’ behavior patterns around accepting or dismissing automated drug alerts. [27]

Limitations

The physicians and pharmacists who agreed to participate in this study may represent a biased group with interest in interprofessional collaboration and/or deprescribing. As interviews were conducted in person with the pharmacists, social desirability bias may have colored their responses. The denseness of the material in the prototype and unfamiliarity with the form may have elicited initial resistance, which may be overcome over time. Additionally, as we only used the sulfonylurea prototype to obtain initial physician feedback, it is possible that different suggestions may have arisen from pharmaceutical opinions on other types of medications. Furthermore, an electronic prescribing system and eHealth record were not available to all community pharmacists in Quebec in 2014, at the time of this study. Perhaps these methods of communication would be preferred over the more traditional facsimile. Automated and semi-automated approaches to improve prescribing patterns among physicians yield a 56% response rate from physicians. [28]

Further research is needed to test the effectiveness of the evidence-based pharmaceutical opinion for deprescribing inappropriate medications in older adults in a

randomized trial. The D-PRESCRIBE cluster randomized trial aims to achieve this goal and is currently underway. [24] The trial will study the processes and outcomes surrounding the distribution of the evidence-based pharmaceutical opinion, such as the rate of use, return rate, and deprescribing endorsement options. Should the evidence-based pharmaceutical opinion prove beneficial for reducing inappropriate prescriptions among older adults, it could be added to the armamentarium of tools designed to promote deprescribing, including the evidence-based deprescribing algorithms developed by the OPEN group [29] or the EMPOWER brochures distributed by the Canadian Deprescribing Network. [30] The evidence-based pharmaceutical opinion template could then be integrated into pharmacy software in the form of automated alerts. It remains to be established whether it would fall within the mandate of the Canadian Pharmacist Association or each individual provincial professional association to develop and update the templates for each potentially inappropriate drug class.

Conclusion

Both physicians and pharmacists endorse the use of a standardized format for evidence-based pharmaceutical opinions that promote interprofessional communication for deprescribing. The outcomes of the D-PRESCRIBE trial will determine the effectiveness of the evidence-based pharmaceutical opinion on deprescribing processes and outcomes.

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Table 1: Physician feedback on the deprescribing prototype for the pharmaceutical opinion (n=32)

Statement:	Agree (%, 95%CI)
1. The prototype is simple and easy to use	96.9% (84.3-99.5)
2. The information is organized efficiently	93.8% (79.9-98.3)
3. The quality of the information is adequate	96.9% (84.3-99.5)
4. The information is relevant to decision-making	96.9% (84.3-99.5)
5. Certain pieces of information were new to me	87.5% (71.9-95.0)
6. Suggestions and recommendations are clear	96.9% (84.3-99.5)
7. References and citations are useful and easily identifiable	90.6% (75.8-96.8)
8. The time required to read and use the tool was acceptable	84.4 (68.3-93.1)
9. I would use this pharmaceutical opinion to guide my practice	93.8% (79.9-98.3)
10. I believe this prototype would be useful in other clinical contexts	96.9% (84.3-99.5)
11. I would appreciate receiving a pharmaceutical opinion like this one from a pharmacist	90.6% (75.8-96.8)
12. I would modify my prescription following receipt of this information	93.8% (79.9-98.3)

Table 2: Pharmacist feedback on a standardized template for the pharmaceutical opinion (n=61)

Statement:	**%, 95% confidence interval (n=61)**
1. I agree with the recommendations in the benzodiazepine and sedative-hypnotics pharmaceutical opinion	93.4% (84.1-98.2)
2. I agree with the recommendations in the first generation anti-histamines pharmaceutical opinion	98.4% (91.2-100)
3. I agree with the recommendations in the long acting sulfonylurea pharmaceutical opinion	98.4% (91.2-100)
4. I agree with the recommendations in the NSAID pharmaceutical opinion	96.7% (88.7-99.6)
When compared to my regular pharmaceutical opinion, the prototype:	
1. Takes less time to fill out	88.5% (77.8-95.3)
2. Is easier to use	95.1% (86.3-99.0)
3. Is more complete/evidence-based	98.4% (91.2-100)
4. Is more likely to be sent out than regular opinions	77.0% (64.5-86.8)
5. Has a greater chance of having an impact on prescription change	80.3% (68.2-89.4)

8.2 Comparison of Interventions to Reduce Sedative-Hypnotic Prescriptions Among Older Adults in the Outpatient Setting: the EMPOWER vs. D-PRESCRIBE Pragmatic Cluster Randomized Trials

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ABSTRACT

Importance: High rates of sedative-hypnotic prescriptions persist among older adults in many outpatient settings, increasing the risk of adverse drug events and drug-related hospitalizations.

Objective: To compare the effectiveness of two interventions on sedative-hypnotic discontinuation among community-dwelling older adults.

Design: Pragmatic cluster randomized D-PRESCRIBE trial (2014-2016, 6-month follow-up), compared to cluster randomized EMPOWER trial (2010-2012, 6-month follow-up). Community pharmacies randomly allocated to the intervention or control arms in non-stratified groups of 2. Participants were screened and enrolled prior to randomization. Participants, physicians, pharmacists, and evaluators were blinded to outcome assessment.

Setting: Outpatient community settings.

Participants: 299 chronic consumers of sedative-hypnotic medication, aged 66-96 years, recruited from 68 community pharmacies in the D-PRESCRIBE trial: 34 pharmacies randomized to the intervention (145 participants) and 34 to wait-list control (154 participants). Comparison with 148 chronic consumers of sedative-hypnotic medication, aged 61-95, recruited from 15 pharmacies, randomized to the EMPOWER intervention.

Interventions: The EMPOWER intervention is a direct-to-consumer educational brochure on the use of sedative-hypnotic medication. The D-PRESCRIBE intervention consists of an evidence-based pharmaceutical opinion template recommending discontinuation of sedative-hypnotics, provided to pharmacists for distribution to physicians, in addition to the EMPOWER educational brochure on sedative-hypnotics for receipt by patients. Control arm is usual care.

Main outcome: Sedative-hypnotic discontinuation at 6 months post-randomization, ascertained by pharmacy medication renewal profiles.

Results: Two-hundred-and-sixty-three participants (88%) completed the 6-month follow-up in D-PRESCRIBE. 44% of the intervention group discontinued sedative-hypnotic use compared to 7% of controls (risk difference 38%, 95% confidence intervals 28-46%, intracluster correlation 0.012, number-needed-to-treat=3). Neither age greater than 80, sex, duration of use, indication for use, dose, previous attempt to taper or concomitant polypharmacy (10 drugs or more/day) had a significant interaction effect with drug discontinuation. The D-PRESCRIBE intervention significantly surpassed EMPOWER, with a 44% versus 27% discontinuation rate (risk difference 17%, 95% confidence intervals 6-28%, odds ratio 2.29, 95% confidence intervals 1.34-3.92)

Conclusion: Sedative-hypnotic reduction occurs most effectively when community pharmacists broker evidence-based practice tools simultaneously to patients and physicians.

Trial registration: ClinicalTrials.gov identifier: NCT02053194

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Introduction

Sedative-hypnotic prescriptions continue to be dispensed inappropriately to older adults at an alarming rate in many primary care settings worldwide [1-9]. Women aged 85 years and overbear a disproportionate burden of these prescriptions [10-13], with point prevalence estimates exceeding 40% in some populations. [2 10 11 13] Emergency department visits, hospitalizations, and unnecessary costs result when sedative-hypnotics are used, [10 12 14 15] and the risk of opioid overdose doubles [16-22]. Choosing Wisely and the American Geriatrics Society recommend avoidance of benzodiazepines and non-benzodiazepine sedative-hypnotics as first-line treatment for insomnia in older adults in order to prevent drug-induced falls, hip fractures, motor vehicle accidents, death and cognitive impairment. [23-26]

Effective strategies for reducing sedative-hypnotic prescribing rates remain elusive. A gamut of promising practices have been proposed to decrease use among community-dwelling seniors [27], however, initiatives such as drug labeling changes by the U.S. Food and Drug Administration, restricted reimbursement of benzodiazepines, audit, and feedback, and financial incentives to physicians yield little to no evidence of success. [28-31] Randomized trial data confirm that when primary care physicians invite patients to discontinue benzodiazepines, 24- 40% of long-term consumers will cease use within 12 to 36 months. [32 33] The challenge in real-life clinical practice is enabling physicians to extend invitations to patients to initiate benzodiazepine tapering on a regular basis. Deterrents include a lack of awareness on the part of primary care physicians of the scale and impact of medication harms, fear of withdrawal symptoms or patient criticism, perceptions of being ill-equipped to deliver non-pharmacological substitutes, and reported lack of time. [34-38] Pharmacists and patients are key players in the physician-pharmacist-patient deprescribing triad with the potential to overcome these barriers. Medication reviews by a pharmacist followed by direct communication to the physician have been shown to motivate physicians to deprescribe [39-44]. Patients can also drive the deprescribing process when provided with education about sedative-hypnotic harms and safer replacement therapies, as illustrated by the EMPOWER

(Eliminating Medications through Patient Ownership of End Results) trial, but report high rates of physician discouragement and lack of support. [45-47]

The objective of the D-PRESCRIBE (Pharmacist-led Research to Educate and Sensitize Community Residents to the Inappropriate prescriptions Burden in the Elderly) cluster randomized trial was to determine the effectiveness of a two-pronged intervention initiated by pharmacists to simultaneously target both older adults and their physicians to reduce sedative-hypnotic use, and then to assess the added value of the D-PRESCRIBE intervention compared to the EMPOWER tool alone.

METHODS

Design, Setting and Participants

A 2-arm parallel group pragmatic cluster randomized clinical trial was conducted in Quebec, Canada. The D-PRESCRIBE trial protocol has been published [48] and ethics approval for the study was obtained on September 17th 2013. Historical comparison is against the EMPOWER trial (2010-2012), which reported the effect of patient education alone on benzodiazepine reduction at 6-months. [45 46] Cluster randomization prevented contamination between participants in the same pharmacy.

Participants for the D-PRESCRIBE trial were recruited in the same manner as in the EMPOWER trial, through partnership with 3 different pharmacy chains in order to avoid overlap with participants from EMPOWER. For D-PRESCRIBE, 68 community pharmacies (cluster units) were recruited from within a 100km radius of the research center in Montreal, Canada. The complete sampling frame of pharmacies within this radius was obtained from the three collaborating drug chains. Pharmacists were contacted in a systematic fashion for eligibility and interest to participate. Eligible pharmacies consisted of all pharmacies whose clientele consisted of ≥20% older adults and who consented to participate. Members of their clientele who were 65 years and older, and who had an active benzodiazepine or z-drug prescription dispensed for at least 3 consecutive months prior to screening were identified using a computer

algorithm from central pharmacy chain drug claims administrative data. Exclusion criteria were a diagnosis of severe mental illness or dementia, participants unable to communicate in English or French, and those living in assisted-living facilities or meeting the threshold for dementia during baseline data collection (score <24 on the Mini-Mental State Exam [49]). Pharmacists asked all eligible clients to participate in the trial. Those who expressed interest were scheduled for an in-home interview with a research assistant to obtain consent and to collect baseline data on demographics, drug duration and indication, health status using the SF-12 [50], and frailty assessed by the Vulnerable Elders Survey VES-13. [51] Recruitment occurred between February 2014 and November 2016. Neither pharmacists nor participants received any financial compensation from the research team for participating in this study.

Intervention

The D-PRESCRIBE intervention encouraged pharmacists to distribute educational materials about sedative-hypnotics to both patients and their prescribers. Pharmacists handed out or mailed study participants the EMPOWER brochure, a customized 8-page educational brochure with information about why sedative-hypnotics may be inappropriate, potential alternative treatments and a visual tapering protocol.46 Pharmacists were also provided with the template of an evidence-based pharmaceutical opinion, which they were invited to send out to each patient's physician [52] [available at https://www.deprescribingnetwork.ca/pharmaceutical-opinions]. In Quebec, the pharmaceutical opinion is a legal and reimbursable pharmacist act aimed at facilitating pharmacist-physician communication around the quality use of medicines [53]. The standardized template was specifically designed to promote deprescribing for sedative-hypnotic drugs among older adults, by including elements requested by primary care providers during testing [52]. These consisted of a clear rationale for why deprescribing was being recommended, by summarizing evidence about drug harms, listing credible sources of the recommendation, providing a choice of safer therapeutic alternatives and highlighting personalized patient data when appropriate. Due to the pragmatic nature of the trial, pharmacists were afforded flexibility in the way they chose to communicate with physicians. For instance, pharmacists could opt to fax physicians an unmodified version

of the evidence-based pharmaceutical opinion provided to them by the research team or to read the template and adapt their communication in a way that better reflected their daily practice. The D-PRESCRIBE intervention was distributed to each participating pharmacist assigned to the intervention group immediately after randomization, and to the wait-list control group 6-months post-intervention.

Outcomes

The primary outcome was complete cessation of a targeted sedative-hypnotic drug 6 months following randomization, measured at the level of the patient. As with the EMPOWER trial 45, discontinuation was defined by the absence of any prescription renewal at the time of the 6-month follow-up sustained for ≥ 3 consecutive months, in the absence of substitution to another sedative-hypnotic drug class. Dose reduction was defined as a ≥25% dose reduction compared to baseline sustained for ≥ 3 consecutive months. Prescription renewals were determined using participants' pharmaceutical drug claims record. A baseline average daily dose was calculated using pharmaceutical profiles spanning a 6-month period pre-randomization, with all doses converted to lorazepam equivalents using the appropriate dose equivalency chart [54 55]. Two investigators, blinded to group allocation, independently assessed outcomes, with differences adjudicated by a third investigator.

Secondary outcomes were the proportion of participants who reported having a conversation about deprescribing with their physician or pharmacist, the proportion of participants who initiated but failed the deprescribing process, and the reasons why the process was thwarted. Fidelity to the intervention was measured by the proportion of patients who received the EMPOWER brochure, and the numbers and types of pharmacy communications sent to physicians. These data were collected from both participants and pharmacists 6 months post-intervention during in-person interviews held at the participants' homes and at the pharmacist's site of practice. Pharmacists also provided information about the proportion of physicians who replied directly to pharmacists about discontinuing sedative-hypnotics.

Randomization and allocation concealment

A 1:1 allocation ratio was assigned by an independent statistician using non-stratified blocked randomization for every two pharmacies recruited using a random number generator. The trial was labeled as a “medication safety in older adults” and sedative-hypnotics were never explicitly mentioned until receipt of the intervention. As such, both participants and pharmacists remained blinded to the intervention during enrollment. Both pharmacists and their clients were blinded to group allocation by being told that the intervention would be delivered during the ensuing 12-month period.

Sample size

We hypothesized that the D-PRESCRIBE intervention would achieve a rate of discontinuation superior by at least 10% to the 27% discontinuation rate achieved by the EMPOWER trial. The D-PRESCRIBE trial was therefore powered at 80% (2-sided test α level of .05) to detect a minimal 20% difference in sedative-hypnotic discontinuation due to the use of the D-PRESCRIBE intervention compared to usual care alone, and a minimal 10% superior discontinuation rate compared to EMPOWER. Based on EMPOWER, we calculated a coefficient of variation [k] of 0.71, an intracluster correlation (ICC) of 0.012 and an average cluster size of 4.4, which resulted in a maximum design effect of 1.02.

Statistical Methods

The baseline characteristics of the D-PRESCRIBE intervention group, the D-PRESCRIBE control group, and the EMPOWER intervention group were compared with chi-square statistics for proportions and t-tests for continuous variables. To assess the primary outcome, we estimated the risk difference and 95% confidence intervals (CI) via generalized estimating equations (GEEs). We used the participant as the unit of analysis, the pharmacy as the cluster, an exchangeable correlation coefficient to account for clustering effects of participants within each pharmacy, and discontinuation as a dichotomous outcome, assessed for each participant at 6 months post-randomization, for both the D-PRESCRIBE intervention group versus control, and the

D-PRESCRIBE versus EMPOWER intervention groups. Both intent-to-treat (ITT) and per protocol (PP) analyses were performed. Participants who were lost to follow-up were designated as not having discontinued in ITT analyses. GEEs with an identity link and an exchangeable correlation structure were used to account for possible correlation between individuals in the same cluster [56]. The number needed to treat was calculated as the inverse of the difference in absolute event rates between the experimental and control groups [57]. Analyses were performed to estimate risk differences for different sub-groups in the D-PRESCRIBE study using interaction terms in the GEE model under ITT and PP conditions for profiles of participants according to age (younger than 80 years versus 80 years and older), sex, education (high school or less versus college or university), health status (fair and poor versus other), vulnerability (VES-13 score 0-2 or ≥ 3) sedative-hypnotic type (Benzodiazepine, Z-drug), use for insomnia (yes, no), dose equivalent (less than 0.8 mg lorazepam equivalent/day versus 0.8 mg or more) [58], previous attempt at tapering (yes/no), duration of sedative-hypnotic use (less than 5 years or 5 years or more), and number of medications (less than 10/day versus 10 or more). Statistical analyses were run using SPSS 25 as well as R Statistics version 3.4.3 with stats sub-package for GEE.

Results

One hundred and fifty-nine community pharmacies were consecutively contacted over a 3-year period for the D-PRESCRIBE trial. Of these, 70 pharmacies (44%) consented to participate. Participating pharmacists identified 1550 potentially eligible participants; 556 expressed interest in the study and 365 accepted an in-person home interview to assess eligibility and sign consent. In total, 299 eligible participants from 68 clusters were randomized. Figure 1 depicts the study flow of the clusters and the participants for the D-PRESCRIBE trial, as well as reasons for withdrawal. The median number of participants per cluster was 4 (range 1-11).

Two-hundred-and-sixty-three participants were available for 6-month follow-up (88%) in D-PRESCRIBE. Baseline characteristics were similar between participants who withdrew or were lost to follow-up. The mean age (SD) of the participants was 76

(6.8) years, 71% were women and 30% of women were 80 years and older. Thirty percent of participants met criteria for frailty. The most common self-reported indications for taking a benzodiazepine were insomnia (73%) and/or anxiety (36%). Participants used benzodiazepines for a mean duration of 10 years and had an average daily dose consumption of 1.4 mg equivalents of lorazepam (Table 1). In comparison to participants in the EMPOWER study, participants in the D-PRESCRIBE study were more educated, reported worse health status, were more likely to have an indication for insomnia and consumed fewer medications per day (Table 1).

Outcomes

In the D-PRESCRIBE trial, complete cessation of sedative-hypnotics was achieved in 44% (64/145) of intervention participants compared to 6.5% (10/154) of controls in intent-to-treat analyses (risk difference 38% (95% CI, 28%-46%, intracluster correlation 0.012, number-needed-to-treat=3) (Table 2). An additional 8% of intervention recipients achieved dose reduction. Figure 2 illustrates the risk differences for discontinuation of benzodiazepines in subgroups of participants by treatment allocation using ITT analysis. No significant interactions were observed between the intervention assignment and participant age, sex, duration of use, indication for use, dose, previous attempt to taper or concomitant polypharmacy (10 drugs or more/day), suggesting that the effect of the D-PRESCRIBE intervention was robust across predisposing characteristics. Per protocol analyses yielded similar results. Compared to the 27% discontinuation rate of sedative-hypnotics among intervention recipients in the EMPOWER trial (39/145), the D-PRESCRIBE intervention was more than twice as likely to result in cessation of sedative-hypnotic medication (risk difference 17%, 95% CI 6-28%, odds ratio 2.29, 95% CI 1.34-3.92) (Table 2).

Process evaluation

One hundred percent of D-PRESCRIBE participants received the educational brochure. Seventy-three percent, compared to 62% of participants in the EMPOWER trial, discussed deprescribing with their physician and/or pharmacist after receipt of the EMPOWER brochure. Sixty-two percent of D-PRESCRIBE participants, compared to

58% in EMPOWER initiated tapering. Of the 77 individuals who attempted discontinuation in the D-PRESCRIBE trial, 58 (75%) compared to 38 (54%) in EMPOWER were successful.

Withdrawal symptoms were reported by 29 (38%) of individuals in the D-PRESCRIBE trial who attempted to discontinue. Almost all discontinuation failures (n=15) were attributed to an intolerance of withdrawal symptoms and/or recommendations from the health professionals to cease the tapering protocol. No major adverse events requiring hospitalization were reported. The 48 participants who did not elect to initiate deprescribing cited reasons linked to dependence (n=18, 38%), lack of concerns about harms (n=14, 29%), and comfort with taking a small dose (n=11, 23%). In contrast to EMPOWER where physician and/or pharmacist discouragement for initiating tapering was reported as the most common reason not to attempt tapering (n=17, 33%), only 5 (10%) of participants in D-PRESCRIBE cited this reason as an impediment. Similar to EMPOWER all participants appreciated the opportunity to participate in shared decision-making around their medication management. Of the 64 participants who discontinued sedative-hypnotic use, substitutions occurred in 8% of cases (n=5) with participants receiving trazodone (n=3) or amitriptyline (n=2).

Only 62% of pharmacists elected to send a pharmaceutical opinion to the treating physician, three-quarters of which adhered to the recommended evidence-based template (Figure 3). Pharmacists who did not communicate with physicians about deprescribing sedative-hypnotics most frequently cited that it was at the request of the patient (n=20, 26%). Additional reasons included lack of time on the part of the pharmacist (n=12, 25%), preference for a different method of communicating with the physician (n=6, 13%) and difficulties reaching physicians by fax or email (n=4, 8%). Pharmacists who chose to modify the recommended pharmaceutical opinion template included/excluded different alternatives (n=11), added a feature to facilitate reimbursement (n=5) or preferred their own template (n=4).

DISCUSSION

Sedative-hypnotic discontinuation occurred among 44% of older adults 6-months after exposure to the D-PRESCRIBE intervention, whereby community pharmacists were invited to communicate evidence-based information about drug harms to both prescribers and patients. This magnitude of effect is significantly higher than the 27% cessation rate achieved by the EMPOWER direct-to-consumer intervention alone. The effect of the intervention was robust across age, sex, indication, dose, and duration of benzodiazepine use.

Strengths and limitations of the study

The trial design was internally rigorous. Similar to the EMPOWER study, the D-PRESCRIBE trial used cluster randomization to prevent contamination between study arms, and blinded participants, pharmacists and physicians to group assignment. Inclusion and exclusion criteria maximized representation of community pharmacists, and older adults who consume sedative-hypnotics. Recruitment rates for pharmacies (44%) and individual participants (19%) were higher than the respective rates of 18% and 11% rates obtained for EMPOWER, suggesting wider external validity. Unlike other studies of sedative-hypnotic discontinuation, the interventions in D-PRESCRIBE were not delivered to patients being seen in sleep disorder clinics or admitted to hospital, and were not labor-intensive [59 60-62] The pragmatic nature of the trial, which afforded latitude to pharmacists on if and how to communicate to physicians, permitted an assessment of the evidence-based pharmaceutical opinion in real-life practice. Although 25% of pharmacists opted not to send the evidence-based pharmaceutical opinion to physicians, exposure to the information still occurred and may have influenced conversations between pharmacists and patients. Neither participants nor healthcare professionals in this trial received financial compensation unless the pharmacist billed for sending a pharmaceutical opinion. Many healthcare jurisdictions do not have reimbursable methods for pharmacist-physician communication, which may diminish uptake of the intervention. A longer follow-up time and the opportunity to gauge physician perspectives may reveal additional insights about the long-term effectiveness

of the intervention on sedative-hypnotic discontinuation. Additionally, subgroup risk difference analyses may have been underpowered to detect differences.

Relevance of the findings and implication for clinicians

Physician's reluctance to deprescribe sedative-hypnotics for older adults is well-documented [36 63 64]. Pharmacist surveys about geriatric prescribing reveal that pharmacists also lack awareness of the potential harms of sedative-hypnotics for older adults and the availability of non-drug substitutes for the treatment of insomnia. [45 65] Both of these barriers were partially overcome in the D-PRESCRIBE trial through provision of an evidence-based pharmaceutical opinion prototype with information requested by physicians to support discontinuation of sedative-hypnotics. The D-PRESCRIBE intervention initiated 11% more deprescribing conversations than EMPOWER and significantly increased healthcare provider support leading to a successful outcome. The educational information directed at healthcare providers, which referenced the credibility of the source of the recommendation and alternative treatment strategies, likely enhanced physician confidence in support of deprescribing. As 50-68% of older adults express a desire to reduce the number of medications they are taking, with 72-92% indicating they would be willing to do so upon recommendation from their prescriber, [66 67] a compelling opportunity exists for healthcare providers to engage patients in conversations around sedative-hypnotic discontinuation. The value of the pharmacist and patient in shared-decision making processes around deprescribing should not be underestimated.

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Figure 1: Flowchart

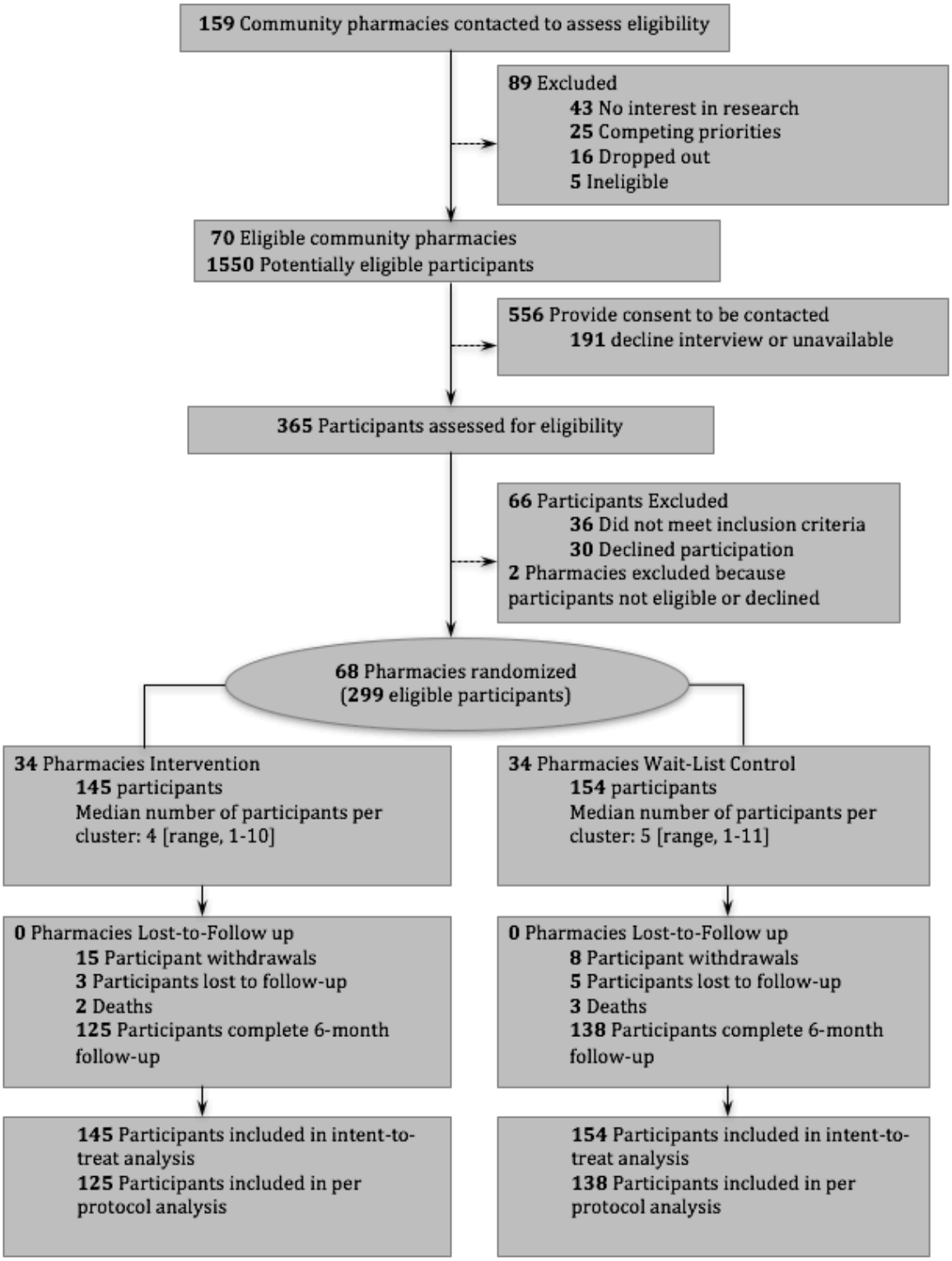


Table 1: Participant characteristics at baseline

Variable	Intervention **(D-PRESCRIBE)** n=145	Control **(D-PRESCRIBE)** n=154	p-value **(D-PRESCRIBE, intervention vs control)**	Intervention **(EMPOWER)** n=145	p-value **(D-PRESCRIBE vs EMPOWER)**
Age in years (mean ± SD, range)	75.9 ± 7.3 (66-96)	75.5 ± 76.4 (66-95)	.571	75.0 ± 6.5 (65-91)	.256
Female (%)	67.6	75.3	.138	70.3	.620
College or university education (%)	48.3	45.5	.625	21.6	.000
Lives alone (%)	40.7	50.0	.106	46.6	.433
Self-reported fair/poor health (%)	13.1	18.2	.228	35.8	.000
Mini-Mental State Examination (mean ± SD, range)	28.8 ± 1.3 (25-30)	29.0 ± 1.1 (25-30)	.185	25.4 ± 2.4 (21-30)[&]	-*
Frail (VES-13 ≥3[560]) (%)	31.7	28.6	.553	-	-
Self-reported indication for benzodiazepine use (%) Insomnia Anxiety Other	73.1 33.8 2.8	72.1 39.0 .6	.445	60.8 45.9 9.5	.008
Mean benzodiazepine dose in mg of lorazepam equivalents/day (mean ± SD, range)	1.4 ± 1.2 (.5-9)	1.4 ± 1.1 (0.4-8)	.656	1.2 ± 0.8 (0-4.8)	.075

Sedative type (%)** Short acting BZD Intermediate acting BZD Long acting BZD Z-drug	27.6 50.3 3.4 18.6	21.4 53.2 5.2 20.1	.595	29.1 66.2 4.7 -	-*
Duration of sedative-hypnotic use (mean number of years ± SD, range)	9.3± 8.44 (0.3-41)	11.3 ± 9.0 (.3-50)	.061	9.6± 8.7 (0.3-48)	.834
Previously attempted cessation (%)	41.2	49.2	.192	45.2	.314
Number of medications/day	8.4 ± 3.8 (1-20)	8.3 ± 3.8 (2-19)	.874	9.9 ± 3.9 (4-24)	.001

* Unable to properly compare group due to difference between studies

** Short-acting benzodiazepines: oxazepam and alprazolam.

Intermediate-acting benzodiazepines: lorazepam, bromazepam, clonazepam, nitrazepam and temazepam.

Long-acting benzodiazepines: flurazepam and diazepam.

Z-drugs: zopiclone, zolpidem

[&] : Montreal Cognitive Assessments score

Figure 2: Risk differences for discontinuation of sedative-hypnotics by subgroups

Subgroup	Risk difference (95% CI)	ICC
Sex		
Men	.48 (0.30-0.62)	.001
Women	.32 (0.21-0.43)	.002
Age, years		
Over 80	.24 (.07-.40)	.008
<80	.43 (.32-.53)	.003
Education level		
University/college	.31 (.11-.49)	.005
High school or less	.40 (.29-.49)	.001
General health status		
Good to excellent	.40 (.30-.49)	0
Poor to fair	.24 (.02-.47)	0
Frailty status		
Frail	.30 (.13-.45)	.007
Non-frail	.41 (.30-.51)	
Sedative type		
Benzodiazepine	.37 (.26-.46)	.001
Z-drug	.42 (.19-.61)	.005
Indication for use		
Insomnia	.36 (.25-.46)	.002
Other reasons	.41 (.24-.57)	.003
Dose		
High (>.8mg/d lorazepam equivalent)	.36 (.26-.46)	0
Low (<.8mg/d lorazepam equivalent)	.44 (.20-.66)	.003
Previously taper attempt		
Yes	.45 (.33-.56)	0
No	.41 (.27-.54)	.002
Duration of sedative hypnotic use, years		
< 5	.37 (.18-.52)	.001
≥ 5	.37 (.25-.48)	0
Number of medications		
< 10	.42 (.29-.53)	.002
≥ 10	.30 (.16-.44)	.003

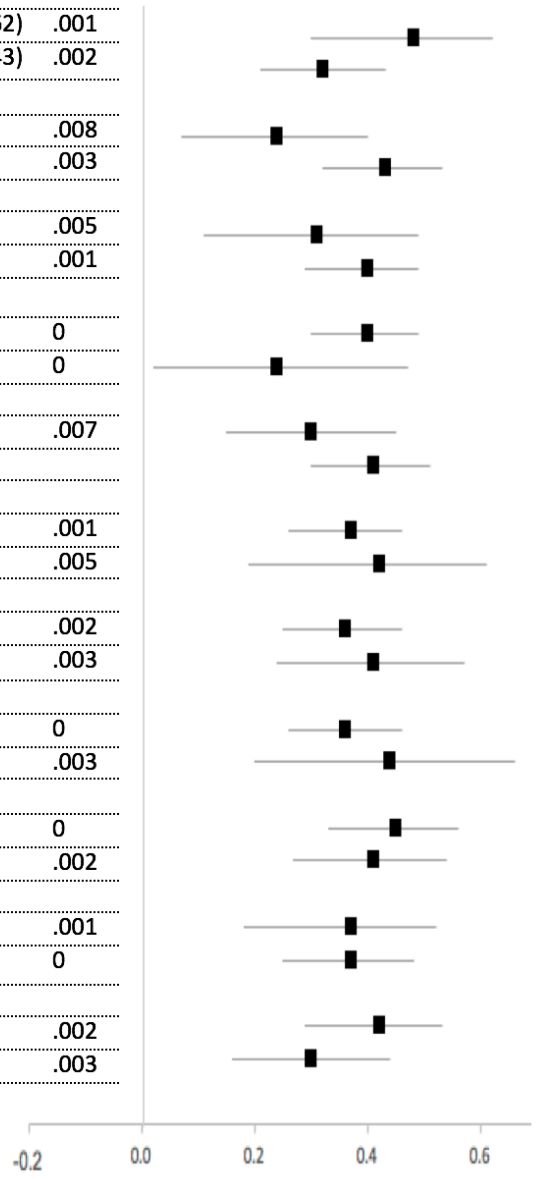


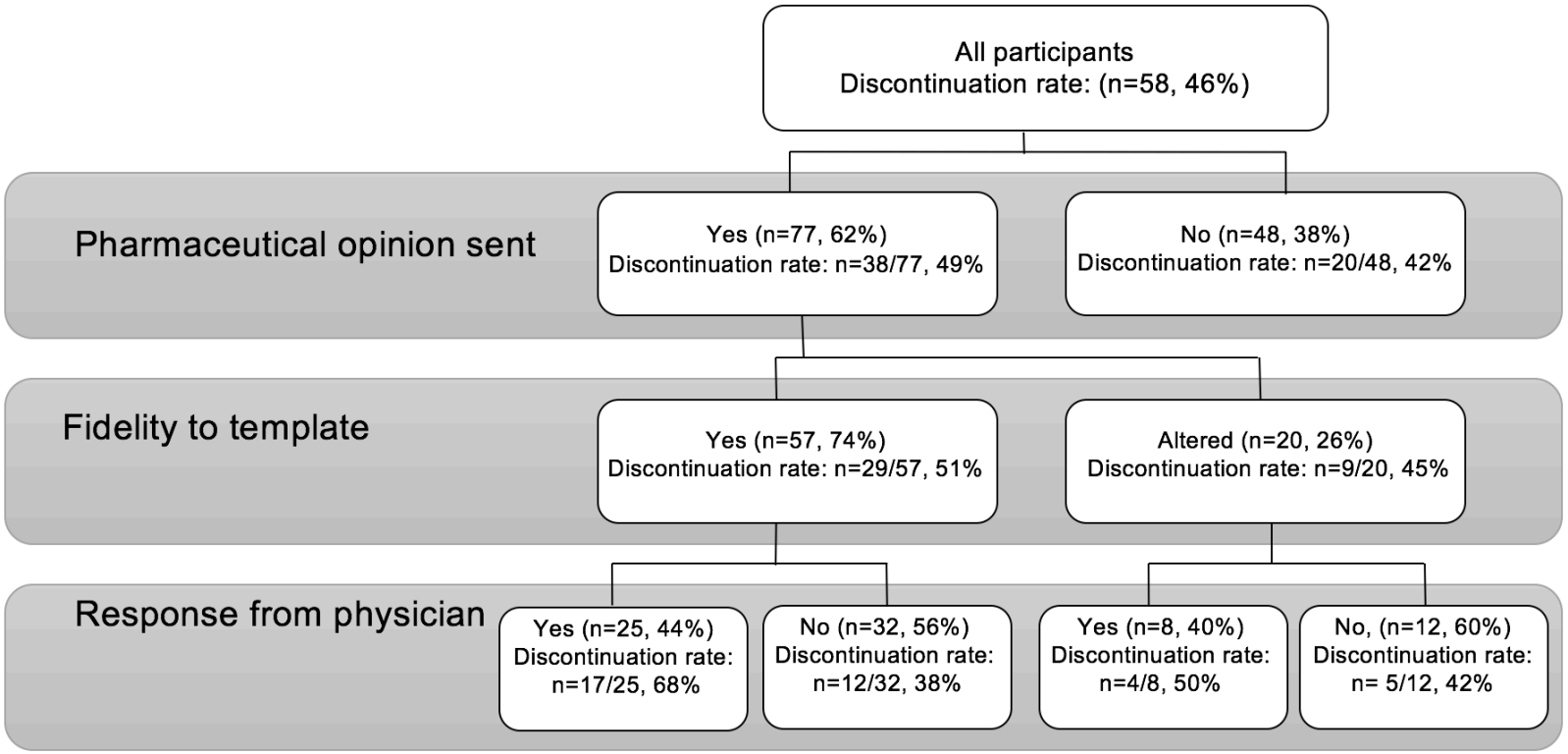
Table 2: Prevalence, risk difference and odds ratios for discontinuation of sedative hypnotics at 6-month follow-up

	Outcome n (%)	Risk difference (95% CI)*	Number-needed-to-treat	Crude OR (95% CI)	Adjusted OR ** (95% CI)
Discontinuation of sedative hypnotic – D-PRESCRIBE					
Intention to treat analysis					
Intervention (n=145)	64 (44.1)	.38		11.38	-
Usual Care (n= 154)	10 (6.5)	(0.28-0.46)	2.63	(5.54-23.37)	
Intracluster correlation		0.012		0.012	-
Per protocol analysis					
Intervention (n=125)	58 (46.4)	0.39	2.56	11.08	-
Usual Care (n= 138)	10 (7.3)	(0.29-0.48)		(5.32-23.07)	
Intracluster correlation		0.044		0.044	-
Discontinuation of sedative hypnotic – D-PRESCRIBE vs EMPOWER					
Intention to treat analysis					
D-PRESCRIBE (n=145)	64 (44.1)	0.17		2.13	2.29
EMPOWER (n=148)	40 (27.0)	(0.06-0.28)	5.84	(1.31-3.48)	(1.34-3.92)
Intracluster correlation		0.005		0.005	0.007
Per protocol analysis					
D-PRESCRIBE (n=125)	58 (46.4)	0.16	6.44	1.94	2.12
EMPOWER (n=123)	38 (30.9)	(0.03-0.27)		(1.15-3.25)	(1.20-3.74)
Intracluster correlation		0.004		0.004	0.008

*95% CI's were calculated using robust standard errors

**Adjusted for education, health status, indication of sedative hypnotic use for insomnia and number of medications.

Figure 3: Pharmacist-Physician Communication during the D-PRESCRIBE trial (per protocol analysis)



Chapter 9 – Discussion

It is now known that Z-drugs and benzodiazepines increase the risk of falls, hip fractures, motor vehicle accidents and cognitive deficits in older adults.[182 186 206 243] As such, they are now being widely recognized as inappropriate for first-line treatment in older adults by all explicit criteria on drugs to avoid in the elderly.[18 25 31-36 47 49 52 561 562] Despite this, there seems to be no end to their use in older adults, with estimated rates of use ranging from 7% to 43%, depending on the country and population studied.[101 104 110-114] Countries such as Israel[109], the United-States[100 116], and Canada[97] have actually seen an increase in sedative-hypnotic use among older adults in recent years.

