Supplementary Online Content

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Supplement 1. Trial protocol

This supplementary material has been provided by the authors to give readers additional information about their work.

EMPOWER_2 / PRESCRIBE study (**P**harmacist-led **R**esearch to **E**ducate and **S**ensitize **C**ommunity **R**esidents to the **I**nappropriate prescriptions **B**urden in the **E**lderly): Effectiveness of a consumer-targeted pharmacist-led educational intervention to reduce inappropriate prescriptions in community older adults

This proposal is the sequel to the EMPOWER study (CIHR-funded 2009-2012), in which our team developed and tested a novel consumer-targeted written knowledge transfer tool aimed at **empowering older adults to act as drivers of safer prescribing practices.** The rationale behind the EMPOWER study was that inappropriate prescribing involves both the prescriber and the consumer. Given that interventions aimed at physicians to curb inappropriate prescriptions have yielded suboptimal results, we hypothesized that: enlisting patients as catalysts of change to collaboratively engage physicians in rethinking high-risk prescriptions would lead to greater rates of medication discontinuation. In Year 1 of EMPOWER we developed and tested the acceptability of a new patient-targeted knowledge transfer tool. In Year 2 we distributed the prototype benzodiazepine tool to 144 chronic benzodiazepine users to determine its impact on medication-related knowledge, beliefs and potential discontinuation. In Year 3 we conducted in-depth qualitative interviews to better understand for whom the medication risk reduction intervention worked best, in what context it worked best and in which situations it failed. We found that:

- A written educational tool based on constructivist learning theory that directly empowered users with knowledge about risks, suggestions for lower-risk therapeutic options, and self-efficacy for implementing tapering protocols, was effective in altering the medication "risk-vs-necessity" perceptions of 45% of chronic benzodiazepine users.
- In over 80% of these cases, new perceptions of increased risk elicited an immediate desire to begin a benzodiazepine tapering protocol and discuss the issue further with a physician.
- Forty-three participants (out of 144) succeeded in tapering off their benzodiazepine medication within 6-months of receiving the knowledge transfer tool.
- The tool worked best for individuals who received support from their physician.
- The tool failed for initially motivated individuals who were discouraged by their physician ("at your age you do not need to worry about it!") or who suffered symptom relapse without access to alternative treatment.
- The tool also failed for patients living through personal/stressful circumstances or suffering from chronic/terminal illnesses who believed that the necessity of the pill outweighed the risks.
- Five patients consulted their pharmacist during the de-prescribing decision-making process. **To our knowledge there was no pharmacist-to-doctor communication during the study.**

EMPOWER provided proof of concept that directly targeting consumers, as drivers of safer prescriptions can be effective for reducing medication risk. However, several challenges and opportunities also became apparent. First, we learned that many physicians were reluctant to change inappropriate prescriptions. 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. The current proposal aims to address these challenges. **We intend to mount a pragmatic randomized controlled trial to test the beneficial effect of enlisting pharmacists to transfer knowledge simultaneously to both patients AND prescribers on reductions in inappropriate prescriptions.**

Why conduct a trial on inappropriate prescribing now?

There are 5 reasons why a trial on inappropriate prescribing is urgently needed.

1. **Older Canadians rank concerns about medication side effects highest on their list of health priorities.** [1, 2] Evidence suggests that seniors have good reason to be concerned: as life expectancy improves and seniors live longer with multiple chronic conditions, they are also more likely to consume multiple medications.[3, 4] Individuals with 1-2 chronic conditions take 3-4 prescription medications on average, while seniors with 3 or more chronic conditions take 6.[3, 4] 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.[3] Polypharmacy is the term commonly used to define the prescription, administration or use of multiple medications (usually 5 drugs or more).[5] There are three types of polypharmacy: *appropriate, inappropriate or redundant*.[5] Polypharmacy can lead to adverse drug reactions, drug-drug interactions, and increased risk of hospitalization even in instances when prescribing is appropriate.[6, 7]

2. **Tragically, far too many seniors are taking *inappropriate prescriptions*, which further increases the risk of adverse drug reactions and unnecessary hospitalization**.[7-11] Inappropriate prescriptions are those where the risks outweigh the benefits, and safer therapeutic alternatives exist that have similar or superior efficacy.[5, 11, 12] Inappropriate prescribing has been estimated to occur in 12-40% of community-dwelling non-hospitalized older adults aged 60+, depending on the criteria used and the country studied.[5, 8, 9, 11, 13-15] In Canada, at least 1-in-4 seniors is currently taking a medication judged to be inappropriate.[14, 15] The cost of inappropriate prescribing among community-dwelling elders has been estimated at $7.2 billion in the United States,[13] and one-tenth the cost in Canada.

3. **No one person is being held accountable for the phenomenon of inappropriate prescribing, and it is not clear who will take responsibility for fixing it.** Consider that industry has a monopoly for evaluating its own products. In countries where drug manufacturers are major contributors to the national economy, no government can afford to delay product approval until the adverse effects of long term use are known.[16] Then consider that after a drug has been released, post-marketing observational and pharmacoepidemiologic studies for determining drug safety take years to complete, and meta-analyses even longer. The results of these studies are frequently critiqued for selection bias, confounding caused by underlying differences among patients, and underreporting of actual adverse events.[17, 18] Rarely are official warnings issued, or medications withdrawn from the market. Linking the incidence of geriatric syndromes such as falls and cognitive impairment to the use of any one medication can therefore be daunting to the healthcare provider, especially in patients with polypharmacy.[19, 20] The evidence base, marketing and guidelines for initiating medications are vast, but few resources exist to support ceasing or reducing medications. Clinicians may feel uncomfortable "de-prescribing" or altering prescriptions initiated by specialists.[21] The pharmacist may wish to intervene, but often has no way of knowing the indication for which the drug was prescribed. Patients themselves may be reluctant to stop their medication because of physical or psychological dependence, or concern about withdrawal symptoms.[22, 23] Clearly a multidisciplinary intervention is required that addresses all of these issues. We believe this initiative must be undertaken by academic researchers who understand the complexity of the problem. We also believe the initiative should be undertaken in close collaboration with the prescribers, pharmacists and patients who are intricately involved in the inappropriate prescribing conundrum.

4. **The climate is ripe for change for both physicians and pharmacists.** The Updated Beers List of Drugs to Avoid in the Elderly was recently released by the American Geriatrics Society in April 2012 and received extensive media attention.[11] These criteria, which have not been updated for the past 10 years, hold world-wide credibility with physicians and pharmacists, providing an easy-to-use reference for inappropriate medications. At the same time, pharmacist organizations across Canada are currently creating momentum for new legislation to expand the scope of practice for pharmacists. The scope aims to include a more independent role in judicious prescribing, justifying issues of patient safety and physician support for going beyond the role of simply dispensing prescriptions.[24] Quebec pharmacists lead the way in this initiative by having been the first to receive payment for sending pharmaceutical opinions or "opinions pharmaceutiques" to physicians.[25] The pharmaceutical opinion consists of a written notice sent to the physician by the pharmacist suggesting changes to the patient's therapeutic regimen.[26] As of 2011, Ontario became the second Canadian province that reimburses pharmacists for sending a pharmaceutical opinion to a physician or for setting up a consultation with a patient to discuss medication safety. Although few studies have examined the outcomes of this policy change, existing data supports the conclusion that pharmaceutical opinions are an effective means of increasing

communication between patients, pharmacists and prescribers, and furthermore allow pharmacists to be paid for their expertise even if a drug is not dispensed (since the pharmaceutical opinion compensates for the loss of income when the pharmacist recommends replacing a prescribed medicine with a nondrug treatment).[27]

5. **In addition to physicians and pharmacists, patients themselves are primed for an intervention on inappropriate prescribing.** As a result of the media coverage surrounding the Beers Update launch, increased access to drug information is available on the internet. The Canadian media also devotes much attention to the cost and consequences of inappropriate drug use in seniors in nursing homes, with resulting public concern about the risks of medication use. Members of the focus groups for the EMPOWER study communicated their concerns about medications quite clearly to us. Additionally, 96% of the patients who participated in the EMPOWER impact study expressed appreciation for involving them more directly in their medication management, even if they decided not to taper their benzodiazepines.

What have we learned from previous interventions to reduce inappropriate prescribing?

To supplement the knowledge gleaned from our previous work, our team studied a recent systematic review of interventions to reduce inappropriate prescribing in the elderly and a new Cochrane review on interventions to improve the appropriate use of polypharmacy for older people.[28, 29] The systematic review by Kaur et al. included 24 studies and the Cochrane review included 10. Various types of interventions were assessed including educational interventions to physicians, online medication reviews, in-hospital geriatrician or pharmacist consultation, complex pharmaceutical care, and computerized support systems. The conclusions from the two 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% , **but did not affect discontinuation of pre-existing prescriptions.**[30-33] 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.[34] 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.[30-32] Consultation and screening by a geriatrician or specialized hospital-pharmacist have also been shown to be effective in reducing inappropriate prescriptions, but are labour-intensive and unaccessible to many community-dwelling patients.[28, 29, 35] Passive interventions such as mailing evidence-based educational bulletins to physicians do not change inappropriate prescribing habits.[36]

The most compelling results from medication discontinuation studies involve medication review by a pharmacist followed by direct communication to the physician.[28, 29, 33, 36-38] 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.[33] The decision varies depending on the type of prescription.[33] All this suggests that pharmaceutical opinions may be an under-utilized tool for pharmacists to sensitize physicians to changing inappropriate prescriptions.