In an attempt to curb sedative-hypnotic use, a wide variety of interventions have been tested.[6 96 382 389 469 563-565] Several approaches yield insignificant results, however other approaches result in discontinuation rates ranging from 16-25%, such as physician-targeted online drug audits, didactic educational activities and letters from physicians to patients with advisories on the risks associated with benzodiazepine use.[107 376 379 500 566] The latter approaches, while effective, are deemed resource intensive, which reduce their feasibility on a large scale and incur extensive fees.

With current research consisting exclusively of top-down approaches targeting health care providers directly, there existed an important knowledge gap in approaches targeting patients first.[470 471] Patient-centered approaches[474 475] involving shared decision-making for deprescribing[392] were virtually unstudied until the launch of the trials presented in this thesis. Since then, there has been a slow but steady increase in patient-centered deprescribing research.[342 345 473]

The EMPOWER cluster-randomized trial was designed to evaluate the effectiveness of a novel patient-centered approach to deprescribing using a theory-based tool (the EMPOWER brochure) aimed at empowering older adults to act as drivers of safer prescribing practices. The results of the realist evaluation, conducted alongside the EMPOWER trial, helped to understand the deprescribing process from

the patient's point of view in order to improve on the initial success of EMPOWER. The findings from EMPOWER informed the design of the D-PRESCRIBE cluster-randomized trial, where we tested whether a two-pronged educational approach stemming from the pharmacist and consisting of the EMPOWER brochure for patients and of a pharmaceutical opinion to prescribers would improve sedative-hypnotic discontinuation rates by reducing healthcare providers' reluctance to support deprescribing efforts. The current thesis on the deprescribing of sedative-hypnotics in older adults can be therefore summarized by three main research questions that we answered to contribute knowledge in this area. The questions and answers are:

1. **Question: Can older adults serve as a catalyst to initiate the benzodiazepine deprescribing process by equipping them with education about sedative-hypnotic risks and potential alternative treatments to chronic benzodiazepine use?**
   Answer: Yes.
2. **Question: Which contexts and mechanisms have an impact on the success or failure of the deprescribing process from the patient's point of view?**
   Answer: Increasing patient motivation, self-efficacy and capacity to taper benzodiazepines are important mechanisms that influence the success or failure of deprescribing. However, motivations are unstable and can vary according to a number of internal and external contexts that can impede or enable patient engagement at different stages of the deprescribing process.
3. **Question: Can the approach explored in EMPOWER be improved by centering the intervention around pharmacists and adding a second educational component directed at physicians?**
   Answer: Yes.

The findings from this thesis provide important information and insights for family physicians, community pharmacists, other decision-makers (professional societies,

university faculties, and pharmacy/clinic owners) as well as government leaders interested in collaborative practice, and more specifically in patient-centered care around medication safety. In this final section of my thesis, I will review and critically appraise the three projects I conducted and discuss implications for future research and practice.

9.1 Development and evaluation of a direct-to-consumer educational brochure to reduce benzodiazepine use in older adults

9.1.1 Summary of results

First, a theory-based educational brochure for discontinuing sedative-hypnotics targeted at older adults was developed and tested. The textual content of the intervention was based on a systematic review of the evidence as well as guidelines concerning the use of benzodiazepines in the elderly. The initial content of the tool was then validated by a panel of colleagues with expertise in geriatric pharmacy and reviewed by a health librarian to ensure that the wording met standards for patient literacy at the Grade 6 level. To determine the readability and comprehension of the information, the tool was field-tested in six focus groups of older adults (n = 60). Based on the focus group feedback, elements of the tool, such as the wording, ordering of the material and the visual presentation were changed in an iterative process until acceptability was reached. The final result was the EMPOWER brochure (Appendix 2).

Proof of concept

We first tested the brochure's effect in an analysis conducted using a sub-sample of all participants having completed the one-week trial follow-up at the time of analysis (n=144). The primary outcome of the study was a self-reported increase in perception of risk associated with benzodiazepine use following receipt of the intervention. This was combined with changes in knowledge, beliefs, self-efficacy, and intent to discuss the intervention with a healthcare professional. A total of 65 (45.1%) participants reported an increased risk perception post-intervention. This increased risk perception was explained by better knowledge acquisition (mean change score 0.9, 95% CI (0.5, 1.3)),

and a change in beliefs (BMQ differential mean change score 5.03, 95% CI (6.4, 3.6)), suggesting elicitation of cognitive dissonance. Self-efficacy for tapering, (mean change score 31.2, 95% CI (17.9, 44.6)), and intent to discuss discontinuation of benzodiazepine with a doctor (83.1% vs 44.3%, $p < 0.001$) were higher among participants who perceived increased risk. Overall, change in risk perception following receipt of the intervention was much lower than anticipated. We hypothesized that this was most probably due to two factors. The first factor explaining these low rates is the psychological dependence associated with chronic benzodiazepine use[4 565 567 568], which may have created resistance to acquiring new knowledge and denial of risks. The second explanation is participants may already have been fully aware of all the information presented in the brochure but decided to continue taking their benzodiazepine anyway. Despite this, we were able to demonstrate a significant effect of the intervention on participants in line with the underlying theories. This provided us with a proof-of-concept for the theoretical components driving the intervention. Further results would allow us to determine if these changes in participants brought on by the intervention would be sufficient to achieve discontinuation.

As this study was the first of its kind to evaluate a novel approach to benzodiazepine deprescribing, and as some of the measures reported were stand-alone questions rather than validated questionnaires, it is difficult to compare our results to other studies. Our findings were nonetheless similar to another study on benzodiazepine discontinuation where the majority of participants rejected the first suggestion of discontinuation.[5] In another study of breast cancer risk, only 50% of participants changed risk perceptions when presented with an educational intervention.[569] Change in risk perception has been shown to affect how receptive participants are to the intervention[570], which supports the underlying theories behind the intervention as well as the observed results.

EMPOWER trial

In order to evaluate the effectiveness of the EMPOWER brochure, we conducted a cluster-randomized trial. A total of 303 chronic users of benzodiazepine medication

aged 65-95 years were recruited from 30 community pharmacies. 15 pharmacies representing 148 participants were randomized to the educational intervention whereas the other 15 pharmacies representing 155 participants were randomized to wait-list control. Two-hundred-and-sixty-one participants were available for 6-month follow-up (86%). There was no difference in the baseline characteristics of participants who withdrew or were lost to follow-up between or within trial arms. At baseline, participants were mostly women (69%), had an average age of 75 years, and one quarter (23.8%) had earned a college degree. The most common self-reported indications for taking a benzodiazepine were insomnia (60%) and/or anxiety (48%). Participants used benzodiazepines for a mean duration of 10 years and had an average daily dose consumption of 1.3 mg equivalents of lorazepam. 62% of recipients in the intervention group initiated a conversation about benzodiazepine cessation with a physician and/or pharmacist, while 58% actually attempted discontinuation. At six months, 27% of the intervention group had discontinued benzodiazepine use compared to 5% of controls (risk difference 23%, 95% confidence intervals 14-32%, intracluster correlation 0.008, number-needed-to-treat=4). Dose reduction occurred in an additional 11% (95% confidence intervals 6-16%). Main reasons for not attempting to cease the medication consisted of discouragement by their physician or pharmacist (33%), followed by fear of withdrawal symptoms (25%), lack of concern about taking benzodiazepines (23%), and difficult life circumstances (12%). Overall, these results suggest that direct-to-consumer education successfully leads to discussions with a health care provider to stop unnecessary or harmful medication and leads to discontinuation or dose reduction of benzodiazepines in over one-third of cases.

At the time of publication, the EMPOWER study was the first of its kind to target the patient as a driver of safer prescribing practices. While patients are now recognized as critical players in the successful outcome of deprescribing processes[431], traditional approaches to deprescribing focused almost exclusively on primary care providers.[6 7 373-375] Following the publication of these results, there has been an increased interest in patient's role in the deprescribing process and in developing additional patient-centered approaches to deprescribing.[341 345] The direct-to-consumer educational approach

yielded similar results to other types of brief interventions by physicians on patient discontinuation of benzodiazepines, as well as pharmacist-initiated communication with general practitioners to de-prescribe potentially inappropriate medication.[6 469 571] With an odds ratio for discontinuing benzodiazepines after exposure to the brochure of 8.05 (95%CI = 3.51-18.47) our intervention seems more promising than pooled estimates of other types of interventions to discontinue benzodiazepines such as gradual dose reduction studies (OR=5.96, 95%CI = 2.08-17.11), brief interventions (OR=4.327, 95%CI = 2.28-8.40), psychological treatment plus gradual dose reduction (OR=3.38, 95%CI = 1.86-6.12) or substitutive pharmacotherapies (OR=1.30, 95%CI = 0.97-1.73).[469] It is worth noting that, in comparison to EMPOWER, these other studies were not conducted exclusively in the geriatric population, with some study populations consisting of mainly of motivated individuals already seeking care in sleep disorder clinics. Few studies of benzodiazepine discontinuation interventions in older adults exist, but of the ones that do, interventions consisting of substitution and psychological support[461-463] have yielded success rates upwards of 80%. However, both studies had very small sample sizes, recruited motivated participants and offered physician support in a supervised clinic setting, which is difficult to reproduce on a large scale in the real-world setting.[388] Additionally, high initial rates of discontinuation dropped to 30% 12-months post-intervention.[463] Studies on physician supervised dose tapering[572] and cognitive behavioral therapy[464 466] also yielded impressive results ranging from 33-80%, however, these again suffered from the inclusion of motivated subjects, low sample size and intensive resources required for follow-up. The most similar intervention at the time of publishing was a resource-intensive study where the intervention consisted of a medication review by a geriatrician plus patient education with gradual tapering compared to usual care, which yielded a 35% (n=12/34) discontinuation rate at 12 months.[384] At the time of publication, the EMPOWER brochure was considered a huge success because of its high discontinuation rate, ease of use, low resource requirements, and simple translation into other languages for distribution. Obstacles to discontinuation, either from failure to initiate or failure to complete the discontinuation process, matched patient and physician barriers to deprescribing reported in the literature.[341 388] From disagreement with the need for deprescribing to fear of withdrawal

and lack of support, it became clear that these barriers impeded the impact of the intervention.

9.1.2 Strengths and weaknesses

Proof of concept study

Strengths of this study include systematically measuring participants' knowledge, beliefs and risk perception about benzodiazepine safety. We used the previously validated specific section of the beliefs about medications questionnaire (BMQ-specific)[573], which we adapted to benzodiazepines to measure beliefs. Limitations mostly stem from the use of other un-validated measurements. As few to no validated instruments exist to measure benzodiazepine knowledge and risk perception, questions to measure these concepts were developed by the research team at face value, with simple, un-validated yes/no answers, and no formal construct validity or psychometric testing. Additionally, the concept of cognitive dissonance was not measured directly but was inferred indirectly according to an operational definition of cognitive dissonance predicated upon a positive change in knowledge and beliefs.[574] A second major weakness of this study stems from a flaw in the original hypothesis. We assumed that all benzodiazepine consumers are unaware of the risks associated with benzodiazepines. However, our study revealed that many chronic benzodiazepine users are indeed aware of the associated risks but prefer to continue the medication due to psychological dependence or fear of withdrawal.[4 341 430] As such, a ceiling effect existed for gains in knowledge and risk perception. Not all participants could be influenced by the intervention in the same way, as not all of them had the potential to gain knowledge or change their perception of risk. We pursued this discovery later on during the realist evaluation.[449] Finally, as one of the questions on the benzodiazepine knowledge questionnaire was on risks associated with benzodiazepine use and as risk perception was the outcome, there is a possibility that the increased knowledge observed in the RISK group is, at least in part, associated with the outcome, further limiting the interpretation associated with a change in knowledge. These limitations constrain the internal validity of study findings. In terms of external validity, benzodiazepine users in the study were typical of chronic users in other studies[4 565 567 568], however, conclusions

are limited to community-dwelling older adults and are not generalizable to frailer patients living in health care facilities or long-term care.

EMPOWER cluster-randomized trial

The first and major strength of this trial is that it exclusively targeted seniors over the age of 65 and was the first to address sedative-hypnotic deprescribing by targeting the consumer with educational materials, rather than the physician[107 380 389 500 501 575]. The second major strength of the trial is the robustness of the cluster randomized design, which is critical in the evaluation of health services in order to prevent contamination between study arms.[487 491 515] The use of a wait-list group[513] and the pragmatic nature of the trial are other advantages[514]. Additionally, recruitment of patients before the randomization of study clusters allowed us to avoid a selection bias previously observed when patients are recruited following randomization.[515-518] Finally, the low rates of loss to follow-up in both study arms solidifies the validity of the observed results by limiting the potential selection bias due to individuals completing the trial differing from those who did not. Additional strengths of this study include the systematic approach to recruitment and blinding of pharmacists and participants which allowed us to minimize selection bias, thus limiting the over-representation of motivated individuals versus unmotivated individuals. The main outcome was measured using objective pharmacy profile analysis by two independent investigators blinded to group assignment, which increases internal validity. The third major strength of this trial was that groups were balanced for baseline data and were similar to other chronic benzodiazepine user populations.[565] Finally, our use of generalized estimating equations is the most reliable statistical method to account for the correlated nature of cluster-randomized clinical trials.[497-499]

The major limitation of the EMPOWER trial lies in the fact that despite our best efforts, recruitment rates for pharmacies (18%) and individual participants (11%) were low and excluded potential participants with major neurocognitive disorders. This suggests that selection bias with a potential over-representation of motivated individuals could have occurred, which is not truly representative of the general chronic

benzodiazepine user population. However, we estimate that this type of bias was unlikely due to the systematic nature of recruitment procedures and as neither pharmacists nor participants were aware of that the primary outcome of the study was benzodiazepine discontinuation. An alternative and more likely explanation is that very few patients and pharmacists have the time or desire to participate in research studies. A second limitation consists of the relatively short duration of the 6-month follow-up time. While similar to the duration of follow-up in some studies[96], this time frame is much shorter than other studies with follow-up periods of up to three years[107 576], which can unmask relapse rates or even detect additional discontinuations in participants still actively working on the tapering process. While we did estimate effect measures of individual subgroups, caution should be taken interpreting these values as sub-group analyses may have been underpowered to detect differences. In addition to the potential confounders we tested such as sex, age, dose etc. we were unable to directly measure the impact of known potential confounders such as socio-economic status prescriber characteristics, hospitalizations or volume of initial prescription[104] due to the design of the study. However, we believe that the randomization and design used in the study serve to greatly limit this potential for confounding and that it does not significantly impact the validity of the conclusion presented. Cursory content analysis of the events that followed receipt of the intervention may have been limited by patient recall and the non-intimate nature of the 6-month telephone follow-up. The process of shared-decision making around benzodiazepine discontinuation, and physicians' motivations for counseling against benzodiazepine discontinuation could not be evaluated as there was no direct contact with physicians during the trial.

9.1.3 Implications for practice and future research

Our results indicate that the aging consumer may be an under-utilized catalyst of change for reducing potentially inappropriate prescriptions. Supplying chronic users with evidence-based information that allows them to question medication overtreatment appears safe and effective. Our research reinforces the notion that patients play a critical role in the deprescribing process.[431] This is supported by research in other fields that shows that patient-centered care improves patient satisfaction, quality of life,

adherence and overall health outcomes.[399-401] The majority of patients wish to be involved in medical decision-making processes, even if the final decisions are taken by their physicians.[398] [399] By having patients initiate and drive conversations around deprescribing benzodiazepines, it is certain that patients will be involved in a shared decision-making process, which has been deemed critical by health care professionals considering to medication discontinuation.[350] [477]

While EMPOWER provided proof of concept that directly targeting consumers as drivers of safer prescriptions can be effective for reducing medication risk, several challenges and opportunities also became apparent. First, we learned that many physicians were reluctant to change inappropriate prescriptions. Second, we realized that not all participants had the same reaction to the intervention. Third, we recognized that pharmacists were greatly under-utilized as a resource in the deprescribing process by participants. Finally, we came to understand that if the de-prescribing process were to become sustainable over the long-term, a new paradigm would have to be entrenched within the pharmaceutical sector and involve the prescriber, the patient, and the pharmacist. All of these considerations led to the design of the D-PRESCRIBE trial.

The uptake of the EMPOWER brochure in practice has exceeded expectations. It is now posted free for download on the Canadian Deprescribing Network website and is being used in many countries. In Canada, several clinics leave copies in patient waiting rooms and Choosing Wisely Canada® has based their patient tool for deprescribing sedative-hypnotics on the EMPOWER brochure. In the US, the American Geriatrics Society Pharmacy Special Interest Group posts links to the brochure on their own website. It has also been adopted by Veterans Affairs in the US to reduce sedative-hypnotics among Veterans with post-traumatic stress disorder, and in Australia for use by the Australian Deprescribing Network. Several research teams have contacted us to adapt and translate the brochure for use in other research studies. The EMPOWER brochure is mentioned regularly in mainstream media. Although it is difficult to track these metrics, we believe that the EMPOWER study has the potential to have an important impact on practice worldwide.

9.2 Identifying mechanisms and contexts responsible for the success and failure of the intervention

9.2.1 Summary of results

Potential impact of cognitive impairment

The first step towards understanding why the intervention succeeded or failed was to explore whether mild cognitive impairment had an impact on the effect of the intervention. This was for two reasons. First, sedative-hypnotic use is associated with cognitive impairment and may contribute to mild neurocognitive disorders in older adults[18 122 162], meaning we can expect a significant portion of chronic sedative-hypnotic users[4,577 578] to suffer from mild cognitive impairment. Second, data show that individuals with mild cognitive impairment may demonstrate deficits in their ability to understand, reason and participate in health-related decisions.[579] Medical decision-making capacity tends to decline over time.[580] We, therefore, had some concern that the EMPOWER brochure might be less effective in individuals with mild cognitive impairment. We conducted a post-hoc analysis of all participants having completed the EMPOWER study follow-up (n=261) and divided them based on their cognitive function, with 122 participants meeting MOCA criteria for mild cognitive impairment[581]. In the end, complete discontinuation of benzodiazepines was achieved in 39 (32.0% 95% CI = 24.4-40.7) participants with mild cognitive impairment and in 53 (38.1% 95% CI = 30.5-46.4) with normal cognition (adjusted OR 0.79, 95% CI [0.45-1.38]). Compared to individuals with normal cognition, mild cognitive impairment had no effect on the acquisition of new knowledge, change in beliefs about benzodiazepines or elicitation of cognitive dissonance. Additionally, cognitive status had no impact on knowledge acquisition, change in beliefs, self-efficacy or decision to discuss the intervention with a healthcare professional.

Interestingly, these results are not in line with previous research showing that individuals with mild cognitive impairment perform significantly worse in multiple aspects of medical decision-making than individuals with normal cognition. [579 580 582] As cognitive impairment is part of the risks detailed in the intervention, we hypothesized that this may

have acted as an enabler to deprescribing[341], with individuals with mild cognitive impairment recognizing drug-induced symptoms and buying into our recommendation that discontinuing sedative-hypnotics may help improve memory and attention. Alternatively, participants with cognitive impairment may have shown the brochure to family members, who encouraged them to deprescribe.[341] Deciding whether to try tapering benzodiazepines is not a terribly complex decision, which is also why our findings may contradict previous research on more serious medical decisions. The good news is that clinicians can be encouraged to use the EMPOWER brochure to engage their patients with mild cognitive impairment in shared decision-making despite declining cognitive status.

Realist evaluation

The realist evaluation aimed to provide us with a better understanding of the factors which played a role in the success and failure of the EMPOWER educational intervention. We tested the three pre-established mechanisms driving the intervention and investigated the contexts that led to positive and negative deprescribing outcomes. This was accomplished using a sequential mixed methods approach. Quantitative data was obtained from the same subsample of all participants from the EMPOWER study having completed the study mentioned above (n=261). Qualitative data was obtained using semi-structured interviews in 21 participants selected strategically using a contrast sample design. The intervention triggered the motivation to deprescribe among 167 (n=64%) participants, demonstrated by improved knowledge (risk difference, 58.50% [95% CI, 46.98%-67.44%]) and increased concern about taking benzodiazepines (risk difference, 67.67% [95% CI, 57.36%-74.91%]). Those who attempted to taper exhibited increased self-efficacy (risk difference, 56.90% [95% CI, 45.41%-65.77%]). Contexts where the deprescribing mechanisms failed included lack of support from a health care provider, a focus on short-term quality of life, intolerance to withdrawal symptoms, and perceived poor health. Overall, our findings support the theory that provision of new knowledge about medication harms can raise concern and augment patients' self-efficacy to deprescribe. However, the analysis also indicates that human motivation to deprescribe is complex and unstable. A variety of internal and

external contexts can interfere with the decision to deprescribe. Internal influences include perceptions about one's health status, long-term health goals, fear of symptom recurrence, and psychological attachment to the drug. The main external influence that blocks consumer-directed deprescribing mechanisms is the lack of support from a health care provider.

The realist review contributes to the body of literature on patient barriers and enablers in the deprescribing process. Similar to results from a systematic review of patient barriers and enablers to deprescribing, we were able to confirm the impact of certain contexts in our study[341]. This included but was not limited to barriers such as lack of primary care support[366 370 436-439 443 444], fear of the deprescribing process[4 366 370 432 434-440 442-444 446] and external influences.[4 366 370 432 434-440 442-444 446] In addition to observing known barriers and enablers to the deprescribing process, we also observed a barrier specific to sedative-hypnotic use consisting of psychological dependence, which has previously been described.[5 430] Finally, we were also able identify new potential enablers and barriers to the deprescribing process in the reported contexts of "positive outlook on aging vs a focus on quality of life during end-of life" as well as "currently stable health status vs poor health".

9.2.2 Strengths and weaknesses

Potential impact of cognitive impairment

The major strength of this study is that is the first study of its kind to explore the association between mild cognitive impairment and the success rates of a patient-centered educational deprescribing intervention in a community-based clinical trial of older adults. The major weakness in this study lies in the fact that the study was not designed specifically to answer this research question, leading to some methodical flaws. The first methodological flaw is the use of a post-hoc design, which exposes the analysis to the well-documented limitations and dangers of subgroup analyses[583 584]. Post-hoc analyses do not conform to the population nor the randomization model of statistical inference. As such, observed differences may be nothing more than simple coincidence.[585] The second major methodological flaw lies in the definition used to

categorize participants as having mild cognitive impairment. As only individuals with a MOCA score of 21 or more were included in the original trial, our results are only generalizable to patients with mild-to-moderate mild cognitive impairment since we excluded the lower spectrum (19-20), which overlaps with early dementia. Additionally, we did not re-measure scores on the MOCA at study endpoint, so were unable to ascertain whether cognition improved after discontinuation. It is also worth pointing out that extensive multivariate analyses were run considering all of the determinants detailed in table 1, with none of the variables other than those associated with MCI at baseline having a significant impact. For the sake of brevity in the article, we only mentioned adjusting for those factors in our analysis, however all determinants were first evaluated and subsequently discarded and only variables significant to $p<0.05$ were left in the adjusted model. Finally, while our study was powered to detect a 15% difference in discontinuation between participants with mild cognitive impairment compared to those with normal cognition, the observed difference was only 6.1%, which gives the study a power of 17.55%. In order for our study to achieve 80% power for the observed 6.1% difference to be significant would have required a sample size of 2104 participants. However, while a study with more participants may have been able to detect a significant difference between participants with mild cognitive impairment compared to those without, the conclusion that patients with mild cognitive impairment still greatly benefit from the intervention with one third stopping their medication would still be valid as baseline discontinuation rates rarely exceed 5% (as described earlier). While a slightly smaller percentage of patients with mild cognitive impairment may stop their medication, it is still quite effective to use this type of approach in this sub-population.

Realist evaluation

The overall main strength of the realist evaluation lies in having taken a robust traditional black-box approach, [528-530] linking the data from a cluster randomized trial to a white-box approach (the realist evaluation)[528 533 535 536] in order to gain a better of the processes underlying the intervention, which is rarely done. An in-depth description of the methodological strengths and weakness of mixed methods studies and the realist

evaluation approach were covered in detail in Chapter 6. In addition, strengths and weaknesses specific to this realist evaluation have already been discussed in section 7.4. In summary, the use of mixed-methods allowed us to increase the robustness of the results observed in the EMPOWER study, while also enabling us to explore dimensions uncaptured by the quantitative data analysis alone.[553] Weaknesses of the study include the fact that as realist evaluation has a relatively narrow scope in the face of the infinite number of possible influencing factors[528], it is almost certain that other mechanisms and contexts trigger motivation to deprescribe beyond what is described and what we were able to capture with our interview questions in this realist evaluation of benzodiazepines. Additionally, another challenge we experienced during the conduct of this realist evaluation was differentiating between the mechanisms and contexts associated with deprescribing, as definitions of the concepts are still debated in the literature.[548] Finally, we recognize that realist evaluations rarely provide a complete explanation of all possible patterns of outcomes but rather provides mid-range theories such as those produced in our refined CMO configuration that require further testing.[528]

9.2.3 Implications for practice and future research

Potential impact of cognitive impairment

Our report illustrates that the EMPOWER brochure can be distributed to community-dwelling older adults with mild cognitive impairment and still work, whether directly through patient comprehension of the material or through the support of caregivers or family. The EMPOWER tool can and should be used in primary care or memory clinics for chronic benzodiazepine users who are candidates for deprescribing sedative-hypnotic medication. Future research on the topic should aim to design the study around cognitive function rather than a post-hoc analysis and should include additional questions evaluating the deprescribing process in order to verify whether or not mild cognitive impairment is compensated for by other enablers of deprescribing.

Realist evaluation

Our realist evaluation contributes to further cycles of inquiry and ongoing theoretical development about the patient's experience of deprescribing. It also provides

proof of the value and importance of conducting realist evaluations alongside large-scale clinical trials. Being the first realist evaluation to explore the deprescribing process from the patient's perspectives, this study may allow physicians and pharmacists to gain a better understanding of the challenges faced by their patients when deprescribing a medication. This, in turn, may allow them to better address some of the patient barriers to deprescribing, while also understanding the role they have to play as an enabler in the process. Future research should aim to see if the model proposed can be faithfully reproduced in the deprescribing of medications other than benzodiazepines.

9.3 Development and evaluation of a combined approach to deprescribing sedative-hypnotics where pharmacists simultaneously educate patients and prescribers

9.3.1 Summary of results

Development of the pharmaceutical opinions

As the intervention required an educational component to be sent to prescribers, we drew upon existing methods of communication between pharmacists and prescribers in Quebec. We decided to use the pharmaceutical opinion program, which has been around for decades in Quebec[586] to facilitate communication around the quality use of medicines.[587] While standardized clinical documentation exists for pharmacists to draft pharmaceutical opinions in Ontario,[588] no such guidance is available in Quebec. We, therefore, had to develop a model for communication using pharmaceutical opinions that would effectively convey information between physicians and pharmacists about drug harms and potential solutions. We initially developed a prototype for a pharmaceutical opinion partly based on Ontario's standard format[588] with lessons learned from evidence-based trials testing different ways of presenting the relative benefits and harms of competing therapeutic approaches.[589 590] We then sought input from a convenience sample of 32 primary care physicians and 61 primary care pharmacists. The majority of physicians (84%-97%) requested that the source of the deprescribing recommendations be cited, that alternative management options be provided, and that the information be tailored to the patient. Sixteen percent of

physicians expressed concern about the information in the opinions being too dense. Pharmacists also questioned the length of the opinion and asked that additional space be provided for the physician's response. A statement was added making the opinion a valid prescription upon receipt of a signature from physicians. Compared to a non-standardized opinion, the majority of pharmacists believed the template was easier to use, more evidence-based, more time efficient and more likely to lead to deprescribing. Overall, use of such a standardized format for evidence-based pharmaceutical opinions was endorsed by both physicians and pharmacist as an effective method to promote interprofessional communication for deprescribing.

Unfortunately, very little information is available on how pharmaceutical opinions are used in Quebec or what their effect is.[591 592] A recent study in Ontario demonstrated a response rate to pharmaceutical opinions of 57% (n=50/87) by physicians[593], which is similar to previously observed rates of 56%.[379]

D-PRESCRIBE cluster-randomized trial

In order to test the effectiveness of our novel two-pronged educational approach stemming from the pharmacist, we conducted the cluster-randomized trial titled D-PRESCRIBE. 299 chronic users of a sedative-hypnotic medication aged 66-96 years, were recruited from 68 community pharmacies (34 randomized to the educational intervention (n=145 participants) and 34 randomized to wait-list control (n=154 participants)). Two-hundred-and-sixty-three participants (88%) completed the 6-month follow-up in D-PRESCRIBE. 44% of the intervention group discontinued sedative-hypnotic use compared to 7% of controls (risk difference 38%, 95% confidence intervals 28-46%, intracluster correlation 0.012, number-needed-to-treat=3). The D-PRESCRIBE intervention significantly surpassed EMPOWER, with a 44% versus 27% discontinuation rate (risk difference 17%, 95% confidence intervals 6-28%, odds ratio 2.29, 95% confidence intervals 1.34-3.92). 62% of pharmacists elected to send a pharmaceutical opinion to the treating physician, three-quarters of which adhered to the recommended evidence-based template. Reasons given for not sending out a pharmaceutical opinion were: at the request of the patient (n=20, 26%), lack of time on the part of the

pharmacist (n=12, 25%), preference for a different method of communicating with the physician (n=6, 13%) and difficulties reaching physicians by fax or email (n=4, 8%). Overall, the D-PRESCRIBE intervention was shown to be significantly more effective than the approach tested in EMPOWER and was robust across multiple factors.

The comparisons between the EMPOWER trial and other studies in the literature also apply indirectly to the D-PRESCRIBE study. Since the initial publication of the EMPOWER results, there have been more studies about discontinuing chronic benzodiazepine use. Notable examples include studies by Bourgeois et al.[460], Kimura et al.[120] and Vicens et al.[576] In the case of Bourgeois et al., this was a pilot prospective observational study where the intervention consisted of physician-initiated and supervised tapering and led to 25/38 (65.8%) of participants to discontinue their sedative-hypnotic use, and 7/38 (18.4%) participants to reduce their dose at 2 months.[460] The Bourgeois study reinforces that patients respond when physicians initiate deprescribing. However, the study consisted mainly of motivated physicians selecting motivated patients and suffers from a small sample size. In 2016, Vicens et al. published results from a cluster-randomized trial on benzodiazepine discontinuation in primary care.[576] At 36 months, 66/168 patients (39.2%) in the structured intervention with written stepped-dose reduction, 79/191 patients (41.3%) in the stepped-dose reduction and follow-up visits group, and 45/173 patients (26.0%) in the control group had discontinued BZD use.[576] Limitations in comparing this study to our results lie in the long duration of the follow-up and the fact that the population did not consist exclusively of older adults. The baseline discontinuation rate of 26% after 36 months in the control group indicates a large difference in spontaneous discontinuation not attributable to the intervention. When comparing the 6-month D-PRESCRIBE results to their 12-month results, we notice their approximate 45% discontinuation rate in the intervention groups in comparison to 15% in their control group for a risk difference of 30%, which is similar to the D-PRESCRIBE risk difference of 38%.[576] Finally, a recent interesting prospective observational study released from Japan by Kimura et al. reported on the effectiveness of an intervention that identified inappropriate medications by pharmacists, who then recommended discontinuation to the prescribing physicians. This led to the

discontinuation of inappropriate benzodiazepines in 37% of cases (n=75/205).[120] The intervention was initiated by a pharmacist, similar to D-PRESCRIBE, but a comparison between the two studies is difficult because of the design and patient population. Participants in the Kimura study were recruited from hospitals and patients were carefully selected by pharmacists. This greatly limits the generalizability of the results and comparability to our study.

9.3.2 Strengths and weaknesses

Development of the pharmaceutical opinions

Strengths of this study include its careful approach to addressing multiple known barriers to deprescribing among pharmacists and prescribers, such as interprofessional communication, lack of knowledge or having the proper tools and necessary time.[388 395] By standardizing, automating and facilitating the pharmaceutical opinion process, we aimed to simultaneously increase the quality of services provided without increasing the workload of pharmacists and physicians. Weaknesses in this study include the fact that we used the prototype from a single medication class to obtain initial physician feedback. It is possible that different suggestions may have arisen from pharmaceutical opinions on other types of medications. It is worth noting that the initial evidence-based pharmaceutical opinion was based on the deprescribing of the oral sulfonylurea hypoglycemic agent glyburide and not on benzodiazepines. This was done purely for practical reasons as D-PRESCRIBE covered four separate medication classes and thus four pharmaceutical opinions were developed on the same concept. At the time of validation, we looked for an opportunity to have the opinions evaluated by a group of physicians. The earliest and best opportunity we were presented with was to run a focus group during a continuing professional development day amongst general practitioners seeking clarification on diabetes management in the elderly. As such it was deemed more appropriate to have them evaluate the pharmaceutical opinion on long acting sulfonylureas rather than benzodiazepines. Physicians and pharmacists who agreed to participate in this study may represent a biased group with interest in interprofessional collaboration and/or deprescribing. As interviews were conducted in person with the pharmacists, social desirability bias may have coloured their responses. The denseness

of the material in the prototype and unfamiliarity with the form may have elicited initial resistance, which could be overcome with time.

D-PRESCRIBE cluster-randomized trial

As with EMPOWER, the trial design was internally rigorous. As previously discussed, the methodological considerations listed in chapter 6, as well as those described in section 9.1.2 for the EMPOWER trial, apply equally to the D-PRESCRIBE trial. In comparison to EMPOWER, we limited the number of potential participants per participating pharmacy, which reduced the workload on participating pharmacists, thus increasing participation rates while simultaneously decreasing the chances of intra-cluster correlation. Recruitment rates for pharmacies (44%) and patients (19%) were higher than the respective 18% and 11% rates observed in EMPOWER, suggesting a lower potential for selection bias. Inclusion and exclusion criteria were kept to a minimum to keep the study as pragmatic and as representative of community-dwelling older adults as possible. As pharmaceutical opinions were only sent out in 62% of cases, with a quarter of those being modified, we did not have as much sample size to determine the effect of the pharmaceutical opinion alone. In retrospect, using a factorial design and removing the pragmatic component of the trial, which afforded pharmacists flexibility in their communication with physicians, would have enabled a better understanding of the impact of the pharmaceutical opinion and to determine if their effect was additive or synergistic with the EMPOWER brochure[594]. On the flip side, we believe that the pragmatic nature of the trial makes the results of the D-PRESCRIBE study more generalizable to real-life clinical practice.