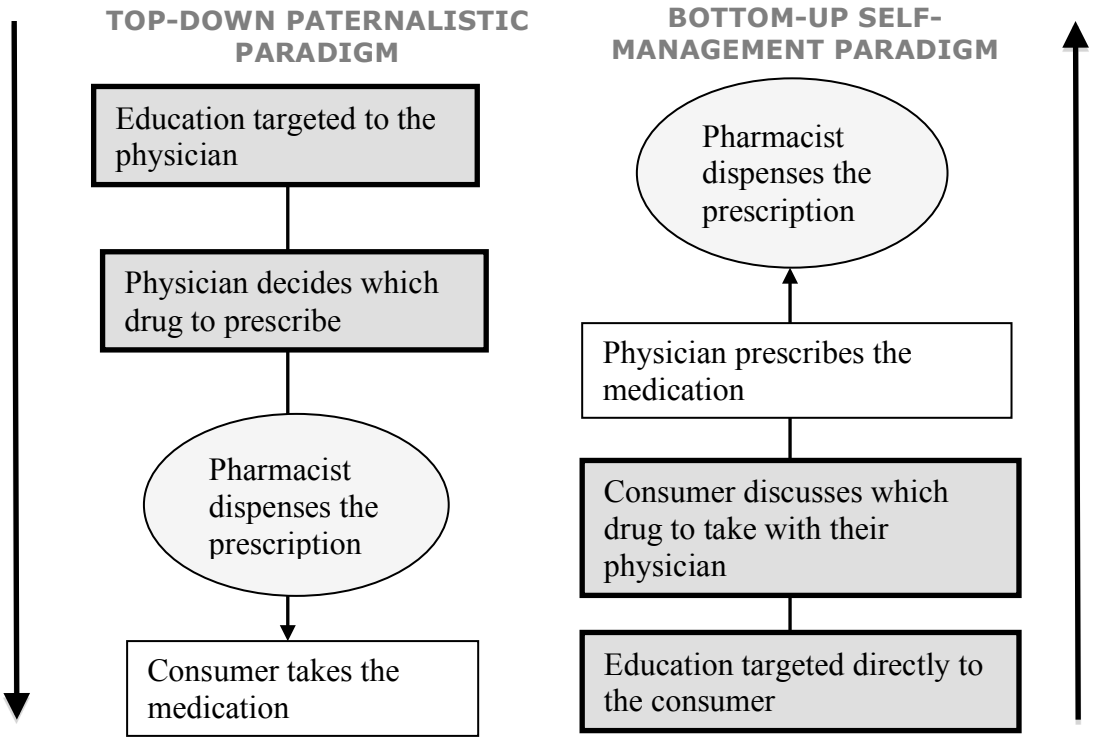
Little is known about the synergy of simultaneously applying more than one intervention to reduce inappropriate prescribing.[28] A systematic review of interventions to change physicians' behavior concluded that interventions that incorporate two or more distinct strategies, target different barriers to change, and that include reminders are most likely to succeed.[39] To our knowledge, no study other than the EMPOWER study has involved the patient in holding physicians accountable to re-think inappropriate prescriptions. As mentioned, results from the EMPOWER study yielded a 30% discontinuation rate of benzodiazepines (the prototype inappropriate prescription) by directly targeting patients with educational material and having them

discuss it with their physicians. **We are therefore very interested in applying and testing a two-pronged intervention initiated by pharmacists to simultaneously target both the patient and the physician to reduce inappropriate prescriptions.**

A new enabling paradigm to optimize medications

Two prescribing paradigms are illustrated in Figure 1. The first paradigm combines the traditional

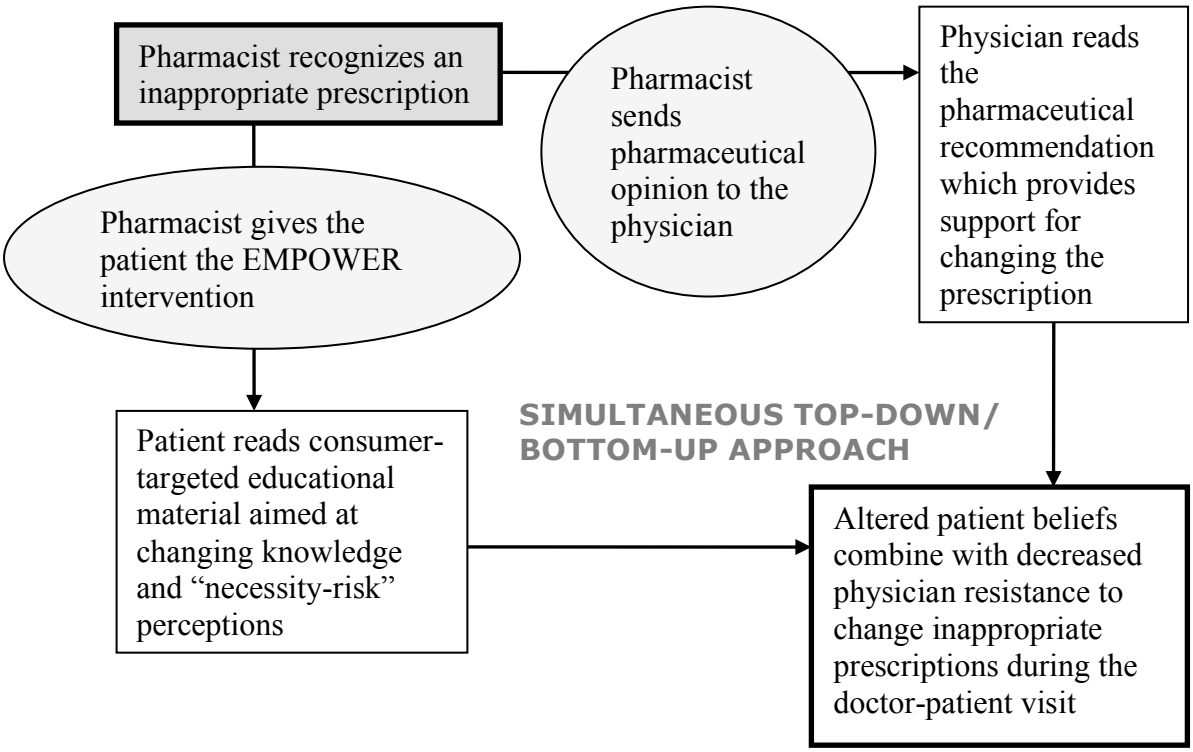
Figure 1:



paternalistic model of patient care with the "top-down" managerial approach described in management and organizational development theory.[40, 41] In this example, the physician acquires information about which medications to prescribe or de-prescribe and decides which drug the patient should take. This paternalistic/top-down model represents the status quo. The second paradigm depicts the approach tested during the EMPOWER study, drawing on theories of self-management and collaborative doctor-patient partnerships and is illustrated as a "bottom-up" change strategy.[40, 41] In the bottom-up approach, the patient drives prescription decisions from information gathered on the internet, through friends, or via an accredited academic body (as in the EMPOWER study). However, as seen in EMPOWER, the physician has potential to negatively influence a patient's desire for change since the physician still holds the prescribing power. This finding parallels observations from organizational change research where resistant managers have killed off the initial enthusiasm of workers for change because the workers challenged the top management prerogative.[41] Note that neither of the two paradigms described above includes the pharmacist as an active player in the decision-making process.

Now consider a **new enabling paradigm** where the "middleman," the pharmacist, initiates and influences the de-prescribing process by simultaneously conveying information bi-directionally to both the physician and the patient *prior* to the doctor-patient encounter. Our hypothesis is that this type of intervention will create the circumstances for elements from the top-down and bottom-up approaches to coincide, a strategy that has previously been shown to facilitate implementation of change in other areas of the public sector.[41] The process would look like this:

Figure 2: Two-pronged pharmacist-led enabling paradigm to optimize medications



In the paradigm described above, the pharmacist will deliver the constructivist learning tool to the patient, which has already been shown to increase knowledge, change beliefs and augment self-efficacy for reducing medication risk in the EMPOWER study. The pharmacist will also educate and offer support to the physician through use of the pharmaceutical opinion, an accepted method of inter-professional collaboration. A small study in Quebec revealed that 58% of physicians implement the drug substitution or drug discontinuation recommendations delivered in pharmacist-initiated pharmaceutical opinions.[27] We therefore hypothesize that this multifaceted intervention will result in a synergistic effect on inappropriate prescriptions.

Pilot work to date

During recruitment for the EMPOWER study we surveyed 20 community pharmacists on their perceptions of whether physicians were receptive to the recommendations issued in their pharmaceutical opinions. On a scale of 0-10 (0 being not at all and 10 being completely receptive), the mean score was 6.5/10 (range 5-9.5), consistent with the degree of physician receptiveness observed in earlier work.[27] Other than these data there is a paucity of evidence on the utility of the pharmaceutical opinion for changing prescriptions among community-dwelling older adults. In order to assess the feasibility of the paradigm proposed for this trial, we sought input from Uniprix, a large pharmacy chain in the province of Quebec, as well as from the Association Quebecoise des Pharmaciens Proprietaires (AQPP or Quebec Association of Pharmacy Owners) on whether or not pharmacists would be interested in taking on the roles envisioned by our paradigm. Amélie Paquette, the educational director at Uniprix is keen to enlist the pharmacists at Uniprix in efforts to reduce inappropriate prescribing. She inquired and informed us that a quarter of the Uniprix pharmacists in Quebec (n=85) have expressed interested in participating in research to evaluate the impact of the pharmaceutical opinion on geriatric pharmacotherapy issues (see letter of collaboration). Normand Cadieux, the Executive Vice-President and General Manager of the AQPP, also expressed enthusiasm about our project and will publicize the opportunity to participate in the research to all pharmacists across Quebec (see letter of collaboration). In the spirit of a **pragmatic trial**, we

therefore intend to determine the effectiveness of the intervention by using it **in real clinical practice**, applied flexibly across pharmacies in a way that is directly relevant to meeting the needs of pharmacists, patients and physicians.[42, 43]

Study objectives and hypothesis

Main Objectives:

1. The first objective of this study is to **test the beneficial effect** of pharmacist-initiated knowledge transfer to both patients and prescribers on the discontinuation of inappropriate prescriptions, compared to usual care.
2. The second objective of this study is to **test the added benefit** of implicating physicians and pharmacists in a patient targeted educational intervention on the discontinuation of inappropriate prescriptions, compared to EMPOWER study results where patients alone were targeted.
3. The third objective of this study is to **test the transferability** of this novel approach to inappropriate prescription discontinuation explored in the EMPOWER study **to other classes of inappropriate medications** by comparing results obtained on benzodiazepines to results in other classes.
4. The fourth objective of this study is to test the economic impact of the tool by comparing cost of the intervention to cost in medical services saved, compared to other interventions currently in use (or considered to be) to reduce inappropriate prescriptions.

Secondary Objectives:

Secondary objectives will include but will not be limited to:

1. To better understand **the mechanisms** by which the educational tool affects participants' risk perception, knowledge and beliefs with respect to inappropriate prescription use.
2. To evaluate the **impact of Pharmaceutical Opinions** on physicians' perception of the prescription as inappropriate as well as document response rates and **overall feasibility** of Pharmaceutical Opinions as a clinical tool to reach physicians in inappropriate prescription discontinuation.
3. To evaluate the **challenges in the patient/physician/pharmacist triad** system for discontinuing inappropriate prescriptions and the **feasibility of implanting** this type of intervention on a large scale in Quebec's health care system.