9.3.3 Implications for practice and future research

Development of the pharmaceutical opinions

Our study provides pharmacists with a standardized format for evidence-based pharmaceutical opinions to recommend deprescribing inappropriate medication in older adults, which was endorsed by both physicians and pharmacists. The template addresses some of the pharmacist and prescriber barriers to deprescribing by providing them with the necessary tools and information to support their patients in the

deprescribing process.[341] [388] In the face of the ever-expanding scope of pharmacist services in Canada, the development, and implementation of such standardized evidence-based tools may lead to an increase in the services offered by pharmacists and lessen physician's burden of optimizing medical management.[393] [394] Not all healthcare jurisdictions reimburse pharmacists for sending out pharmaceutical opinions, which limit widespread uptake and implementation.

Future research should aim to test the effectiveness of such standardized pharmaceutical opinions on deprescribing processes and outcome. Additionally, research should focus on increasing the uptake rate of pharmaceutical opinions. The fax system is not an ideal method of communication between pharmacists and physicians as faxes can get lost, forgotten or ignored by one or both parties. As the electronic health record and electronic prescribing systems become mainstream, it may be easier to automate the template and more readily use it in e-prescribing and e-deprescribing systems.

D-PRESCRIBE cluster-randomized trial

The findings from the D-PRESCRIBE trial confirm that pharmacists can play a significant role in managing patients' health.[394] With the expansion of the scope of pharmacy practice in the past few years, pharmacists are now able to provide more services than ever across Canada.[394] Evidence provided by the D-PRESCRIBE trial will help inform governments and professional societies that pharmacists can broker the deprescribing process by addressing both patient and prescriber barriers to deprescribing.[341] [388] [395] With growing recognition of the need for interprofessional collaboration in healthcare management, pharmacists are stepping up to rightly share some of the physician's burden of optimizing medical management.[393] [394] Their value and accessibility as an intermediary/ mediator between the patient and the physician in the shared decision-making process around deprescribing should not be underestimated.[395]

Future research should fall in the realm of implementation science, in order to investigate scale and spread of the D-PRESCRIBE intervention in deprescribing efforts in other settings, provinces, and countries.[379] We designed the intervention in a way that it should be easy to scale-up and be implemented on a provincial, national or even international level using systems already in place. For example, both pharmaceutical opinions and patient brochures can easily be implemented into pharmacy software and distributed to entire chains at a moment's notice. However, it is important to note that depending on how the intervention is used in everyday practice, it may not be sustainable. In fact, as in previous cases, the overuse of the educational material may lead to physicians and patients being bombarded with material and eventually lead patients and physicians to ignore alerts as it was with other computerized decision support interventions.[376] [379] While the role and impact of the pharmacist on the deprescribing process is gaining momentum, future efforts should also focus on identifying pharmacists' barriers and enablers in the deprescribing process as there is little research on the subject.[395] Additionally, the effect of the D-PRESCRIBE intervention on other types of inappropriate medication needs to be explored to evaluate the transferability of the effect. Finally, the next logical step in researching approaches to benzodiazepine discontinuation in older adults would be to evaluate the impact of successful discontinuation on both patient health outcomes and the economic impact of such an intervention in order to justify its large-scale implementation and reimbursement as an official service offered by pharmacists.

Chapter 10 – Conclusion

This thesis discussed the development and evaluation of novel patient-centered approaches to deprescribing sedative-hypnotics in older adults. We provided proof-of-concept that a simple educational intervention was sufficient to impact chronic sedative-hypnotic's user's perceptions of the risks associated with benzodiazepines. In the EMPOWER study, one out of every four participants receiving the intervention discontinued their medication. Post-hoc analysis of our results demonstrated that the intervention was equally successful among participants with mild cognitive impairment. We then conducted a realist evaluation, which helped us identify and target barriers and enablers to the deprescribing process from the patient's perspective. One modifiable barrier was discouragement from pharmacists and physicians to initiate and sustain deprescribing. To help patients obtain support from healthcare providers, we developed the evidence-based pharmaceutical opinion to educate pharmacists and physicians on sedative-hypnotic harms and substation therapies. The D-PRESCRIBE trial revealed that as expected, a two-pronged educational approach brokered by the pharmacist to patients and their physicians was even more successful than the patient-centered approach alone by diminishing physician reluctance to deprescribe during patient-initiated conversations.

Results from this thesis support the need and importance of involving all three stakeholders in the deprescribing triad. We first demonstrated that patients can play a key role in catalyzing and initiating deprescribing. We then showed that pharmacists can be critical communication mediators between the prescriber and the patient to ensure that everyone is, literally, on the same page. Finally, while the physician has always played an essential role in the deprescribing process, there is a growing recognition that deprescribing sedative-hypnotics is somewhat out of their comfort zone and that they need tools and support to be able to fully engage in shared decision-making with their patients.

Future efforts should focus on evaluating the transferability of the EMPOWER brochure and evidence-based pharmaceutical opinion template to other types of inappropriate prescriptions. Scale up and spread to other contexts, provinces and countries will require adaptation and an appreciation of the value patients and pharmacists can bring for managing health and medication use. We hope these approaches will eventually be implemented on a large scale through government level policies or by integrating the educational resources within automated quality indicator systems in electronic prescribing software.

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Appendix 1

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TRIALS

STUDY PROTOCOL Open Access

An educational intervention to reduce the use of potentially inappropriate medications among older adults (EMPOWER study): protocol for a cluster randomized trial

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Abstract

Background: Currently, far too many older adults consume inappropriate prescriptions, which increase the risk of adverse drug reactions and unnecessary hospitalizations. A health education program directly informing patients of prescription risks may promote inappropriate prescription discontinuation in chronic benzodiazepine users.

Methods/Design: This is a cluster randomized controlled trial using a two-arm parallel-design. A total of 250 older chronic benzodiazepine users recruited from community pharmacies in the greater Montreal area will be studied with informed consent. A participating pharmacy with recruited participants represents a cluster, the unit of randomization. For every four pharmacies recruited, a simple 2:2 randomization is used to allocate clusters into intervention and control arms. Participants will be followed for 1 year. Within the intervention clusters, participants will receive a novel educational intervention detailing risks and safe alternatives to their current potentially inappropriate medication, while the control group will be wait-listed for the intervention for 6 months and receive usual care during that time period. The primary outcome is the rate of change in benzodiazepine use at 6 months. Secondary outcomes are changes in risk perception, self-efficacy for discontinuing benzodiazepines, and activation of patients initiating discussions with their physician or pharmacist about safer prescribing practices. An intention-to-treat analysis will be followed.

The rate of change of benzodiazepine use will be compared between intervention and control groups at the individual level at the 6-month follow-up. Risk differences between the control and experimental groups will be calculated, and the robust variance estimator will be used to estimate the associated 95% confidence interval (CI). As a sensitivity analysis (and/or if any confounders are unbalanced between the groups), we will estimate the risk difference for the intervention via a marginal model estimated via generalized estimating equations with an exchangeable correlation structure.

Discussion: Targeting consumers directly as catalysts for engaging physicians and pharmacists in collaborative discontinuation of benzodiazepine drugs is a novel approach to reduce inappropriate prescriptions. By directly empowering chronic users with knowledge about risks, we hope to imitate the success of individually targeted anti-smoking campaigns.

Trial registration: ClinicalTrials.gov identifier: NCT01148186

Keywords: Patient education, Benzodiazepine use, Inappropriate prescription, Older adult health, Cognition disorders, Drug therapy, Polypharmacy

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Background

Appropriate and safe prescribing for older adults is rendered difficult by the increased risk of side effects, drug-drug interactions and adverse events, due to associated comorbidities and high prevalence polypharmacy in this population [1,2]. Prescriptions are considered inappropriate when potential risks outweigh potential benefits, and safer therapeutic alternatives exist that have similar or superior efficacy [3-5]. Avoiding the use of inappropriate and high-risk drugs is an important, simple and effective strategy in reducing medication-related problems and adverse drug events in older adults [5]. The Beers Criteria for Potentially Inappropriate Medication Use in Older Adults identifies, grades and qualifies potentially inappropriate medications. The criteria were developed by a panel of geriatric pharmacy experts who applied a modified Delphi method to a systematic review of all medications and graded the evidence to reach a consensus on a recommended list of drugs to avoid in older people [5-7].

Currently, far too many older adults are taking inappropriate prescriptions, which further increases the risk of adverse drug reactions and unnecessary hospitalizations [5,8-11]. Inappropriate prescribing has been estimated to occur in 12 to 40% of community-dwelling non-hospitalized older adults aged over 60 years, depending on the criteria used and the country studied [3,5,9-14]. A conservative estimate of the incremental healthcare expenditures related to inappropriate prescribing among community-dwelling older adults is $7.2 billion in the United States [12].

Benzodiazepines represent one of the most prevalent inappropriate prescriptions, consumed by 19% of older adults (range 10 to 42%) [15]. The new Beers list, released in 2012, recommends that all short- and long-acting benzodiazepine sedative-hypnotic drugs used for the treatment of anxiety and insomnia should be avoided in older adults, due to an excessive risk of delirium, falls, fractures and motor vehicle accidents [5,16-19]. Benzodiazepines have also been shown to increase the risk of amnestic and non-amnestic cognitive impairment and may lead to incident dementia [20,21].

Previous research has attempted to define the best strategy to inform and educate relevant parties, to try and implement safer prescribing practices, and to eliminate benzodiazepine use. The problem is that chronic benzodiazepine users develop a psychological dependence to benzodiazepines, and both physicians and consumers have difficulty implementing tapering protocols [22]. Many patients deny or minimize side effects, or express reluctance to risk suffering without these medications [22]. For these reasons physicians are hesitant about insisting on benzodiazepine discontinuation for fear of upsetting the doctor-patient relationship or because they believe that the patient tolerates the medication with minimal side effects [23].

Interventions to reduce benzodiazepine use in older people have been tested [24-47]. Several approaches have yielded insignificant results; other approaches, such as physician-targeted online drug audits, didactic educational activities and letters from physicians advising on risks associated with benzodiazepine use, have resulted in discontinuation rates ranging from 16 to 25% [43-47]. Despite achieving mild success in benzodiazepine discontinuation, these approaches are rarely feasible on a large scale and can be linked to extensive fees.

Targeting consumers directly as catalysts for engaging physicians and pharmacists in collaborative discontinuation of benzodiazepine drugs is a novel approach to reduce inappropriate prescriptions that has never been tested. Studies have shown that collaborative efforts to taper benzodiazepine use do not result in an increased workload for family physicians [48]. This type of approach could empower patients to participate in medication safety, diminish physician workload and do so at lower costs than current approaches in changing medical practice.

The aim of the current cluster randomized controlled trial is to determine the effectiveness of an educational tool directed at older adults on subsequent cessation of benzodiazepine use.

Methods/Design

Trial design

Study objectives

The primary objective of the EMPOWER trial is to evaluate the effectiveness of a new knowledge transfer tool on a community-based sample of chronic benzodiazepine users, as measured by the rate of benzodiazepine discontinuation at 6 months with 1-year follow-up, to determine whether change rates are sustained over the long-term. The acronym EMPOWER stands for "Eliminating Medications through Patient OWnership of End Results".

Secondary objectives are to determine whether receipt of a knowledge transfer tool by chronic benzodiazepine users changes risk perceptions and self-efficacy for discontinuing benzodiazepines, and leads patients to initiate discussions about safer prescribing practices with their physician or pharmacist.

Design

This is a cluster randomized controlled trial. The rationale for choosing a cluster design is to prevent contamination across the intervention and control arms by individual clients served by the same pharmacy. The cluster and unit of randomization is the community pharmacy. There are two arms in this parallel randomized controlled trial: the educational intervention arm and the control arm. A 50:50 ratio of participants will be used in each study arm. Figure 1 illustrates the study flow.

Study site: clusters and characteristics

The study is being conducted in the greater Montreal area in Quebec, Canada. Collaboration with a drugstore chain was established, and all pharmacies within a 3-hour driving radius (approximately 200 km) of Montreal were identified and listed. Pharmacies were listed in random order by a computer generated program, contacted sequentially and screened for eligibility criteria. Clusters consist of community pharmacies with ≥20% older adults. In order to prevent small or empty clusters, pharmacies with ≤50 eligible participants following the initial screening process are not recruited to the trial.

Study population

The study population comprises chronic benzodiazepine users aged 65 years and older.

Eligibility criteria for individual patients to enroll in the study

Selection of participants will be according to the following inclusion and exclusion criteria.

Inclusion criteria

1. Men and women aged 65 years and older.
2. With at least five active prescriptions (polypharmacy).
3. Of which one is an active benzodiazepine prescription that has been dispensed for at least 3 consecutive months prior to screening, based on pharmacy records.
4. Patients who are willing to participate in the study.

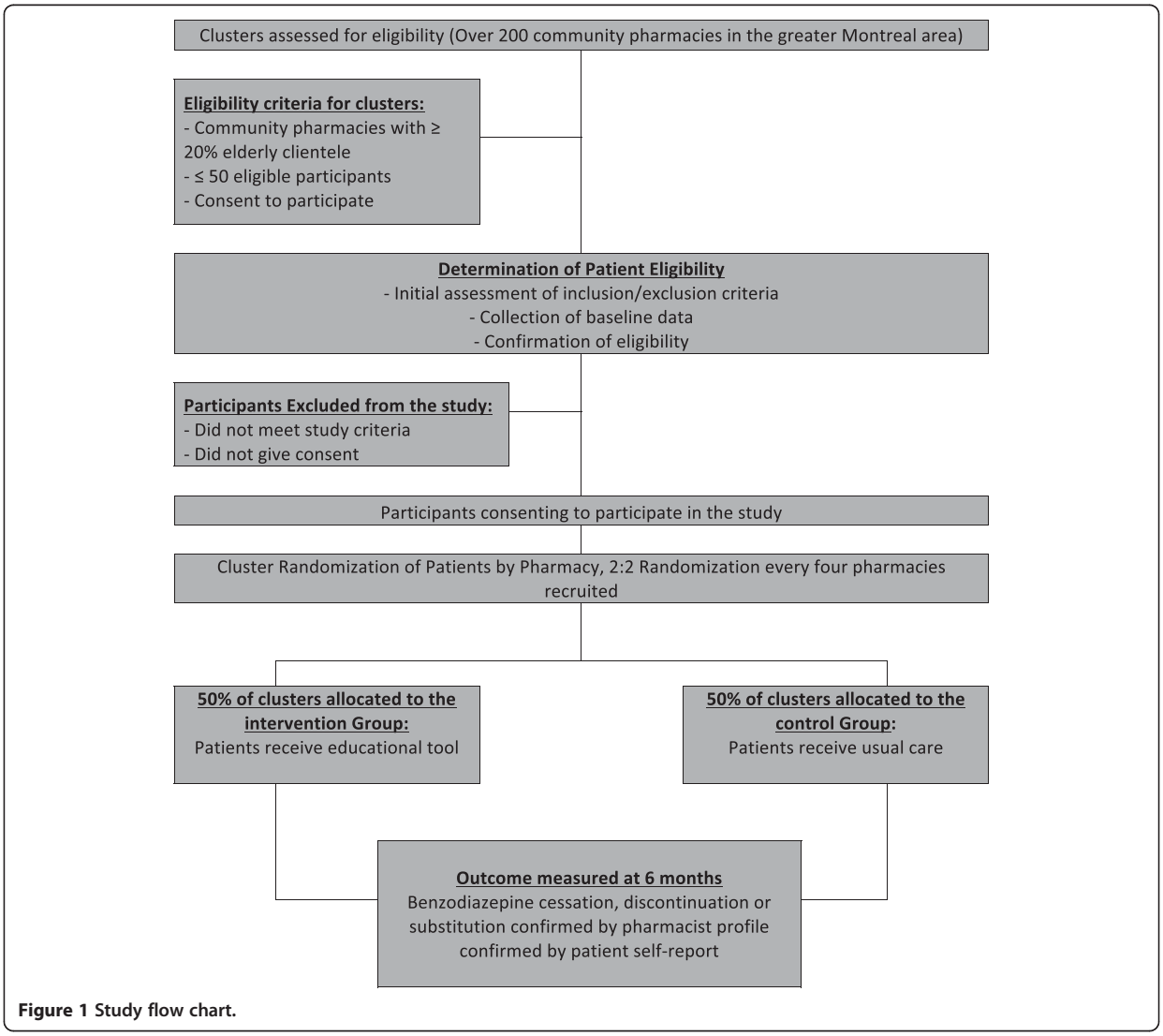

Figure 1 Study flow chart.

Exclusion criteria

1. A diagnosis of severe mental illness or dementia ascertained by the presence of an active prescription for any antipsychotic medication, and/or a cholinesterase inhibitor or memantine in the preceding 3 months.
2. Unable to communicate in French and/or English.
3. Evidence of significant cognitive impairment (score under 21 on the Montreal Cognitive Assessment (MoCA) [49]).
4. Patients living in a long-term care facility.

Ethical approval

The study protocol was approved on 26 July 2009 by the Research Ethics Board of the Centre de Recherche de l'Institut Universitaire de Gériatrie de Montreal, Canada (ClinicalTrials.gov identifier: NCT01148186).

Enrollment

Enrollment in the trial is conducted in collaboration with a regional pharmacy chain. A letter from the vice-president of the chain was sent to all affiliated pharmacies inviting pharmacists to participate in the trial by recruiting eligible clients served by their medication dispensing units. Company headquarters then identified a list of all chain drugstores within a 3-hour driving radius of the research center and sent a list to the research team. This list was sorted in random order by a computer generated program and pharmacies are contacted systematically to ascertain their interest in participating in the study. Pharmacies interested in participating are supplied with a list of eligible participants identified from the company's centralized electronic database by a preset inclusion/exclusion filter that applies all inclusion and most exclusion criteria. Any pharmacy found to have less than 50 potential candidates is excluded from the project to avoid small or empty clusters. Otherwise, pharmacies are enrolled in the study and proceed with participant recruitment.

Recruitment of participants and application of eligibility criteria

Recruitment of participants occurs through a three-step screening process. First, pharmacy clients are filtered by the company's centralized computer system using preset eligibility criteria for age and medication use. Second, participating pharmacists receive a list of eligible clients with a matching set of personalized name and address labels from company headquarters through internal mail, and are asked to review the list to exclude patients with undetected dementia or those living in care facilities. Using the final list of potential participants, pharmacists tally the numbers and contact the research team to request an appropriate number of English and French study invitational materials intended for mailed distribution to participants.

Invitational materials consist of a headquarters pre-approved invitation letter personalized on behalf of the pharmacist and an accompanying brochure describing a study on 'better drug management'. The flyer invites participants to contact either their pharmacist directly or the study coordinator by phone if they have any questions or are interested in participating in the study. Letters and invitations are put in envelopes by the pharmacy personnel, affixed with the address labels provided by company headquarters and mailed to all eligible participants.

One week after sending out the invitations, the pharmacist notes all replies spontaneously received from potential participants indicating their willingness or refusal to participate in the study. The pharmacist then calls the remaining candidates to ascertain their interest in participating in the study and, if so, to obtain permission to give their names and phone numbers to the study coordinator. According to protocol, a maximum of three phone calls and voice messages must be attempted over a 2-week time period in order to reach participants, after which time potential participants are declared not interested. All affirmative responses are recorded by the pharmacist, and the names and phone numbers of interested clients are transferred to the research staff at the end of the 3-week period following the invitation mail-out to participants.

The study coordinator then contacts all potential participants referred by the pharmacists (with the client's permission) and arranges an appointment at the person's residence to complete the third screening stage: signed consent if eligible and collection of baseline data. During the home visit, a research assistant reviews the medication currently taken by the patient, queries the medical history and administers the MoCA. Signed consent to participate in the study is then obtained from individuals who meet the study criteria after baseline cognitive and health status screening. All baseline data are collected from the questionnaires indicated in Table 1 under T0 at this time.

Randomization

Randomization

A statistician, blinded to pharmacy and cluster size, generates a random allocation sequence using computer generated random digit numbers. For every four pharmacies recruited, a simple 2:2 randomization is used to allocate the four clusters into intervention and control groups. Towards the end of recruitment, randomization might be skewed to favor the least populated study arm to allow the desired 50:50 allocation ratio.

Concealment of allocation

Prior to random allocation into either arm of the study, informed consent, agreement to enroll in the study and

Table 1 Overview of data collection and measurements in both trial arms

	Baseline	Follow-up post-intervention			
Visit number	T0	T1	T2	T3	T4
Time	**1-7 months pre-intervention**	7 days	6 weeks	6 months	1 year
Inclusion and exclusion criteria	X				
Socio-demographic characteristics	X				
SMAF questionnaire	X				
GHS questionnaire	X				
MoCA	X				
Rey 15-Item Memory Test	X				
GAI	X		X	X	X
Depression PHQ-9	X[a]		X	X	X
Insomnia questionnaire	X[a]		X	X	X
Medication use characteristics	X				
Benzodiazepine tapering questionnaire		X	X	X	X
Medication knowledge questionnaire	X	X			
BMQ-Specific	X	X			
Self-efficacy scale	X	X			
Intervention related questionnaire		X	X	X	
Intervention appreciation questionnaire				X	

[a]Only administered if related outcome present. BMQ-Specific, Beliefs about Medicines Questionnaire - Specific segment; GAI, Geriatric Anxiety Inventory; GHS, general health status; MoCA, Montreal Cognitive Assessment; PHQ, Patient Health Questionnaire; SMAF, functional autonomy measurement system.

ascertainment of eligibility will all be obtained from the pharmacists and their clients. Up until the point of randomization, neither the research assistant, the cluster representative (the pharmacist), nor the client will know the allocation of the clusters. After randomization, only the research assistant will be aware of treatment allocation. Pharmacists and participants will not be informed, and will remain unaware of the fact that there is another group in the study; nor will they be informed of the procedures for the other arm. Participants' link to the project will be the pharmacist, but participants of the same pharmacy will not normally be in contact with each other. Randomization is performed in clusters to prevent bias in case this happens. Therefore all participants from the same pharmacy will be randomized as a single cluster, thereby receiving the same treatment and remaining blinded to treatment allocation.

Blinding

As the intervention is educational in nature, blinding of the intervention is impossible. However, to preserve a certain level of blinding and to protect sources of bias, the following measures are taken.

For participants, blinding is achieved by presenting the project to participants as a project on optimizing medication management. Consenting participants understand that their medication profiles will be transmitted to the research team within the following months and that they will receive a customized letter at some point during the year which may contain recommendations for change, which they can then decide to take to their physician or pharmacist for discussion.

For pharmacists, blinding is achieved by presenting the same study timeline. Pharmacists are aware that their clients will receive an intervention at some point during the following year and remain blinded to group allocation throughout the course of the study. Pharmacists also remain blinded to other participating pharmacies. Since pharmacies are randomized as clusters, they are located in distinct geographic locations and generally have no reason to interact with one another.

Thus, blinding pertains to both the individual and cluster level.

The educational intervention

The educational intervention consists of a seven-page letter-size paper brochure developed specifically for this trial. The language for the intervention is set at a grade six reading level and written in 14 point font to facilitate accessibility of the material. The brochure is mailed to the intervention group within 1 week of group allocation. The control/wait-list group receives the educational tool 6 months later. As the intervention is sent individually to participants and participants within each cluster are

unknown to one another, the intervention only pertains to the individual participant.

Theory and development of the intervention

The tool aims to promote active learning by using constructivist learning theory principles, incorporated during the development of the intervention. Constructivist learning theory activates users to create new knowledge in order to make sense out of the presented material. The goal of this approach is to allow the learner to interact with the academic material, fostering their own selecting, organizing and information integrating processes [50]. Many other learning theories were integrated in the different parts of the intervention, such as cognitive dissonance, social comparison, peer champion theories and self-assessment theory. Cognitive dissonance theory confronts two inconsistent cognitions held simultaneously by the same individual. This process aims to create an aversive motivational state in the individual who will then seek to alter one of these perceptions to remove the pressure caused by this conflict [51]. The tool also includes elements of social comparison and peer champion theories [52]. Social comparison consists of comparing oneself to others in order to evaluate or enhance personal aspects [53]. Thus, the evaluation of the ability or inability to accomplish a certain action depends on a proxy performer's success. The efficacy of social comparison depends on whether the comparer assimilates or contrasts him/herself to others [52]. Thus, aspects such as previous agreement with the peer's views and comparability with the peer champion are paramount for the comparison to work [53]. A self-assessment component was also introduced to promote insight about potential misinformation or beliefs held about benzodiazepine use [54,55]. A common idea in models of risk perception is that risk is perceived from two dimensions: knowledge of and beliefs. Information about the risks associated with benzodiazepine use was therefore in incorporated into the tool. It has also been shown that pre-existing beliefs frequently supersede information transfer about risks [56]. In order to understand the drivers and consequences of risk perception the behavior motivation hypothesis was used. This hypothesis, which is endorsed by most models of health behavior, describes the determinants of risk perception and their effects on behavior change [57]. It is important to note that perception of risk has been shown to be positively related to preventive health behavior in conditions where expectations of success in dealing with the risk are acceptable and when recommendations for preventive behavior are presented as effective [58].

The textual content of the intervention was based on guidelines concerning the use of benzodiazepines in older people as well as a systematic review of the evidence. The initial content of the tool was drafted by a geriatrician and graduate student, and then validated by a panel of colleagues with expertise in geriatric pharmacy. Following validation, a health librarian reviewed the content to ensure that the wording met standards for patient literacy. The tool was initially developed in English then backward-forward translated into French.

Components of the intervention

The cover page of the brochure has an image of a pillbox filled with several medications titled 'You May Be At Risk', followed by 'You are currently taking (name of benzodiazepine)'. Brochures are customized according to each patient's medication profile. The first page of the intervention lists four true or false questions regarding the safety, side effects, withdrawal symptoms and alternatives to the use of the benzodiazepines, and is entitled 'Test Your Knowledge'. The second page contains the correct answers as well as an explanation for each statement. The goal is to create cognitive dissonance and challenge the patient's beliefs for each incorrect answer by incorporating elements of constructivist learning theory into the answers. The third page incorporates a self-assessment component as well as educational facts on potential inappropriate use, side effects, drug-drug interactions and information about physiological changes that occur with age that affect drug metabolism. Suggestions for equally or more effective therapeutic substitutes, as well as evidence-based risks associated with benzodiazepine use in older people, are presented on the fourth and fifth pages. The sixth page highlights one woman's success story in weaning herself off benzodiazepines. The last page outlines a simple 21-week tapering program that can be adapted to the patient's medication use. For contrast and visual enhancement, visual such as color shading and several pictures of older adults and medication are used throughout the tool. In order to make sure the intervention is used appropriately, the words 'Please Consult your Doctor or Pharmacist Before Stopping Any Medication' appear as a warning in large lettering on four different occasions throughout the tool.

Acceptability of the intervention

To determine the readability and comprehension of the information, the tool was field-tested in six focus groups of older adults (n = 60). Based on the focus group feedback, elements of the tool, such as the wording, ordering of the material and the visual presentation were changed in an iterative process until acceptability was reached.

Study arms

Participants allocated to the experimental group receive the written educational program via mail immediately following randomization. Telephone follows-ups are conducted 1 week, 1 month, 6 months and 1 year post-intervention, and last 5 to 10 minutes. Participants in

the control 'wait-list' group are monitored during the first 6 months following randomization and then receive the same intervention as the experimental group.

Study outcomes

Outcomes are measured at all study follow-up points. At baseline, questionnaires are completed at the participants' homes during an interview with the research coordinator. Follow-up is by telephone interview with the same coordinator. Self-reported socio-demographic variables, health status variables and prescription details are collected at baseline.

Primary outcomes

Prescription change rate at 6 months

The primary outcome of the study is cessation of benzodiazepines in the 6 months following receipt of the intervention, ascertained by pharmacy renewal profiles and confirmed by patient self-report. A 1-year follow-up will be undertaken to determine whether change rates are sustained over the long-term. The definition of discontinuation will be an absence of any benzodiazepine prescription renewal at the time of the 6-month follow-up. Dose reductions will also be measured and will be defined as ≥50% reductions in the renewal profile for at least 3 consecutive months beginning at the time of the 6-month follow-up. The discontinuation/dose reduction rate among participants in the experimental arm will be compared to the discontinuation/dose reduction rate among participants in the control arm. In this way we will be able to determine the absolute rate of discontinuation attributable to the intervention. This outcome measure pertains to the individual level.

The 6-month period and 1-year follow-up were chosen because although there is no agreement on the time frame of change, the trans-theoretical model supposes that, typically, once people start thinking about changing their behavior, decision and planning of the action is usually done within the following 6 months. Maintenance of the new behavior begins after 6 months of being in the active stage of changing and continues for at least 6 months [59]. Pharmacy profiles, supplied monthly by fax to the research center by the pharmacist, were chosen to measure prescription change rates because of the high amount of information they contain. Pharmaceutical profiles vary in the information they contain between pharmacies of the same chain depending on the owners. However, vital information to determine change rates, such as the date of renewal, the dose and the quantity of the prescription are always listed. Using this objective measure allows comparison and validation of patient reported outcomes, and thus more accurately and objectively determines the effect of the intervention.

Secondary outcomes

Change in risk perception

Change in perception of risk associated with benzodiazepine use will be evaluated through a self-reported measure, along with change in knowledge and change in beliefs. The self-reported measure will consist of participants answering whether they perceived the same, increased or no risk from consumption of their benzodiazepine medication after having read the brochure, and will be collected 1 week post-intervention. Change in knowledge will be measured by comparing the pre- and post-intervention (T1) answers from the four true or false questions in the 'Test Your Knowledge' section of the questionnaire. The first statement targets safety of long-term benzodiazepine and reads, '(Example: Valium®) . . . is a mild tranquilizer that is safe when taken for long periods of time'. The second statement focuses on side effects and is phrased, 'The dose of Valium® that I am taking causes no side effects'. The third statement, focusing on withdrawal, is worded, 'Without Valium® I will be unable to sleep or will experience unwanted anxiety', and the fourth, on alternative treatment options, states, 'Valium® is the best available option to treat my symptoms'. Change in beliefs is measured by comparing the pre- and post-intervention (T1) total scores on the Specific section of the beliefs about medicines questionnaire (BMQ-Specific) adapted for benzodiazepines [60,61]. Statements remained identical to the originals with the exception that the word 'medicines' was replaced by 'benzodiazepine' in each statement. The beliefs in medications questionnaire is a validated measure used to assess cognitive representations of medications [60,61]. These outcome measures pertain to the individual level.

Change in risk perception was chosen as a secondary outcome in order to reflect the behavior motivation hypothesis described earlier. As patient reported outcomes are not always objective, two additional and more objective outcomes were chosen to evaluate risk perception: change in knowledge and change in beliefs about benzodiazepines. This was done because a common idea in models of risk perception states that risk is perceived from two dimensions: knowledge of and beliefs about that risk, as mentioned earlier. The rationale for choosing the score for the knowledge questionnaire was that it allows a quantification of the knowledge transfer aspects of the intervention. The rationale for choosing the BMQ-Specific instrument to measure beliefs relates to its ability to isolate and score participants' beliefs about a specific medication; both in terms of the dangers and concerns participants have regarding their prescription (Specific-Concerns), and the necessity they attribute to this same prescription (Specific-Necessity). The BMQ-Specific consists of two 5-item factors belonging to each sub-score. Participants indicate their degree of agreement with each statement on a 5-point Likert scale (1 = strongly disagree to 5 = strongly

agree). Both scales are then summed into their respective scores (5 to 25 scale) with higher scores indicating stronger beliefs in that concept. A necessity-concerns differential can also be derived from these scales by subtracting the concern sub-score from the necessity sub-score. This differential can be considered as the cost benefit analysis for each patient, where costs (concerns) are weighed against perceived benefits (necessity beliefs) [60,61].

Change in self-efficacy

The second secondary outcome measure will be change in self-efficacy. Self-efficacy will be measured pre- and post-intervention (T1) with the medication reduction self-efficacy scale, a scale that was developed and tested in the context of previous benzodiazepine tapering studies [62]. Participants will indicate their level of confidence for achieving a pre-determined medication reduction goal on a scale of 0 to 100 (0 = not at all confident to 100 = extremely confident), which is based on Bandura's original guidelines for the development of task-specific self-efficacy scales. Post-intervention, participants will also be asked to rate on this same scale their level of confidence about eventually discontinuing using the tapering program provided. This outcome measure pertains to the individual level. The rationale is that self-efficacy gives a clear indication of a patient's belief about their capability to discontinue benzodiazepines and may be a potential predictor of benzodiazepine discontinuation.

Initiation of discussion with a physician or pharmacist about the decision to taper benzodiazepines

The third secondary outcome will be the potential of the intervention to activate participants to discuss safer prescribing options with their physician or pharmacist. At T1 to T3 participants will be asked to indicate: if they had spoken to friends and/or family about the intervention, and if they had spoken to or intended to discuss medication discontinuation with either their physician or pharmacist. Reactions and results of these behaviors will be noted. These intentions are considered as measures of self-initiated medication risk reduction behaviors. This outcome measure pertains to the individual level.

The intervention was designed to target consumers directly as catalysts for engaging physicians and pharmacists in collaborative discontinuation of their benzodiazepine drugs or other inappropriate medications. Observing this outcome will allow us to determine the intervention's potential for engaging participants in collaborative medication management. Furthermore, it will also allow us to identify at which point the intervention failed, and whether psychological dependence on the part of consumers or obstructive behavior on the part of the physicians or pharmacists was the cause of the intervention's failure.

Sample size

The main question driving the sample size for this study is whether chronic inappropriate medication users who receive the knowledge transfer tool are more likely to discontinue use at 6-month follow-up compared to users who do not receive the intervention. A systematic review was undertaken to identify similar studies and compare discontinuation rates for benzodiazepine drugs. Inclusion criteria were: rigorous randomized controlled trial methodology, inclusion of adults aged 65 years and older, community setting, a non-imposed intervention, and interventions that targeted inappropriate benzodiazepine prescriptions and included a prescription discontinuation measure. Eight studies met the inclusion criteria and were used in the sample size calculation estimates. Many other studies were identified that presented very different estimates, however these varied greatly in setting, population or measure and were irrelevant to the current study.

We expect our intervention to achieve a rate of discontinuation that is at least as great as that achieved in previous studies by medication review by pharmacist and contact with physician (range 19 to 24%, mean 22%) [29,43,63] or by simple discontinuation letters (range 13 to 20%, mean 16%) [47,64-67]. However, it is possible that individuals who do not receive the intervention may have rates of discontinuation as high as 6% for inappropriate prescriptions (range 2 to 6%, mean 4%) [29,43,47,64-66]. Our study will therefore be powered to detect a minimal 20% increase in inappropriate medication discontinuation due to use of the intervention and an absolute minimal rate of discontinuation of 25%. Based on an alpha of 0.05 and 80% power to detect a 20% difference, 58 participants are needed for each group. To detect greater differences, a lower sample size is needed. However, due to the cluster design of this study, adjustments need to be made to account for both clustering and for the effect of the coefficient of variation of the cluster size [68]. Based on current recruitment data (16 clusters, cluster sizes 6 to 27), the coefficient of variation was established at 0.527 using the minimum/maximum cluster size estimation method [68] and estimated intra-cluster correlation set at 0.05. After computing the coefficient by which to multiply our sample size to account for these factors we obtained 1.79 [69]. Current loss to follow-up in the study (in the first 185 recruited participants) was established at 9%. Therefore 114.2 (58 × 1.79 × 1.10 = 114.2) participants will be needed for each group. A sample of 250 individuals will be recruited.

Analysis plan

Data will be analyzed using an intention-to-treat approach. Descriptive statistics (means, proportions) will first be calculated to assess the balance between the groups on important confounders, such as age, sex, health status,

baseline beliefs about medications and benzodiazepine use. In order to answer the main research question driving this study - whether an educational intervention targeting consumers directly as catalysts for engaging physicians and pharmacists in collaborative discontinuation achieves an inappropriate prescription discontinuation rate of at least 20% compared to usual care - we will use a marginal model estimated via generalized estimating equations (GEE) with a binary outcome and an identity link, with an exchangeable correlation structure to account for correlation between participants in the same cluster [69]. Risk differences between the control and experimental groups will be calculated and the robust variance estimator will be used to estimate the associated 95% confidence interval (CI) and *P* value [70]. As a sensitivity analysis (and/or if any confounders are unbalanced between the groups), we will estimate the risk difference for the intervention via a marginal model estimated via GEE with an exchangeable correlation structure. The robust variance estimator will again be used. In secondary analyses, we will calculate risk differences in subgroups of interest (for example, very older people, women, baseline beliefs about medication and degree of polypharmacy). The analysis will be carried out at both the cluster and individual levels.