Hypothesis:

We hypothesize that:

1. Implementation of this two-pronged approach will reduce inappropriate prescriptions compared to usual care, of a magnitude at least as great as interventions directed to physicians alone (25%)[33].
2. Implementation of this two-pronged approach will improve inappropriate prescriptions discontinuation compared to targeting patients alone by addressing barriers of discontinuation.
3. This novel approach to inappropriate prescription discontinuation will not only be transferable to other classes of inappropriate medications but should obtain even greater results due to the absence of the dependence factor present in benzodiazepine use.[44]
4. This novel approach to inappropriate prescription discontinuation will lead to significant savings in medical costs and will do so at lower cost than current or hypothesized approaches to inappropriate prescription.
5. This educational tool will increase risk perceptions among recipients, and that increased risk perceptions will be associated with changes in knowledge and beliefs about their medication use.[45]
6. Pharmaceuticals opinions should at least reach the majority of physicians as in previous studies[33] and shouldn't have a significant impact on workload.
7. Simplicity of the intervention should simplify/favourite its implementation on a large scale if challenges in the patient/physician/pharmacist triad are properly identified and addressed.

Methods

Trial design: A 3-year pragmatic cluster randomized, two-arm, parallel-group controlled trial enlisting 46 pharmacies and 400 of their community-dwelling clients consuming inappropriate medications. 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, as well as by pharmacists working within the same pharmacy.

Participants: The study population is community-dwelling older adults recruited from community pharmacies in Quebec. Pharmacists who consent to participate in the project will be asked to solicit from RAMQ (Quebec's public health insurance program) a list of all eligible participants from their practice who meet the inclusion and exclusion criteria listed below.

Inclusion criteria will be:

1) Men and women 65 years of age and older (no upper age limit)
2) Polypharmacy (5 or more active prescriptions)
3) Individuals for whom prescription claims derive from only one pharmacy identifier
4) **Chronic consumption (> 3 month claims)** of one of 3 target inappropriate prescriptions. The choice of these 3 medication classes was based on high quality evidence and the strength of the recommendations presented in the 2012 Updated Beers Guidelines for Inappropriate Prescriptions,[11] as well as their frequency of use in the general population.[33, 46] There is strong rationale for targeting the following 3 drug classes:

- **All short, intermediate and long-acting benzodiazepines + Nonbenzodiazepine hypnotics**. Clear epidemiologic evidence indicates that benzodiazepines are associated with a five-fold increased risk of cognitive events[47-50], a 30% to two-fold increased risk of falls[51-53], a 50% increased risk of hip fractures[53-57], and a 25% to 2-fold increased risk of motor vehicle accidents.[58-60] Similar evidence has also been detected in Nonbenzodiazepine hypnotics.[11] Short-acting benzodiazepines are a recent addition to the updated 2012 Beers list. [11]
- **Anticholinergic agents including first-generation antihistamines** (as single agents or as part of combination products such as hydroxyzine or diphenhydramine), and the **tertiary amine tricyclic antidepressant amitriptyline.** First-generation antihistamines cause can cognitive impairment,[50] and have been associated with an increased risk of confusion, dry mouth, constipation, and functional decline.[61-66] Amitriptyline should be avoided in the elderly because of an increased risk of sedation, cognitive impairment and confusion,[50, 63-66] as well as their potential to cause orthostatic hypotension and falls.[67]
- **The long-acting sulfonylurea oral hypoglycemic agents chlorpropamide or glyburide** used for the treatment of diabetes. Oral hypoglycemic agents are estimated to be responsible for 11% of emergency hospitalizations for adverse drug events in older adults.[7] 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.[68, 69] Chlorpropramide has potential to cause SIADH (syndrome of inappropriate antidiuretic hormone secretion).[70] Glyburide is a new addition to the Beers list this year.[11, 71]

All inappropriate prescriptions that will be targeted by the intervention are listed by medication class in table 1.

Table 1: List of inappropriate prescriptions targeted by the intervention

Benzodiazepines	Anticholinergic Agents	Long Acting Sulfonylurea
Alprazolam	Hydroxyzine	Chlorpropamide
Estazolam	Promethazine	Glyburide
Lorazepam	Amitriptyline	
Oxazepam	Chlordiazepoxide-amitriptyline	
Temazepam	Clomipramine	

Triazolam	Doxepin > 6 mg/d
Clorazepate	Imipramine
Chlordiazepoxide	Perphenazine-amitriptyline
Chlordiazepoxide-amitriptyline	Trimipramine
Clidinium-chlordiazepoxide	
Clonazepam	
Diazepam	
Flurazepam	
Quazepam	
Eszopiclone	
Zolpidem	
Zaleplon	

Exclusion criteria will be:

1) A probable diagnosis of dementia (persons without the capacity to provide informed consent), as determined by a) a prescription for memantine or a cholinesterase inhibitor; b) report from a caregiver or family-member; or c) a baseline screening score < 23 on the Montreal Cognitive Assessment (MoCA)[72].
2) Inability to understand English or French

Recruitment procedure

Participants will be recruited to the trial in a systematic fashion. As per previous studies conducted by R. Tamblyn, potentially eligible patients from consenting pharmacy will be identified from the RAMQ (Régie de l'assurance maladie du Québec) prescription claims database with permission from participating pharmacists.[31, 73, 74] The RAMQ is the universal healthcare public insurance agency in Quebec. Currently, 91% of Quebec seniors (65+) are covered by the RAMQ drug plan.[73] Each pharmacy in Quebec has a unique identifier and patients eligible under RAMQ have a record of all prescriptions filled at each pharmacy.[73] Medication dispensations have been demonstrated to be accurately and reliably recorded in the RAMQ prescription claims database.[73] Participating pharmacists will provide consent for the research team to request from RAMQ a list of clients who meet eligibility criteria for the study based on prescription claims data from their pharmacy. The pharmacists will receive a copy of this list and a second encrypted copy will be sent to the research team. The research team will stratify the encrypted identifiers by drug class and randomize each stratum. Participants taking one or more or the targeted drug classes will be randomly assigned to receive the intervention for one drug class only. The randomized list with encrypted identifiers will be sent back to the pharmacist to sequentially contact clients from each of the 3 drug classes to invite them to participate in the study. 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. 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. The pharmacist records all affirmative responses, 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 assess cognitive function. Signed consent to participate in the study is then obtained from individuals who meet the study criteria after baseline cognitive and

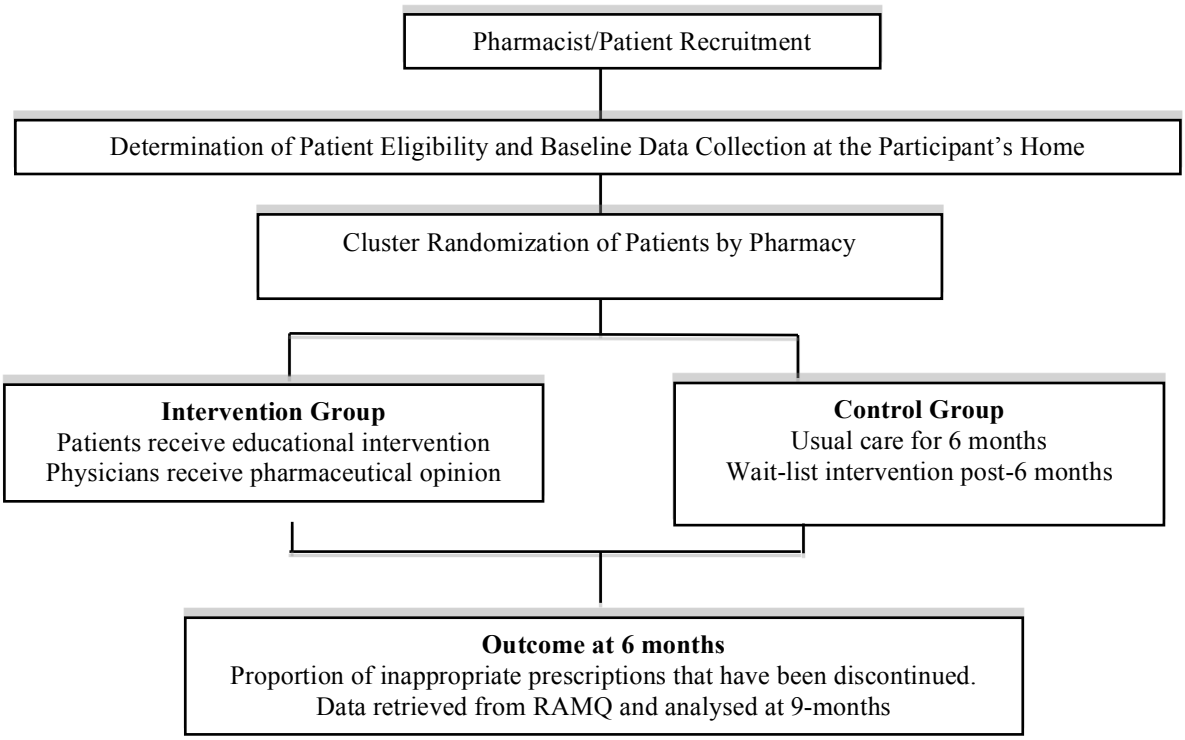
health status screening. This procedure will be followed until 3 clients from each drug class have been recruited, screened by the research coordinator for eligibility (including a cognitive screen that rules out dementia) and enrolled in the trial, or until such time as there are no more eligible clients at that pharmacy or clusters have been filled.

The 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 the educational material to the patient in the form of a written educational brochure that was developed and tested during the EMPOWER study. 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 by consumers during Year 1 of the EMPOWER study (only the benzodiazepine intervention was used for the impact study in Year 2). When handing the intervention to patients, pharmacists will also join a letter explaining why they are receiving an intervention and a pamphlet detailing pharmacist services inviting them to a consultation regarding the intervention after reading it should they have any questions. 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 pharmaceutical opinions that could be sent to the patient's physician depending on the type of inappropriate medication consumed. The examples will provide reference to the Beers criteria and include suggestions for safer therapeutic alternatives for the inappropriate prescription under consideration. The pharmacist will be allowed flexibility in their choice of whether to use the examples provided by the research team or to draft their own pharmaceutical opinion for the physicians. The educational materials for the patients and examples of pharmaceutical opinions about the 3 inappropriate prescriptions will be distributed to each pharmacist assigned to the intervention group immediately after randomization.

The Control Group: 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. After enrolment, all pharmacists will be informed that the project materials will be delivered "sometime over the next year." Based on our experience with the EMPOWER study, we expect that the pharmacists will consider this "wait-list" delay to be reasonable as it takes time to contact potentially eligible research participants once their pharmacist has obtained permission from them to give the research team their contact details (patients go on vacation, visit relatives, feel sick etc.). It also takes time to arrange a baseline data collection home visit at a time that is mutually convenient to the patient and research interviewer. Many eligible participants will refuse to participate in the study or be deemed ineligible because of the cognitive screen and the pharmacist will need to select new candidates. We will explain to the pharmacists that these delays may take 3-6 months so the recruitment process for the study is long, and 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.

Randomization and blinding: Randomization will be by pharmacy cluster after 9 clients from each pharmacy have consented to participate in the trial or all eligible patients have been screened. Randomization to the experimental or control group will be achieved by computer-generated random digits generated by a research assistant not involved in participant recruitment. Randomization will be balanced in non-stratified block groups of four, every time four pharmacies and their patients have completed enrolment and baseline data collection. Allocation of the intervention by a third party will be blinded, 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 it will be aware that the intervention is being delivered. We will do our best to ensure that participants are blinded to the purpose of the study during enrolment and baseline data collection (prior to randomization) by informing them that the study is about safe use of medication in general.

Study flow: The trial flow is depicted in the figure below.



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 Primary Outcome: The primary outcome for the trial is discontinuation of any inappropriate prescription. The time period chosen for ascertainment of the outcome is 6-months post-intervention. The 6-month time period was chosen 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 behaviour, they usually make a decision and implement their plan of action within 6 months.[75] Provincial insurance administrative (RAMQ) data will be used to measure the outcome for participants in the intervention and control groups.[73] The RAMQ database includes coverage for physician services and payment to the pharmacist for all pharmaceutical opinion sent 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. RAMQ data has been previously used to measure discontinuation of inappropriate medications in studies by R. Tamblyn, so the results of this study will be directly comparable to previous interventions targeting physicians only.[34] 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) during the nine months following receipt of the intervention (e.g. claims data will only be retrieved 9 months post-intervention for the preceding year at a single time point for each participant).

Secondary Outcomes and Measures: The new 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.[76] 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. This will be ascertained from the pharmacists at the end of the six-month study period and corroborated by patient self-report during 3 and 6-month telephone follow-up interviews with the patient participants. The 3-month phone call is required to reduce recall bias.
- *The prevalence, timing and type of pharmaceutical opinions sent* by the pharmacists to the patients' primary care providers. The occurrence and delivery date of any pharmaceutical opinion sent to the patient's physician will be ascertained by the presence of a RAMQ billing code recorded within 6 months after randomization of pharmacies to the intervention group. The type of opinion (example provided by the research team vs customized by the pharmacist) will be established by obtaining a photocopied paper copy of the pharmaceutical opinion from the patient's record at the end of the study (by law, the pharmacist must keep a copy in the patient's dossier). The dates of the paper copy will be matched to the date of the billing registered in the RAMQ database to validate that the latter relates to the drug under study.
- *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. Baseline and post-intervention evaluation of participants' beliefs about their medication will be assessed with the **Beliefs about Medicines Questionnaire (BMQ).** The BMQ is a validated index, commonly used with older adults, comprising two five-item scales (BMQ-specific) assessing patients' beliefs about the necessity of the prescribed medication for controlling their medical symptoms and their concerns about the potential adverse consequences of taking it as well as two four-item scales (BMQ-general) assessing patients' beliefs about medications in general (harm and overuse).[77-79] The BMQ allows calculation of a necessity-concern differential which can be used to gauge a change in risk perception over time, as in the EMPOWER study. We will also query the patient's intent to discuss discontinuation with their doctor or pharmacist as in the EMPOWER study. Two telephone follow-ups to patients will occur: once at 3-months and once at 6-months post-intervention. If the patient reports having received material from their pharmacist at the 3-month phone call, then the BMQ and behavioral intentions questions will be queried. If the answer is negative, then the same process will be repeated at the 6-month follow-up.
- *Effect of the pharmaceutical opinion on the prescriber's behaviour.* Pharmacists will be provided with a "study response card" to accompany any pharmaceutical opinion sent to a physician for study patients with inappropriate prescriptions. The "response card" will ask the physician to endorse one of the following three options: 1) I agree with the proposed recommendation and have signed the prescription recommendation you have provided to discontinue or substitute the inappropriate prescription (or institute a benzodiazepine tapering protocol, etc.); 2) I will discuss with the patient at the next visit; or 3) No change required. The physician will be asked in the pharmaceutical opinion to fax back the response card to the pharmacist. A copy of all response cards received by the pharmacist will be collected by the research team at the end of the study. The pharmacist will also be asked whether the physician acknowledged the pharmaceutical opinion in any other way. Lack of acknowledgment of the pharmaceutical opinion by the physician will be coded as a non-response. We expect that physician contamination will be minimal, as only 3 clients per drug class will be selected from each pharmacy and it is likely that physicians serving a given geographic area will have clients served within the same cluster.
- *Patient-physician encounters to discuss inappropriate prescriptions.* Patient visits to their primary care provider within the 6-months post-intervention will be ascertained by RAMQ billing codes. Visits to

physicians where discussions about inappropriate prescriptions occurred will be determined by patient self-report during the 6-month semi-structured telephone follow-up interview by asking whether patients met with their physician to discuss their prescriptions and what happened during these encounters. We will also query any phone call discussions with physician on this subject and conversations with pharmacists to discuss prescription changes.

- *Self-Efficacy/Change in self-efficacy*. Self-efficacy will be measured pre- and post-intervention with the medication reduction self-efficacy scale, a scale that was developed and tested in the context of previous benzodiazepine tapering studies.[80] 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.[81] 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. 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.

Other Measures: Various measures will also be collected to assess effects of the intervention with some of these being medication class specific. These will include:

For benzodiazepine users:

- **Geriatric Anxiety inventory (GAI):** As anxiety is the main reason for benzodiazepine use in the elderly, measurement of this dimension may play a critical role in understanding study results[82]. The GAI is a 20 item, 5 minutes, self- or nurse-administered scale that measures dimensional anxiety in elderly people. Its Cronbach's α was 0.91 among normal elderly people and 0.93 in the psychogeriatric sample[83]. Concurrent validity with a variety of other measures was demonstrated in both the normal sample and the psychogeriatric sample[83]. Inter-rater and test–retest reliability were found to be excellent. Receiver operating characteristic analysis indicated a cut-point of 10/11 for the detection of DSM-IV Generalized Anxiety Disorder (GAD) in the psychogeriatric sample, with 83% of patients correctly classified with a specificity of 84% and a sensitivity of 75%.[83] When comparing the psychometric properties of a variety of anxiety measures administered to older adults, The Geriatric Anxiety Inventory (GAI) demonstrated the strongest psychometric properties.[84]

- **Insomnia Severity Indeex (ISI)**: As insomnia is the second most common reason for benzodiazepine use in the elderly, measurement of this dimension may play a critical role in understanding study results.[82] The ISI is a brief self-report instrument measuring the patient's perception of his or her insomnia. Psychometric evaluation of the ISI showed that it has adequate internal consistency and is a reliable self-report measure to evaluate perceived sleep difficulties and that the ISI is a valid and sensitive measure to detect changes in perceived sleep difficulties with treatment[85]. The questionnaire is approximately 5 minutes and only administered if subjects previously report insomnia.

- **Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ):** As benzodiazepine withdrawal is linked to side effects due to physiological dependence of patients to the medication, measurement of this dimension may play a critical role in understanding study results. The BWSQ is a self-report questionnaire is described which records the main symptoms experienced during withdrawal from benzodiazepines in pharmacologically dependent patients. It has shown to have reliability coefficients between 0.84 and 0.88 and the test-retest correlations between 0.75 and 0.88 during withdrawal[86]. Mean scores on the BWSQ during withdrawal has been shown to differentiate between completers and failures ($p = 0.036$) and low scores during the last phase of tapering off predicted no, or limited, use of benzodiazepines in the first years following discontinuation ($p = 0.003$)[86].

For long-acting sulfonylurea users:

- **Diabetes Treatment Satisfaction Questionnaire (DTQSs):** As diabetes treatment satisfaction is likely to be linked to patients' decision to or not to change treatment, measurement of this dimension may play a critical role in understanding study results. The DTSQ is a measure of satisfaction with diabetes treatment regimens. Designed and developed in the 1980s[87], the DTSQ is now in a form suitable for people with either Type 1 or 2 diabetes mellitus and is widely used in clinical trials.[88] It has shown to have reliability coefficients of 0.80 and 0.83 for English and French respectively.[89]

For all three categories of medication:

- **Patients' Attitudes Towards Deprescribing (PATD) questionnaire**: As attitude towards deprescribing may be an important predictor of patient's decisions, measurement of this dimension may play a critical role in understanding study results. The PATD is a 15-item (~5-7 minutes) questionnaire, which aims to capture the views and beliefs of patients regarding cessation of medications.[90] The PATD was determined to be valid through piloting, expert review and gamma rank correlation with the previously validated beliefs about medicines questionnaire and reliable since test-retesting resulted in a total concordance of 71.3 % (95 % confidence interval, 64.1–78.5 %). [90]

- **PHQ-9 (Depression diagnostic and severity measure)**: As depression may play an important role in patient's decisions, measurement of this dimension may play a critical role in understanding study results. At 9 items, the PHQ depression scale (which we call the PHQ-9) is half the length (~5mins) of many other depression measures, has comparable sensitivity and specificity, and consists of the actual nine criteria on which the diagnosis of DSM-IV depressive disorders is based[91]. (Clearly defined cut-off scores of 5, 10, 15, and 20 represent mild, moderate, moderately severe, and severe depression, respectively.[91]) The latter feature distinguishes the PHQ-9 from other two-step depression measures for which, when scores are high, additional questions must be asked to establish DSM-IV depressive diagnoses. The PHQ-9 is thus a dual-purpose instrument that, with the same nine items, can establish provisional depressive disorder diagnoses as well as grade depressive symptom severity[92]. Using the MHP re-interview as the criterion standard, a PHQ-9 score > or =10 has a sensitivity of 88% and a specificity of 88% for major depression. [91] When compared to other psychometric measures in the elderly, The PHQ-9 had an area under the curve (AUC) of 0.87 (95% confidence interval [CI], 0.74-1.00) for major depression, while the PHQ-2 and the 15-item Geriatric depression scale (GDS) each had an Area under the curve (AUC) of 0.81 (95% CI for PHQ-2, 0.64-0.98, and for 15-item GDS, 0.70-0.91; P = 0.551). For major and minor depression combined, the AUC for the PHQ-9 was 0.85 (95% CI, 0.73-0.96), for the PHQ-2, 0.80 (95% CI, 0.68- 0.93), and for the 15-item GDS, 0.71 (95% CI, 0.55-0.87; P = 0.187)[93]. As the PHQ-9 performs comparably to the PHQ-2 and the 15-item GDS in identifying depression among elderly while taking half the length, it was preferred here.