In order to determine whether the patient intervention altered beliefs about the necessity-concern ratio, knowledge or risk perception for the inappropriate prescriptions, as well as self-efficacy, paired t-tests will be used to evaluate change scores pre- and post-intervention. The potential of the intervention to engage participants in preventive health behaviors will be evaluated via chi-square tests comparing intervention and control groups. These analyses will be carried out at the individual level.

Discussion

To date there is no effective or sustainable approach to reduce benzodiazepine use in older adults [24-42]. Previous research on strategies to reduce benzodiazepine consumption has applied paternalistic approaches to patient care, similar to the 'top-down' managerial approach described in management and organizational development theory [71,72]. An example of this approach is when physicians acquire warning letters from study investigators and send these letters to patients asking them to schedule an office visit to discuss benzodiazepine discontinuation. Our educational intervention draws on theories of self-management and collaborative doctor-patient partnerships, and provides a means to test a 'bottom-up' change strategy [71,72]. In the bottom-up model, patients drive prescription decisions from information gathered on the Internet, through friends or via an accredited academic body. To our knowledge, no published study to date has targeted the patient as a driver of safer prescribing practices. By directly empowering chronic users with knowledge about risks, suggestions for lower-risk therapeutic options and self-efficacy for implementing tapering protocols, we hope to imitate the success of individually targeted anti-smoking campaigns [73].

To maintain the generalizability of the findings from our study, exclusion criteria have been kept to a minimum. In order to fulfill recruitment needs, no limits on cluster size were imposed to pharmacies meeting the cluster eligibility criteria. Since some pharmacies identified over 200 potential participants, while others barely covered the 50 potential candidate minimum to qualify as a cluster, cluster sizes are expected to vary. However, this was considered both in the sample size calculations and analyses.

The study has been designed as a pragmatic trial that takes place in the real-world setting. The intervention is theoretically-based and incorporates a practical and contemporary learning and psychological approach to help participants overcome hard-to-achieve lifestyle modifications. Thus, we expect that implementing an educational intervention trial in a practical setting will yield both internally and externally valid evidence for reducing inappropriate benzodiazepine use, by directly targeting and activating community-dwelling older adults in a previously unexplored approach.

Trial status

The trial is currently recruiting participants and was approximately 80% complete at time of publication.

Abbreviations

BMQ-Specific: Beliefs about Medicines Questionnaire - Specific segment; CI: Confidence interval; GAI: Geriatric Anxiety Inventory; GEE: Generalized estimating equations; GHS: General health status; MoCA: Montreal Cognitive Assessment; PHQ: Patient Health Questionnaire; SMAF: Functional autonomy measurement system.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

CT conceived the study, participated in its design and coordination, and helped to revise the manuscript. PM was involved in drafting and revising the manuscript. RT and SA contributed to the conception and design of the study, and were involved in manuscript revision. All authors read and approved the final manuscript.

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Appendix 2

You May Be at Risk

You are taking one of the following sedative-hypnotic medications:

- ○ Alprazolam (Xanax®)
- ○ Bromazepam (Lectopam®)
- ○ Chlorazepate
- ○ Chlordiazepoxide-amitriptyline
- ○ Clidinium-chlordiazepoxide
- ○ Clobazam
- ○ Clonazepam (Rivotril®, Klonopin®)
- ○ Diazepam (Valium®)
- ○ Estazolam
- ○ Flurazepam
- ○ Loprazolam
- ○ Lorazepam (Ativan®)
- ○ Lormetazepam
- ○ Nitrazepam
- ○ Oxazepam (Serax®)
- ○ Quazepam
- ○ Temazepam (Restoril®)
- ○ Triazolam (Halcion®)
- ○ Eszopiclone (Lunesta®)
- ○ Zaleplon (Sonata®)
- ○ Zolpidem (Ambien®, Intermezzo®, Edluar®, Sublinox®, Zolpimist®)
- ○ Zopiclone (Imovane®, Rhovane®)

CIHR IRSC Canadian Institutes of Health Research / Instituts de recherche en santé du Canada
Centre de recherche iugm Institut universitaire de gériatrie de Montréal
AFFILIATED WITH Université de Montréal
Michel Saucier Chair in Pharmacy, Health & Aging
La Chaire pharmaceutique Michel-Saucier en santé et vieillissement
CaDeN Canadian Deprescribing Network

TEST YOUR KNOWLEDGE ABOUT THIS MEDICATION

QUIZ

SEDATIVE-HYPNOTIC DRUGS

1. The medication I am taking is a mild tranquilizer that is safe when taken for long periods of time. ○ TRUE ○ FALSE

2. The dose that I am taking causes no side effects. ○ TRUE ○ FALSE

3. Without this medication I will be unable to sleep or will experience unwanted anxiety. ○ TRUE ○ FALSE

4. This medication is the best available option to treat my symptoms. ○ TRUE ○ FALSE

ANSWERS

1. FALSE

It is no longer recommended to take a sedative-hypnotic drug to treat insomnia or anxiety. People who take it are putting themselves at a:

- 5-fold higher risk of memory and concentration problems
- 4-fold increased risk of daytime fatigue
- 2-fold increased risk of falls and fractures (hip, wrist)
- 2-fold increased risk of having a motor vehicle accident
- Risk of problems with urine loss

2. FALSE

Even if you think that you have no side effects, and even if you take only a small dose, a sedative-hypnotic drug worsens your brain performance and slows your reflexes.

3. TRUE

Your body has probably developed a physical addiction to this medication. If you stop it abruptly, you may have trouble sleeping and feel greater anxiety. Millions of people have succeeded in slowly cutting this drug out of their lives and finding alternatives to help their problem.

4. FALSE

Although it is effective over the short term, studies show that sedative-hypnotic drugs are not the best long-term treatment for your anxiety or insomnia. Sedative-hypnotic medication covers up the symptoms without actually solving the problem. Please keep on reading to learn more about developing healthier sleep patterns and diminishing stress.

DID YOU KNOW?

Your medication is in a family of drugs that bind to the receptors in the brain that cause sedation. Sedative-hypnotic drugs can be highly addictive and can cause many side effects. Except in special circumstances, these medications should never be taken.

These drugs remain longer and longer in your body as you age. This means that they can stay for up to several days and could be making you tired, weak, impair your balance, and reduce your other senses.

Sedative-hypnotic drugs can also be associated with hip fractures, memory problems, and involuntary urine loss. Their sedative properties can cause you to be drowsy during the day which can lead to car accidents and sleep walking. Even if you are not experiencing these symptoms, be sure to speak to your doctor or pharmacist so that you do not develop them in the future.

Alternate therapies are available to relieve your anxiety or improve your sleep with fewer side effects on your quality of life.

Please Consult your Doctor or Pharmacist Before Stopping Any Medication.

SO ASK YOURSELF:

YES OR NO?

Have you been taking this sedative-hypnotic drug for a while?	○Y	○N
Are you tired and often groggy during the day?	○Y	○N
Do you ever feel hungover in the morning, even though you have not been drinking?	○Y	○N
Do you ever have problems with your memory or your balance?	○Y	○N

AS YOU AGE

Age-related changes take place in your body and modify the way you process medications. Your chances of taking more than one medication increase as you age, as well as the possibility of a history of illness. Drugs stay in your body longer and diminished liver function and poor blood flow to your kidneys may increase side effects.

Unfortunately this is important information that is often not passed on to patients who are taking this drug. Please consult your physician or pharmacist to discuss this further. Alternative therapies could relieve your anxiety or improve your sleep with less side effects on your quality of life.

ALTERNATIVES

If you are taking this sedative-hypnotic drug to help you sleep:

There are lifestyle changes that can help.

- Do not read or watch TV in bed. Do so in a chair or on your couch.
- Try to get up in the morning and go to bed at night at the same time every day.
- Before going to bed, practice deep breathing or relaxation exercises.
- Get exercise during the day, but not during the last three hours before you go to bed.
- Avoid consuming nicotine, caffeine and alcohol as they are stimulants and might keep you awake.
- Ask your doctor for the use of a sleep diary, which can help you understand disruptive sleep patterns.
- Check out the website Sleepwell Nova Scotia (sleepwellns.ca), which offers online cognitive behavioural therapies to improve sleep.
- See our brochure, ***How to get a good night's sleep without medication*** (www.criugm.qc.ca/fichier/pdf/Sleep_brochure.pdf).

ALTERNATIVES

If you are taking this sedative-hypnotic drug to help reduce your anxiety:

There are other solutions to deal with your stress and anxiety.

- Talking to a therapist is a good way to help you work out stressful situations and talk about what makes you anxious.
- Support groups help to relieve your stress and make you feel you are not alone.
- Try relaxation techniques like stretching, yoga, massage, meditation or tai chi that can help relieve you of everyday stress and help you work through your anxiety.
- Talk to your doctor about other anti-anxiety medications that have less serious side effects.

MRS. ROBINSON'S STORY

She had been taking lorazepam, a sedative-hypnotic drug just like yours

"I am 65 years old and took lorazepam for 10 years. A few months ago, I fell in the middle of the night on my way to the bathroom and had to go to the hospital. I was lucky and, except for some bruises, I did not hurt myself. I read that lorazepam puts me at risk for falls. I did not know if I could live without lorazepam as I always have trouble falling asleep and sometimes wake up in the middle of the night.

I spoke to my doctor who told me that my body needs less sleep at my age – 6 hours of sleep per night is enough. That's when I decided to try to taper off lorazepam. I spoke to my pharmacist who suggested I follow the step-by-step tapering program (on the next page).

I also applied some new sleeping habits I had discussed with my doctor. First I stopped exercising before bed; then I stopped reading in bed, and finally, I got out of bed every morning at the same time whether or not I had a good nights sleep.

I succeeded in getting off lorazepam. I now realize that for the past 10 years I had not been living to my full potential. Stopping lorazepam has lifted a veil, like I had been semi-sleeping my life. I have more energy and I don't have so many ups and downs anymore. I am more alert: I don't always sleep well at night, but I don't feel as groggy in the morning. It was my decision! I am so proud of what I have accomplished. If I can do it, so can you!"

TAPERING-OFF PROGRAM

We recommend that you follow this schedule under the supervision of your doctor or your pharmacist.

WEEKS	TAPERING SCHEDULE							✓
	MO	TU	WE	TH	FR	SA	SU	
1 and 2	½	1	1	1	½	1	1	
3 and 4	½	1	½	½	1	½	½	
5 and 6	½	½	½	½	½	½	½	
7 and 8	½	¼	½	½	¼	½	½	
9 and 10	½	¼	½	¼	½	¼	½	
11 and 12	¼	¼	½	¼	¼	½	¼	
13 and 14	¼	¼	¼	¼	¼	¼	¼	
15 and 16	✕	¼	✕	✕	¼	✕	¼	
17 and 18	✕	✕	✕	✕	✕	✕	✕	

EXPLANATIONS

Full dose · Half dose · Quarter of a dose · ✕ No dose

5 QUESTIONS TO ASK YOUR HEALTH CARE PROVIDER

1. Do I need to continue my medication?
2. How do I reduce my dose?
3. Is there an alternative treatment?
4. What symptoms should I look for when I stop my medication?
5. With whom do I follow up with and when?

Questions I want to ask my health care provider about my medication

Use this space to write down questions you may want to ask:

This brochure can be found online at:

www.deprescribingnetwork.ca/useful-resources

Appendix 3

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TRIALS

STUDY PROTOCOL Open Access

A consumer-targeted, pharmacist-led, educational intervention to reduce inappropriate medication use in community older adults (D-PRESCRIBE trial): study protocol for a cluster randomized controlled trial

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Abstract

Background: Medication safety for older persons represents an ongoing challenge. Inappropriate prescriptions – those with a high risk of evidence-based harm – persist in up to 25 % of seniors, and account for a significant proportion of avoidable emergency department visits. This project is the sequel to the EMPOWER study, in which a novel consumer-targeted written knowledge transfer tool aimed at empowering older adults to act as drivers of benzodiazepine de-prescription resulted in a 27 % reduction of inappropriate benzodiazepine use at 6-month follow-up (number needed to treat (NNT) = 4). Failure to discontinue in the EMPOWER study was attributable to re-emerging symptoms among participants, prescribing inertia, and lack of knowledge and skills for substituting alternate therapy among physicians and pharmacists. To maximize de-prescription of inappropriate therapy, educational medication-risk reduction initiatives should be tested that simultaneously include patients, physicians and pharmacists. The objective of this trial is to: 1) test the beneficial effect of a new de-prescribing paradigm enlisting pharmacists to transfer knowledge to both patients and prescribers in a 2-pronged approach to reduce inappropriate prescriptions, compared to usual care and 2) evaluate the transferability of the EMPOWER study concept to other classes of inappropriate prescriptions.

Methods: We intend to conduct a 3-year pragmatic cluster randomized parallel-group controlled trial to test the effect of the new de-prescribing intervention compared to usual care for reducing 4 classes of inappropriate prescriptions from the 2012 Beers criteria among 450 community-dwelling older adults with polypharmacy. Inappropriate prescriptions will include benzodiazepines, sulfonylurea hypoglycemic agents, first generation antihistamines and non-steroidal anti-inflammatory drugs. The study population is community-dwelling older adults recruited from community pharmacies in Quebec, Canada. The intervention was developed based on a systematic review of the evidence for each medication. Participants in the experimental group will receive the written educational program following randomization and have their pharmacist send their physicians an evidence-based pharmaceutical opinion to recommend de-prescription and be followed for a year. The control group will be wait-listed for 6 months.

Discussion: System change to effectively reduce medication risk among community-dwelling seniors requires a coordinated approach targeting physicians, pharmacists and patients. This trial will test the feasibility and effectiveness of a tripartite approach to de-prescribing.

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Trial registration: Registered via ClinicalTrials.gov on 31 January 2014, identifier: NCT02053194.

Keywords: Patient education, Inappropriate prescription, Pharmaceutical opinion, Cognition disorders/drug therapy, Polypharmacy

Background

Older adults rank concerns about medication side effects highest on their list of health priorities, with 89 % of those with chronic conditions willing to attempt cessation of one of their medications if deemed appropriate by a physician [1–3]. Seniors have good reason to be concerned: as life expectancy improves and older adults live longer with chronic conditions, they are also more likely to consume multiple medications [4, 5]. Polypharmacy is a risk factor for adverse drug events including drug-drug interactions, emergency department visits due to therapeutic competition, hospitalization and death [6–8]. Some medications confer greater risk than others, and are termed inappropriate when their risks outweigh the benefits, and when safer therapeutic alternatives exist that have similar or superior efficacy [9–11].

Despite the development of guidelines identifying inappropriate medications among older adults such as the Beers criteria [9], inappropriate prescriptions persist in up to 25 % of community-dwelling non-hospitalized older adults aged 65+, depending on the criteria used and the country studied [10, 12]. Interventions aimed at physicians and pharmacists for reducing inappropriate medication use include medication reviews and software alerts [13, 14]. In a previous study [15], we developed and tested a consumer-targeted written knowledge transfer tool aimed at empowering older adults to act as drivers of safer prescribing practices. This resulted in a 27 % discontinuation rate in the intervention group independent of patient factors [15] and thus EMPOWER provided proof of concept that directly targeting consumers as drivers of safer prescriptions can be effective for reducing medication risk.

Several challenges and opportunities became apparent in the EMPOWER study. Patients stated in 33 % of cases that physicians were reluctant to change their prescription. Second, we realized that if the de-prescribing process were to become sustainable over the longterm, the new paradigm would have to be entrenched within the pharmaceutical sector and involve the prescriber, the patient and the pharmacist.

A tripartite approach to de-prescribing is supported by a recent systematic review on the barriers of de-prescribing, which suggests that the decision to stop a medication by an individual is influenced by multiple competing barriers and enablers [16]. In this review, a total of four enablers and barriers to de-prescribing were identified. Enablers consisted of agreement with appropriateness of cessation, positive influences such as support from the pharmacist and/or physician, dislike of medication as well as the presence of a clear cessation process. Barriers to cessation consisted of fear of cessation, negative influences such as discouragement from the pharmacist and/or physician, disagreement over the appropriateness of cessation, as well as the absence of a clear cessation process. Using this knowledge as well as our own findings from the EMPOWER study, which also demonstrated barriers to cessation such as prescribing inertia and a lack of knowledge and skills for substituting alternate therapy, we developed the current approach to the patient de-prescribing process. This trial aims to address these barriers and to test the beneficial effect of enlisting pharmacists to transfer knowledge on inappropriate prescriptions simultaneously to both patients and prescribers.

Methods/Design

Trial design

Study objectives

The primary objective of the trial is to evaluate the effectiveness of a pharmacist-initiated educational knowledge transfer intervention to both patients and prescribers on the discontinuation of inappropriate prescriptions on a community-based sample of chronic inappropriate prescription users as measured by the rate of targeted medication discontinuation at 6 months, with 1-year follow-up to determine whether change rates are sustained over the longterm. The acronym D-PRESCRIBE stands for "*D*eveloping *P*harmacist-led *R*esearch to *E*ducate and *S*ensitize *C*ommunity *R*esidents to the *I*nappropriate prescription *B*urden in the *E*lderly."

Secondary objectives of the study include: evaluating the added benefit of implicating physicians and pharmacists in a patient-targeted educational intervention on the discontinuation of inappropriate prescriptions in comparison to the EMPOWER [15, 17] study, where patients alone were targeted; to test the transferability of this novel approach to inappropriate prescription discontinuation explored in the EMPOWER study to other classes of inappropriate medications; to better understand the mechanisms by which the educational tool affects participants' risk perception, knowledge and

beliefs with respect to inappropriate prescription use; to evaluate the impact of evidence-based pharmaceutical opinions on physicians' perception of the prescription as inappropriate; and to document response rates and the overall feasibility of using pharmaceutical opinions as a clinical tool to catalyze physicians to de-prescribe inappropriate prescriptions.

Design

This is a pragmatic, cluster randomized, parallel-group controlled trial. A cluster design was chosen to prevent contamination across the intervention and control arms by individual clients served by the same pharmacy. The cluster and unit of randomization consists of each community pharmacy. There are two arms in this parallel-randomized controlled trial for each of the four medication categories targeted: the educational intervention arm and the control arm. A 50:50 ratio (intervention: control) of participants will be used in each medication class arm. Figure 1 illustrates the flow chart.

Study site: clusters and characteristics

The study is being conducted in the greater Montreal area in Quebec, Canada. Collaboration was established with the pharmacies of 3 local drugstore chains within a 2-hour driving radius (approximately100 km) of Montreal. Pharmacies are randomly ordered via a computer-generated program, and subsequently invited to participate in the trial in that order. Clusters consisted of community pharmacies that are able to track medication dispensing, that have a ≥ 20 % older person clientele, and that consent to participate in the project.

Study population

The study population comprises chronic users of the four targeted classes of inappropriate prescriptions among community-dwelling older adults recruited from community pharmacies in Quebec.

Men and women 65 years of age and older with chronic consumption (>3-month claims) of one of 4 targeted inappropriate prescriptions classes are eligible for participation in this trial. The choice of these 4 medication classes was based on moderate to high quality evidence and the strength of the recommendations presented in the *2012 Updated Beers Guidelines for Inappropriate Prescriptions* [9], as well as their frequency of use in the general population [18–20]. There is a strong recommendation for avoiding the four classes of prescription medications chosen in this trial (see Table 1) with moderate to strong evidence backing these recommendations [9].

Patients with a diagnosis of severe mental illness or dementia ascertained by the presence of an active prescription for any antipsychotic medication and/or a cholinesterase inhibitor or memantine in the preceding 3 months, those unable to communicate in French and/or English as well as patients showing evidence of significant cognitive impairment (a baseline screening score < 24 on the Mini-Mental State Exam (MMSE) [21]) are excluded. Additionally, patients in assisted-living facilities will be excluded from the study population.

Ethical approval

The study protocol was approved by the Research Ethics Board of the Centre de Recherche de l'Institut Universitaire

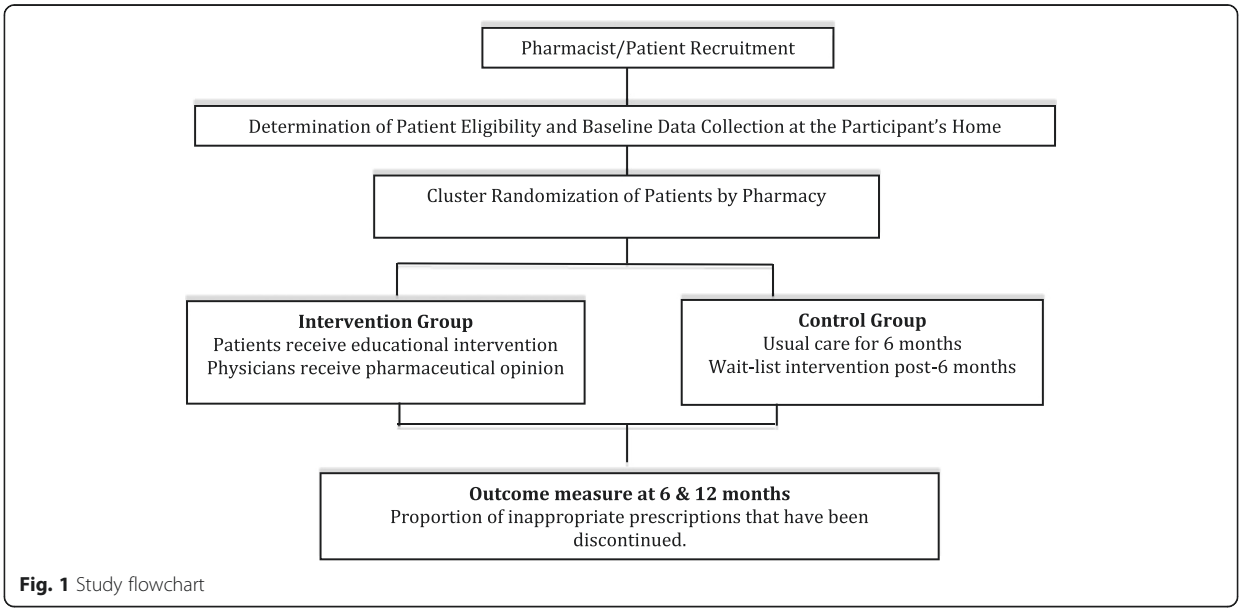

Fig. 1 Study flowchart

Table 1 Targeted medication classes

Medication class	Rationale
All benzodiazepines as well as non-benzodiazepine hypnotics	• Associated with: ○ A 5-fold increased risk of cognitive events [36–39] ○ A 30 % to 2-fold increased risk of falls [40–42], a 50 % increased risk of hip fractures [42–46] ○ A 25 % to 2-fold increased risk of motor vehicle accidents [47–49] ○ Increased risk of Alzheimer's disease by up to 80 % [50] • Similar evidence of harm exists for non-benzodiazepine hypnotics [9] • Hypnotics are associated with a greater than 3-fold increased risk of death even when prescribed < 18 pills/year [51]
Anticholinergic agents including first-generation antihistamines (as single agents or as part of combination products)	• Can cause cognitive impairment [39] • Have been associated with an increased risk of [52–57]: ○ Confusion ○ Dry mouth ○ Constipation ○ Functional decline
Long-acting sulfonylurea oral hypoglycemic agents chlorpropamide or glyburide used for the treatment of diabetes	• Estimated to be responsible for 11 % of emergency hospitalizations for adverse drug events in older adults [58] • Glyburide is associated with a 52 % greater risk of experiencing at least one episode of hypoglycemia compared with other secretagogues and with 83 % greater risk compared with other sulfonylureas [59, 60] • Chlorpropramide has potential to cause SIADH (syndrome of inappropriate antidiuretic hormone secretion) [61] • Glyburide was a new addition to the Beers list in 2012 [9, 62]
Chronic non-COX-selective non-steroidal anti-inflammatory drug (NSAIDs)	• Increased risk of gastro-intestinal bleeding/peptic ulcer disease in older adults • Ulcers, bleeding, or perforation caused by NSAIDs occur in approximately 1 % of patients treated for 3–6 months, and in about 2–4 % of patients treated for 1 year with trends continuing with longer duration of use [63–65] • Use of misoprostol or a proton pump inhibitor reduces this risk, it does not eliminate it

A full list of medication associated with these drug classes is presented in Appendix 1: Table 3

de Gériatrie de Montréal, Canada on 17 September 2013 (ClinicalTrials.gov identifier: NCT02053194).

Enrollment

Enrollment in the trial was conducted in collaboration with three regional pharmacy chains. Company headquarters provided the research team with a list of all chain drugstores with an appropriate version of the pharmacy software within a 100-km radius of the research center. Following this, a high-ranking company representative of each of the three banners circulated an announcement to all pharmacist owners to participate in the project. Following these announcements, pharmacy lists were randomized and then each one contacted systematically in that order to assess interest in participation. Pharmacists interested in participating then met in person with a research coordinator to sign a collaboration engagement, thus confirming their participation in the trial.

Recruitment of participants and application of eligibility criteria

Participants will be recruited to the trial in a systematic fashion. Participating pharmacists will approve the extraction from the pharmacy software of a comprehensive list of all clients meeting eligibility criteria for the study, divided according to the four targeted drug classes, and listed in random order by drug class. An extraction algorithm was developed and validated to reflect the inclusion and exclusion criteria of participants for the study, and applied across all participating pharmacies. The pharmacist then systematically and sequentially phones each client from each of the four drug classes to invite them to be contacted by the research team for more information about participating in a study on safe medication management, to a maximum of seven consenting participants per drug class or until no more names remain on the lists. The pharmacist records all responses and transfers the names and phone numbers

of those who responded affirmatively to the research staff. Research assistants then contact all potential participants referred by the pharmacists (with the client's permission), re-explains the details to confirm interest in participation and then arrange an appointment at the participant's residence or at the research center (based on patient preference) to complete the third screening stage: signed consent if eligible and collection of baseline data. During this visit, a research assistant reviews the medication currently taken by the patient, queries the medical history and assesses cognitive function. Signed informed consent to participate in the study is then obtained from individuals who meet the study criteria after baseline cognitive and health status screening. This procedure is followed until three clients from each drug class have been recruited per pharmacy, or until such time as there are no more eligible clients at that pharmacy or clusters have been filled. Participants taking one or more of the targeted drug classes will be randomly assigned to only one group and receive the intervention for a single drug class only.

Randomization

Randomization/Concealment of allocation

Randomization will be by pharmacy cluster after recruitment procedures are complete for the cluster. Randomization will be done in blocks using a 1:1 ratio every time to pharmacies and their patients' complete enrollment and baseline data collection. Allocation of the intervention by a third party will be blinded via a computer-generated random digit generated by a research assistant not involved in participant recruitment, as will data analysis and ascertainment of the outcome. The trial is, nonetheless, considered open-label because both the research assistant who delivers the interventions and the study participants and pharmacists who receive the educational materials will be aware that the intervention is being delivered.

Blinding

As the intervention is educational in nature, blinding of the intervention is impossible. However, to preserve a certain level of blinding and to protect against sources of bias, the following measures are taken. For participants, blinding is achieved by presenting the project to participants as a project on optimizing medication management. Consenting participants understand that their medication profiles will be transmitted to the research team within the following months and that they will receive a customized letter at some point during the year that may contain recommendations for change, which they can then decide to take to their physician or pharmacist for discussion. For pharmacists, blinding is achieved by presenting the same study timeline. Pharmacists are aware that their clients will receive an intervention at some point during the following year and remain blinded to group allocation throughout the course of the study. Pharmacists also remain blinded to other participating pharmacies. Since pharmacies are randomized as clusters, they are located in distinct geographic locations and generally have no reason to interact with one another. Thus, blinding pertains to both the individual and cluster level.

Intervention

The intervention is multifaceted, consisting of the delivery of educational materials about inappropriate prescriptions to both patients and their prescribers by the pharmacist. The pharmacist will deliver in person or by mailing the educational material to the patient in the form of a written educational brochure that was developed and tested during the EMPOWER study [15]. All educational material will be customized to the type of inappropriate prescription being consumed by the patient. All materials have already been developed and tested for acceptability [17]. Pharmacists will also provide a letter to their clients explaining why they are receiving an intervention, and a pamphlet inviting them to schedule a consultation. The pharmacist will deliver the educational material to the physician in the form of a faxed pharmaceutical opinion 2 weeks after having delivered the intervention to patients. The research team will provide the pharmacist with the customized educational materials for their patients, and examples of evidence-based pharmaceutical opinions that could be sent to the patient's physician depending on the type of inappropriate medication consumed. The evidence-based pharmaceutical opinions were developed by the research team, reviewed by experts, field-tested among a cohort of physicians as well as a team of pharmacists, and adapted until consensus was reached on the content and format for the final versions. The evidence-based opinions refer to the Beers criteria and other literature detailing the risk of harm associated with use of each targeted drug class for older adults, and include suggestions for safer therapeutic alternatives. The pharmacist is allowed flexibility in their choice of whether to use the pharmaceutical opinions provided by the research team, adapt it to their needs, draft their own pharmaceutical opinion for the physicians or not send out any opinion at all. All study materials are distributed to each participating pharmacist assigned to the intervention group immediately after randomization.

The comparator for this study will be usual care during the 6-month time period postrandomization. Usual care is a common comparator for a pragmatic trial, since it captures a wide, realistic range of alternate practice

scenarios [22]. After enrollment, all pharmacists will be informed that the project materials will be delivered "sometime over the next year." We will explain to the pharmacists that delays with various study procedures may take 3–6 months and that the recruitment process for the study is long. We will request that no action be taken by the pharmacist other than usual care until such time as the study materials are delivered to them. The control group pharmacists will be given all the educational materials at the end of their 6-month wait period postrandomization.

Study follow-up

Study follow-ups include 2 telephone calls 1 week and 6 weeks post randomization, and a single in-person interview at 6 months postintervention. Telephone interviews last from 5 to 10 minutes while the final in-person interview may take up to 30 minutes.

Outcomes

Prescription discontinuation rates at 6 months

The primary outcome for the trial is discontinuation of any of the targeted inappropriate prescriptions. The time period for ascertainment of the outcome is 6-months post-intervention. The 6-month time period was selected according to data obtained in the EMPOWER study and is consistent with the transtheoretical model of change, which predicts that once people start thinking about changing their behavior they usually make a decision and implement their plan of action within 6 months [23]. A follow-up at 1 year will be obtained to monitor long-term changes and to assess whether discontinuation persists.

Outcomes will be measured from the administrative database used for public drug claims reimbursement for both the intervention and control groups. This database includes all prescriptions filled at the pharmacy as well payment claims to pharmacists for all services rendered, such as the delivery of pharmaceutical opinions to physicians. Prescription data contain information on all dispensed prescriptions including drug name, dispensation date, dosage, drug form, duration and quantity of the drug dispensed, as well as the license number of the physician who wrote the prescription. Discontinuation of an inappropriate prescription will be defined as the lack of a claims renewal for that medication during a minimum of 3 or more consecutive months (with no subsequent renewals) as well as the absence of initiation of another inappropriate prescription of the same class.

Secondary outcomes

Medical Research Council guidance for complex intervention studies recommends that process evaluations be conducted within the trial to assess the fidelity and quality of implementation of the intervention, to clarify causal mechanisms, and to identify contextual factors associated with variation in outcomes [24]. We therefore intend to track the sequence of events stemming from the delivery of the knowledge transfer tools to each pharmacist in the intervention group. The following parameters will be measured:

- *Delivery of the educational brochures to the patients* by their pharmacists
- *Prevalence, timing and type of pharmaceutical opinions sent* by the pharmacists to the patients' primary care providers
- *Effect of the patient knowledge transfer tool* on patients' beliefs about the use of their inappropriate medications and their intent to discuss cessation with their doctor or pharmacist
- *Effect of the pharmaceutical opinion on the prescriber's behavior*
- *Patient-physician encounters to discuss inappropriate prescriptions*
- *Patient self-efficacy and improvement in self-efficacy in ability to change medication*

Table 2 illustrates the time points for measurement of each outcome during the study.

Sample size

The main question driving the sample size is whether the delivery of a knowledge transfer intervention by pharmacists to consumers of inappropriate prescriptions and their prescribers is more likely to result in discontinuation of inappropriate prescription over a 6-month time period compared to usual care. We hypothesize that our intervention will achieve a rate of discontinuation that is at least as great as that achieved in previous studies by medication review by a pharmacist and contact with a physician (maximum rate 27 % in EMPOWER [15]) compared to usual care (maximum rate of discontinuation 6 %) [13, 14, 18, 25–29]. These figures were derived from published studies in older people conducted in the community setting with a non-imposed intervention targeting inappropriate prescriptions, and included a prescription discontinuation measure. We therefore intend to power our study to detect a minimal 20 % increase in any inappropriate medication discontinuation over usual care, and an absolute minimal rate of discontinuation of 25 %, which would compare to EMPOWER. We are also interested in conducting sub-group analyses by drug class as the four drug classes we have chosen have different indications and may have different rates of discontinuation due to the intervention. Our calculations also account for the cluster design, with adjustments made for both

Table 2 Overview of data collection and measurements in both trial arms

	Baseline	Follow-up		
Visit number	T0	T1	T2	T3
Time	Day 0	7 days post	6 weeks post	6 months post
Inclusion and exclusion criteria	X			
Sociodemographic characteristics	X			
SF-12	X			X
VES-13	X			X
MMSE	X			
PATD	X			X
Blood glucose monitoring		X[c]	X[c]	X[c]
Medication use characteristics	X			
Benzodiazepine Tapering Questionnaire		X[a,b]	X[a,b]	X[a,b]
DTSQs		X[c]		X[c]
Medication risk assessment	X	X		
BMQ-Specific	X	X		
Patient Self-Efficacy Scale	X	X		X
Intervention-related questionnaire		X	X	X
Intervention Appreciation Questionnaire				X

BMQ-Specific, Beliefs about Medicines Questionnaire - Specific segment [66]; *DTSQs*, Diabetes Treatment Satisfaction Questionnaire [67]; *MMSE*, Mini-Mental State Exam [68]; *PATD*, Patients Attitude Towards De-prescribing Questionnaire [69]; *SF-12*, 12-Item Short Form Survey to measure health status and health-related quality of life [70]; *VES-13*, Vulnerable Elders Survey [71]. [a]Only administered if in benzodiazepine group
[b]Only administered if benzodiazepine tapering had begun
[c]Only administered if in sulfonylurea group

clustering and for the effect of the cluster size [30]. We assume that the intracluster correlation coefficient (ICC) will be similar to the ICC observed in the EMPOWER study (0.008) [31]. Based on pilot work from EMPOWER [17], we have chosen the minimal number of participants per drug class (n = 3) in order to augment the likelihood that each consenting pharmacy will achieve the required number of participants. Limiting the number of participants per pharmacy and per drug class should also lower design effects when compared to the EMPOWER study where clusters varied from 2 to 27 participants per pharmacy [30]. With an estimated ICC of 0.05 (worst-case scenario) for the 3 participants recruited per drug class, we would require 17 pharmacies per group (51 participants per arm) to be able to estimate a 20 % absolute discontinuation rate difference between trial arm by drug class with 80 % power and alpha 0.05 [31]. To detect greater differences, a lower sample size is needed. Thus we would have ample power for the overall comparison. Based on preliminary recruitment rates for the D-PRESCRIBE trial during a run-in period, we have observed that only 1 out of every 10 pharmacies that participate are able to recruit the desired number of participants with a participant range per pharmacy of 3–12 and a mean of 6 participants per pharmacy. This may be because smaller pharmacy chains are eligible for inclusion, compared to the EMPOWER trial. Based on our previous research we assume that 10 % of participants will withdraw or be lost to follow-up. We have, therefore, inflated our sample size to 450 participants (112 per medication class) from an estimated 75 pharmacies. Additionally, to compare the added benefit of the pharmaceutical opinion in comparison to the educational material alone, we chose to recruit an additional three participants from the benzodiazepine group. This was powered to detect a minimal 12.5 % difference between participants in this study and the EMPOWER study and accounted for the previously mentioned sample size considerations.

Analysis

To determine whether randomization was effective, descriptive statistics (means, proportions) will be calculated to assess the balance between the groups on important confounders such as age, sex, health status, baseline beliefs about medications and the degree of polypharmacy. The primary analysis will focus on answering the main research question driving this study - whether the intervention results in an increased discontinuation rate of inappropriate prescriptions of at least 20 % compared to usual care. We will use a marginal model estimated via generalized estimating equations (GEE) with a binary outcome and an identity link, with an exchangeable correlation structure to account for correlation between participants in the same cluster. Participants will be analyzed as randomized (ie, intention to treat). Risk differences between the control and experimental groups will be calculated and the robust variance estimator will be used to estimate the associated 95 % confidence interval and *P*-value [32]. If any confounders (age, sex, degree of polypharmacy or health status) are unbalanced between the groups, we will estimate the unadjusted and adjusted odds ratios for the intervention via a marginal model estimated via GEE with an exchangeable correlation structure. The robust variance estimator will again be used. All analyses described above will be repeated for each drug class during sub-analysis. As a sensitivity analysis, we will compare results obtained with the GEE to other procedures that account for clustering such as generalized linear mixed models.

The fidelity and quality of implementation of the intervention by the pharmacists will be assessed by rates of delivery of the educational materials to the participants

and their primary care providers. The types of pharmaceutical opinions delivered and the patients' and physicians' responses to receipt of the knowledge transfer tools will be reported as proportions, along with 95 % confidence intervals, and will be stratified by type of prescription. In order to determine whether the patient intervention altered beliefs about the necessity-concern ratio for the inappropriate prescriptions, linear mixed models will be used to evaluate change-scores preintervention and postintervention for each medication class with the pharmacist as a random effect. To better understand the explanatory mechanisms driving the success or failure of the intervention, we will track the sequence of events following randomization for each patient in the intervention group. The chronological order of billings for pharmaceutical opinions, prescription changes, and patient visits to the physician for each participant and each type of prescription will be ascertained. These will be compared to the dates and content of the response cards returned by the physicians and the patients' reports of what transpired during any discussions with health providers about their medication. Analysis of these temporal "pathways" will provide valuable insight into *how* and *why* the de-prescribing process occurred or did not occur for each participant.

Discussion

The EMPOWER study demonstrated that direct-to-consumer education is effective at eliciting shared decision-making around the overuse of medications that increase the risk of harm in older adults. Our hope here is to demonstrate the added value of using pharmacists as a bidirectional conduit of evidence-based knowledge to patients and physicians to drive the reduction of inappropriate prescriptions. In various countries, legislative and regulatory changes have led to a wider scope of pharmacist practice for substituting or discontinuing certain medications [27]. Data from randomized trials indicate that patients benefit from increased pharmacist involvement in their care [33].

The patient-centered process developed for this study aims to reinforce known enablers and address barriers to medication cessation. By providing the patient with evidence-based information in the educational brochures we expect to increase patient's endorsement of appropriate cessation, increase their dislike of the medication, reduce the fear of re-emerging symptoms, and equip them with the skills to safely taper their medication. Patient empowerment is a key mechanism for increasing patient responsibility in shared decision-making with health care providers [34]. Use of an evidence-based pharmaceutical opinion aims to catalyze and support pharmacists and physicians by providing them with the appropriate tools and information to positively influence and encourage patients to initiate de-prescribing. Only 41 % of community pharmacists admit familiarity with the Beers criteria of drugs to avoid in older people [35]. As such, the evidence-based pharmaceutical opinion serves a dual purpose in educating both pharmacists and physicians about the latest pharmacogeriatric recommendations. This tripartite educational approach to pharmacists, physicians and patients is intended to achieve synergistic impact.

Strengths

Strengths of the study include but are not limited to its pragmatic design, which will allow the observed process to reflect real world practice as accurately as possible. Systematic recruitment of participants via community pharmacies, blinding of the study hypothesis from participants, physicians, pharmacists, and evaluators as well as objective assessment of drug discontinuation rates from pharmacy prescription renewal profiles will increase the trial's internal validity. Comparison with EMPOWER and other studies will allow us to examine the synergic effects of our intervention compared to direct-to-consumer and direct-to-prescriber interventions alone. Additionally, a comparison of discontinuation rates for the four different drug classes may allow us to identify different barriers and/or enablers that need to be addressed for different medication indications.

Limitations

Limiting the list of inappropriate medications to four drug classes only will restrict the study's potential generalizability to all inappropriate prescription. Contamination between the experimental and control groups is possible, but we expect it to be minimal. Pharmacists will be informed that the intervention will be staggered over the course of a year and they should follow usual care until receipt of the study materials. Physicians may end up with patients in both the control and experimental arms of the study, but this is unlikely as pharmacies generally serve a specific geographic area and patients will be recruited throughout Quebec. The physician will not be contacted directly because of the potential to influence the outcome of the intervention during the study period and/or to interfere with the pharmacist-doctor relationship. Information on what occurs during the physician-patient encounter will, therefore, be limited.

Trial status

The trial is currently recruiting participants and is approximately 60 % complete at the time of publication.

Appendix 1

Table 3 Complete list of medications

Benzodiazepines	First generation antihistamines	Long-acting sulfonylurea	Non-COX-selective NSAIDs
Alprazolam	Hydroxyzine	Chlorpropamide	Aspirin (>325 mg/day)
Estazolam	Promethazine	Glyburide	Diclofenac
Lorazepam	Brompheniramine		Diflunisal
Oxazepam	Carbinoxamine		Fenoprofen
Temazepam	Chlorpheniramine		Etodolac
Triazolam	Clemastine		Ibuprofen
Clorazepate	Cyproheptadine		Ketoprofen
Chlordiazepoxide	Dexbrompheniramine		Meclofenamate
Chlordiazepoxide-amitriptyline	Dexchlorpheniramine		Mefenamic acid
Clidinium-chlordiazepoxide	Diphenhydramine (oral)		Meloxicam
Clonazepam	Doxylamine		Naproxen
Diazepam	Triprolidine		Oxaprozin
Flurazepam			Piroxicam
Quazepam			Sulindac
Eszopiclone			Tolmetin
Zolpidem			
Zaleplon			

Abbreviations
D-PRESCRIBE: Developing Pharmacist-led Research to Educate and Sensitize Community Residents to the Inappropriate prescription Burden in the Elderly; GEE: generalized estimating equations; ICC: intracluster correlation coefficient; MMSE: Mini-Mental State-Exam; NSAIDs: non-steroidal anti-inflammatory drugs.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
PM and CT conceived the study, participated in its design/coordination and helped to revise the manuscript. PM was involved in drafting the manuscript. RT, SA, AB contributed to conception and design of the study and were involved in manuscript revision. All authors read and approved the final manuscript.

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Appendix 4

Institut universitaire

CERTIFICAT D'ÉTHIQUE

Le comité d'éthique de la recherche de l'IUGM a examiné la demande pour le projet intitulé:

« La gestion des médicaments: passez à l'action » (réf. : 2009-0801A)

présenté par : **Dre Cara Tannenbaum**

et juge la recherche acceptable au point de vue éthique.

Johane de Champlain, Présidente

1er septembre 2009

Ce rapport est valide jusqu'au : 1er septembre 2010

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Institut universitaire
de gériatrie de Montréal

Montréal, le 16 septembre 2013.

Docteure Cara Tannenbaum, MD, Ph.D.
Centre de recherche – IUGM
4545, chemin Queen-Mary
Montréal (Québec) H3W 1W5

Objet: CER IUGM 13-14-10 : Approbation finale

EMPOWER_2/ PRESCRIBE study (Pharmacist-led research to educate and sensitize community residents to inappropriate prescriptions burden in the elderly)): Effectiveness of consumer-targeted pharmacist-led educational intervention to reduce inappropriate prescriptions in older adults community.

Docteure,

Vous avez soumis au Comité d'éthique de la recherche de l'IUGM, une demande d'évaluation pour votre projet de recherche cité en rubrique. À cet effet, vous avez soumis au Comité les documents suivants :

- Lettres de présentation datée du 18 juin 2013.
- Formulaire de soumission d'un projet de recherche, dûment complété.
- Protocole de recherche intitulé : EMPOWER_2/ PRESCRIBE study (Pharmacist-led Research to Educate and sensitize Community Residents to Inappropriate prescriptions Burden in the Elderly)): Effectiveness of consumer-targeted pharmacist-led educational intervention to reduce inappropriate prescriptions in older adults community.
- Formulaire d'information et de consentement, daté du 6 mai 2013
- Informed consent form, daté du 17 juin 2013.
- Questionnaire - Socio-demographic data, daté du 7 juin 2013.
- Questionnaire - Moca, daté du 7 juin 2013.
- Questionnaire - VES-13, daté du 7 juin 2013.
- Questionnaire - Health status + SF-12, daté du 7 juin 2013.
- Questionnaire - Anxiety, daté du 7 juin 2013.
- Questionnaire - PHQ - 9, daté du 7 juin 2013.
- Questionnaire - Insomnia, daté du 7 juin 2013.
- Questionnaire - General beliefs in medicines, daté du 7 juin 2013.
- Questionnaire - PATD, daté du 7 juin 2013.
- Questionnaire - BMQ - specific, daté du 7 juin 2013.
- Questionnaire - Associated risk, daté du 7 juin 2013.
- Questionnaire - Use of (type of medication) (T1), daté du 7 juin 2013.
- Questionnaire - Vrai ou faux, daté du 7 juin 2013.
- Questionnaire T2, daté du 7 juin 2013.
- Questionnaire T3, daté du 7 juin 2013.
- Questionnaire - BWSQ, daté du 7 juin 2013.
- Questionnaire - BeQuestionnaire T4, daté du 7 juin 2013.
- Questionnaire - The Diabetes Treatment Satisfaction Questionnaire (DTSQs), daté du 7 juin 2013.
- Questionnaire - Profil pharmacologique.
- Un danger vous guette, soyez vigilant! - Vous prenez Amitriptyline® (Elavil®).
- Un danger vous guette, Soyez vigilant! - Vous prenez du Celecoxib®.
- Un danger vous guette, Soyez vigilant! - Vous prenez Diphenhydramine®.
- Un danger vous guette, Soyez vigilant! - Vous prenez Tylenol codéine®.

- Un danger vous guette, Soyez vigilant! - Vous prenez Vesicare®.
- Un danger vous guette, Soyez vigilant! - Vous prenez Glyburide® (Diabeta®).
- You May Be at Risk - You are currently taking Ativan® (Lorazepam®).
- Your Uniprix Pharmacist is there for you! List of offered services.
- Your pharmacist-owner affiliated to Jean-Coutu invites you to participate in the PRESCRIBE Study – « Am I taking the best medication possible? ».
- Votre pharmacien affilié à Uniprix vous invite à participer à l'étude « La gestion des médicaments : passez à l'action ».
- Lettre modèle pour le recrutement.
- Details of financial assistance requested.
- Lettre d'appui au projet signée par Madame Paquette, datée du 10 août 2012.
- Lettre d'appui au projet signée par Monsieur Cadieux, datée du 31 août 2012.
- Curriculum vitae du Docteure Cara Tannenbaum, MD.
- Curriculum vitae de Madame Robyn Tamblyn, Ph.D.
- Curriculum vitae de Madame Andrea Benedetti, Ph.D.

Une approbation conditionnelle vous a été émise en date du 2 août 2013. Vous nous avez soumis en date du 19 août 2013, le document suivant :

- Formulaire d'information et de consentement, daté du 2 août 2013 – mode révision

Vous nous avez en date du 8 septembre 2013, les documents suivants :

- Formulaire d'information et de consentement, daté du 8 septembre 2013 – mode révision.
- Informed consent form, daté du 8 septembre 2013.
- Your pharmacist-owner affiliated to Jean-Coutu invites you to participate in the PRESCRIBE Study – « Am I taking the best medication possible? ».
- Votre pharmacien affilié à Uniprix vous invite à participer à l'étude « La gestion des médicaments : passez à l'action ».

Vos réponses et les modifications apportées à votre projet de recherche ont fait l'objet d'une évaluation. Le tout ayant été jugé satisfaisant, nous avons le plaisir de vous informer que votre projet de recherche a été approuvé à l'unanimité par le Comité d'éthique de la recherche de l'IUGM.

Les documents que le Comité d'éthique de la recherche de l'IUGM a approuvés et que vous pouvez utiliser pour la réalisation de votre projet sont les suivants :

- Protocole de recherche intitulé : EMPOWER_2/ PRESCRIBE study (Pharmacist-led Research to Educate and sensitize Community Residents to Inappropriate prescriptions Burden in the Elderly)): Effectiveness of consumer-targeted pharmacist-led educational intervention to reduce inappropriate prescriptions in older adults community.
- Formulaire d'information et de consentement, daté du16 septembre 2013.
- Informed consent form, daté du 16 septembre 2013.
- Questionnaire - Socio-demographic data, daté du 7 juin 2013.
- Questionnaire - Moca, daté du 7 juin 2013.
- Questionnaire - VES-13, daté du 7 juin 2013.
- Questionnaire - Health status + SF-12, daté du 7 juin 2013.
- Questionnaire - Anxiety, daté du 7 juin 2013.
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- Un danger vous guette, Soyez vigilant! - Vous prenez Diphenhydramine®.
- Un danger vous guette, Soyez vigilant! - Vous prenez Tylenol codéine®.
- Un danger vous guette, Soyez vigilant! - Vous prenez Vesicare®.
- Un danger vous guette, Soyez vigilant! - Vous prenez Glyburide® (Diabeta®).
- You May Be at Risk - You are currently taking Ativan® (Lorazepam®).
- Your Uniprix Pharmacist is there for you! List of offered services.
- Your pharmacist-owner affiliated to Jean-Coutu invites you to participate in the PRESCRIBE Study – « Am I taking the best medication possible? ».
- Votre pharmacien affilié à Uniprix vous invite à participer à l'étude « La gestion des médicaments : passez à l'action ».

Cette approbation éthique est valide pour un an à compter du 16 septembre 2013. Un mois avant la date d'échéance, vous devrez faire une demande de renouvellement auprès du Comité d'éthique de la recherche de l'IUGM, en utilisant le formulaire du Comité prévu à cet effet.

Dans le cadre du suivi continu, le Comité vous demande de vous conformer aux exigences suivantes en utilisant les formulaires du Comité prévus à cet effet :

- De soumettre, pour approbation préalable au Comité, toute demande de modification au projet de recherche ou à tout document approuvé par le Comité pour la réalisation de votre projet.
- De soumettre, dès que cela est porté à votre connaissance, les incidents thérapeutiques graves, les réactions indésirables graves, les réactions indésirables et inattendues et les accidents observées en cours de recherche.
- De soumettre, dès que cela est porté à votre connaissance, tout nouveau renseignement sur des éléments susceptibles d'affecter l'intégrité ou l'éthicité du projet de recherche ou d'accroître les risques et les inconvénients des sujets, de nuire au bon déroulement du projet ou d'avoir une incidence sur le désir d'un sujet de recherche.
- De soumettre, dès que cela est porté à votre connaissance, toute modification constatée au chapitre de l'équilibre clinique à la lumière des données recueillies.
- De soumettre, dès que cela est porté à votre connaissance, la cessation prématurée du projet de recherche, qu'elle soit temporaire ou permanente.
- De soumettre, dès que cela est porté à votre connaissance, tout problème identifié par un tiers, lors d'une enquête, d'une surveillance ou d'une vérification interne ou externe.
- De soumettre, dès que cela est porté à votre connaissance, toute suspension ou annulation de l'approbation octroyée par un organisme de subvention ou de réglementation.
- De soumettre, dès que cela est porté à votre connaissance, toute procédure en cours de traitement d'une plainte ou d'une allégation de manquement à l'intégrité ou à l'éthique ainsi que des résultats de la procédure.

Vous pouvez obtenir les formulaires du Comité téléchargeables à partir du site web du Centre de recherche IUGM, à l'adresse suivante http://www.criugm.qc.ca/fr/la-recherche/ethique.html

De plus, nous vous rappelons que vous devez conserver pour une période d'au moins un an suivant la fin du projet, un répertoire distinct comprenant les noms, prénoms, coordonnées, date du début et de fin de la participation de chaque sujet de recherche.

Finalement, nous vous rappelons que la présente décision vaut pour une année et pourra être suspendue ou révoquée en cas de non-respect de ces exigences.

Le Comité d'éthique de la recherche de l'IUGM est désigné par le ministère de la Santé et des Services sociaux, en vertu de l'application de l'article 21 du Code civil du Québec et suit les règles émises par l'Énoncé de politique des trois conseils et les Bonnes pratiques cliniques.

Avec l'expression de nos sentiments les meilleurs.

Johane de Champlain
Présidente du Comité d'éthique de la recherche
IUGM

JdeC/kb

p. j. Formulaires d'information et de consentement, approuvés
Lettre pour le recrutement, approuvée

Comité d'éthique de la recherche de l'IUGM
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Site du Comité : http://www.criugm.qc.ca/fr/la-recherche/ethique.html

Appendix 5

Interview Guide

EMPOWER Study - Qualitative section

6 months post-intervention

I. INTRODUCTION

Mr. X / Mrs. Y, Hi,

First off, we would like to thank you for taking the time to participate in all the steps of the EMPOWER study. During the course of this research project you received an educational brochure which allowed you to come to your own conclusions on your use of medication XY. The objective of the interview today is to collect your opinion of the whole intervention process in order to better evaluate what happened with the intervention. As you already know, we wish to discuss with you your experience during this process and to collect your opinion on various aspects of your experience.

This interview is conducted for a University study and all information shared today will be confidential and anonymized. There are now right or wrong answers here, all that is important to us is to capture your honest opinion and experiences.

If you have no objections, we would like to record this conversation in order to facilitate the full collection of this interview.

Lets start with a small introduction, my name is…. And here is ….

Our colleague XX, the person who previously contacted you has indicated that you would be a good candidate to be interviewed. Although you have already discussed some of your experiences with her, we would like to start over from the start in order to capture all the details of your experience.

II. Aging, disease and medication

1. How old are you? Are you still active? Do you still work? Do you volunteer? Are you close to your family?

   Relaunch on:

   Perception of aging

   Physical psychological and social difficulties associated with aging.

2. How would you describe your current health status?
3. I would like to discuss your attitude towards medications in general.

What do medications represent at your age? Tell me about your current prescriptions. How do you manage taking your daily medications?

Relaunch:

Do they take/manage them themselves?

Do they use a Dispill?

Do you get any help managing them?

Do you ever forget them?

4. Now, let's talk about the medication for which you received the educational brochure. Tell me, how do you take your benzodiazepine? For which reasons do you take them and under which circumstances did you start taking this medication?

Relaunch:

- *Sleeping pill?*
- *Anxiolytic?*

5. How long have you been taking this medication for? How has the use of this medication evolved over time?
6. Do you still find this medication effective? Why? Do you have any side effects from this medication?

Relaunch:

Falls?

Dizziness?

Etc.

(As a whole, what are the advantages and disadvantages associated with taking this medication?)

7. Have you ever intended on ceasing your benzodiazepine (or actually attempted to) before receiving the educational brochure?
    a. If yes, how did it go?
    b. If no, why?
8. *Question only for those who <u>intended to but did not try ceasing medication</u>:*
    a. How important is ceasing your medication to you

b. How confident if your ability to stop using this medication?

c. How do you think you would feel if you ceased the medication?

For the interviewer: If the participant mentions having attempted of ceased the medication AFTER the brochure, just mention that this will be discussed later on in the interview.

III. Prescription and the patient-physician relation

9. Who prescribed your benzodiazepine? Tell me about your experience (first interaction? and after?). What did your doctor tell you about taking this medication?
10. Do you see your doctor often? Tell me about your relation with him/her?
11. Is it always the same physician who prescribes you your medications? (Multiple physicians? Family doctor?)
12. Before receiving the brochure, had you previously discussed or been approached by your physician about the possibility to switch/stop your benzodiazepine?
    a. If so, what were your expectations? What was their reaction? How did it go?
    b. If not, why?

IV. Acquisition and relation with the pharmacist

13. Now let's talk about your pharmacist.

How do you manage buying your benzodiazepine? Tell me about your experiences.

→Do you go see your pharmacist yourself? Do you have your medications delivered? At what frequency?

What has your pharmacist told you about this medication? How does he interact with you?

14. Before receiving the brochure, had you previously discussed or been approached by your pharmacist about the possibility to switch/stop your benzodiazepine?
    a. If so, what were your expectations? What was their reaction? How did it go?
    b. If not, why?

V. Reaction to the intervention

15. What was your first reaction when you read the information contained in the brochure that we sent you?
    a. What did you learn about the potential alternative treatments?

b. What did you learn about benzodiazepine cessation and withdrawal?

c. How do you now perceive the potential risks associated with your benzodiazepine prescription?

16. Please explain to me what happened once you read the brochure? (Did you read it more than once, discuss it with others?)

Relaunch:

Did you intend on initiating the tapering protocol after reading the brochure? Why?

17. Did you try implementing the tapering protocol suggested at the last page?

    a. If yes: For what reasons did you decide to initiate the tapering program?

    How was the process? (What were your withdrawal symptoms?) What helped you succeed your tapering? What were the obstacles? How do you feel since tapering off the medication?

    b. If no: For what reasons did you decide not to initiate the tapering program?

    What were the barriers? Do you have any questions or preoccupations regarding the tapering process? Do you think you could change your mind in the future? What would be the required criteria for you to stop your benzodiazepine?

18. For you, what are the important criteria/results that are most important to determine the success of a stopping a medication?

19. To conclude, what is your appraisal of the intervention? In what measure was the information provided useful to you? Would you recommend this intervention to someone else? Why?

20. To what degree do you value the importance of your implication in the management of your medication?

21. Are there any other subjects that were not discussed in the context of this interview but that you feel are important and that you would like to discuss?

Appendix 6

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Medication information

A drug education tool developed for older adults changes knowledge, beliefs and risk perceptions about inappropriate benzodiazepine prescriptions in the elderly

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ABSTRACT

Objective: To develop and test an educational tool for older adults that increases risk perception about benzodiazepines through knowledge acquisition and change in beliefs.
Methods: A written educational tool was mailed to 144 benzodiazepine consumers aged ≥65 years recruited from community pharmacies. Knowledge and beliefs about inappropriate prescriptions were queried prior to and 1-week after the intervention. Primary outcome was a change in risk perception. Explanatory variables were a change in knowledge and beliefs about medications. Self-efficacy for tapering and intent to discuss discontinuation were also measured.
Results: Post-intervention, 65 (45.1%) participants perceived increased risk. Increased risk perceptions were explained by better knowledge acquisition (mean change score 0.9, 95% CI (0.5, 1.3)), and a change in beliefs (BMQ differential mean change score −5.03, 95% CI (−6.4, −3.6)), suggesting elicitation of cognitive dissonance. Self-efficacy for tapering, (mean change score 31.2, 95% CI (17.9, 44.6)), and intent to discuss discontinuation of benzodiazepine with a doctor (83.1% vs 44.3%, $p < 0.001$) were higher among participants who perceived increased risk.
Conclusion: Risk perception surrounding inappropriate prescriptions can be altered through direct delivery of an educational tool to aging consumers.
Practice implications: Patients should be targeted directly with information to catalyze discontinuation of inappropriate prescriptions.

1. Background

Medication safety in the elderly population represents a unique challenge. Older adults are at increased risk of drug side effects, drug-drug interactions and adverse events due to age-related changes and associated disease [1,2]. The 2012 updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults lists all drugs-to-avoid in the elderly to reduce the risk of drug-related adverse events [3,4]. All benzodiazepine sedative-hypnotic drugs used for the treatment of anxiety and insomnia feature on this list due to an excessive risk of delirium, falls, fractures and motor vehicle accident [5].

With every update to the Beers criteria, significant efforts are made to inform and educate relevant parties to try and implement safer prescribing practices. We sought to develop an educational intervention to inform consumers directly about the risk of benzodiazepine drugs. We chose benzodiazepine drugs because qualitative research suggests that chronic users develop a psychological dependence to benzodiazepines, attributing them qualities that extend beyond their ordinary capacity [6]. Most consumers deny or minimize side effects while expressing subtle reluctance to outright refusal for being left suffering without these medications [6]. For these reasons physicians often express reticence for insisting on benzodiazepine discontinuation for fear of upsetting the doctor-patient relationship or because they believe that the patient tolerates the medication with minimal side effects [7].

The objective of this study was to develop and test an educational tool targeted directly to older consumers on the risks associated with benzodiazepine use in the geriatric population. By applying constructivist learning theory to the development of the educational intervention, we aimed to evaluate the potential of this tool for increasing the patient's risk perception by eliciting cognitive dissonance through knowledge acquisition and belief alteration. We hypothesized that improvements in patient

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knowledge, beliefs and perceived medication risk would lead to greater motivation for initiating discussions about drug discontinuation with a doctor or pharmacist and greater self-efficacy for tapering benzodiazepine use.

2. Methods

A quasi-experimental study was conducted among a cohort of chronic benzodiazepine users aged 65 years and older in Montreal, Canada. Participants were randomized to immediately receive an educational intervention to reduce inappropriate prescriptions or to a six-month wait-list group. The current analysis presents interim results on short-term changes in risk perceptions about benzodiazepines due to the intervention. The study was approved by the Institut Universitaire de Gériatrie de Montréal Ethics Committee in Montreal, Quebec, Canada.

2.1. Participants

The study population included community-dwelling men and women aged 65 years and older, consuming at least five prescription medications including a benzodiazepine dispensed for at least three consecutive months. Exclusion criteria were a diagnosis of severe mental illness or dementia ascertained by the presence of an active prescription for any antipsychotic medication and/or a cholinesterase inhibitor or memantine. Participants unable to communicate in French and/or English or showing evidence of significant cognitive impairment (score under 21 [8] on the MOCA (Montreal Cognitive Assessment)) were also excluded.

2.1.1. Recruitment

Participants were recruited from community pharmacies in the greater Montreal area. Pharmacists identified eligible patients from their databases and invited them to enroll in the study through personalized mailed invitations, referring them to the study coordinator. A telephone follow up from the pharmacist (or delegate) aimed to ascertain interest in the study from eligible participants who had not spontaneously contacted the coordinator. An appointment was made with the study coordinator at participant's residence for those who provided permission to be contacted for the study. Signed consent was obtained from individuals who met study criteria after baseline cognitive and health status screening.

2.2. The educational intervention

2.2.1. Theory and development of the intervention

Social cognitive theory, which consists of health promotion through social cognitive means, guided the development of the intervention [9]. The specific learning model that was applied was constructivist learning. Constructivist learning theory aims to promote active learning through creation of knowledge that seeks to make sense out of the material presented. The goal of this approach is to create an environment where the learner can interact with academic material, fostering their own selecting, organizing and information integrating processes [10]. Such theories have already proven successful in other health promotion interventions such as in educational materials for smoking cessation [11].

A critical component of constructivist learning theory is elicitation of cognitive dissonance [12]. Cognitive dissonance occurs when a person's preconceived notions about the self and the world clash with new knowledge acquisition; the discrepancy that is evoked results in a state of tension known as cognitive dissonance [12]. Our educational intervention for reducing benzodiazepine use was developed to create cognitive dissonance by soliciting an aversive motivational state in recipients by confronting two inconsistent cognitions on benzodiazepine use. The theory holds that as the experience of dissonance is unpleasant, the individual will be motivated to remove the pressure caused by this conflict by altering one of these perceptions to achieve consonance [12]. For instance, if an individual previously believed that benzodiazepines were safe, the threatening content of the tool challenges this belief by providing information that benzodiazepines incur several harmful risks, thus putting into question whether consumption should be continued [13,14] We also incorporated social comparison theory into the content of the intervention to reassure participants about their newfound uncertainty regarding benzodiazepine use. Social comparison states that: "people evaluate their opinions and abilities by comparison respectively with the opinions and abilities of others"[15]. It thus consists of comparing oneself with others in order to evaluate or to enhance some aspects of the self [16]. Here, the evaluation of the ability or inability to do a specific action relies on the success of a proxy performer. The efficacy of this theory depends on whether the comparer assimilates or contrasts him/herself to others [17]. Comparability with a peer champion's narrative and previous agreement with the peer's views are important factors for the comparison to work [16]. A self-assessment component was also introduced, which aimed to promote insight about potential misinformation or beliefs held about benzodiazepine use by providing feedback on incorrect assumptions [18,19].

Textual content of the intervention was based on a systematic review of the evidence as well as guidelines concerning the use of benzodiazepines in the elderly. A geriatrician and graduate student drafted the initial content of the tool, which was then validated by a panel of colleagues with expertise in geriatric pharmacy and reviewed by a health librarian to ensure that the wording met standards for patient literacy at the Grade 6 level. The tool was developed in English, and backward and forward translated into French.

2.2.2. Components of the intervention

The cover page of the brochure states "You May Be At Risk" with a picture of a pillbox with several medications in it, followed by "You are currently taking (name of the patient's benzodiazepine)". The first page of the intervention is entitled "Test Your Knowledge" and consists of four true or false questions on the use of the benzodiazepines. The second page lists the correct answers. Elements of constructivist learning theory are incorporated into the answers to create cognitive dissonance and challenge the patient's beliefs for each incorrect answer. The third page incorporates self-assessment and education about potential inappropriate use, side effects, drug-drug interactions and information about physiologic changes that occur with age that affect drug metabolism. The fourth and fifth pages present evidence-based risks associated with benzodiazepine use in the elderly and suggestions for equally or more effective therapeutic substitutes. The sixth page describes a case scenario highlighting one woman's success at weaning herself off benzodiazepines. The last page outlines a simple 21-week tapering program. The reader is encouraged on four occasions and is warned in large, red lettering to "Please Consult your Doctor or Pharmacist Before Stopping Any Medication."

2.2.3. Acceptability of the intervention

The tool was field-tested with a convenience sample of older adults to determine the readability and comprehension of the information. Six focus-groups ($n = 60$ adults) were conducted. Based on the focus group discussions, the wording, ordering of the material and visual presentation of the intervention was changed

in an iterative process until acceptability was reached. The final educational intervention consisted of a seven-page letter-size paper brochure written in 14-point font. The educational tool was mailed to the study participants within six months of the initial assessment.

2.3. Study outcomes

2.3.1. Primary outcomes

The primary outcome was a self-reported change in perception of risk associated with benzodiazepine use one week post-intervention. Participants were asked whether they perceived the same, increased, or no risk from consumption of their benzodiazepine following the intervention. A common idea in models of risk perception is that risk is perceived from two dimensions: the first being knowledge about the risk, and the second, beliefs about that risk [20]. To explain changes in perception of risk we therefore measured changes in knowledge and beliefs about medications as a mechanism through which cognitive dissonance could occur.

Change in knowledge was measured by comparing the pre-intervention and post-intervention answers from the four-item true or false questions listed in the "Test Your Knowledge" section of the questionnaire. The first statement on the safety of long-term benzodiazepine was "(Example: Ativan®)...is a mild tranquilizer that is safe when taken for long periods of time". The second statement focused on side effects and was worded, "The dose of Ativan® that I am taking causes no side effects." The third statement on withdrawal was phrased, "Without Ativan® I will be unable to sleep or will experience unwanted anxiety," and the fourth statement on alternative treatment options reads: "Ativan® is the best available option to treat my symptoms".

Change in beliefs was measured by comparing the pre- and post-intervention total scores on the specific section of the beliefs about medicines questionnaire (BMQ-Specific) adapted for benzodiazepines [21,22]. The rationale for choosing the BMQ-Specific instrument to measure beliefs relates to its ability to isolate and score participants' beliefs (second dimension of risk perception) about a specific medication, both in terms of the necessity of taking their prescription (Specific-Necessity) and the dangers of this same prescription, such as long term toxicity, side-effects and dependence (Specific-Concerns). The BMQ-specific consists of two five-items factors belonging to each sub-score. Participants indicate their degree of agreement with each statement on a 5 point Likert scale (where 1 = strongly disagree through 5 = strongly agree). Scores are then summed into their respective sub-category (5–25 scale) with higher scores indicating stronger beliefs. A necessity-concerns differential can also be calculated by subtracting the concern sub-score from the necessity sub-score. This differential can be thought of as the cost benefit analysis for each patient, where costs (concerns) are weighed against perceived benefits (necessity beliefs) [21,22]. A negative change in BMQ-differential score thus indicates a greater perception of risk.

2.3.2. Secondary outcomes

Two secondary outcomes were selected to measure anticipated behaviors potentially resulting from a change in risk perception: self-efficacy for tapering benzodiazepines and the intent to discuss benzodiazepine discontinuation with a doctor or pharmacist. The behavior motivation hypothesis was used to understand the drivers and consequences of risk perception. This hypothesis describes the determinants of risk perception and their effects on behavior change, and is endorsed by most models of health behavior [23]. Perception of risk has been shown to be positively related to preventive health behavior when expectations of success in dealing with the risk are acceptable, and when recommendations for preventive behavior are presented as effective [24]. Self-efficacy for tapering benzodiazepines was measured pre- and post-intervention on the Medication Reduction Self-efficacy scale, which allows the respondent to rate on a scale of 0 to 100 their degree of confidence for tapering and discontinuing benzodiazepines [25].

In order to measure anticipated behavior as a function of the participant's willingness to empower themselves in health-related decisions following the intervention, participants were asked to indicate (yes/no) post intervention: if they had spoken to friends and family about the intervention, and if they had spoken to or intended to discuss medication discontinuation with their doctor and/or pharmacist. These intentions were considered as a preliminary measure of preventive health behavior. Finally, initial reaction to the questionnaire and whether they had read it more than once was also collected.

Outcomes were measured at baseline and one week following receipt of the intervention. At baseline, questionnaires were completed at the participants' homes during an interview with the research coordinator. Follow up was by telephone interview with the same coordinator. Self-reported socio-demographic variables, health status variables and prescription details were collected at baseline.

2.4. Statistical analysis

Participant characteristics were summarized using means with standard deviations for continuous data and percentages for categorical data. The number of participants reporting increased risk perceptions one week after the intervention was reported as a proportion of all participants. To examine potential differences in the baseline characteristics of participants who perceived increased risk versus those who did not, group comparisons were conducted. There were few missing baseline data ($n = 0$–5 per variable), which were replaced by the mean group value.

To determine whether a change in knowledge or beliefs explained changes in risk perception as a result of receiving the educational intervention, changes in knowledge and beliefs from pre- to post-intervention were computed for each individual, as well as within and between groups of individuals who reported increased risk perceptions versus those who did not. Correct knowledge pre- and post-intervention was reported as the proportion of individuals endorsing the correct answer for each question. A sub-analysis among participants with potential for change, denoted by CAIA, or Change in the Answer from an Incorrect Answer, was also conducted to determine change in knowledge among participants who initially answered a question incorrectly, but subsequently changed to the correct answer at 1-week follow-up. Participants with correct answers at both time-points were thus excluded from the CAIA measure, as there was no potential for cognitive dissonance. An overall score for knowledge was computed as the sum of correct answers (0–4 range). A change in belief was measured by comparing the BMQ-specific-necessity score, specific-concern score and necessity-concern differentials both within and between the increased risk and no increased risk group. Participants who had evidence of both a change in knowledge and a change in beliefs were denoted as having experienced cognitive dissonance.

Self-efficacy scores for discontinuing benzodiazepines were compared both within and between RISK groups from baseline to post intervention, as were responses to the query about self-efficacy for tapering benzodiazepines. Participants with missing data for any of the BMQ-specific variables ($n = 3$) or the self-efficacy variables ($n = 7$–8) were withdrawn from these analyses. In order to determine the increased likelihood of anticipated preventive behaviors according to risk perception, the odds of

endorsing a behavior were regressed against risk perception using univariate logistic regression. Missing data were replaced by a negative answer for the latter analyses,

A chi-square test was used when comparing groups while McNemar's test was used to examine changes within groups from baseline to post-intervention for categorical variables. Independent *t*-tests were used to compare groups while paired *t*-tests were used to examine changes within groups from baseline to post-intervention for continuous variables. The statistical significance for all analyses was set at $p < 0.05$ (two-sided). SPSS Version 20.0 (SPSS Inc. Chicago, IL, USA) was used for all analyses.

3. Results

3.1. Recruitment

Participants were recruited from 12 pharmacies. The response rate to the mailed invitation to enroll in the study among eligible participants identified by their pharmacists was 15%. A total of 144 participants who received the educational intervention are included in this analysis.

3.2. Baseline characteristics

Table 1 shows demographic, general health status and prescription-related characteristics of the entire cohort at baseline. Participants were mostly female (73%), had an average age of 75, and the majority (83%) had no formal college or university education. Half of all participants had previously attempted benzodiazepine discontinuation, 25% of whom had successfully weaned off the drug at some point.

3.3. Change in risk perceptions

Post-intervention, 45.1% ($n = 65$) of participants reported increased perceived risk from consumption of benzodiazepines. There were no statistical differences in baseline characteristics between individuals perceiving an increased risk (RISK) and those with no perceptions of increased risk (NO RISK), except for a trend showing a shorter duration of benzodiazepine use among the RISK group ($p = 0.08$) (Table 1).

3.4. Change in knowledge

Knowledge about benzodiazepines was similar between groups at baseline. Changes in knowledge both within and between risk groups are described in Table 2. Eighty percent (52/65) of participants in the RISK group changed an answer from incorrect to correct on at least one knowledge question from pre- to post-intervention compared to only 41% (33/79) in the NO RISK group. The RISK group demonstrated a significantly higher proportion of correct answers post-intervention on the safety, side effects and alternatives questions compared to the NO RISK group ($p < 0.001$). Only participants in the RISK group who had the potential for knowledge acquisition showed a statistically significant increase on the overall knowledge score (mean change score 1.77 SD (1.3)). The change in overall score was significantly greater among these individuals in the RISK group post-intervention compared to the NO RISK group (mean change score 0.91 95% CI (0.5, 1.3)).

3.5. Changes in beliefs

Beliefs about benzodiazepines were similar between groups at baseline. Tables 3a and 3b show changes in beliefs about the necessity, perceived negative consequences, and risk-benefit ratio of benzodiazepine use. Eighty-three percent (54/65) of participants in the RISK group had an improved BMQ-differential score (negative change) from baseline to follow-up, indicating increased risk perception, compared to 27% (31/79) of participants in the NO RISK group. The RISK group showed statistically significant group differences across all three of these BMQ outcomes ($p < 0.001$) while no significant group changes were detected in the NO RISK group. Post-intervention, the RISK group reported significantly lower scores on the necessity subscale (mean change score −1.31, 95% CI (−2.3, −0.4)), significantly higher scores on the concerns subscale (mean change score 3.72, 95% CI (2.9, 4.5)) and a statistically greater necessity-concerns differential (mean change score −5.03, 95% CI (−6.4, −3.6)), compared to the NO RISK group.