- **Montreal Cognitive Assessment (MoCA)**: As proper cognitive function is crucial for the administration of any educational intervention, a measurement of this dimension is critical in assessing patient's eligibility to the study. The MoCA test is a one-page 30-point test administered in approximately 10 minutes validated in the setting of mild cognitive impairment.[72] The MoCA has shown consistently superior psychometric properties when compared with the Mini-mental State Exam (MMSE), and higher diagnostic accuracy to discriminate between Mild cognitive impairment (MCI) (area under the curve=0.856; 95% confidence interval, 0.796-0.904) and Alzheimer's Disease (AD) patients (area under the curve=0.980; 95% confidence interval, 0.947-0.995). The MoCa showed that at an optimal cut-off of below 22 for MCI and below 17 for AD, it achieved significantly superior values in comparison with MMSE for sensitivity, specificity, positive predictive value, negative predictive value, and classification accuracy[94]. This robust evidence that the MoCA is a better cognitive tool than the widely used MMSE for the screening and monitoring of MCI and AD and will be preferred here despite its longer administration time (10-12 minutes) vs the MMSE (~8 minutes). All patients showing signs of MCI (MoCA score ≤17) will not be included in the study.

- **The Short-Form-12 Health Survey (SF-12)**: As health status may play an important role in patient's decisions, measurement of this dimension may play a critical role in understanding study results. The SF-12 is an abbreviation 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 complete Survey.[95] 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. The correlation between the Physical health composite score (PCS) scores on the two instruments in another study was 0.95; the correlation for the Mental health composite score (MCS) was 0.97. Cronbach's alpha was 0.84 for the MCS items and 0.81 for the PCS. The 12 items predicted PCS scores on the complete SF-36 ($R^2 = 0.91$), whereas the R^2 for the MCS was 0.92. Ware et al. compared SF-12 scores with SF-36 scores derived from the same data set; the correlation between the SF-12 and SF-36 PCS was 0.95 and was 0.97 for the MCS. They reported that, in a number of international studies, the PCS correlations ranged from 0.94 to 0.96, and those for the MCS ranged from 0.94 to 0.97. [95] The SF-12 has been used extensively in health care 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 sample.[96, 97]

- **Vulnerable Elders Survey (VES-13):** As patient autonomy may play an important role in patient's decisions, measurement of this dimension may play a critical role in understanding study results. The Vulnerable Elders Survey (VES-13) is a simple function-based tool for screening community-dwelling populations to identify older persons at risk for health deterioration. The VES considers age, self-rated health, limitations in physical function and functional disabilities. It is a validated function-based targeting system that effectively and efficiently identifies older people at risk of functional decline and death[98]. The questionnaire takes approximately 5 minutes.

- Baseline patient measures as well as socio-demographic data such as age and educational status will be collected at initial screening conducted in the patient's home by the research assistant after the pharmacist has relayed the names and contact numbers of patients wishing to participate in the trial. The consent form for the trial, permission to access each patient's RAMQ administrative data for follow-up. A breakdown of measurements collected at each visit is illustrated in Table 2.

Table 2. Summary of Data collection per study visit

Visit number	**T0**	**T1**	**T2**	**T3**	**T4**
Time	**1-7 months pre-intervention**	**- 7 days**	**7 days**	**6 weeks**	**6months**
Inclusion/exclusion criteria	X				
Informed Consent	X				
Socio-demographic characteristics	X				
VES-13	X				
SF-12	X				X
MoCA	X				
GAI	X				X
Depression PHQ-9	X				X
ISI	X[a]				X[a]
Medications profile	X				
BMQ-General	X				X
PATD	X				X
Risk Assessment		X	X		X
Targeted medication use characteristics		X			X

DTSQs		X[b]	X[b]		X[b]
Medication knowledge questionnaire		X	X		
BMQ-Specific		X	X		X
Self-efficacy scale		X	X		X
Intervention related questionnaire			X	X	X
Benzodiazepine tapering questionnaire				X[a]	X[a]
Intervention appreciation questionnaire					X
Additional PIPs screening information					X[a]

[a]Only administered if related outcome present. [b]Only administered if in Sufonylurea group. BMQ, Beliefs about Medicines Questionnaire; GAI, Geriatric Anxiety Inventory; SF-12, Short Form Health Survey; MoCA, Montreal Cognitive Assessment; PHQ, Patient Health Questionnaire; SMAF-ADL, Functional Autonomy Measurement System - Activities of Daily Living; ISI, Insomnia Severity Index; PIPS, Potentially inappropriate prescriptions.

Visits: As shown in table 2, there will be a total of 5 data collection requiring patient input.

- **Baseline (T0)**: Baseline will be collected in the patient's homes by the research assistant after the pharmacist has relayed the names and contact numbers of patients wishing to participate in the trial. In this visit, informed consent is obtained from patients. Visit duration should vary between 45-60 minutes depending on participants.
- **On study (T1-T3)**: Time points one to three will be collected over the phone by the same research assistant and should last no longer than 5-20 minutes depending on the time point and participant dispositions.
- **On study (T4)**: Time point 4 will be collected in the participant's homes by the same research assistant. Visit duration should vary between 45-60 minutes depending on participants. At this point, participants may also be asked if they would wish to meet again to further discuss their experience during the study in the context of gathering qualitative data in association with the project.
- **Additional visits**: Patients with more/different inappropriate prescriptions detected in their medication will be queried for their specific medication at T4, receive additional intervention material for these medications and be followed up on 6 months later (T5: 1 year post-intervention). Follow up will be similar to the one done at T3, will also be done over the phone and should last no longer than 5-10 minutes. Patients agreeing to the qualitative interview will arrange a meeting with the research assistant. This extra meeting will be perfectly voluntary and participants receiving additional intervention material after T4 will not be asked until after their optional T5 as to avoid causing prejudice in their decision to participate or not in the qualitative interview process.

Sample size calculation

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 25%) compared to usual care (maximum rate of discontinuation 6%).[28, 29, 33, 34, 99-102] 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%. We are also interested in conducting sub-group analyses by drug class as the three 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.[103] We assume that the intracluster correlation (ICC) will 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.[104, 105] For example, Thompson et al. report an ICC of 0.01 for the intent to quite smoking and an ICC of 0.2 to reduce drinking within 61 physician practices.[104] Table 3 shows the number of pharmacies required for both the subgroup analysis and the main analysis based on different ICC's and the minimum numbers of patients per drug class identified from each pharmacy.[106]

Table 3: Sample size calculation with varying ICC and number of participants per pharmacy

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

Based on our pilot work from EMPOWER, we have chosen the minimal number of subjects per drug class (n=3) in order to augment the likelihood that each consenting pharmacy will achieve the required number of participants. With an estimated ICC of 0.05 for the 3 participants recruited per drug class, we require 20 pharmacies per group (60 participants per arm) to be able to estimate discontinuation rates by drug class with 80% power and alpha 0.05. Recruiting nine participants from each of these pharmacies yields 180 participants per arm. With an ICC of 0.2, even just 20 pharmacies per arm would allow 90% power to detect a 20% difference at alpha 0.05. To detect greater differences, a lower sample size is needed. Thus we would have ample power for the overall comparison. Based on our experience with EMPOWER we assume that 1 out of every 10 pharmacies who wishes to participate will not be able to recruit the desired number of participants (insufficient numbers of eligible participants who consent to participate), and that 10% of participants will withdraw or be lost to follow-up. We have therefore inflated our sample size to 400 participants from 46 pharmacies.

Recruitment feasibility: Our experience with the EMPOWER study makes us confident that we will achieve the recruitment target for the current study. We anticipate being able to complete recruitment and baseline data collection within a 2 year time period (200 patients/year) by recruiting pharmacists throughout the entire catchment area of Quebec. We will be working in close collaboration with the Uniprix chain (n=85 pharmacists have already expressed interest in participating) as well as the AQPP to reach out to potentially interested pharmacists from other chains. Pharmacists who participated in EMPOWER will be excluded from participating in the current proposal.

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. Subjects 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.[107] 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 the adjusted chi-squared, ratio estimator and parametric modeling approaches.

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 RAMQ 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.

Timeline

The project will take 4 years. Six months to obtain ethics approval and set up procedures with RAMQ for recruitment and follow-up. Two years for recruitment, screening and patient enrolment to the trial. Although we anticipate being able to quickly recruit the pharmacists, it will take 2 years to obtain the lists from RAMQ, contact 2000 clients (only 1/5 clients consents to participate based on EMPOWER data) and arrange baseline interviews. Nine-month follow-up is required for outcome ascertainment, and 3-months and 6-months for analysis and dissemination of the findings respectively.

Limitations

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. Comparison with EMPOWER and previous studies by Dr. Tamblyn's group will allow us to examine the synergic effects of our intervention compared to direct-to-consumer and direct-to-prescriber interventions alone.

The Team

The investigators from the EMPOWER study form the core team for this proposal to which they have added Dr. Andrea Benedetti, a biostatistician jointly appointed in the departments of Medicine and Epidemiology & Biostatistics at McGill University. Dr. Benedetti has extensive experience in the modelling of epidemiologic and clustered data and will direct the statistical analyses. Two stakeholder collaborators, Amélie Paquette from Uniprix and Normand Cadieux from the Association Quebecoise de Pharmaciens Proprietaires will also participate. The team will be led by Dr. Cara Tannenbaum, a practicing geriatrician, clinical researcher and Endowed Chair of Geriatric Pharmacology, Health and Aging at the University of Montreal. Dr. Sara Ahmed will contribute expertise in health outcomes research in patient populations with chronic disease. Dr. Robyn Tamblyn is a world leader in intervention studies aimed at reducing inappropriate prescribing.