3.6. Frequency of cognitive dissonance

According to an operational definition of cognitive dissonance predicated upon a change in knowledge and a change in beliefs about benzodiazepine consumption due to receipt of the intervention, 44/65 (68%) of participants in the RISK group and 19/79 (24%) of participants in the NO RISK group experienced cognitive dissonance. The experience of cognitive dissonance was associated with a six-fold higher likelihood of patients reporting increased risk perception about their benzodiazepine prescription (OR = 6.61 95%CI (3.2, 13.8)).

Table 1
Descriptive demographic and health status characteristics at baseline. Values are mean, standard deviation (SD) or number (%).

Characteristics	All ($N = 144$)	RISK[a] ($N = 65$)	NO RISK[a] ($N = 79$)	*p*-Value
Female, *n* (%)	105 (73%)	47 (72%)	58 (73%)	0.88
Age (years), mean (SD)	74.9 (6.5)	75.3 (6.1)	74.6 (6.8)	0.52
College or University education, *n* (%)	25 (17%)	11 (17%)	14 (18%)	0.90
Living alone, *n* (%)	69 (48%)	29 (45%)	40 (51%)	0.47
MOCA[b], mean (SD)	25.4 (2.4)	25.4 (2.4)	25.4 (2.5)	0.94
General health status (fair to bad), *n* (%)	43 (30%)	19 (29%)	24 (30%)	0.88
Comorbidities, mean (SD)	7.0 (2.5)	6.8 (2.3)	7.1 (2.6)	0.62
Indication for taking Benzodiazepines, *n* (%)				
Insomnia	94 (65%)	42 (65%)	52 (66%)	0.88
Anxiety	64 (44%)	27 (42%)	37 (47%)	0.52
Duration of benzodiazepine use (years), mean (SD)	10.5 (8.2)	9.2 (7.8)	11.6 (8.4)	0.08
Previous attempts at cessation, *n* (%)	80 (56%)	32 (49%)	48 (61%)	0.24
Successful attempts, *n* (%)	20 (25%)	5 (16%)	15 (31%)	0.11

Independent sample *t*-test for continuous variables, chi square for categorical variables.
[*] Level of significance, $p < 0.05$ [28].
[a] RISK: Perceived an increased risk vs NO RISK: perceived no risk or same risk as pre-intervention.
[b] MOCA: The Montreal Cognitive Assessment (scale 0–30)

Table 2
Effect of the educational tool on knowledge. Values are number (%), mean or standard deviation (SD).

Variables		Within groups at one week						Between groups at week 1			
Questions		Group	Baseline	*p*-Value (between groups)	Post-intervention	CAIA[b], n (%)	*p*-Value (CAIA[b)]	Difference (%)	*p*-Value	Difference in CAIA[b] (%)	*p*-Value (CAIA[b)]
1 – safety, *n*		RISK[a] (*n* = 65)	23 (35.4%)	0.75	56 (86.2%)*	33/42 (78.6%)*	<0.001	34.3*	<0.001	39.9*	<0.001
(% with correct answer)		NO RISK[a] (*n* = 79)	26 (32.9%)		41 (51.9%)*	24/62 (38.7%)*	0.014				
2 – side-effects, *n*		RISK[a] (*n* = 65)	4 (6.2%)	0.51[c]	28 (43.1%)*	26/63 (41.3%)*	<0.001	30.4*	<0.001	30.5*	<0.001
(% with correct answer)		NO RISK[a] (*n* = 79)	3 (3.8%)		10 (12.7%)*	8/77 (10.4%)*	0.039				
3 – withdrawal, *n*		RISK[a] (*n* = 65)	13 (20.0%)	0.69	32 (49.2%)*	21/55 (38.2%)*	<0.001	11.6	0.13	11.7	0.17
(% with correct answer)		NO RISK[a] (*n* = 79)	18 (22.8%)		29 (36.7%)*	18/68 (26.5%)*	0.043				
4 – alternatives, *n*		RISK[a] (*n* = 65)	7 (10.8%)	0.17	41 (63.1%)*	35/60 (58.3%)*	<0.001	29.8*	<0.001	32.6*	<0.001
(% with correct answer)		NO RISK[a](*n* = 79)	15 (19.0%)		27 (34.2%)*	18/70 (25.7%)*	0.023				
Test score	Group	Baseline	*p*-Value (between groups)	Post-intervention	CAIA[b], Mean (SD)	*p*-Value (CAIA[b)]	Difference (95% CI)	*p*-Value	CAIA[b] (95% CI)	*p*-Value (CAIA[b)]	
Overall (/4), mean (SD)	RISK[a](*n* = 65)	0.72 (0.9)	0.69	2.42 (1.3)	1.77 (.1.3)*	<0.001	1.06 (.6, 1.5)*	<0.001	0.91 (.5, 1.3)*	<0.001	
	NO RISK[a] (*n* = 79)	0.79 (0.9)		1.35 (1.3)	0.86 (1.10)	0.682					

Within groups: Paired *t*-test for continuous Variables, McNemar's test for categorical variables. Between groups: Independent sample *t*-test for continuous variables, chi square for categorical variables.
[a] RISK: perceived an increased risk vs NO RISK: perceived no risk or same as pre-intervention.
[b] CAIA: change among those with an incorrect answer (excludes participants with correct answers at both time-points).
[c] Wilcoxon non-parametric test.
* Level of significance, $p < 0.05$ [28].

3.7. Change in self-efficacy for tapering benzodiazepines

The RISK group reported significantly greater improvements in self-efficacy for discontinuing benzodiazepines following the intervention (mean change score 31.24 95% CI (17.9, 44.6)) compared to the NO RISK group. The added benefit of the tapering protocol on self-efficacy scores for discontinuing benzodiazepines within the RISK group was an extra 6.05 points on the self-efficacy scale, 95% CI (3.0, 9.1). No statistically significant differences in self-efficacy were found in the NO RISK group.

3.8. Change in health behaviors aimed at discontinuing benzodiazepine use

Fig. 1 shows correlates and anticipated behaviors associated with an increased risk perception post-intervention. The RISK group reported a significantly higher likelihood of reading the tool more than once (OR = 8.34 95% CI (3.9, 17.9)), intention to discuss the intervention with family and friends (OR = 2.65 95% CI (1.3, 5.5)), and intention to discuss discontinuation with a physician (OR = 6.17 95% CI (2.8, 13.5)), or pharmacist (OR = 6.29 95% CI (2.8, 14.3)), compared to the NO RISK group.

4. Discussion and conclusion

Findings from this study indicate that a personalized patient-targeted benzodiazepine educational intervention delivered directly to the individual consumer via written material was effective in changing medication risk perceptions in 45% of older chronic users. Heightened risk perception was explained by significant changes in knowledge and beliefs about benzodiazepines due to receipt of the tool. Our study suggests that participants in whom the intervention elicited changes in knowledge and beliefs may have experienced cognitive dissonance as the mechanism underlying increased risk perception. Participants with increased risk perception reported greater self-efficacy for tapering benzodiazepines, and marked intent to engage in preventive health behaviors by discussing medication safety with a health professional.

The participants in this study are representative of other older chronic benzodiazepine users reported in previous studies, with a mean age of 77 years and a 10-year average duration of benzodiazepine use [6,9,26]. Neither age nor duration of use were significant predictors of the ability to perceive increased risk, suggesting that our intervention is effective in a wide range of individuals regardless of entrenched habits or beliefs. To the best of our knowledge, this study is the first to demonstrate a positive effect of targeting older adults directly about medication appropriateness, thereby bypassing health professionals and engaging patients as drivers of change to catalyze physicians and/or pharmacists in a collaborative effort to reduce medication-related risk.

4.1.1. Mechanisms underlying the change in risk perception

The educational intervention developed in the current study aimed to change risk perception by creating cognitive dissonance

Table 3a
Change in beliefs associated with risk perception post-intervention. Values are mean or standard deviation (SD).

Variables	Within groups at one week					Between groups at week 1	
	Group	Baseline	Post-intervention	Difference (95% CI)	*p*-Value	Difference (95% CI)	*p*-Value
Belief about necessity of the drug[b], Mean (SD)	RISK[a]	14.22 (3.3)	12.60 (2.4)	−1.62 (−2.5, −0.8)*	<0.001	−1.31 (−2.3, −0.4)*	0.007
	NO RISK[a]	13.97 (3.7)	13.91 (3.3)	−0.06 (−0.9, 0.8)	0.883		
Belief about side-effects of the drug[b], Mean (SD)	RISK[a]	13.40 (2.3)	16.14 (2.5)	2.75 (2.0, 3.5)*	<0.001	3.72 (2.9, 4.5)*	<0.001
	NO RISK[a]	12.71 (2.1)	12.42 (2.3)	−0.28 (−0.8, 0.3)	0.296		
Necessity Concern[c] differential, Mean (SD)	RISK[a]	0.83 (4.3)	−3.54 (3.8)	−4.37 (−5.6, −3.1)*	<0.001	−5.03 (−6.4, −3.6)*	<0.001
	NO RISK[a]	1.27 (4.6)	1.49 (4.4)	0.22 (−.9, 1.3)	0.697		
Self-efficacy for discontinuation of drug[d], Mean (SD)	RISK[a]	32.42 (33.4)	68.71 (36.6)	36.29 (24.8, 47.8)*	<0.001	31.24 (17.9, 44.6)*	<0.001
	NO RISK[a]	31.9 (35.1)	37.47 (42.4)	5.56 (−4.5, 15.6)	0.276		

Table 3b
Added impact of tapering tool on self-efficacy for discontinuation post-intervention.

Variables	Group	On their own	With Tapering tool	Added value of tool (95% CI)	*p*-Value	Difference (95% CI)	*p*-Value
Self-efficacy for discontinuation of drug[d], mean (SD)	RISK[a]	68.71 (36.6)	74.80 (32.3)	6.05 (3.0, 9.1)*	<0.001	32.66 (20.1, 45.2)*	<0.001
	NO RISK[a]	40.68 (42.4)	42.09 (41.6)	1.42 (−1.7, 4.5)	0.368		

Within groups: paired *t*-test, between groups: independent sample *t*-test.
[a] RISK: perceived an increased risk vs NO RISK: perceived no risk or same as pre-intervention.
[b] Specific-necessity and concern scales range from 5 to 25, higher scores indicating more agreement with the concept.
[c] "Benefit-risk ratio", necessity – concern scale, ranges from −20 to 20.
[d] Scaled from 0 to 100.
* Level of significance, $p < 0.05$ [28].

through self-assessment, new knowledge provision, and social comparison. We hypothesized that a change in knowledge and beliefs would create cognitive dissonance, thus leading to a change in risk perception. Unfortunately our study was not designed to ascertain cognitive dissonance directly. By operationalizing cognitive dissonance as a change in both knowledge and beliefs, we were able to show that individuals who experienced cognitive dissonance were six times more likely to report increased risk, thus supporting the application of constructivist learning theory. Interestingly, the intervention was only effective in changing risk perceptions in 45% of participants. This may be explained by the fact that many benzodiazepine users are psychologically dependent on their medication. This psychological dependence likely creates compelling opposition to new learning and denial of risk, possibly explaining the lack of significance across all components of the tool for the 55% of participants who reported no increase in risk perception. Our findings are consistent with another study on medication discontinuation where the majority of participants tended to reject the first suggestion of discontinuation [6], as well as with studies on breast cancer risk by Alexander et al. where only 50% of participants changed risk perceptions when presented with an educational intervention [27].

Baseline knowledge was similar across all participants, with the greatest knowledge change occurring in participants who perceived increased risk. Participants who correctly answered the knowledge questions post-intervention were eight times more likely to reread the tool (OR = 8.34, 95% CI (3.9, 17.9)) than those who perceived no increased risk suggesting that rereading the intervention may be associated with better learning.

4.1.2. Preventive health behavior

Our results also showed a significant difference between groups on self-reported intent to discuss medication discontinuation with a family member, pharmacist or physician. These measures signify readiness to engage in preventive health behaviors. Whether or not these intentions translate into action remains to be determined.

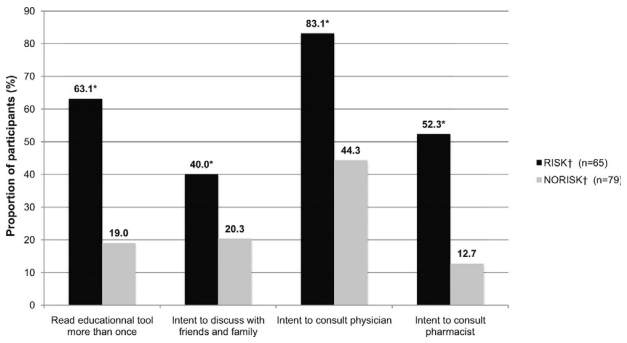

Fig. 1. Correlates and anticipated behaviors associated with risk perception. † RISK: perceived an increased risk vs NO RISK: perceived no risk or same as pre-intervention. *$p < 0.01$ for difference between groups using chi-square.

4.1.3. Strengths and limitations

The major strength of this study was systematic measurement of knowledge, beliefs and risk perceptions. Missing data was imputed to reflect a worst-case scenario, and at best underestimated the impact of the intervention. Few validated instruments exist to reliably measure benzodiazepine-related knowledge, beliefs and behaviors. Although the BMQ-Specific questionnaire has been previously tested, the benzodiazepine-related knowledge questions were not. Similarly, risk perception was measured with a single self-reported item and not a full instrument, and the elicitation of cognitive dissonance was assumed rather than measured directly. Finally, this study was conducted in community pharmacies and thus is not generalizable to frailer patients living in health care facilities or long-term care.

4.2. Conclusion

In conclusion, a home-based educational program consisting of a document mailed to participants demonstrated significant effects on medication knowledge, beliefs and risk perception in a cohort of older benzodiazepine users. By changing knowledge and increasing perceived risk, consumer-targeted drug information elicited a desire among many older adults to discuss medication safety with their health care providers. The results of an ongoing randomized trial will demonstrate whether these changes wrought by the educational intervention are sufficient to result in discontinuation of inappropriate prescriptions.

4.3. Practice implications

The aging consumer may be an under-utilized catalyst of change for reducing potentially inappropriate prescriptions.

Funding

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Conflict of interest

None.

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Appendix 7

Original Investigation

Reduction of Inappropriate Benzodiazepine Prescriptions Among Older Adults Through Direct Patient Education
The EMPOWER Cluster Randomized Trial

Cara Tannenbaum, MD, MSc; Philippe Martin, BSc; Robyn Tamblyn, PhD; Andrea Benedetti, PhD; Sara Ahmed, PhD

IMPORTANCE The American Board of Internal Medicine Foundation Choosing Wisely Campaign recommends against the use of benzodiazepine drugs for adults 65 years and older. The effect of direct patient education to catalyze collaborative care for reducing inappropriate prescriptions remains unknown.

OBJECTIVE To compare the effect of a direct-to-consumer educational intervention against usual care on benzodiazepine therapy discontinuation in community-dwelling older adults.

DESIGN, SETTING, AND PARTICIPANTS Cluster randomized trial (EMPOWER [Eliminating Medications Through Patient Ownership of End Results] study [2010-2012, 6-month follow-up]). Community pharmacies were randomly allocated to the intervention or control arm in nonstratified, blocked groups of 4. Participants (303 long-term users of benzodiazepine medication aged 65-95 years, recruited from 30 community pharmacies) were screened and enrolled prior to randomization: 15 pharmacies randomized to the educational intervention included 148 participants and 15 pharmacies randomized to the "wait list" control included 155 participants. Participants, physicians, pharmacists, and evaluators were blinded to outcome assessment.

INTERVENTIONS The active arm received a deprescribing patient empowerment intervention describing the risks of benzodiazepine use and a stepwise tapering protocol. The control arm received usual care.

MAIN OUTCOMES AND MEASURES Benzodiazepine therapy discontinuation at 6 months after randomization, ascertained by pharmacy medication renewal profiles.

RESULTS A total of 261 participants (86%) completed the 6-month follow-up. Of the recipients in the intervention group, 62% initiated conversation about benzodiazepine therapy cessation with a physician and/or pharmacist. At 6 months, 27% of the intervention group had discontinued benzodiazepine use compared with 5% of the control group (risk difference, 23% [95% CI, 14%-32%]; intracluster correlation, 0.008; number needed to treat, 4). Dose reduction occurred in an additional 11% (95% CI, 6%-16%). In multivariate subanalyses, age greater than 80 years, sex, duration of use, indication for use, dose, previous attempt to taper, and concomitant polypharmacy (10 drugs or more per day) did not have a significant interaction effect with benzodiazepine therapy discontinuation.

CONCLUSIONS AND RELEVANCE Direct-to-consumer education effectively elicits shared decision making around the overuse of medications that increase the risk of harm in older adults.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT01148186

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The US Patient Protection and Affordable Health Care Act encourages greater use of shared decision making in health care through provision of evidence-based information that apprises patients of the risks and benefits of different treatments.[1] Based on the concepts of patient-centered medicine and patient preferences, consumer education is a core tenet of promoting collaborative self-management for cost containment and health improvement.[2,3] However, the effect of involving patients in the decision to curtail medical treatments and resources is viewed by some as expecting too much.[4]

In 2012, the American Board of Internal Medicine (ABIM) Foundation launched its Choosing Wisely campaign to help physicians and patients select which interventions should be discontinued to reduce the overuse of medical resources that increase the risk of harm.[5] As part of this campaign, the American Geriatrics Society advised physicians and patients to refrain from using benzodiazepines as first-line treatment for insomnia in older adults.[6] The decision to target benzodiazepines derives from the potential for benzodiazepines to elicit cognitive deficits and increase the risk of falls and hip fractures.[7-10] Benzodiazepines comprise 20% to 25% of inappropriate prescriptions in the elderly,[11,12] with a reported prevalence of use ranging from 5% to 32% in community-dwelling older adults.[13-15] Although physicians recognize the risks associated with benzodiazepines, almost 50% continue to renew prescriptions, citing patient dependence and benefit as justification for their actions.[16-19]

The effect of direct-to-consumer patient education and empowerment to reduce benzodiazepine prescriptions has not yet been fully examined.[20] Direct-to-consumer advertising of prescription drugs by the pharmaceutical industry has clearly been shown to influence patient demand for medicines.[21] However, there is concern that inconsistent enforcement of the US Food and Drug Administration (FDA) requirement to provide consumers with a balanced presentation of risks and benefits in the drug information package, and the lack of subsequent revision to include data on drug harms from postmarketing pharmacoepidemiological research, has led to inappropriate overuse of some prescription drugs.[21,22] Educational interventions aimed at achieving patient empowerment around medication overtreatment has potential to catalyze shared decision making to deprescribe. Patient empowerment is a process that aims to "help people gain control, which includes people taking the initiative, solving problems, and making decisions, and can be applied to different settings in health and social care and self-management."[23]

The objective of the EMPOWER (Eliminating Medications Through Patient Ownership of End Results) cluster randomized trial was to test the effectiveness of direct patient education about drug harms on benzodiazepine therapy discontinuation among community-dwelling adults 65 years and older receiving long-term benzodiazepine therapy. Secondary objectives were to assess rates of dose reduction in addition to complete cessation and to conduct a process evaluation of subsequent events after receipt of the intervention. Cluster randomization served to prevent contamination between participants in the same pharmacy.

Methods

Design, Setting, and Participants

A 2-arm, parallel-group, pragmatic cluster randomized clinical trial was conducted in Quebec, Canada. The trial protocol has been published.[24] The Research Ethics Board of the Centre de Recherche de l'Institut Universitaire de Gériatrie de Montreal approved the study protocol on July 26, 2009. All patients signed an informed consent form prior to the screening interview. Recruitment occurred between July 2010 and November 2012.

The study included 30 community pharmacies (cluster units) in the greater Montreal area. Eligibility criteria for clusters included local community pharmacies with 20% or more of their clientele consisting of older adults and a minimum of 50 eligible participants. A full list of pharmacies within 200 km of the research center was obtained through collaboration with the pharmacy chain's headquarters. This list was randomized, and pharmacies were systematically contacted by the research team to assess interest in participating.

The sampling frame for individual participants was a list of all adults 65 years and older receiving long-term benzodiazepine therapy from each participating pharmacy, provided to pharmacists by the central database system of the pharmacy chain. Eligibility criteria for individual participants included a minimum of 5 active prescriptions, one being an active benzodiazepine prescription (short, medium, or long acting) dispensed for at least 3 consecutive months prior to screening. Participants with polypharmacy (>5 medications) were recruited to extend the generalizability of the findings from this trial to the typical elderly benzodiazepine user with multimorbidity and associated polypharmacy. Exclusion criteria included a diagnosis of severe mental illness or dementia, an active prescription for any antipsychotic medication and/or a cholinesterase inhibitor or memantine in the preceding 3 months, and residence in a long-term care facility. All clients meeting study criteria received a recruitment mailing followed by telephone call invitations from their pharmacists. Patients who expressed interest in participating in the study were directed to the study team and screened for eligibility via in-home interviews with a research assistant. Clients who were unreachable after 3 attempts were not recontacted. During the in-home interview, patients with evidence of cognitive impairment, defined by a screening score less than 21 on the Montreal Cognitive Assessment, were excluded.[25] Baseline demographic data and information on the indication for and duration of benzodiazepine use, as well as any previous attempts at discontinuation, were collected. Health status was determined (excellent, very good, good, fair, or poor). The presence of an anxiety disorder was ascertained by a score of 9 or higher on the Geriatric Anxiety Inventory.[26]

Intervention

The patient empowerment intervention consisted of an 8-page booklet based on social constructivist learning and self-efficacy theory, and its development and testing have been previously detailed.[24] The intervention comprises a self-

assessment component about the risks of benzodiazepine use, presentation of the evidence for benzodiazepine-induced harms, knowledge statements designed to create cognitive dissonance about the safety of benzodiazepine use, education about drug interactions, peer champion stories intended to augment self-efficacy, suggestions for equally or more effective therapeutic substitutes for insomnia and/or anxiety, and stepwise tapering recommendations.[24] Tapering recommendations consist of a visual 21-week tapering protocol showing a picture-based diminishing schedule of full-pill, half-pill, and quarter-pill consumption. The visual schematic for the deprescribing protocol was proposed by consumers during the development and usability testing of the intervention to enable application to any benzodiazepine, regardless of dose. The intervention asks participants to discuss the deprescribing recommendations with their physician and/or pharmacist. The information is included in a letter-size paper handbook, with the language set at a sixth-grade reading level and written in 14-point font to facilitate accessibility to the material. The intervention was personalized according to the participant's pharmacy profile to include the name of the specific benzodiazepine the participants was taking. The intervention was mailed to the intervention group within 1 week of group allocation while the usual care (wait list) group received the educational tool 6 months following group allocation. A full version of the intervention is available in the eAppendix in the Supplement.

Outcomes

The primary outcome was complete cessation of benzodiazepine use in the 6 months following randomization. Cessation was defined as an absence of any benzodiazepine prescription renewal at the time of the 6-month follow-up that was sustained for 3 consecutive months or more, in the absence of substitution to another benzodiazepine. This was ascertained via pharmacy renewal profiles, which contained information on drugs purchased, dates of purchase, dose, and quantity served. Dose reduction was defined as a 25% or greater dose reduction compared with baseline sustained for 3 consecutive months or more. A baseline average daily dose per month was established using pharmaceutical profiles for the 6 months before randomization. Dose reduction was then calculated by comparing patients' average daily dose per month at 6 months after randomization compared with baseline. All doses were converted to lorazepam equivalents. To ensure an accurate representation of the pharmaceutical profiles, a list of pharmacies visited by participants was collected at baseline. At follow-up, patients were queried whether they switched pharmacies. A complete follow-up with the pharmacy in use at the 6-month follow-up was completed for all study participants. One investigator (P.M.) and 1 research nurse, blinded to group allocation, independently assessed outcomes according to a prespecified protocol. Agreement was obtained in 94% of cases, with differences adjudicated by a third investigator (C.T.).

Process Evaluation

After the primary end point had been ascertained using the pharmacy renewal profiles and in order to understand the events that occurred after receipt of the intervention, a 6-month semistructured interview was conducted by telephone with participants in the intervention group. Interviews lasted approximately 30 minutes. Participants were queried whether they had discussed the possibility of tapering their benzodiazepine medication with a physician, pharmacist, or both (yes/no); what was decided during these discussions (open ended); whether tapering was attempted (yes/no); if any difficulties were encountered during the tapering process (open ended); reasons why any attempts failed (open ended); justification of why participants felt they did not want to discontinue their benzodiazepine medication (open ended); and satisfaction about learning about the risks of benzodiazepine use (yes/no).

Randomization and Allocation Concealment

A 1:1 allocation ratio was assigned by an independent statistician using nonstratified blocked randomization for groups of 4 pharmacies using computer-generated random digits. The study was described as a "medication safety study for older adults" without mention of benzodiazepines in particular; thus, participants remained blinded to the intervention at the time of enrollment. Group allocation was concealed from both the pharmacists and their clients by telling them that the intervention would be delivered to the clients at some point during the next year.

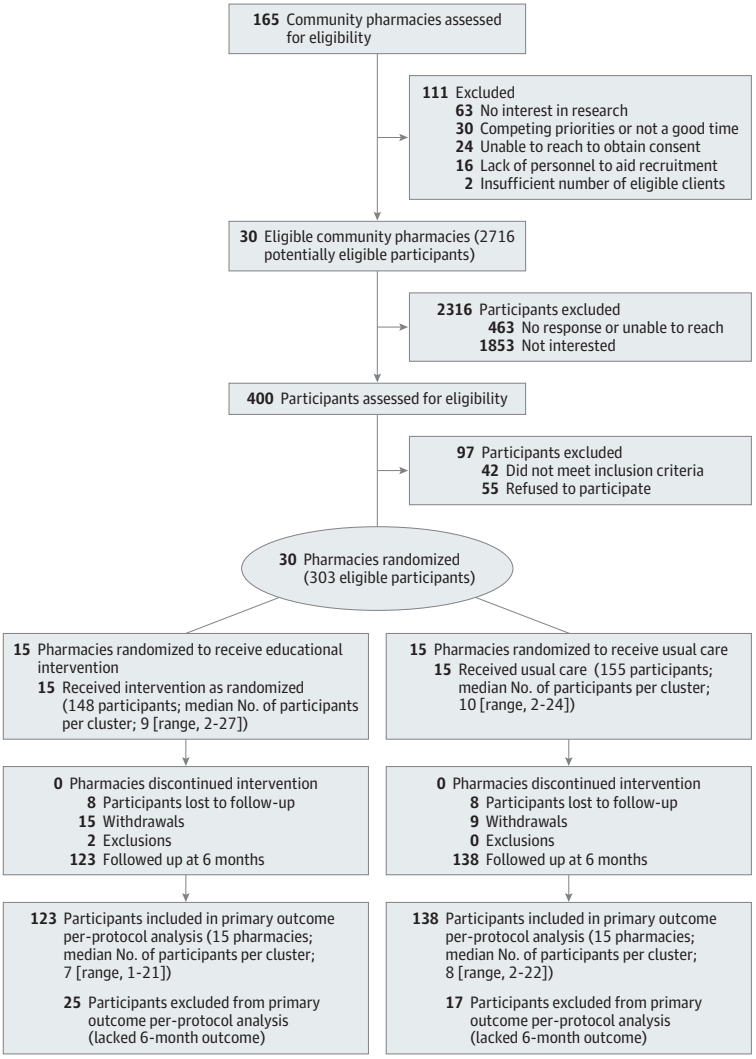
Sample Size

The study was powered at 80% (2-sided test α level of .05) to detect a minimal 20% difference in benzodiazepine therapy discontinuation due to the use of the intervention.[19,27-33] On the basis of the study results, we calculated a coefficient of variation (kappa) of 0.62, an intracluster correlation (ICC) of 0.008, and a median cluster size of 10.1, which resulted in a maximum design effect of 1.03. A minimal sample size per group of 60 individuals was therefore required.[34]

Statistical Methods

Differences in baseline characteristics between groups were compared. To assess the primary outcome, we estimated the unadjusted risk difference (prevalence of the outcome) and 95% confidence intervals via generalized estimating equations (GEEs) using the participant as the unit of analysis, the pharmacy as the cluster, an exchangeable correlation coefficient to account for clustering effects of participants within each pharmacy, and discontinuation as a dichotomous outcome, assessed for each participant at 6 months after randomization. Both intent-to-treat (ITT) and per-protocol analyses were performed. Participants who were lost to follow-up were designated as having neither discontinued nor reduced the dose of benzodiazepines in ITT analyses. Generalized estimating equations with an identity link and an exchangeable correlation structure were used to account for possible correlation between individuals in the same cluster.[35] The number needed to treat was calculated as the inverse of the difference in absolute event rates between the experimental and control groups.[36] In secondary analyses, to control for possible confounding effects between groups, multiple logistic regression

Figure 1. Trial Flow



models were used, with age (<80 years vs ≥80 years), sex, education (high school or less vs college or university), health status (fair and poor vs other), benzodiazepine use for insomnia (yes/no), anxiety disorder detected with the Geriatric Anxiety Inventory (yes/no), benzodiazepine dose (<0.8-mg/d lorazepam equivalent vs ≥0.8 mg/d),[37] previous attempt at tapering (yes/no), duration of benzodiazepine use (<5 years or ≥5 years), and number of medications (<10 per day vs ≥10 per day) included in the model. To determine whether any of the aforementioned-listed characteristics differentially impacted on cessation rates, analyses were performed to estimate risk differences for each of the subgroups using interaction terms in the GEE model under ITT and per-protocol conditions. Proportions of participants reporting having discussed discontinuation with a physician or pharmacist were calculated. Responses to the open-ended questions about failure to initiate discontinuation or abandonment of the tapering protocol were analyzed by content analysis according to emergent themes. All statistical analyses were run using RStudio 0.97.310.0, R-3.0.2, with statistics subpackage for GEE (RStudio Inc), an integrated development environment for R.

Results

Study Participants and Follow-up

A total of 165 community pharmacies were consecutively contacted over a 2-year period. Of these, 30 pharmacies (18%) consented. The most common reasons for nonparticipation in the project included lack of interest in participating in a research project (n = 63 [38%]), competing priorities (n = 30 [27%]), inability to reach the pharmacy owner to obtain consent (n = 24 [15%]), and inadequate personnel to aid recruitment (n = 16 [10%]) (**Figure 1**). The centralized electronic pharmacy records database identified 2716 potentially eligible clients in the participating pharmacies who were 65 years and older and who

Table 1. Participant Characteristics at Baseline

Variable	Intervention (n = 148)	Control (n = 155)
Age, mean (SD) [range], y	75.0 (6.5) [65-91]	74.6 (6.2) [65-95]
Female, %	70.3	68.4
College or university education, %	21.6	25.8
Lives alone, %	46.6	54.8
Self-reported fair or poor health, %	35.8	34.8
Montreal Cognitive Assessment, mean (SD) [range], score	25.4 (2.4) [21-30]	25.4 (2.5) [21-30]
Self-reported indication for benzodiazepine use, %		
Insomnia	60.8	60.0
Anxiety	45.9	49.0
Pain	2.7	3.2
Other	6.8	6.5
Anxiety disorder, %[a]	32.4	30.3
Benzodiazepine dose in mg of lorazepam equivalents per day, mean (SD) [range]	1.2 (0.8) [0-4.8]	1.3 (0.8) [0-4]
Benzodiazepine type, %[b]		
Short acting	29.1	24.5
Intermediate acting	66.2	72.9
Long acting	4.7	2.6
Duration of benzodiazepine use, mean (SD) [range], y	9.6 (8.7) [0.3-48.0]	11.2 (8.3) [0.5-40.0]
Previously attempted cessation, %	45.2	49.4
No. of medications per day	9.9 (3.9 6) [4-24]	9.9 (3.4) [4-21]

[a] Score of 9 or greater on the Geriatric Anxiety Index.

[b] Short-acting benzodiazepines: oxazepam and alprazolam; intermediate-acting benzodiazepines: lorazepam, bromazepam, clonazepam, and temazepam; and long-acting benzodiazepines: flurazepam and diazepam.

regularly renewed benzodiazepine prescriptions. Approximately 1 in 6 spoke with their pharmacist and agreed to meet with the research team. Four hundred clients were screened for eligibility, and 75% agreed to participate and were eligible to enroll in the trial. In total, 30 clusters and 303 eligible participants were randomized. Figure 1 depicts the study flow of the clusters and the participants for the trial. The median (range) number of participants per cluster was 10 (2-27).

Of the 303 participants randomized, 261 were available for 6-month follow-up (86%). There was no difference in the baseline characteristics of participants who withdrew or were lost to follow-up between or within trial arms. The mean (SD) age of the participants at baseline was 75 (6.3) years, 69% were women, and one-quarter (24%) had earned a college degree. The most common self-reported indications for taking a benzodiazepine were insomnia (60%) and/or anxiety (48%). Participants used benzodiazepines for mean duration of 10 years and had an average daily dose consumption of 1.3-mg equivalents of lorazepam (**Table 1**).

Outcomes

In ITT analyses, complete cessation was achieved in 40 of 148 participants (27%) compared with 7 of 155 controls (5%) (prevalence difference, 23%; 95% CI, 14%-32%) (**Table 2**). There was a crude 8-fold higher likelihood of achieving discontinuation among those who received the intervention compared with controls (odds ratio, 8.1; 95% CI, 3.5-18.5) and an adjusted odds ratio of 8.3 (95% CI, 3.3-20.9) when all baseline characteristics were accounted for. **Figure 2** illustrates the risk differences for discontinuation of benzodiazepines in subgroups of participants by treatment allocation using ITT analysis. No significant interactions were observed between the intervention assignment and participant characteristics, suggesting that the effect of the intervention was robust across variable predisposing characteristics. An additional 11% (95% CI, 6%-16%) of individuals who received the intervention achieved dose reductions. The number needed to treat for any discontinuation or dose reduction was 3.7 in ITT analyses (Table 2). Per-protocol analysis yielded similar results.

Patient Empowerment and Process Evaluation

Six-month telephone follow-up interviews with all participants in the intervention group who completed the trial (n = 123) revealed that 62% initiated discussions about benzodiazepine therapy discontinuation with their physician and/or pharmacist, and 58% attempted discontinuation (**Table 3**). The majority (72%) of participants desiring discontinuation opted to follow the tapering protocol provided. Others required a customized tapering protocol because more than 1 benzodiazepine was being used or because the type of benzodiazepine pills or capsules could not easily be halved or quartered and substitution was required to appropriately taper. Of the 71 participants who attempted cessation, 38 (54%) were successful; 16 (22%) achieved dose reduction, of which one-third was continuing the tapering process; and 17 (24%) failed. Withdrawal symptoms such as rebound insomnia or anxiety occurred in 42% of participants attempting to taper. No major adverse effects requiring hospitalization were reported. Of the 40 participants, 5 (13%) who discontinued benzodiazepine therapy received substitutions with trazodone (3 cases), paroxetine (1 case), or amitriptyline (1 case). In 7 individuals who attempted to taper, complete discontinuation was discouraged by their health professional. Among the 52 recipients who elected not to taper, discouragement by their physician or pharmacist was the most common reason provided (n = 17 [33%]), followed by fear of withdrawal symptoms (n = 13 [25%]), lack of concern about taking benzodiazepines (n = 12 [23%]), and difficult life circumstances (n = 6 [12%]). Several participants reported that their physician discouraged use of the tapering protocol because of a perceived absence of adverse effects from their benzodiazepine use. Of the 123 participants, 120 (98%) acknowledged satisfaction with receiving medication risk information.

Discussion

Delivery of an empowerment intervention to engage older adults in discussing the harms of benzodiazepine use with their physician and/or pharmacist yielded a benzodiazepine discontinuation rate of 27% compared with 5% in the control group

Table 2. Prevalence, Risk Difference, and Odds Ratios for Discontinuation and Discontinuation Plus Benzodiazepine Dose Reduction at the 6-Month Follow-up

Variable	Participants, No.	Outcome, No. (%)	Risk Difference (95% CI)[a]	No. Needed to Treat	Crude OR (95% CI)	Adjusted OR (95% CI)[b]
Discontinuation of benzodiazepine use						
Intention to treat analysis						
Intervention	148	40 (27.0)	0.23 (0.14-0.32)	4.35	8.05 (3.51-18.47)	8.33 (3.32-20.93)
Usual care	155	7 (4.5)				
Intracluster correlation			0.008		0.008	0.010
Per protocol analysis						
Intervention	123	38 (30.9)	0.26 (0.16-0.36)	3.85	8.53 (3.69-19.76)	8.10 (3.34-19.66)
Usual care	138	7 (5.1)				
Intracluster correlation			0.007		0.007	0.005
Discontinuation plus benzodiazepine dose reduction						
Intention to treat analysis						
Intervention	148	56 (37.8)	0.27 (0.18-0.37)	3.70	5.05 (2.66-9.59)	5.49 (2.78-10.84)
Usual care	155	17 (11.0)				
Intracluster correlation			0.006		0.006	0.010
Per protocol analysis						
Intervention	123	54 (43.9)	0.34 (0.22-0.45)	2.94	6.33 (3.10-12.92)	6.73 (3.12-14.55)
Usual care	138	16 (11.6)				
Intracluster correlation			0.030		0.030	0.020

[a] 95% Confidence intervals were calculated using robust standard errors.