Project Oversight

The trial will have a steering committee made up of its academic investigators, a member of the private pharmaceutical sector (Amélie Paquette), a pharmacist representative (Normand Cadieux), a primary care

provider, a representative from the Ordre des Pharmaciens de Quebec and a patient representative. The steering committee will meet every two months to review the progress of the study and identify macro-level problems and solutions. C. Tannenbaum will oversee the day-to-day management of the project. She will meet weekly with the study coordinator to monitor participant recruitment and flow.

Expected Contribution and Knowledge Transfer Plan

The results of this trial will determine whether the new enabling paradigm to optimize medications is an effective strategy to reduce inappropriate prescriptions. Our study will set the stage for future work on the assessment of health outcomes as a result of this paradigm. At a policy and health services level, our collaborator from the Association Quebecoise de Pharmaciens Proprietaires and additional networking with the Ordre des Pharmaciens de Quebec will help inform decision-makers about the utility of pharmaceutical opinions for reducing inappropriate prescribing in the elderly. We foresee rapid dissemination of the results to pharmacist and patient stakeholders with the help of our steering committee, and to other provinces through presentations at the Canadian Pharmacy Association National Conference. We believe the timing of our project falls within a window of opportunity during which the scope of the pharmacist's practice is expanding. At the same time, pressure is on physicians to improve the quality of care delivered to patients and to reduce drug-related hospitalizations. Increased support from pharmacists has potential to alleviate this burden. Hopefully this trial will provide Level 1 evidence to catalyze a new culture of pharmacist-led communication to patients and prescribers to improve the problem of inappropriate prescribing for the individual and society at large.

1. Tannenbaum C. Effect of age, education and health status on community dwelling older men's health concerns. The aging male : the official journal of the International Society for the Study of the Aging Male. 2012 Jun;15(2):103-8. PubMed PMID: 22103599. Epub 2011/11/23. eng.
2. Tannenbaum C, Mayo N, Ducharme F. Older women's health priorities and perceptions of care delivery: results of the WOW health survey. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne. 2005 Jul 19;173(2):153-9. PubMed PMID: 16027431. Pubmed Central PMCID: 1174854.
3. Reason B, Terner M, Moses McKeag A, Tipper B, Webster G. The impact of polypharmacy on the health of Canadian seniors. Family practice. 2012 Aug;29(4):427-32. PubMed PMID: 22223743.
4. Terner M, Reason B, McKeag AM, Tipper B, Webster G. Chronic conditions more than age drive health system use in Canadian seniors. Healthcare quarterly. 2011;14(3):19-22. PubMed PMID: 21841372.
5. Gallagher P, Barry P, O'Mahony D. Inappropriate prescribing in the elderly. Journal of clinical pharmacy and therapeutics. 2007 Apr;32(2):113-21. PubMed PMID: 17381661.
6. Gurwitz JH, Field TS, Harrold LR, Rothschild J, Debellis K, Seger AC, et al. Incidence and preventability of adverse drug events among older persons in the ambulatory setting. JAMA : the journal of the American Medical Association. 2003 Mar 5;289(9):1107-16. PubMed PMID: 12622580.
7. Budnitz DS, Lovegrove MC, Shehab N, Richards CL. Emergency hospitalizations for adverse drug events in older Americans. The New England journal of medicine. 2011 Nov 24;365(21):2002-12. PubMed PMID: 22111719.
8. Zhan C, Sangl J, Bierman AS, Miller MR, Friedman B, Wickizer SW, et al. Potentially inappropriate medication use in the community-dwelling elderly: findings from the 1996 Medical Expenditure Panel Survey. JAMA : the journal of the American Medical Association. 2001 Dec 12;286(22):2823-9. PubMed PMID: 11735757.
9. Liu GG, Christensen DB. The continuing challenge of inappropriate prescribing in the elderly: an update of the evidence. Journal of the American Pharmaceutical Association. 2002 Nov-Dec;42(6):847-57. PubMed PMID: 12482007.
10. Jano E, Aparasu RR. Healthcare outcomes associated with beers' criteria: a systematic review. The Annals of pharmacotherapy. 2007 Mar;41(3):438-47. PubMed PMID: 17311835.

11. American Geriatrics Society Beers Criteria Update Expert P. American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. Journal of the American Geriatrics Society. 2012 Apr;60(4):616-31. PubMed PMID: 22376048. Pubmed Central PMCID: 3571677.
12. McLeod PJ, Huang AR, Tamblyn RM, Gayton DC. Defining inappropriate practices in prescribing for elderly people: a national consensus panel. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne. 1997 Feb 1;156(3):385-91. PubMed PMID: 9033421. Pubmed Central PMCID: 1226961.
13. Fu AZ, Jiang JZ, Reeves JH, Fincham JE, Liu GG, Perri M, 3rd. Potentially inappropriate medication use and healthcare expenditures in the US community-dwelling elderly. Medical care. 2007 May;45(5):472-6. PubMed PMID: 17446834.
14. Information CIFH. Drug Claims by Seniors: An Analysis Focusing on Potentially Inappropriate Medication Use, 2000 to 2006. In: Information CIFH, editor. Canada: Canadian Government; 2007.
15. Médicament Cd. Étude sur la prévalence d l'usage d'ordonnances potentiellement non appropriées (OPNA) chez les aînés du Québec, de 2000 à 2006. In: Médicament Cd, editor.: Gouvernement du Québec; 2009.
16. Garattini S, Chalmers I. Patients and the public deserve big changes in evaluation of drugs. Bmj. 2009;338:b1025. PubMed PMID: 19336489.
17. Freemantle N, Irs A. Observational evidence for determining drug safety. Bmj. 2008 Mar 22;336(7645):627-8. PubMed PMID: 18356209. Pubmed Central PMCID: 2270986.
18. Avorn J. In defense of pharmacoepidemiology--embracing the yin and yang of drug research. The New England journal of medicine. 2007 Nov 29;357(22):2219-21. PubMed PMID: 18046025.
19. Gnjidic D, Hilmer SN, Blyth FM, Naganathan V, Waite L, Seibel MJ, et al. Polypharmacy cutoff and outcomes: five or more medicines were used to identify community-dwelling older men at risk of different adverse outcomes. Journal of clinical epidemiology. 2012 Sep;65(9):989-95. PubMed PMID: 22742913.
20. Shah BM, Hajjar ER. Polypharmacy, adverse drug reactions, and geriatric syndromes. Clinics in geriatric medicine. 2012 May;28(2):173-86. PubMed PMID: 22500537.
21. Gnjidic D, Le Couteur DG, Abernethy DR, Hilmer SN. A pilot randomized clinical trial utilizing the drug burden index to reduce exposure to anticholinergic and sedative medications in older people. The Annals of pharmacotherapy. 2010 Nov;44(11):1725-32. PubMed PMID: 20876826.
22. Iliffe S, Curran HV, Collins R, Yuen Kee SC, Fletcher S, Woods B. Attitudes to long-term use of benzodiazepine hypnotics by older people in general practice: findings from interviews with service users and providers. Aging & mental health. 2004 May;8(3):242-8. PubMed PMID: 15203405. Epub 2004/06/19. eng.
23. Gnjidic D, Le Couteur DG, Kouladjian L, Hilmer SN. Deprescribing trials: methods to reduce polypharmacy and the impact on prescribing and clinical outcomes. Clinics in geriatric medicine. 2012 May;28(2):237-53. PubMed PMID: 22500541.
24. Schindel TJ, Given LM. The pharmacist as prescriber: A discourse analysis of newspaper media in Canada. Research in social & administrative pharmacy : RSAP. 2012 Jul 24. PubMed PMID: 22835707. Epub 2012/07/28. Eng.
25. Poirier S, Gariepy Y. Compensation in Canada for resolving drug-related problems. Journal of the American Pharmaceutical Association. 1996 Feb;NS36(2):117-22. PubMed PMID: 8742009.
26. Kroger E, Moisan J, Gregoire JP. Billing for cognitive services: understanding Quebec pharmacists' behavior. The Annals of pharmacotherapy. 2000 Mar;34(3):309-16. PubMed PMID: 10917375.
27. Dumas J, Matte J. Characteristics of pharmaceutical opinions written in a Quebec community pharmacy. The Annals of pharmacotherapy. 1992 Jun;26(6):835-9. PubMed PMID: 1611169.
28. Kaur S, Mitchell G, Vitetta L, Roberts MS. Interventions that can reduce inappropriate prescribing in the elderly: a systematic review. Drugs & aging. 2009;26(12):1013-28. PubMed PMID: 19929029. Epub 2009/11/26. eng.