[b] Adjusted for age, sex, education, health status, indication of benzodiazepine use for insomnia, anxiety disorder, benzodiazepine dose, previous attempt at tapering, duration of benzodiazepine use, and number of medications.

6 months after the intervention. An additional 11% of recipients achieved dose reductions. The effect of the intervention was robust across age, indication, dose, and duration of benzodiazepine use.

Strengths and Weaknesses of the Study

Strengths of this study include systematic recruitment of participants via community pharmacies; blinding of the study hypothesis from participants, physicians, pharmacists, and evaluators; and objective assessment of drug discontinuation rates from pharmacy prescription renewal profiles. Compared with previous studies, this trial exclusively targeted seniors older than 65 years, examined patient empowerment as a means of initiating shared decision making around potentially harmful medication, and addressed the issue from the patient's rather than the physician's perspective.[19,27-29,38,39] One limitation is the 6-month time frame for outcome reporting. Longer follow-up times could reveal relapse rates or higher discontinuation rates as several participants who achieved dose reductions were still following the tapering protocol at study end point. Recruitment rates for pharmacies (18%) and individual participants (11%) were low and excluded potential participants with cognitive impairment. Despite this, selection bias is unlikely because neither pharmacists nor participants were aware of the primary outcome of the study other than it being a medication safety study for older adults. Pharmacies were recruited systematically across socioeconomic and geographic living areas around Montreal, and although data on participant income could not be collected, no differences between groups were observed on other variables that correlate with poverty in the senior population such as female sex, educational status, and polypharmacy.[40,41] Subgroup analyses may have been underpowered to detect differences. Cursory content analysis of the events that followed receipt of the intervention may have been limited by patient recall and the nonintimate nature of the 6-month follow-up. The process of shared decision making around benzodiazepine therapy discontinuation and physicians' motivations for counseling against benzodiazepine therapy discontinuation could not be evaluated because there was no direct contact with physicians during the trial.

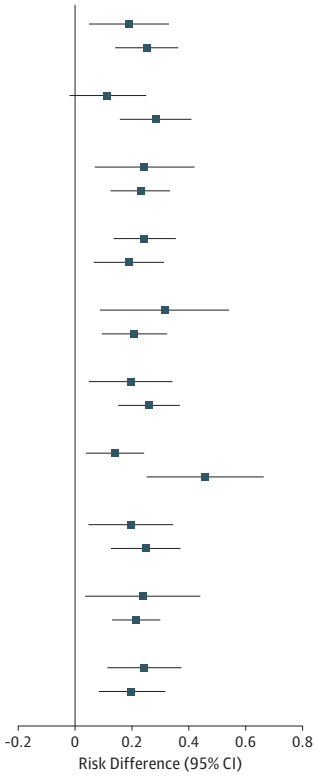
Relevance of the Findings and Implications for Clinicians

Our findings suggest that direct-to-consumer education successfully leads to discussions with physicians and/or pharmacists to stop unnecessary or harmful medication. Discontinuation or dose reduction of benzodiazepines occurred in more than one-third of the participants who received the empowerment intervention. The Beers criteria for inappropriate use of medications provide guidance for 53 drugs to be avoided in the elderly.[10] This trial only addressed deprescription of benzodiazepine medication, which arguably may be one of the most difficult classes of medication to withdraw because of psychological and physical dependence.[15,42]

Previous studies have examined the effect of other types of brief interventions by physicians on patient discontinuation of benzodiazepine use, as well as pharmacist-initiated communication with general practitioners to deprescribe potentially inappropriate medication.[31,43,44] Sending a letter of advice from family physicians to patients achieved a discontinuation rate of 24% at 6 months, but the effect size was reported as much lower because 12% of participants in the con-

Figure 2. Risk Differences for Discontinuation of Benzodiazepines in Subgroups

Subgroup	Risk Difference, (95% CI)	ICC
Sex		
Men	0.19 (0.06 to 0.32)	0
Women	0.25 (0.15 to 0.35)	0.022
Age, y		
≥80	0.11 (-0.01 to 0.24)	0
<80	0.29 (0.17 to 0.40)	0.038
Education level		
University or college	0.25 (0.08 to 0.41)	0.126
<High school	0.23 (0.14 to 0.32)	0.012
General health status		
Good to excellent	0.24 (0.15 to 0.345)	0
Poor to fair	0.19 (0.08 to 0.30)	0
Anxiety disorder		
Yes	0.32 (0.10 to 0.53)	0.150
No	0.21 (0.10 to 0.31)	0.010
Indication for benzodiazepine use		
Insomnia	0.20 (0.06 to 0.33)	0.030
Other reasons	0.26 (0.16 to 0.36)	0
Dose		
High (>0.8-mg/d equivalent dose)	0.14 (0.05 to 0.23)	0.010
Low (≤0.8-mg/d equivalent dose)	0.46 (0.26 to 0.66)	0.110
Previously attempted to cease benzodiazepine use		
Yes	0.20 (0.06 to 0.33)	0.020
No	0.25 (0.14 to 0.36)	0
Duration of benzodiazepine use, y		
<5	0.24 (0.05 to 0.43)	0
≥5	0.22 (0.14 to 0.29)	0
No. of medications		
<10	0.24 (0.13 to 0.36)	0
≥10	0.20 (0.10 to 0.31)	0



Forest plot of risk differences (95% CIs) for benzodiazepine discontinuation due to the intervention within subgroups of interest. ICC indicates intracluster correlation.

Table 3. Effect of the Empowerment Intervention on Self-reported Participant Empowerment

Self-reported Participant Empowerment	Participants, No. (%)		
	All (n = 123)	Discontinuation of Benzodiazepine Use (n = 38)	Discontinuation or Benzodiazepine Dose Reduction (n = 54)
Discussion with a health professional after receipt of the intervention			
Physician only	44 (35.8)	14 (36.8)	20 (37.0)
Pharmacist only	5 (4.0)	2 (5.3)	2 (3.7)
Both	27 (21.9)	13 (34.2)	18 (33.3)
Neither	47 (38.2)	9 (23.6)	14 (25.9)
Attempt to discontinue			
Yes, using the tapering protocol in the brochure	51 (41.4)	26 (68.4)	32(59.3)
Yes, using a customized protocol from a physician or pharmacist	18 (14.6)	10 (26.3)	14 (25.9)
Yes, method not stated	2 (1.6)	2 (5.3)	2 (3.7)
No	52 (42.3)	0	6 (11.1)
Patient satisfaction with receipt of the intervention			
Appreciated receiving medication risk information	120 (97.5)	38 (100)	54 (100)

trol group also achieved discontinuation.[28] Our use of a cluster randomized design with prerandomization enrolment of participants may help explain the larger effect seen in the present study. Furthermore, the added value of directly educating the patient, in the absence of initial physician involvement, likely promotes patient buy-in for discontinuation at an early stage and allows the patient to act as a catalyst for initiating discussions about medication management, which is a more effective approach than the traditional paternalistic approach to patient care.[23] The booklet used for this trial, which directly delivers information on drug harms to patients, could be distributed in the nonresearch environment in pharma-

cies or on the Internet in conjunction with other community education initiatives such as the American Geriatrics Society website (http://www.healthinaging.org), thus achieving widespread reach.

Three issues arise for future consideration. First, participants reported that their physician discouraged discontinuation of benzodiazepines in several cases. Many physicians continued to perceive the benefits of benzodiazepines as outweighing their risks.[19] Second, benzodiazepines were sometimes substituted with equally harmful sedative medication. A similar phenomenon was found to occur in US nursing home residents when coverage for benzodiazepine medications was interrupted during implementation of the Medicare Part D reimbursement policy in 2006.[45] Continuing medical education to physicians about the harms of all sedative hypnotic medication may eventually overcome this obstacle. Third, pharmacists were solicited less often than physicians to discuss benzodiazepine therapy discontinuation. With the expanding scope of pharmacists' practice and an increasing emphasis on interprofessional models of care, community pharmacists may be underutilized players to participate in efforts to reduce costly and unnecessary medical treatments.[46]

Conclusions

Supplying older adults with evidence-based information that allows them to question medication overtreatment appears safe and effective and is consistent with the priorities expressed by the ABIM Choosing Wisely campaign. Without a direct-to-patient educational component, promotional efforts for deprescription to physicians may fail or have a smaller impact. In an era of multimorbidity, polypharmacy, and costly therapeutic competition, direct-to-consumer education is emerging as a promising strategy to stem potential overtreatment and reduce the risk of drug harms. The value of the patient as a catalyst for driving decisions to optimize health care utilization should not be underestimated.

ARTICLE INFORMATION

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Additional Information: Patient-level data and the full dataset are available on request from the authors.

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Appendix 8

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BMC Geriatrics

RESEARCH ARTICLE Open Access

Use of the EMPOWER brochure to deprescribe sedative-hypnotic drugs in older adults with mild cognitive impairment

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Abstract

Background: Evidence-based mailed educational brochures about the harms of sedative-hypnotic use lead to discontinuation of chronic benzodiazepine use in older adults. It remains unknown whether patients with mild cognitive impairment (MCI) are able to understand the information in the EMPOWER brochures, and whether they achieve similar rates of benzodiazepine discontinuation.

Methods: Post-hoc analysis of the EMPOWER randomized, double-blind, wait-list controlled trial that assessed the effect of a direct-to-consumer educational intervention on benzodiazepine discontinuation. 303 community-dwelling chronic users of benzodiazepine medication aged 65–95 years were recruited from general community pharmacies in the original trial, 261 (86%) of which completed the trial extension phase. All participants of the control arm received the EMPOWER brochure during the trial extension. Normal cognition ($n = 139$) or MCI ($n = 122$) was determined during baseline cognitive testing using the Montreal Cognitive Assessment questionnaire. Changes in knowledge pre- and post-intervention were assessed with a knowledge questionnaire and changes in beliefs were calculated using the Beliefs about Medicines Questionnaire. Logistic regression was used to compare knowledge gained, change in beliefs and benzodiazepine cessation rates between participants with and without MCI.

Results: Complete discontinuation of benzodiazepines was achieved in 39 (32.0% [24.4,40.7]) participants with MCI and in 53 (38.1% [30.5,46.4]) with normal cognition (adjusted OR 0.79, 95% CI [0.45–1.38]). Compared to individuals with normal cognition, MCI had no effect on the acquisition of new knowledge, change in beliefs about benzodiazepines or elicitation of cognitive dissonance.

Conclusions: The EMPOWER brochure is effective for reducing benzodiazepines in community-dwelling older adults with mild cognitive impairment.

Trial registration: Our ClinicalTrials.gov identifier is NCT01148186, June 21st 2010.

Keywords: Patient education, Benzodiazepines, Inappropriate prescription, Deprescribing, Discontinuation

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Background

Sedative-hypnotic use is associated with cognitive impairment, and may contribute to mild neurocognitive disorders in older adults [1–3]. For this reason, both long and short-acting benzodiazepines are listed in the 2015 Beers criteria of medications to avoid in older adults [3]. A mild neurocognitive disorder is defined in the DSM-5 as a noticeable decrement in cognitive function beyond that of normal aging, which requires individuals to engage in compensatory strategies to maintain independence [4]. The term is meant to replace the previously used diagnosis of mild cognitive impairment (MCI). Over 1-in-5 community dwelling older adults have MCI at any given time, although the exact prevalence is difficult to estimate due to the variability in the criteria used, the source of subjects, the fluctuating nature of the condition and the reference standards [5, 6]. Individuals with MCI may demonstrate significant impairments in their ability to understand, reason and participate in health related decisions [7]. Longitudinal data suggest that medical decision-making capacity in patients with MCI tends to decline over time [8].

The majority of long-term benzodiazepine users aged 65 years of age and older report not being concerned about side effects, mainly because they have never been alerted to the risks [9]. However, when provided with evidence-based information about harm in the form of a mailed educational brochure, 27% of chronic users discontinued benzodiazepines within 6 months in the EMPOWER trial [10]. It remains unknown whether patients with MCI retain capacity to understand the material in the brochure, and whether they respond equally well to the educational intervention. The objective of this report is to examine whether cognitive status affected the comprehension and success rates of the EMPOWER patient-centered educational approach to the deprescribing of benzodiazepines.

Design & methods

Study population

Participants in the EMPOWER trial were adults aged 65 years and older with polypharmacy (≥5 medications), taking at least one chronic benzodiazepine prescription (≥3 months). Participants with self-reported epilepsy, a diagnosis of established dementia, or a mental health disorder requiring treatment with antipsychotic medication, were deemed ineligible. In order to exclude patients with undiagnosed dementia from the study, the Montreal Cognitive Assessment (MoCA) was administered at an in-home baseline screening interview. The MoCA was chosen due to its high sensitivity and specificity for distinguishing normal individuals from those with MCI [11]. Participants with a MoCA score of 26 and over were qualified as having normal cognition, while those with scores of 21 to 25 were classified as having mild cognitive impairment (MCI) [11]. Participants with scores under 21 were excluded in order to eliminate all potential cases of dementia [11]. In the original EMPOWER trial, participants randomized to the control group were wait-listed to receive the EMPOWER brochure at the end of the 6-month study period. In an extension to the trial, participants in the control arm were followed for an additional 6 months after study completion in order to evaluate their response to the EMPOWER brochure. This paper analyses all EMPOWER participants (from the intervention and control arm) having received the EMPOWER brochure and having completed the post-intervention EMPOWER assessment by 1-year ($n = 261$) [10].

Intervention

The EMPOWER brochure consists of an 8-page paper-based benzodiazepine deprescribing tool embedded with program theories which participants received by mail. Development of the intervention has previously been described in detail [10, 12]. A generic version of the EMPOWER tool is available at http://www.criugm.qc.ca/fichier/pdf/BENZOeng.pdf. The deprescribing tool was individualized with the name of the participant's benzodiazepine on the front page. It included true and false questions about the harms of benzodiazepines, a short paragraph describing changes in drug metabolism with age, suggestions for alternate non-drug therapies for anxiety and insomnia, a peer champion story, and a standard 21-week tapering protocol showing a picture-based diminishing schedule of full-pill, half-pill, and quarter-pill consumption. The pictogram was proposed by consumers during the development of the intervention and allows participants to apply the benzodiazepine tapering protocol regardless of the type or dose of sedative-hypnotic consumed.

Data collection

Baseline data, including demographic characteristics and prescription details were recorded during the initial in-person interview. Follow-up data was collected by phone 1 week, 6 weeks and 6 months after each participant received the EMPOWER brochure by mail. Benzodiazepine cessation or dose reduction was ascertained using pharmacy renewal profiles, which contained information on drugs purchased, dates of purchase, dose, and quantity served. Cessation was defined as an absence of any benzodiazepine prescription renewal, sustained for a minimum of 3 months during the follow-up period. A significant dose reduction consisted of a >25% dose reduction, sustained over a minimum of 3 months when compared to baseline use. Withdrawal symptoms were measured using the benzodiazepine withdrawal

symptom questionnaire 6 weeks and 6 months post-intervention. Participants reporting any withdrawal symptoms at either time point were qualified as having experienced withdrawal symptoms [13].

Change in knowledge, beliefs and self-efficacy to taper benzodiazepines

In order to evaluate whether MCI participants understood and reacted similarly to the content of the deprescribing intervention, we measured knowledge gained, change in beliefs, improvements in self-efficacy and frequency of outreach to a healthcare professional. Change was calculated by comparing responses on the pre and post-intervention questionnaires. For knowledge, this consisted of scores on four true or false questions [12]. Beliefs about the necessity of taking benzodiazepines versus associated harms were measured by comparing the total scores on the specific section of the beliefs about medicines questionnaire [14]. Change in self-efficacy was evaluated with the Medication Reduction Self-efficacy scale [12]. Outreach to a healthcare professional was measured by self-report.

Analysis

Participant characteristics were described using means with standard deviations for continuous data and percentages for categorical data. A chi-square test was used when comparing baseline characteristics of MCI vs non-MCI participants. Univariable logistic regression was used to determine the odds of all reported outcomes comparing participants with normal cognitive function to those with MCI. Multivariate analyses were adjusted for variables that were significantly associated with MCI at baseline, namely living arrangement, education, baseline self-efficacy and anxiety as an indication for therapy (Table 1). The results are reported as proportions with 95% confidence intervals (CI), and odds ratios (OR) with 95% CI, as appropriate. By combining participants who were randomized to the intervention, as well as the wait-list control group who received the brochure during the trial extension, the sample was powered to detect a 15% difference in proportions of individuals with and without MCI who discontinued benzodiazepines, based on an alpha of 0.05 and 80% power. The statistical significance for all analyses was set at $p < 0.05$ (two-sided). SPSS

Table 1 Participant characteristics at baseline by cognitive status

Characteristics	All ($N = 261$)	MCI ($n = 122$)	Normal cognition ($n = 139$)	*p*-value
Female, *n* (%)	187 (71.6)	90 (73.8)	97 (69.8)	.494
Age years, Mean (SD)	74.4 (6.3)	75.3 (6.7)	73.7 (5.8)	.08
Education – college or university degree, *n* (%)	67 (25.6)	21 (17.2)	46 (33.1)	.003*
Living alone, *n* (%)	137 (52.4)	75 (61.5)	62 (44.6)	.01*
MOCA[b], Mean score (SD)	24.5 (2.4)	23.3 (1.4)	27.4 (1.3)	.000*
General health status (poor or fair), *n* (%)	88 (32.8)	49 (32.8)	44 (31.7)	.895
Comorbidities, Mean (SD)	7.4 (2.5)	7.2 (2.4)	7.6 (2.7)	.335
Self-reported indication for benzodiazepine:				
Insomnia[c], *n* (%)	159 (60.9)	73 (59.8)	86 (61.9)	.417
Anxiety[c], *n* (%)	126 (48.3)	70 (57.4)	56 (40.3)	.006*
Duration of benzodiazepine use (years), Mean (SD)	10.7 (8.8)	10.3 (8.0)	10.9 (9.4)	.548
Previous attempts at cessation, *n* (%)	119 (45.6)	52 (42.6)	67 (48.2)	.321
Successful attempts, *n* (%)	41 (15.7)	14 (11.5)	27 (19.4)	.123
Benzodiazepine type[d], *n* (%):				
Short-acting	70 (26.8)	36 (29.5)	34 (24.5)	.358
Intermediate acting	180 (70.0)	81 (66.4)	99 (71.2)	.400
Long acting	11 (4.2)	5 (4.1)	6 (4.3)	.888
Benzodiazepine Equivalent dose[a], Mean (SD)	1.24 (.85)	1.27 (.75)	1.25 (.82)	.571
Number of medications at baseline	9.86 (3.7)	9.72 (3.8)	9.98 (3.6)	.574
Baseline Self-efficacy in tapering benzodiazepine (/100), Mean (SD)	38.1 (35.6)	31.2 (34.8)	44.1 (35.4)	.004*

*Level of significance, $p < 0.05$
[a]Benzodiazepine dose in mg of lorazepam equivalents/day
[b]MOCA: The Montreal Cognitive Assessment (scale 0–30)
[c]Based on medical diagnosis but self-reported by patients
[d]Short-acting = half-life <6 h, Intermediate acting = half-life 6–20 h, Long-acting = half-life >20 h

Version 20.0 (SPSS Inc. Chicago, IL, USA) was used for all analyses.

Results

Participants in the post-hoc analysis consisted of older adults aged 74.4 years (6.3 year standard deviation) (Table 1). Participants were taking an average of 10 different medications and reported a mean of 7 comorbidities, with almost one third classifying their health status as unfavorable. The mean duration of benzodiazepine use was 10.7 years, indicated for insomnia and/or anxiety. Almost half (45.6%) of patients reported a previous attempt to taper their benzodiazepine. One third of the latter (15.7%) succeeded in the attempt, prior to re-initiating the drug at a later date.

One hundred twenty-two (46.7%) participants were classified as having MCI at baseline. Participants with MCI were less well educated, more likely to live alone, more likely to be taking their benzodiazepine to treat anxiety, and expressed a lower level of confidence for successful tapering than their counterparts with normal cognitive function (Table 1).

Complete discontinuation of benzodiazepines was achieved in 92 participants, with 39 (32.0% [24.4,40.7]) meeting MOCA criteria for mild cognitive impairment and 53 (38.1% [30.5,46.4]) having normal cognition (Adjusted OR = 0.79, 95% CI 0.45 to 1.38). An additional 28 participants significantly reduced their benzodiazepine dose during the same time period (12 in the normal group and 16 MCI participants). In total, 65 (46.8% [38.7–55.0]) participants with normal cognition and 55 (45.1% [36.5,53.9] MCI participants achieved dose reduction or complete discontinuation (Adjusted OR = 1.07, 95% CI 0.62 to 1.83) (Table 2).

Compared to participants with normal cognition, those with MCI exhibited the same ability to acquire new knowledge and change their beliefs following the intervention. Self-efficacy to taper and experience of withdrawal symptoms was the same in both groups. Additionally, cognitive status did not affect the participants' decision to partake in a discussion about the intervention with their healthcare provider (Table 2).

Discussion

Although previous research indicates that individuals with MCI perform significantly worse than controls in multiple aspects of medical decision-making [7, 8, 15], we did not detect any difference in response to the EMPOWER deprescribing brochure among older adults who met MOCA criteria for MCI. Participants with MCI demonstrated improvements in knowledge and self-efficacy, were able to change their beliefs about benzodiazepines, and initiated discussions about deprescribing with a health care provider. Clinicians should be encouraged to distribute the EMPOWER brochure to their MCI patients in order to engage patients in conversations about deprescribing sedative hypnotics, leading to shared decision-making despite declining cognitive status.

Strengths and limitations

This is the first study of its kind to explore the association between MCI and the success rates of a patient-centered educational deprescribing intervention in a community-based clinical trial of older, community-dwelling adults. As the mild neurocognitive disorder diagnosis was not yet developed at the time of the study and the MoCA's usefulness in detecting mild neurocognitive disorder is modest [16], we categorized participants according to the older

Table 2 Outcomes of the EMPOWER intervention by cognitive status

Primary outcome	All (*n* = 261) (*n*, %)	MCI (*n* = 122) (*n*, %)	Normal cognition (*n* = 139) (*n*, %)	Univariable OR (95% CI)	Multivariable OR (95% CI)[a]
Cessation	92 (35.2)	39 (32.0)	53 (38.1)	0.76 [.46–1.27]	.79 [.45–1.38]
Dose Reduction	28 (10.7)	16 (13.1)	12 (8.6)	1.60 [.72–3.53]	2.04 [.86–4.83]
Cessation + Dose Reduction	120 (45.9)	55 (45.1)	65 (46.8)	.94 [.57–1.52]	1.07 [.62–1.83]
Process Outcomes					
Improvement in knowledge	157 (60.2)	75 (61.5)	82 (59.0)	1.11 [.68–1.82]	1.06 [.62–1.80]
Change in beliefs	147 (56.3)	67 (54.9)	80 (57.6)	.89 [.54–1.47]	.84 [.48–1.43]
Improved self-efficacy for tapering	144 (55.2)	68 (55.7)	76 (54.7)	1.04 [.64–1.70]	.89 [.52–1.54]
Discussed intervention with a physician	102 (39.1)	43 (35.2)	59 (42.6)	.73 [.44–1.22]	.75 [.43–1.32]
Discussed intervention with a pharmacist	55 (21.1)	26 (21.3)	29 (20.8)	1.02 [.57–1.86]	.89 [.46–1.72]
Experienced withdrawal symptoms during cessation	31 (11.9)	12 (9.8)	19 (13.7)	.69 [.32–1.49]	.60 [.27–1.35]

[a]Analyses adjusted for living arrangement, education, anxiety as an indication for benzodiazepine treatment and baseline self-efficacy

MCI diagnosis. Our results are only generalizable to patients with mild-to-moderate MCI since we used a MoCA cut-off score of 21, thus excluding the lower spectrum of MCI (19–20), which overlaps with early dementia. Additionally, as we did not re-measure scores on the MOCA at study endpoint, and were unable to ascertain whether cognition improved after discontinuation. The mean lorazepam equivalent dose was only 1.25 mg/day in both groups of participants, which may have facilitated tapering.

Conclusions

This report illustrates that the EMPOWER brochure can be distributed to community-dwelling older adults with MCI and still work, whether directly through patient comprehension of the material or through the support of caregivers or family. The EMPOWER tool can and should be used in primary care or memory clinics for chronic benzodiazepine users who are candidates for deprescribing sedative-hypnotic medication.

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Availability of data and materials

Philippe Martin (Faculty of Pharmacy – University of Montreal & Centre de recherche de l'Institut universitaire de gériatrie) had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Patient level data and the full dataset are available upon reasonable request from the authors. Consent or data sharing was not obtained but the presented data are anonymised and the risk of identification is low.

Authors' contribution

PM participated in the data analysis and interpretation and wrote the manuscript. CT designed the study, participated in the data interpretation and manuscript revision. Both authors read and approved the final manuscript.

Competing interests

Both authors declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years, and no other relationships or activities that could appear to have influenced the submitted work. Philippe Martin received a bursary from the Michel Saucier Endowed Chair in Pharmacology, Health and Aging of the Faculty of Pharmacy of the Université de Montréal and Cara Tannenbaum is a clinician scientist funded by the Fonds de Recherche en Santé de Quebec. Cara Tannenbaum has on occasion been an advisory board member and received speaker honoraria from Pfizer, Astellas, Allergen and Ferring pharmaceuticals in the past 5 years.

Consent for publication

Consent or data sharing was not obtained but the presented data are anonymised and the risk of identification is low.

Ethics approval and consent to participate

Signed informed consent was obtained from all participants. The Research Ethics Board of the Centre de Recherche de l'Institut Universitaire de Gériatrie de Montreal approved the study protocol on July 26, 2009.

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Appendix 9

BMJ Open

A realist evaluation of patients' decisions to deprescribe in the EMPOWER trial

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ABSTRACT

Background and objectives Successful mechanisms for engaging patients in the deprescribing process remain unknown but may include: (1) triggering motivation to deprescribe by increasing patients' knowledge and concern about medications; (2) building capacity to taper by augmenting self-efficacy and (3) creating opportunities to discuss and receive support for deprescribing from a healthcare provider. We tested these mechanisms during theEliminating Medications through Patient Ownership of End Results (EMPOWER) () trial and investigated the contexts that led to positive and negative deprescribing outcomes.

Design A realist evaluation using a sequential mixed methods approach, conducted alongside the EMPOWER randomised clinical trial.

Setting Community, Quebec, Canada.

Participants 261 older chronic benzodiazepine consumers, who received the EMPOWER intervention and had complete 6-month follow-up data.

Intervention Mailed deprescribing brochure on benzodiazepines.

Measurements Motivation (intent to discuss deprescribing; change in knowledge test score; change in beliefs about the risk–benefits of benzodiazepines, measured with the Beliefs about Medicines Questionnaire), capacity (self-efficacy for tapering) and opportunity (support from a physician or pharmacist).

Results The intervention triggered the motivation to deprescribe among 167 (n=64%) participants (mean age 74.6 years±6.3, 72% women), demonstrated by improved knowledge (risk difference, 58.50% (95% CI 46.98% to 67.44%)) and increased concern about taking benzodiazepines (risk difference, 67.67% (95% CI 57.36% to 74.91%)). Those who attempted to taper exhibited increased self-efficacy (risk difference, 56.90% (95% CI 45.41% to 65.77%)). Contexts where the deprescribing mechanisms failed included lack of support from a healthcare provider, a focus on short-term quality of life, intolerance to withdrawal symptoms and perceived poor health.

Conclusion Deprescribing mechanisms that target patient motivation and capacity to deprescribe yield successful outcomes in contexts where healthcare providers are supportive, and patients do not have internal competing desires to remain on drug therapy.

Trial registration number ClinicalTrials.gov: NCT01148186.

Strengths and limitations of this study

- ► Use of a mixed methods approach enabled us to explore the breadth, depth and complexity of the patient's experience of deprescribing.
- ► Use of the realist evaluation allowed us to investigate how the mechanisms underlying deprescribing interventions interact with specific contexts to yield positive or negative outcomes.
- ► This study was conducted alongside a large cluster randomised clinical trial.

INTRODUCTION

Deprescribing refers to the collaborative process of tapering, discontinuing, stopping or withdrawing medications in order to reduce adverse drug events and improve outcomes.[1–5] Deprescribing has many steps,[1 3 6] with one key component being the engagement of patients in shared decision-making.[1 7–15] Research suggests that older adults have conflicted feelings about medications[4 14]: 78% of older adults believe that medications are necessary to improve health, but at the same time, 68% would like to reduce their current medication use, with 92% willing to stop a regular medication if advised to do so by their physician.[14] A better understanding of the mechanisms that trigger patient motivation and capacity to engage in the deprescribing process could reduce the use of potentially inappropriate medications.

The aim of realist evaluation is to reveal how an intervention might generate different outcomes in different circumstances, and how mechanisms work in particular contexts, by enabling or motivating participants to make different choices.[16] Educational strategies to increase patients' knowledge, beliefs and motivation are hypothesised to influence deliberate action on the part of the patient to curtail the use of a drug.[10] However, what works, for whom, under which circumstances and why are questions that have never been explored systematically from the patient's

point of view. Recent reviews on deprescribing call for a realist evaluation of large deprescribing trials to investigate how the mechanisms underlying deprescribing interventions interact with specific contexts to yield positive or negative outcomes.[17 18] The Eliminating Medications through Patient Ownership of End Results (EMPOWER) trial, which demonstrated a number-needed-to-treat of 4 for the effectiveness of mailing a benzodiazepine deprescribing brochure on complete cessation of benzodiazepines at 6 months, provides a timely opportunity to examine which deprescribing mechanisms worked under which circumstances.[12]

The initial theory underpinning the development of the EMPOWER intervention was that most, if not all, older adults are unaware of the age-related harms of taking benzodiazepine anti-anxiety drugs and sleeping pills. Side effects of sedative-hypnotics are well documented in the literature but rarely talked about in practice as being a potential cause of memory impairment, falls and fractures[19–24] feared by many older adults.[25 26] Not understanding why medications should be discontinued is a patient barrier to deprescribing.[4 27] As most patients are uninformed of the potential risks associated with the use of benzodiazepines, we hypothesised a linear behaviour change process whereby providing patients with an interactive educational brochure detailing associated risks, safer alternatives and steps for tapering would trigger patients' motivation, capacity and opportunity to initiate the deprescribing process through discussion of medication discontinuation with a healthcare provider.

This paper reports a realist evaluation of the deprescribing process from the patient's perspective. The realist evaluation tests the following mechanisms: (1) whether the EMPOWER intervention triggered patients' motivation to deprescribe by increasing knowledge and concern about benzodiazepines; (2) augmented patients' capacity and self-efficacy to taper benzodiazepines and (3) created opportunities for the patient to discuss and receive support from a healthcare provider to engage in the deprescribing process. We also determined in which contexts successful and failed deprescribing outcomes occurred.

METHODS

Study design

A realist evaluation was conducted alongside the EMPOWER randomised controlled trial.[12] This report follows online supplementary material 2 RAMESES II guidelines for realist evaluation.[16] The approach was chosen to inform the implementation of future deprescribing initiatives by examining the possible causes and contextual factors associated with change.[28] Realist evaluation is a theory-based, sequential mixed methods approach that seeks to gain a deeper understanding of contexts, mechanisms and outcomes. This is accomplished through the identification and examination of underlying generative mechanisms (M) associated with the intervention or programme, the conditions or contexts (C) under which the mechanisms operate, and the pattern of outcomes (O) produced. These may be expressed as linked Contexts–Mechanisms–Outcomes configurations (or C+M=O).[28] In this case, the (C) consist of all internal and external factors that can influence the deprescribing process and the (O) refer to whether or not the deprescribing intervention was successful. The (M) that we aimed to test were whether the EMPOWER brochure: (1) triggered older adults' motivation to deprescribe by increasing knowledge and concern about benzodiazepines; (2) built capacity to taper by augmenting self-efficacy and (3) drove opportunities to receive support from a healthcare provider to deprescribe.

The study was approved by the Institut Universitaire de Gériatrie de Montréal Ethics Committee in Montreal, Quebec, Canada.

Environment surrounding the evaluation

The EMPOWER trial was a pragmatic randomised trial that examined the effectiveness of a direct-to-consumer, written educational brochure mailed directly to patients on subsequent discontinuation of sedative-hypnotic medication.[29] The EMPOWER trial was rolled out between July 2010 and November 2013, with community-dwelling participants randomly recruited via pharmacists located within a 200 km radius of the Montreal urban area in Quebec, Canada. Participants were 303 older, community-dwelling, chronic users of benzodiazepine medication and agreed to home visits and telephone follow-up interviews by the research team. All benzodiazepine prescriptions for seniors were covered under the publicly financed drug plan in the province of Quebec, excluding the programme's deductible (if applicable). Provincial governments covered physician reimbursements for patient visits, and drug dispensing fees for pharmacists, as part of Canada's universal healthcare programme.

The EMPOWER intervention

The eight-page EMPOWER brochure, available at http://www.criugm.qc.ca/fichier/pdf/BENZOeng.pdf,[30] aims to promote active learning by incorporating and using constructivist learning principles.[31] The brochure includes a self-assessment component and presentation of the evidence-based risks associated with benzodiazepine use in an effort to elicit cognitive dissonance.[10] Elements of social comparison theory,[32] through the use of peer champion stories, are also integrated in the intervention. The brochure provides a self-guided tapering schedule, consisting of a visual tapering protocol showing pictures of full pills, halved pills and quartered pills.[30]

Evaluation of mechanisms and contexts

The mechanisms embedded in the EMPOWER intervention are based on Michie *et al*'s behaviour change wheel,[33] targeting motivation, capacity and opportunity. Michie *et al* define motivation as the mental process that energises

Table 1 Programme mechanisms embedded in EMPOWER intervention

Mechanisms	Components of the EMPOWER brochure		
Increase motivation to deprescribe by changing knowledge and beliefs	Messaging on the front page 'You May be at Risk' to raise awareness of the harms of benzodiazepines	Interactive knowledge test with four true/false questions and answers about the harms of benzodiazepines, aimed at increasing knowledge	Information about changes in drug metabolism with age that can lead to a higher risk of side effects, meant to change beliefs and elicit concern about the safety of the medication in older adults
Increase capacity to taper by augmenting self-efficacy	A list of alternative non-pharmacological approaches to sleep and anxiety that patients can use as substitutes	An inspirational story using social comparison and peer championing to increase self-efficacy for tapering	Provision of an easy-to-use visual 16–20 weeks tapering tool showing when to take a whole, half or quarter pill, and when to skip the dose completely
Drive opportunities to discuss and initiate deprescribing with a healthcare provider	Instruction to 'Please consult your doctor or pharmacist before stopping any medication' in a large red box	Logos on the brochure provide source credibility for the patient to initiate conversations	The printed format of the eight-page brochure makes it an effective knowledge transfer piece to take and show to a healthcare provider

and directs behaviours. Capability refers to the psychological and physical capacity of the individual to engage in the behaviour. Opportunity refers to the internal and external factors that permit or promote a behaviour to happen, and include both the physical and social environment of the individual. Table 1 links the programme mechanisms to the corresponding intervention components.

The evaluation of mechanisms and contexts consisted of quantitative data collection and analysis, qualitative data collection and analysis and triangulation of the quantitative and qualitative results.[34] Data collection was conducted between July 2010 and November 2013 as part of the EMPOWER clinical trial. Analysis, triangulation and refinement of the Context–Mechanism–Outcome configuration took place subsequent to completion of the trial.

Data collection methods

Quantitative data included preintervention and 1-week postintervention information on knowledge about benzodiazepine-related harms, beliefs about the necessity of taking benzodiazepines versus concern about harms, self-efficacy for tapering and intent to discuss deprescribing with a healthcare provider. We measured gains in knowledge with the four true or false questions listed in the 'Test Your Knowledge' section of the questionnaire.[29 30] Correct answers were summed to a maximum of 4 points, and answers were compared prior to and after receiving the intervention. Participants' beliefs about consuming benzodiazepines were measured with the Beliefs about Medicines Questionnaire (BMQ-Specific) at both time points. The BMQ-Specific consists of two validated five-item subscales assessing the respondents' perceptions about the necessity and concerns associated with taking benzodiazepines.[35] Participants indicate their degree of agreement with each statement on a five-point Likert scale (1=strongly disagree, 5=strongly agree). Scores are summed into their respective subcategory (5–25 point scale) with higher scores indicating stronger beliefs. Risk perception was assessed using a single question 1-week postintervention in which participants were asked whether they perceived the same, increased or no risk from consumption of their benzodiazepine following the intervention. In order to determine whether the EMPOWER brochure increased capacity to taper by augmenting self-efficacy, we measured self-efficacy for tapering on the Medication Reduction Self-efficacy scale, which allows the respondent to rate on a scale of 0 to 100 their degree of confidence for tapering benzodiazepines.[36] Higher scores indicate greater self-efficacy. Participants were also asked to indicate (yes/no) postintervention if they had spoken to or intended to discuss medication discontinuation with their doctor and/or pharmacist. Health status was assessed at baseline using the first item of the Short-Form-12 Health Survey and dichotomised by categorising poor to fair responses as poor health.[37]

Qualitative data were collected after the 6-month follow-up, using semistructured interviews conducted at participants' homes to determine the contexts under which the deprescribing mechanisms succeeded or failed. Twenty-one participants were strategically sampled for the interviews using a contrast sample design, based on cessation of benzodiazepines (yes or no) combined with intent to discuss tapering (yes or no).[38] Interviews lasted approximately 1 hour, were recorded with consent and professionally transcribed verbatim. The interviews were based on a pre-established discussion guide, the major themes of which included initial reactions to the intervention, reasons underlying the decision to taper, experience with the tapering process and personal interactions with healthcare providers (see online supplementary material 1).

Analysis

The three mechanisms of increasing motivation, capacity and opportunity were tested using quantitative analysis.

Participants with complete follow-up data were included in the quantitative analysis (n=261, mean age 74.6±6.3, 72% women). Data were described and compared using means with SD and independent t-tests for continuous data, and percentages and χ^2 tests for categorical data, according to each of three outcomes: intent to deprescribe with successful discontinuation, intent to deprescribe with failed discontinuation and no intent to deprescribe. Individuals who achieved a dose reduction were classified as intent to deprescribe with failed discontinuation. Participant changes in knowledge, in the BMQ necessity and concerns subscales and in self-efficacy scores for tapering were computed from baseline to postintervention. Risk differences with 95% CIs were calculated for the proportion of participants in each group who demonstrated increased knowledge, heightened concern about benzodiazepine use and augmented self-efficacy for tapering. The statistical significance for all analyses was set at p<0.05 (two-sided).[39] SPSS V.21.0 was used for all analyses.

Qualitative data from the semistructured interviews were analysed using thematic content analysis to explore the contexts under which the programme mechanisms led to positive or negative outcomes.[40] Discourses were contrasted according to whether participants discontinued benzodiazepines and/or expressed the intent to discuss discontinuation. Interviews were coded using Dedoose software. Contextual themes were derived from the data and supported by quotes. Initially, two researchers independently read the transcripts and field notes, then collaboratively developed first order codes, which were subsequently verified by double coding. Second order thematic coding was performed for the purpose of building concepts.

Quantitative and qualitative results about context were combined and analysed in an iterative fashion through use of a triangulation protocol using a convergence coding matrix,[41] as described by Farmer *et al*.[42] The convergence matrix served to inform which contexts favourably or unfavourably influenced a patient's decision to deprescribe based on agreement, partial agreement or dissonance between the quantitative and qualitative data.[41 42] Differences were adjudicated via discussion and consensus.[42] The convergence-coding matrix is available from the authors on request.

RESULTS

Linking mechanisms to outcomes

The mechanism of triggering motivation to deprescribe occurred in 167 of 261 individuals (64%) who received the EMPOWER intervention (table 2).Participants who expressed an intent to deprescribe postintervention had improved knowledge (risk difference, 58.50% (95% CI 46.98% to 67.44 %)), lower perceived necessity scores (risk difference, 56.03% (95% CI 44.63% to 64.81%)), increased concern (risk difference, 67.67% (95% CI 57.36% to 74.91%)) and a greater perception of risk about their benzodiazepine medication than those who were not motivated to attempt deprescribing (risk difference, 35.14% (95% CI 23.06% to 45.39%)). Individuals who decided to deprescribe exhibited higher capacity for tapering after receipt of the EMPOWER brochure, with enhanced self-efficacy compared with those in whom the intervention did not trigger motivation (risk difference, 56.90% (95% CI 45.41% to 65.77%)) (table 2). Approximately half of individuals with augmented motivation and capacity to deprescribe initiated a conversation with their physician, and 25% spoke to a pharmacist about deprescribing. Neither postintervention self-efficacy scores nor creating the opportunity to discuss deprescribing with a healthcare provider distinguished between positive or negative outcomes among motivated individuals.

Contexts associated with positive deprescribing outcomes

Table 3 shows the results of the qualitative analysis, describing the contexts that enabled the EMPOWER mechanisms to achieve positive deprescribing outcomes. Favourable personal contexts included stable health status and a positive outlook on ageing. Individuals who were not dealing with acute health issues were more receptive to tapering off benzodiazepines, as were individuals who prioritised long life expectancy over the short-term benefits of continued use or the transient discomfort associated with deprescribing benzodiazepines. Individuals who succeeded in tapering had the highest baseline self-efficacy for being able to discontinue (table 2). External influences associated with successful discontinuation were previous and ongoing support or encouragement from a healthcare provider (table 3).

Contexts in which the EMPOWER mechanisms failed

Thirty-six per cent of the participants in the trial reported no desire to deprescribe after receipt of the EMPOWER brochure. These individuals showed no gain in knowledge and no increase in perceived risk post-intervention (table 2). Failure for the EMPOWER intervention to elicit motivation to deprescribe was more likely among individuals who reported poor health (40% vs 28%, 12.28% (95% CI 0.44% to 24.18%)). During the qualitative interviews, participants dealing with ongoing health issues expressed a strong reliance on benzodiazepines for everyday coping (table 4). Other contexts associated with the decision not to attempt deprescribing included previous reassurance by a physician that benzodiazepines were safe or necessary and the belief that the benefits of benzodiazepines outweighed the risks for immediate symptom relief (table 4). Contexts that led participants to abort the deprescribing process once they showed initial motivation, capacity and opportunity to deprescribe included the lack of support from a healthcare provider, intolerance to withdrawal symptoms and a sudden loss of confidence to live without sleeping pills (table 4).

Table 2 Linking mechanisms to outcomes

Mechanisms	Outcomes: All (n=261)	Successful deprescribing (n=92)	Intent but failed deprescribing (n=75)	No attempt to deprescribe (n=94)	Successful and failed intent versus no attempt* p value/ risk difference (95% CI)	Successful completion versus failed intent to deprescribe p value/ risk difference (95% CI)
Increased motivation						
Change in knowledge:						
Baseline knowledge (/4), mean (SD)	0.85 (0.99)	0.97 (1.08)	0.87 (0.97)	0.71 (0.90)	0.10	0.54
Postintervention knowledge (/4), mean (SD)	1.92 (1.40)	2.64 (1.23)	2.01 (1.34)	1.13 (1.20)	0.00*	0.00*
Increase in knowledge postintervention, n (%)	156 (59.8)	80 (86.9)	55 (73.3)	21 (22.3)	58.5 (47.0 to 67.4)*	13.6 (1.6 to 25.9)*
Beliefs about benzodiazepines						
Baseline belief about necessity† (/25), mean score (SD)	13.8 (3.4)	13.0 (0.3)	14.3 (0.4)	14.1 (0.4)	0.23	0.01*
Postintervention belief about necessity†, mean score (SD)	12.58 (3.32)	11.07 (0.30)	12.55 (0.32)	14.05 (0.35)	0.00*	0.10
Participants with a decrease in score about necessity postintervention, n (%)	138 (52.8)	75 (81.5)	47 (62.7)	16 (17.4)	56.0 (44.6 to 64.8)*	18.9 (5.3 to 32.0)*
Baseline concern†, (/25), mean score (SD)	13.4 (2.7)	13.4 (0.3)	14.1 (0.3)	12.9 (0.3)	0.00*	0.01*
Postintervention concern†, mean score (SD)	14.42 (3.41)	15.60 (0.37)	15.34 (0.36)	12.56 (0.28)	0.00*	0.62
Participants with increased concern postintervention, n (%)	138 (52.8)	70 (76.1)	59 (78.7)	9 (9.7)	67.7 (57.3 to 74.9)*	–2.6 (–15.0 to 10.4)
Risk perception:						
Participants perceiving increased risk postintervention, n (%)	118 (44.8)	51 (55.4)	45 (60.0)	21 (22.3)	35.1 (23.1 to 45.4)*	–4.6 (–19.1 to 10.4)
Building capacity						
Self-efficacy for tapering						
Baseline self-efficacy (/100), mean (SD)	37.8 (35.7)	47.3 (34.6)	35.0 (37.4)	31.0 (33.6)	0.03*	0.02*
Postintervention increase in self-efficacy score, mean change (SD)	25.44 (42.78)	35.78 (36.80)	36.03 (44.63)	6.00 (40.93)	0.00*	0.97
Participants with increased self-efficacy postintervention, n (%)	145 (55.5)	70 (76.1)	57 (76.0)	18 (19.1)	56.9 (45.4 to 65.8)*	0 (–12.6 to 13.3)
Creating opportunity						
Outreach to a healthcare professional:						
Discussed with physician, n (%)	103 (39.5)	42 (45.6)	38 (50.6)	23 (25.0)	23.4 (11.3 to 34.1)*	–5.0 (–19.8 to 10.0)
Discussed with pharmacist, n (%)	56 (20.1)	25 (27.1)	22 (28.9)	9 (9.7)	18.6 (8.7 to 27.1)*	–2.2 (–15.9 to 11.3)

*Level of significance, $p<0.05$.
†As some participants selected more than one condition, total does not equal 100%.
Independent sample t-test for continuous variables, χ^2 for categorical variables.

Table 3 Contexts associated with positive outcomes

	Outcomes			
Contexts	Successful deprescribing (n=7)	Failed deprescribing (n=7)	No attempt to deprescribe (n=7)	Supporting citation
Previous support from physician/positive attitude towards discontinuation	5 (71%)	4 (57%)	1 (14%)	*'He (my doctor) told me the drug was not good for me and that I could experience side effects while taking it'.* (72-year-old man, successful taper)
Stable health status	5 (71%)	4 (57%)	2 (29%)	*'I don't have as much pain as I used to. It's now under control so it was easier for me to stop. Before—no way'.* (68-year-old woman, successful taper)
Certainty and confidence about tapering (postintervention)	6 (86%)	4 (57%)	1 (14%)	*'I persuaded myself that I needed to get rid of this, no matter what*'. (84-year-old man, successful taper)
Perception of increased risk	6 (86%)	5 (71%)	1 (14%)	*'My physician told me it (the drugs) could cost me my memory. My memory has become very important to me'.* (79-year-old man, successful taper)
Lack of psychological attachment	5 (71%)	3 (43%)	1 (14%)	*'I understood I could stop taking it (after I read the brochure), that it was not an obligation (to take it)*'. (72-year-old woman, successful taper)
Positive outlook on ageing	3 (43%)	1 (14%)	0	*'At my age I don't believe in miracles such as being able to sleep for 8, 9 or 10 hours each night. It would be impossible for me, so I content myself with the hours of sleep I get'.* (84-year-old man, successful taper)
Tapering tool provides support	5 (71%)	3 (43%)	0	*'In the past I tried to stop the pill all at once. But using the tapering tool, I understood that it need to be a gradual and not a drastic process'.* (84-year-old man, successful taper)
Supportive healthcare provider	3 (43%)	2 (29%)	0	*'When I told my doctor I wanted to stop, he said, 'no problem, let's do it'.* (87-year-old woman, successful taper)

Refining the context–mechanism–outcome configuration for deprescribing interventions

The initial context–mechanism–outcome configuration that drove the development of the EMPOWER intervention was a simple, linear progression along different stages of readiness to deprescribe, similar to Prochaska & DiClemente's transtheoretical model of change (figure 1A).[43] We believed that the EMPOWER brochure would trigger motivation and capacity to deprescribe, moving patients from precontemplation about deprescribing to action and maintenance, by increasing knowledge about the harms of benzodiazepines, enhancing self-efficacy and creating opportunities to discuss deprescribing with a healthcare professional. We assumed that the healthcare provider would provide a supportive context, encouraging the patient to deprescribe, thereby yielding a positive outcome. This initial configuration oversimplified the stages through which individuals transitioned after receiving the deprescribing intervention. Figure 1B depicts a revised, non-linear context–mechanism–outcome configuration that takes into account the complexity of internal and external contexts on initiating and completing the deprescribing process from the consumer's perspective. The revised model recognises that new information influences beliefs and actions only if the information generates a desire strong enough not to be overwhelmed by competing motivations arising from other sources. In many instances, the desire for risk reduction, which was the prime motivator behind the development of the EMPOWER intervention, did not supersede concerns about symptom recurrence, or other psychological and health factors, as well as interpersonal relationships with healthcare providers, which played critical contextual roles in the outcome of the intervention.

DISCUSSION

This realist evaluation tested the mechanisms embedded in the EMPOWER intervention and showed that motivation and capacity to deprescribe were triggered in 64% of older chronic benzodiazepines consumers, the majority of whom created an opportunity to discuss

Table 4 Contexts associated with negative outcomes

Key theme	Successful deprescribing (n=7)	Failed deprescribing (n=7)	No attempt to deprescribe (n=7)	Supporting citation
Previous discouragement from physician	1 (14%)	1 (14%)	5 (71%)	*'I asked him (my doctor), 'Are there any of my medications I could stop?' He told me, 'No, we're not taking anything away, you are doing well'. I then told him my medication was getting very expensive to which he replied, 'You know Mr., life is priceless'.* (75-year-old man, no intent to taper)
Poor health status	0	1 (14%)	4 (57%)	*'If anyone stops my pills, poof, I would die for sure because of my poor health'.* (70-year-old woman, no intent to taper)
Unquestioning belief in their physician	1 (14%)	1 (14%)	3 (43%)	*'If you take all your pills as prescribed, you'll never have problems in your life […] When my doctor prescribes something for me, I know it's not junk, I know it's good for me. And I don't question it'.* (72-year-old man, no intent to taper)
Lack of perception of personal risk	1 (14%)	2 (29%)	5 (71%)	*'I recall that he (my doctor) told me that in the long-term my benzodiazepine could affect my memory. But my memory is fantastic'.* (72-year-old man, no intent to taper)
Reliance on medication for coping/everyday function	1 (14%)	1 (14%)	4 (57%)	*'Without this medication, I know that my life would be plagued by anxiety, of this I am certain'.* (68-year-old woman, no intent to taper)
Quality of life focus during end of life	0	2 (29%)	3 (43%)	*'At my age I don't care about the risks. I don't care if I live to 100 or not'.* (85-year-old woman, failed tapering)
Discouragement from a physician	1 (14%)	3 (43%)	5 (71%)	*'My doctor told me: 'At your age, don't worry about it. You've been taking this pill for a while and you are fine. You aren't taking a dangerous dose at all'*. (85-year-old woman, failed tapering)
Intolerance to recurrence of symptoms/withdrawal effects	0	5 (71%)	_	*'When I decreased the dose I started getting headaches. I felt miserable not being able to sleep at night'.* (85-year-old man, failed tapering)
Loss of confidence to complete the tapering process (postintervention)	0	4 (57%)	4 (57%)	*'I knew that I'd be in trouble without my pills. It's been a long time now. How can I put it in words? If I ran out of pills I'd be in trouble'.* (85-year-old man, failed tapering)

deprescribing with a healthcare provider. These findings support the theory that provision of new knowledge about medication harms can raise concern and augment patients' self-efficacy to deprescribe. However, the analysis also indicates that human motivation to deprescribe is complex and unstable. A variety of internal and external contexts can interfere with the decision to deprescribe. Internal influences include perceptions about one's health status, long-term health goals, fear of symptom recurrence and psychological attachment to the drug. The main external influence that blocks consumer-directed deprescribing mechanisms is the lack of support from a healthcare provider.

Our findings contribute to the literature by illustrating that linear progression along different stages of readiness to deprescribe does not fully explain successful deprescribing from the patient's perspective. This conclusion is consistent with other critiques of the transtheoretical model, which claim that the stages of readiness are arbitrary, that human beings do not make logical and stable plans to change their behaviour and that setbacks can occur along the trajectory of change.[44] Education appears to be necessary but insufficient for many individuals, and new strategies will be needed to trigger deprescribing in prohibitive contexts where the EMPOWER mechanisms failed. As capacity and motivations change over time,

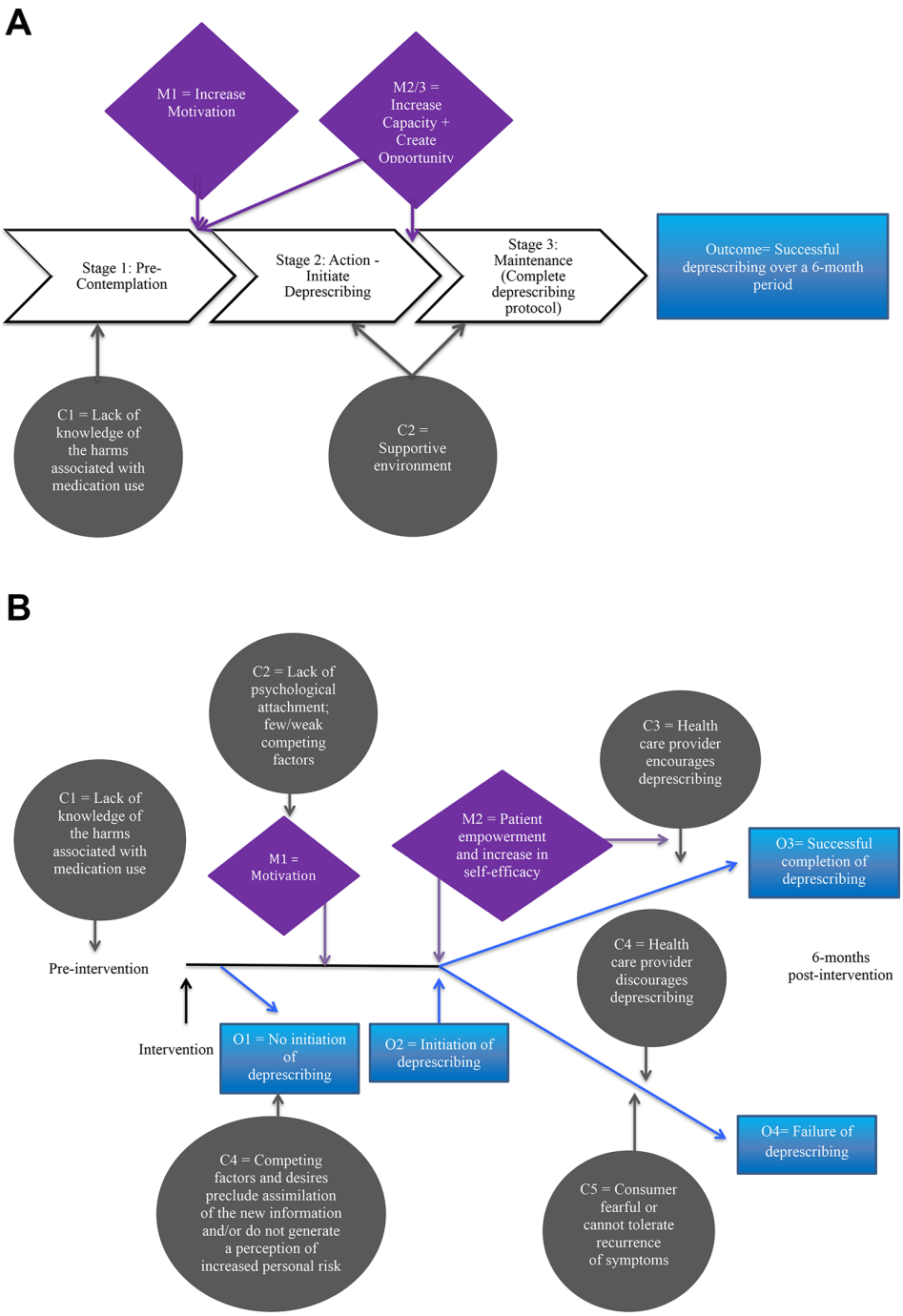

Figure 1 (A) Initial deprescribing context–mechanism–outcome configuration. (B) Refined deprescribing context–mechanism–outcome configuration.

reminders and ongoing discussions about the risks of inappropriate medications may progressively trigger and sustain patients' commitments to engage in the deprescribing process. Some competing factors may wane, such as poor health. Offering cognitive behavioural therapy to patients during the most difficult last quarter period of the tapering protocol may augment self-efficacy for overcoming withdrawal symptoms.[36] Interventions can be directed at healthcare providers who discourage deprescribing efforts. Continuing medical education to inform health providers about the mounting evidence on the harms of benzodiazepine use may curtail the phenomenon of physicians who continue to promote the use of inappropriate medication.[20 45] Future research directions should also include measurement of cognitive dissonance, which lies at the heart of constructivist learning.[46] Methods to measure cognitive dissonance, defined as a feeling of tension between two sets of competing beliefs and motivations, may shed light on the way in which tensions about deprescribing are played out and drive behaviour change.[46 47] As we did not directly ask patients if they felt internal tension, we were unable to record feelings or processes of cognitive dissonance.

Use of a mixed methods approach enabled us to explore the breadth, depth and complexity of the patient's experience of deprescribing from a social, behavioural and health perspective, allowing stronger inferences about the various contexts affecting patients' decisions than could be achieved through a quantitative or qualitative lens alone.[48] However, other mechanisms and contexts may trigger motivation to deprescribe beyond what is described in this realist evaluation. One untested mechanism is provision of information about the lack of drug benefits in certain populations, such as statins to reduce cholesterol levels in palliative care patients with limited life expectancy.[49 50] Another challenge that we experienced during the conduct of this realist evaluation was differentiating between the mechanisms and contexts associated with deprescribing.[51] For instance, when participants stated that their physician or pharmacist undermined their decision to deprescribe, it was clear this factor changed the reasoning of the participants. However, we were not sure whether this factor should be labelled as a mechanism or a context. Since the mechanism of action is defined as the 'how' behind the generation of outcomes, we initially thought that healthcare provider support was a mechanism that brought about deprescribing.[51] On iterative reflection and discussion of the C–M–O configurations, we came to the conclusion that healthcare provider support was actually a context that enabled or hindered the consumer's motivation, capacity and opportunity to deprescribe, as triggered by the EMPOWER intervention. We drew this conclusion by subscribing to Pawson and Tilley's initial approach to realist evaluation, which seeks to identify mechanisms at the level of the individual's human reasoning.[52] Others such as Dalkin *et al* posit that interpersonal relationships between stakeholders are a key factor that influence human reasoning, and argue that mechanisms can also be evaluated through the social lens of human and systems interactions.[51] Deprescribing in particular is a complex social process that involves patients, prescribers and pharmacists, so our analysis may be faulted by some for studying the consumer's decision-making processes in isolation. For this reason, we chose not to make a table listing discrete C–M–O relationships in this paper but instead focused on broadly describing and testing the mechanisms embedded in the EMPOWER intervention and outlining the different personal, interpersonal and external contexts that led to positive or negative outcomes. We created figure 1A,B with difficulty, and some scepticism about whether these complex interactions could be illustrated in simple form. As the field of realist evaluation evolves, new terminology and formats may emerge that better capture a way of graphically illustrating the science of human interactions and behaviour change.

In conclusion, this realist evaluation conducted alongside a clinical trial provides important insights about deprescribing from the patient's perspective and increases current understanding about the specific mechanisms and contexts that generate positive or negative outcomes when attempting to engage patients in curbing the overuse and potentially inappropriate use of medicines.

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A realist evaluation of patients' decisions to deprescribe in the EMPOWER trial

Philippe Martin and Cara Tannenbaum

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Appendix 10

Evidence-Based Pharmaceutical Opinion

Date (dd/mm/yy):_____

To the attention of Dr. _____
Address:_____
Tel: (___)_____ Fax: (___)_____

Pharmacist name:_____
Address:_____
Tel: (___)_____ Fax: (___)_____

Your patient, _____ (DOB (dd/mm/yy)_____), is currently taking _____ to treat his/her insomnia and/or anxiety. The use of sedative-hypnotics is associated with an increased risk of falls, fractures and memory impairment and is not recommended in adults over the age of 65, safer alternatives may be considered. Your patient is at risk because:_____.

Suggested alternatives ➡ indicate all that apply

- ☐ Provide information to this patient on cognitive behavioral therapy (e.g. download this brochure: http://www.criugm.qc.ca/fichier/pdf/Sleep_brochure.pdf, see http://sleepwellns.ca/), which has been shown to be effective for the treatment of both insomnia and anxiety and helps patient with sedative-hypnotic discontinuation.
- ☐ Provide this patient with information on other behavioral changes to treat insomnia and anxiety such as relaxation exercises, managing eating habits, etc.
- ☐ I will consider adding an SSRI or SNRI at the next visit if required. Note: These medications are also associated with falls in the elderly, but are preferred over benzodiazepines, non-benzodiazepine hypnotics and trazodone because of their lower risk profile. Beware: substitution with trazodone or any of the Z-drug hypnotics is not recommended.
- ☐ Implement and follow the 16-week tapering schedule for this patient (see next page)
- ☐ Please cease current prescription and switch to:
  Medication:_____ Dose:_____
  Quantity:_____ Refills:_____
- ☐ No change to current prescription

I certify that:

- ***This prescription is an original prescription***
- ***The identified pharmacist pre-cited is the sole recipient***
- ***The original will not be re-used***

Physician:_____
No of license:_____
Date (dd/mm/yy):_____

Clinical guidelines*	Rationale*
The 2015 American Geriatrics Society Beers List of drugs to avoid in the elderly considers all short-, medium- and long-acting benzodiazepines as well and non-benzodiazepine hypnotics as a potentially inappropriate medication for use in adults aged 65+ due to a greater risk of falls, fractures, memory/cognitive impairment and motor vehicle crashes, based on high quality evidence.	• Older adults are at an increased risk for cognitive impairment. • Sedative-hypnotics increase the risk of falls by 50%. • Fractures may be increased 2-fold even with PRN use and especially if other CNS agents are prescribed. • Sedative-hypnotics are also associated with an increased risk of motor vehicle crashes. • May increase the risk of Alzheimer's disease by 50%

PLEASE RETURN TO _____PHARMACY VIA FAX NUMBER (___)_____

WEEKS	TAPERING SCHEDULE							✓
	MO	TU	WE	TH	FR	SA	SU	
1 and 2	½	1	1	1	½	1	1	
3 and 4	½	1	½	½	1	½	½	
5 and 6	½	½	½	½	½	½	½	
7 and 8	½	¼	½	½	¼	½	½	
9 and 10	½	¼	½	¼	½	¼	½	
11 and 12	¼	¼	½	¼	¼	½	¼	
13 and 14	¼	¼	¼	¼	¼	¼	¼	
15 and 16	✕	¼	✕	✕	¼	✕	¼	
17 and 18	✕	✕	✕	✕	✕	✕	✕	

EXPLANATIONS

1 Full dose ½ Half dose ¼ Quarter of a dose ✕ No dose

***REFERENCES:** American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults, http://onlinelibrary.wiley.com/doi/10.1111/jgs.13702/pdf; Otto *et al.* (2010). Efficacy of CBT for benzodiazepine discontinuation in patients with panic disorder: Further evaluation. *Behav Res Ther.* 2010 Aug;48(8):720-7. Finkle *et al.* (2011). Risk of fractures requiring hospitalization after an initial prescription of zolpidem, alprazolam, lorazepam or diazepam in older adults. J Am Geriatr Soc 2011;59(10):1883-1890. Billioti de Gage S, Moride Y, Ducruet T, *et al*. Benzodiazepine use and risk of Alzheimer's disease: case-control study. Bmj. 2014;349:g5205.

Date of revision: May 16th, 2017

Evidence-Based Pharmaceutical Opinion

Date (dd/mm/yy):_____

To the attention of Dr. _____
Tel: (___)_____ Fax: (___)_____

Pharmacist name:_____
Tel: (___)_____ Fax: (___)_____

Your patient, _____ (DOB (dd/mm/yy)_____ , is currently taking _____ to treat his/her diabetes. The use of glyburide is associated with an increased risk of hypoglycemia in adults aged 65 and older. Safer alternatives should be considered.

Patient information (if available): HbA1c: _____ Hypoglycemic episodes: _____ CrCl: _____
Self-monitored blood glucose: _____

Suggested alternatives ➡ indicate all that apply

☐ **Cease glyburide WITHOUT substitution** (re-assess at the next follow-up visit – glucose, HbA1c, nutrition, exercise)

☐ **Cease glyburide and substitute with (Clarify dose, qty, duration, renewals):**

☐ Metformin (Glucophage®) ***first line treatment*** *RAMQ covered, based on tolerance and CrCl*

DPP-4 Inhibitor
- ☐ Saxagliptin (Onglyza®) *based on CrCl; EN148 or EN149*
- ☐ Linagliptin (Trajenta®) **Fill out restricted medications form*
- ☐ Sitagliptin (Januvia®) based on CrCl **Fill out restricted medications form*
- ☐ Repaglinide (GlucoNorm®) ***with meals****; EN24 or EN25*

Other Sulfonylureas (based on CrCl)
- ☐ Gliclazide (Diamicron®) *EN23 or EN24*
- ☐ Gliclazide MR (Diamicron MR®) *EN23 or EN24*
- ☐ Glimiperide (Amaryl®) *EN23 or EN24*

☐ **Cease Glyburide/Metformin combination and substitute with another metformin combination (Clarify dose, qty, duration, renewals):**
- ☐ Sitagliptin/Metformin (Janumet®) EN150
- ☐ Saxagliptin/Metformin (Komboglyze®) *EN150*
- ☐ Linagliptin/Metformin (Jentadueto®) EN150

☐ **Other: Cease glyburide and substitute with: _____ (Clarify dose, qty, duration, renewals)**

☐ **No change to glyburide prescription**

Dose: _____
(Details on back page)

Qty: _____

Duration tx: _____

Renewals #: _____

I certify that:

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- ***The aforementioned pharmacist is the only recipient***
- ***The original will not be re-used***

Physician signature:

_____

No license: _____

Date:

Clinical guidelines*	Rationale*
The 2015 American Geriatrics Society Beers List of drugs to avoid in the elderly considers glyburide as a potentially inappropriate medication because of the risk of severe prolonged hypoglycemia in adults aged 65 years and older (high quality evidence). In 2013, the Canadian Diabetes Association raised the concern that the use of glyburide in the elderly is associated with an increased risk of severe or fatal hypoglycemia	• Older adults are at an increased risk for hypoglycemia. • Glyburide increases the risk of severe hypoglycemia by 50% compared to other sulfonylureas. • Hypoglycemia may exacerbate physical and cognitive functioning in the frail elderly or in those with cognitive impairment. • Hypoglycemia increases the risk of fall-related fractures by 70%.

PLEASE RETURN TO _____PHARMACY VIA FAX NUMBER (___)_____

Managing glyburide deprescribing in type-2 diabetic patients aged 65+
Review goals

Usual target	HbA1c < 7%
Frail older adults*	Target HbA1c: 7% - 8.5% Pre-prandial glucose: 5-12 mmol/L Post-prandial glucose: 10-14 mmol/L
Older adults with cognitive impairment	Priority: avoid hypoglycemia < 5.0 mmol/L at all times

* Frailty defined by: unintentional weight loss, reported exhaustion, low physical activity, slow waking speed, weakness, need of help for ADLs/IADLs, symptoms of chronic diseases limiting activities

Preferred alternatives

Class	Efficacy & Advantages	Precautions	Drug Dose range	RAMQ coverage Cost/month
Biguanide	↓ HbA1c by 1.5-2% 1st line treatment		Metformin (Glucophage®) 250 -1000 mg PO BID *CrCl 30-60 mL/min: reduce dose* *CrCl <30 mL/min – do not use*	RAMQ – Covered ~12-15 $
Sulfonylurea	↓ HbA1c 1-1.5%	Risk of hypoglycemia CI in severe hepatic impairment	Gliclazide (Diamicron®)* 80-160 mg PO BID Glclazide (Diamicron®)* MR 30-120 mg PO daily *CrCl 15-30 mL/min: reduce dose* *CrCl < 15 mL/min:not recommended*	EN 23 or EN 24 ~5-6 $
			Glimiperide (Amaryl®)* 2-8 mg PO daily *CrCl 15-30 mL/min: reduce dose CrCl<15 mL/min: not recommended*	EN 23 or EN 24 ~12 $
Meglitinide	↓ HbA1c by 0.5-1.0% Flexible dosing (taken with meals)	CI if patient taking gemfibrozil	Rapeglinide (Gluconorm®)* 0.5-4 mg PO TID **with meals** *Renal impairment: no dosage adjustment needed*	EN 24 or EN 25 ~10 $
DPP-4 inhibitors	↓ HbA1c by 0.5-1% Lower risk of hypoglycemia Combination with metformin available.	Precaution: history of pancreatitis, heat failure For combinations: Renal impairment: Dose of DPP-4 inhibitor and metformin must be adjusted as per CrCl.	Sitagliptin (Januvia®) *100 mg PO daily *CrCl 30-50 mL/min: 50 mg PO daily* *CrCl<30 mL/min: 25 mg PO daily* Sitagliptin / Metformin (Janumet®) * 50/500 mg PO BID; 50/850 mg PO BID; 50/1000 mg PO BID	EN150 ~70-90 $
			Saxagliptin (Onglyza®)* 2.5-5 mg PO daily *CrCl<15 mL/min: 2.5 mg PO daily* Saxagliptin /Metformin (Komboglyze®)* 2,5/500 mg PO BID 2,5/850 mg PO BID 2,5/1000 mg PO BID	EN 148 or EN 149 ~70-90 $ EN 150 ~70-90 $
			Linagliptin (Trajenta®)* 5 mg PO daily *Renal impairment: no dosage adjustment needed* Linagliptin /Metformin (Jentadueto®)* 2.5/500 mg PO BID 2.5/850 mg PO BID 2.5/1000 mg PO BID	EN 150 ~70-90 $ EN 150 ~70-90 $

* Restricted medications – RAMQ application codes:
EN23 : Another sulfonylurea is not tolerated or is ineffective. **EN24**: For treatment of non-insulin dependent patients suffering from renal failure
EN25: When a sulfonylurea is contraindicated, not tolerated or is ineffective. **EN148**: In association with Metformin, when a sulfonylurea is contraindicated, not tolerated or ineffective. **EN149**: In association with a sulfonylurea, when Metformin is contraindicated, not tolerated or ineffective
EN150: When sulfonylurea is contraindicated, not tolerated of ineffective and daily doses of Metformin have been stable for 3 months.

[v]**REFERENCES :** Kirkman *et al.* (2012). Diabetes in older adults : A consensus Report. *JAGS*, *60*, 2342-2356.;Meneilly *et al.* (2013). Clinical Practice Guidelines ; Diabetes in the Elderly. *Can J Diabetes*, *37*, S184-; American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults, http://onlinelibrary.wiley.com/doi/10.1111/jgs.13702/pdf.

Evidence-Based Pharmaceutical Opinion

Date (dd/mm/yy):_____

To the attention of Dr._____
Tel: (___)_____ Fax: (___)_____

Pharmacist name:_____
Tel: (___)_____ Fax: (___)_____

Your patient, _____(DOB (dd/mm/yy):_____), is currently taking _____to treat itching or allergies. First-generation antihistamines are associated with an increased risk of drowsiness and anticholinergic side effects. They are not recommended for people over the age of 65. Other safer alternatives should be considered.

Suggested alternatives ➨ indicate all that apply

1) For allergies

☐ Discontinue the current prescription and replace it with 2nd or 3rd generation antihistamines (circle your selection):

2nd generation:
- Cetirizine (Reactine®) → 5-10 mg daily
- Loratadine (Claritin®) → 10 mg daily

3rd generation:
-Desloratadine (Aerius®) → 5 mg daily
-Fexofenadine (Allegra®) → 180 mg or 60 mg daily

☐ Discontinue the current prescription and prescribe:
Name:_____ Dose : ____ Qty:____ Duration tx:_____ Renewal # : _____

2) For pruritus due to cutaneous dryness (xerosis)

☐ Discontinue the current prescription and replace it with a urea-based cream
Name:_____ Dose : ____ Qty:____ Duration tx:_____
Renewal #: _____

☐ Provide patient with information on non-pharmacological solutions to reduce itching and dry skin:
- Use mild soap and detergents
- Replace soap with shower/bath gel
- Apply a hydrating cream after bathing, and up to three times per day as needed to hydrate the skin (ointments or thick creams with a high lipid content)
- Use a humidifier in winter

NOTE: *There is no sustained evidence to validate the use of antihistamines to treat pruritus that is not caused by mast cells.*

☐ No change to the prescription.

I certify that:

- ***This prescription is an original prescription***
- ***The aforementioned pharmacist is the only recipient***
- ***The original will not be re-used***

Physician signature:
_____
License #: _____
Date: _____

Clinical guidelines*	Rationale*
The 2015 American Geriatrics Society Beers List of drugs to avoid in the elderly recommends not prescribing first-generation antihistamines to adults aged 65 and older. To treat itching or chronic allergies, the list recommends prescribing second- and third-generation antihistamines.	• Older patients are at greater risk of anticholinergic side effects, such as confusion, dry mouth, constipation, urinary retention, dry eyes (quality evidence). • The use of first-generation antihistamines may cause memory impairment and attention or concentration problems.

PLEASE RETURN TO _____PHARMACY VIA FAX NUMBER (___)_____

*REFERENCES: American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults, http://onlinelibrary.wiley.com/doi/10.1111/jgs.13702/pdf; Garibyan *et al.* Advanced aging skin and itch: addressing an unmet need. Dermatologic Therapy 2013; 26:92-103. Tannenbaum *et al.* A systematic review of amnestic and non-amnestic mild cognitive impairment induced by anticholinergic, antihistamine, GABAergic and opioid drugs. Drugs Aging 2012; 29(8):639-58.