29. Patterson SM, Hughes C, Kerse N, Cardwell CR, Bradley MC. Interventions to improve the appropriate use of polypharmacy for older people. Cochrane database of systematic reviews (Online). 2012;5:CD008165. PubMed PMID: 22592727. Epub 2012/05/18. eng.
30. Tamblyn R, Huang A, Taylor L, Kawasumi Y, Bartlett G, Grad R, et al. A randomized trial of the effectiveness of on-demand versus computer-triggered drug decision support in primary care. Journal of the American Medical Informatics Association : JAMIA. 2008 Jul-Aug;15(4):430-8. PubMed PMID: 18436904. Pubmed Central PMCID: 2442270.
31. Tamblyn R, Huang A, Perreault R, Jacques A, Roy D, Hanley J, et al. The medical office of the 21st century (MOXXI): effectiveness of computerized decision-making support in reducing inappropriate prescribing in primary care. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne. 2003 Sep 16;169(6):549-56. PubMed PMID: 12975221. Pubmed Central PMCID: 191278.
32. Isaac T, Weissman JS, Davis RB, Massagli M, Cyrulik A, Sands DZ, et al. Overrides of medication alerts in ambulatory care. Archives of internal medicine. 2009 Feb 9;169(3):305-11. PubMed PMID: 19204222.
33. Monane M, Matthias DM, Nagle BA, Kelly MA. Improving prescribing patterns for the elderly through an online drug utilization review intervention: a system linking the physician, pharmacist, and computer. JAMA : the journal of the American Medical Association. 1998 Oct 14;280(14):1249-52. PubMed PMID: 9786375. Epub 1998/10/24. eng.
34. Tamblyn R, Eguale T, Buckeridge DL, Huang A, Hanley J, Reidel K, et al. The effectiveness of a new generation of computerized drug alerts in reducing the risk of injury from drug side effects: a cluster randomized trial. Journal of the American Medical Informatics Association : JAMIA. 2012 Jul-Aug;19(4):635-43. PubMed PMID: 22246963. Pubmed Central PMCID: 3384117.
35. Gallagher PF, O'Connor MN, O'Mahony D. Prevention of potentially inappropriate prescribing for elderly patients: a randomized controlled trial using STOPP/START criteria. Clinical pharmacology and therapeutics. 2011 Jun;89(6):845-54. PubMed PMID: 21508941.
36. Allard J, Hebert R, Rioux M, Asselin J, Voyer L. Efficacy of a clinical medication review on the number of potentially inappropriate prescriptions prescribed for community-dwelling elderly people. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne. 2001 May 1;164(9):1291-6. PubMed PMID: 11341138. Pubmed Central PMCID: 81019.
37. Krska J, Cromarty JA, Arris F, Jamieson D, Hansford D, Duffus PR, et al. Pharmacist-led medication review in patients over 65: a randomized, controlled trial in primary care. Age and ageing. 2001 May;30(3):205-11. PubMed PMID: 11443021.
38. Hanlon JT, Weinberger M, Samsa GP, Schmader KE, Uttech KM, Lewis IK, et al. A randomized, controlled trial of a clinical pharmacist intervention to improve inappropriate prescribing in elderly outpatients with polypharmacy. The American journal of medicine. 1996 Apr;100(4):428-37. PubMed PMID: 8610730.
39. Grimshaw JM, Shirran L, Thomas R, Mowatt G, Fraser C, Bero L, et al. Changing provider behavior: an overview of systematic reviews of interventions. Medical care. 2001 Aug;39(8 Suppl 2):II2-45. PubMed PMID: 11583120.
40. Bodenheimer T, Lorig K, Holman H, Grumbach K. Patient self-management of chronic disease in primary care. JAMA : the journal of the American Medical Association. 2002 Nov 20;288(19):2469-75. PubMed PMID: 12435261.
41. Sminia H, Van Nistelrooij A. Strategic management and organizational development: Planned change in a public sector organization. Journal of Change Management. 2006;6(1):99-113.
42. Treweek S, Zwarenstein M. Making trials matter: pragmatic and explanatory trials and the problem of applicability. Trials. 2009;10:37. PubMed PMID: 19493350. Pubmed Central PMCID: 2700087.
43. Godwin M, Ruhland L, Casson I, MacDonald S, Delva D, Birtwhistle R, et al. Pragmatic controlled clinical trials in primary care: the struggle between external and internal validity. BMC medical research methodology. 2003 Dec 22;3:28. PubMed PMID: 14690550. Pubmed Central PMCID: PMC317298. Epub 2003/12/24. eng.

44. Cook JM, Biyanova T, Masci C, Coyne JC. Older patient perspectives on long-term anxiolytic benzodiazepine use and discontinuation: a qualitative study. Journal of general internal medicine. 2007 Aug;22(8):1094-100. PubMed PMID: 17492325. Pubmed Central PMCID: PMC2305752. Epub 2007/05/12. eng.
45. Martin P, Tamblyn R, Ahmed S, Tannenbaum C. A drug education tool developed for older adults changes knowledge, beliefs and risk perceptions about inappropriate benzodiazepine prescriptions in the elderly. Patient education and counseling. 2013 Mar 28. PubMed PMID: 23541509. Epub 2013/04/02. Eng.
46. Brekke M, Rognstad S, Straand J, Furu K, Gjelstad S, Bjorner T, et al. Pharmacologically inappropriate prescriptions for elderly patients in general practice: How common? Baseline data from The Prescription Peer Academic Detailing (Rx-PAD) study. Scandinavian journal of primary health care. 2008;26(2):80-5. PubMed PMID: 18570005. Pubmed Central PMCID: PMC3406653. Epub 2008/06/24. eng.
47. Glass J, Lanctot KL, Herrmann N, Sproule BA, Busto UE. Sedative hypnotics in older people with insomnia: meta-analysis of risks and benefits. Bmj. 2005 Nov 19;331(7526):1169. PubMed PMID: 16284208. Pubmed Central PMCID: 1285093.
48. Glass JR, Sproule BA, Herrmann N, Streiner D, Busto UE. Acute pharmacological effects of temazepam, diphenhydramine, and valerian in healthy elderly subjects. Journal of clinical psychopharmacology. 2003 Jun;23(3):260-8. PubMed PMID: 12826988.
49. Rummans TA, Davis LJ, Jr., Morse RM, Ivnik RJ. Learning and memory impairment in older, detoxified, benzodiazepine-dependent patients. Mayo Clinic proceedings Mayo Clinic. 1993 Aug;68(8):731-7. PubMed PMID: 8331973.
50. Tannenbaum C, Paquette A, Hilmer S, Holroyd-Leduc J, Carnahan R. A systematic review of amnestic and non-amnestic mild cognitive impairment induced by anticholinergic, antihistamine, GABAergic and opioid drugs. Drugs & aging. 2012 Aug 1;29(8):639-58. PubMed PMID: 22812538.
51. Ensrud KE, Blackwell TL, Mangione CM, Bowman PJ, Whooley MA, Bauer DC, et al. Central nervous system-active medications and risk for falls in older women. Journal of the American Geriatrics Society. 2002 Oct;50(10):1629-37. PubMed PMID: 12366615.
52. Landi F, Onder G, Cesari M, Barillaro C, Russo A, Bernabei R. Psychotropic medications and risk for falls among community-dwelling frail older people: an observational study. The journals of gerontology Series A, Biological sciences and medical sciences. 2005 May;60(5):622-6. PubMed PMID: 15972615. Epub 2005/06/24. eng.
53. Coutinho ES, Fletcher A, Bloch KV, Rodrigues LC. Risk factors for falls with severe fracture in elderly people living in a middle-income country: a case control study. BMC geriatrics. 2008;8:21. PubMed PMID: 18727832. Pubmed Central PMCID: 2532993.
54. Tamblyn R, Abrahamowicz M, du Berger R, McLeod P, Bartlett G. A 5-year prospective assessment of the risk associated with individual benzodiazepines and doses in new elderly users. Journal of the American Geriatrics Society. 2005 Feb;53(2):233-41. PubMed PMID: 15673346.
55. Ray WA, Griffin MR, Downey W. Benzodiazepines of long and short elimination half-life and the risk of hip fracture. JAMA : the journal of the American Medical Association. 1989 Dec 15;262(23):3303-7. PubMed PMID: 2573741.
56. Cumming RG, Le Couteur DG. Benzodiazepines and risk of hip fractures in older people: a review of the evidence. CNS drugs. 2003;17(11):825-37. PubMed PMID: 12921493.
57. Finkle WD, Der JS, Greenland S, Adams JL, Ridgeway G, Blaschke T, et al. Risk of fractures requiring hospitalization after an initial prescription for zolpidem, alprazolam, lorazepam, or diazepam in older adults. Journal of the American Geriatrics Society. 2011 Oct;59(10):1883-90. PubMed PMID: 22091502.
58. Barbone F, McMahon AD, Davey PG, Morris AD, Reid IC, McDevitt DG, et al. Association of road-traffic accidents with benzodiazepine use. Lancet. 1998 Oct 24;352(9137):1331-6. PubMed PMID: 9802269. Epub 1998/11/05. eng.

59. Thomas RE. Benzodiazepine use and motor vehicle accidents. Systematic review of reported association. Canadian family physician Medecin de famille canadien. 1998 Apr;44:799-808. PubMed PMID: 9585853. Pubmed Central PMCID: PMC2277821. Epub 1998/05/20. eng.
60. Hemmelgarn B, Suissa S, Huang A, Boivin JF, Pinard G. Benzodiazepine use and the risk of motor vehicle crash in the elderly. JAMA : the journal of the American Medical Association. 1997 Jul 2;278(1):27-31. PubMed PMID: 9207334. Epub 1997/07/02. eng.
61. Agostini JV, Leo-Summers LS, Inouye SK. Cognitive and other adverse effects of diphenhydramine use in hospitalized older patients. Archives of internal medicine. 2001 Sep 24;161(17):2091-7. PubMed PMID: 11570937. Epub 2001/09/26. eng.
62. Guaiana G, Barbui C, Cipriani A. Hydroxyzine for generalised anxiety disorder. Cochrane database of systematic reviews (Online). 2010 (12):CD006815. PubMed PMID: 21154375.
63. Han L, McCusker J, Cole M, Abrahamowicz M, Primeau F, Elie M. Use of medications with anticholinergic effect predicts clinical severity of delirium symptoms in older medical inpatients. Archives of internal medicine. 2001 Apr 23;161(8):1099-105. PubMed PMID: 11322844. Epub 2001/04/27. eng.
64. Rudolph JL, Salow MJ, Angelini MC, McGlinchey RE. The anticholinergic risk scale and anticholinergic adverse effects in older persons. Archives of internal medicine. 2008 Mar 10;168(5):508-13. PubMed PMID: 18332297.
65. Gnjidic D, Bell JS, Hilmer SN, Lonnroos E, Sulkava R, Hartikainen S. Drug Burden Index associated with function in community-dwelling older people in Finland: a cross-sectional study. Annals of medicine. 2012 Aug;44(5):458-67. PubMed PMID: 21495785.
66. Hilmer SN, Mager DE, Simonsick EM, Ling SM, Windham BG, Harris TB, et al. Drug burden index score and functional decline in older people. The American journal of medicine. 2009 Dec;122(12):1142-9 e1-2. PubMed PMID: 19958893. Pubmed Central PMCID: 3263511.
67. Darowski A, Chambers SA, Chambers DJ. Antidepressants and falls in the elderly. Drugs & aging. 2009;26(5):381-94. PubMed PMID: 19552490.
68. Gangji AS, Cukierman T, Gerstein HC, Goldsmith CH, Clase CM. A systematic review and meta-analysis of hypoglycemia and cardiovascular events: a comparison of glyburide with other secretagogues and with insulin. Diabetes care. 2007 Feb;30(2):389-94. PubMed PMID: 17259518.
69. Shorr RI, Ray WA, Daugherty JR, Griffin MR. Individual sulfonylureas and serious hypoglycemia in older people. Journal of the American Geriatrics Society. 1996 Jul;44(7):751-5. PubMed PMID: 8675920.
70. Clarke BF, Campbell IW. Long-term comparative trial of glibenclamide and chlorpropamide in diet-failed, maturity-onset diabetics. Lancet. 1975 Feb 1;1(7901):246-8. PubMed PMID: 8667857.
71. Bramlage P, Gitt AK, Binz C, Krekler M, Deeg E, Tschope D. Oral antidiabetic treatment in type-2 diabetes in the elderly: balancing the need for glucose control and the risk of hypoglycemia. Cardiovascular diabetology. 2012;11:122. PubMed PMID: 23039216. Pubmed Central PMCID: 3508810.
72. Nasreddine ZS, Phillips NA, Bedirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. Journal of the American Geriatrics Society. 2005 Apr;53(4):695-9. PubMed PMID: 15817019.
73. Tamblyn R, Lavoie G, Petrella L, Monette J. The use of prescription claims databases in pharmacoepidemiological research: the accuracy and comprehensiveness of the prescription claims database in Quebec. Journal of clinical epidemiology. 1995 Aug;48(8):999-1009. PubMed PMID: 7775999. Epub 1995/08/01. eng.
74. Tamblyn R, Huang A, Kawasumi Y, Bartlett G, Grad R, Jacques A, et al. The development and evaluation of an integrated electronic prescribing and drug management system for primary care. Journal of the American Medical Informatics Association : JAMIA. 2006 Mar-Apr;13(2):148-59. PubMed PMID: 16357357. Pubmed Central PMCID: 1447542.
75. James O. Prochaska, Norcross JC, Diclemente CC. Changing for Good: The Revolutionary Program That Explains the Six Stages of Change and Teaches You How to Free Yourself from Bad Habits. New York: William Morrow & Co 1994.

76. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: the new Medical Research Council guidance. Bmj. 2008;337:a1655. PubMed PMID: 18824488. Pubmed Central PMCID: PMC2769032. Epub 2008/10/01. eng.
77. Horne R, Weinman J. Patients' beliefs about prescribed medicines and their role in adherence to treatment in chronic physical illness. J Psychosom Res. 1999 Dec;47(6):555-67. PubMed PMID: 10661603. English.
78. Horne R, Weinman J, Hankins M. The Beliefs about Medicines Questionnaire: The development and evaluation of a new method for assessing the cognitive representation of medication. Psychology & Health. 1999 Jan;14(1):1-24. PubMed PMID: Peer Reviewed Journal: 1999-05846-001. English.
79. Modig S, Kristensson J, Ekwall AK, Hallberg IR, Midlov P. Frail elderly patients in primary care--their medication knowledge and beliefs about prescribed medicines. European journal of clinical pharmacology. 2009 Feb;65(2):151-5. PubMed PMID: 18958457. Epub 2008/10/30. eng.
80. Belanger L, Morin CM, Bastien C, Ladouceur R. Self-efficacy and compliance with benzodiazepine taper in older adults with chronic insomnia. Health psychology : official journal of the Division of Health Psychology, American Psychological Association. 2005 May;24(3):281-7. PubMed PMID: 15898864. Epub 2005/05/19. eng.
81. Sherer M, Maddux JE, Mercandante B, Prentice-dunn S, Jacobs B, Rogers RW. The Self-efficacy Scale: Construction and validation. Psychological Reports. 1982 Oct;51(2):663-71.
82. Bogunovic OJ, Greenfield SF, Goldstein MZ. Use of Benzodiazepines Among Elderly Patients. Psychiatric Services. 2004 Mar;55(3):233-5. PubMed PMID: Peer Reviewed Journal: 2004-11806-011.
83. Pachana NA, Byrne GJ, Siddle H, Koloski N, Harley E, Arnold E. Development and validation of the Geriatric Anxiety Inventory. International psychogeriatrics / IPA. 2007 Feb;19(1):103-14. PubMed PMID: 16805925.
84. Diefenbach GJ, Tolin DF, Meunier SA, Gilliam CM. Assessment of anxiety in older home care recipients. The Gerontologist. 2009 Apr;49(2):141-53. PubMed PMID: 19363010. Pubmed Central PMCID: 2667674.
85. Bastien CH, Vallieres A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. Sleep medicine. 2001 Jul;2(4):297-307. PubMed PMID: 11438246. Epub 2001/07/05. Eng.
86. Couvee JE, Zitman FG. The Benzodiazepine Withdrawal Symptom Questionnaire: psychometric evaluation during a discontinuation program in depressed chronic benzodiazepine users in general practice. Addiction. 2002 Mar;97(3):337-45. PubMed PMID: 11964110.
87. Lewis KS, Bradley C, Knight G, Boulton AJ, Ward JD. A measure of treatment satisfaction designed specifically for people with insulin-dependent diabetes. Diabetic medicine : a journal of the British Diabetic Association. 1988 Apr;5(3):235-42. PubMed PMID: 2967144. Epub 1988/04/01. eng.
88. Bradley C. Handbook of Psychology and Diabetes: a guide to psychological measurement in diabetes research and practice. 1 ed. Chur, Switzerland: Harwood Academic Publishers; 1994. 424 pages p.
89. Plowright R, Witthaus E, Bradley C. Psychometric evaluation of Diabetes Treatment Satisfaction Questionnaire in 8 languages. Proceedings of the British Psychological Society. 2000;8(2).
90. Reeve E, Shakib S, Hendrix I, Roberts MS, Wiese MD. Development and validation of the patients' attitudes towards deprescribing (PATD) questionnaire. International journal of clinical pharmacy. 2013 Feb;35(1):51-6. PubMed PMID: 23054137.
91. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. Journal of general internal medicine. 2001 Sep;16(9):606-13. PubMed PMID: 11556941. Pubmed Central PMCID: 1495268.
92. Kroenke K, Spitzer RL. The PHQ-9: A new depression diagnostic and severity measure. Psychiatric Annals. 2002 Sep;32(9):509-15. PubMed PMID: Peer Reviewed Journal: 2002-04400-002.
93. Phelan E, Williams B, Meeker K, Bonn K, Frederick J, Logerfo J, et al. A study of the diagnostic accuracy of the PHQ-9 in primary care elderly. BMC family practice. 2010;11:63. PubMed PMID: 20807445. Pubmed Central PMCID: 2940814.

94. Freitas S, Simoes MR, Alves L, Santana I. Montreal cognitive assessment: validation study for mild cognitive impairment and Alzheimer disease. Alzheimer disease and associated disorders. 2013 Jan-Mar;27(1):37-43. PubMed PMID: 22193353.
95. McDowell I. Measuring health: A guide to rating scales and questionnaires (3rd ed.). New York, NY: Oxford University Press; US; 2006.
96. Ware J, Jr., Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Medical care. 1996 Mar;34(3):220-33. PubMed PMID: 8628042.
97. Hopman WM, Towheed T, Anastassiades T, Tenenhouse A, Poliquin S, Berger C, et al. Canadian normative data for the SF-36 health survey. Canadian Multicentre Osteoporosis Study Research Group. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne. 2000 Aug 8;163(3):265-71. PubMed PMID: 10951722. Pubmed Central PMCID: 80287.
98. Saliba D, Elliott M, Rubenstein LZ, Solomon DH, Young RT, Kamberg CJ, et al. The Vulnerable Elders Survey: a tool for identifying vulnerable older people in the community. Journal of the American Geriatrics Society. 2001 Dec;49(12):1691-9. PubMed PMID: 11844005. Epub 2002/02/15. eng.
99. Stewart R, Niessen WJ, Broer J, Snijders TA, Haaijer-Ruskamp FM, Meyboom-De Jong B. General Practitioners reduced benzodiazepine prescriptions in an intervention study: a multilevel application. Journal of clinical epidemiology. 2007 Oct;60(10):1076-84. PubMed PMID: 17884604.
100. Gorgels WJ, Oude Voshaar RC, Mol AJ, van de Lisdonk EH, van Balkom AJ, van den Hoogen HJ, et al. Discontinuation of long-term benzodiazepine use by sending a letter to users in family practice: a prospective controlled intervention study. Drug and alcohol dependence. 2005 Apr 4;78(1):49-56. PubMed PMID: 15769557. Epub 2005/03/17. eng.
101. Holden JD, Hughes IM, Tree A. Benzodiazepine prescribing and withdrawal for 3234 patients in 15 general practices. Family practice. 1994 Dec;11(4):358-62. PubMed PMID: 7895961.
102. Bashir K, King M, Ashworth M. Controlled evaluation of brief intervention by general practitioners to reduce chronic use of benzodiazepines. The British journal of general practice : the journal of the Royal College of General Practitioners. 1994 Sep;44(386):408-12. PubMed PMID: 8790654. Pubmed Central PMCID: PMC1238990. Epub 1994/09/01. eng.
103. Eldridge SM, Ashby D, Kerry S. Sample size for cluster randomized trials: effect of coefficient of variation of cluster size and analysis method. International journal of epidemiology. 2006 Oct;35(5):1292-300. PubMed PMID: 16943232.
104. Thompson DM, Fernald DH, Mold JW. Intraclass correlation coefficients typical of cluster-randomized studies: estimates from the Robert Wood Johnson Prescription for Health projects. Annals of family medicine. 2012 May-Jun;10(3):235-40. PubMed PMID: 22585888. Pubmed Central PMCID: 3354973.
105. Evans CD, Eurich DT, Taylor JG, Remillard AJ, Shevchuk YM, Blackburn DF. A pragmatic cluster randomized trial evaluating the impact of a community pharmacy intervention on statin adherence: rationale and design of the Community Pharmacy Assisting in Total Cardiovascular Health (CPATCH) study. Trials. 2010;11:76. PubMed PMID: 20615235. Pubmed Central PMCID: 2912883.
106. Dupont WD, Plummer WD, Jr. Power and sample size calculations. A review and computer program. Controlled clinical trials. 1990 Apr;11(2):116-28. PubMed PMID: 2161310.
107. Ukoumunne OC, Forbes AB, Carlin JB, Gulliford MC. Comparison of the risk difference, risk ratio and odds ratio scales for quantifying the unadjusted intervention effect in cluster randomized trials. Statistics in medicine. 2008 Nov 10;27(25):5143-55. PubMed PMID: 18613226.