Official Title: Engaging Patients to Promote Deprescribing
NCT Number: NCT04294901
Document Date: July 18, 2023

Study overview

We propose a multi-site, mixed-methods, quasi-experimental Hybrid Type I effectiveness implementation trial of a patient-centered intervention. A Hybrid Type I trial "tests a clinical intervention while gathering information on its potential for implementation in a real-world situation." Modeled on our Institutional Review Board (IRB)-approved pilot study procedures[1], Veterans at three intervention sites will each receive a medication-specific brochure adapted for VA prior to a scheduled primary care appointment. For the up to 6,800 subjects, we will use pharmacy dispensing data to measure deprescribing (primary outcome).

Intervention design

The intervention is an evidence-informed practice: a medication-specific brochure (adapted from Canadian Deprescribing Network EMPOWER brochures) designed to educate and activate patients. [2,3] These brochures provide detailed medication information, allow self-testing of indications for use, prompt reflection of experiences with potential side effects, discuss alternative therapies (medication and non-pharmacologic options), and provide a vignette of a patient who successfully stopped the medicine. They were designed for a 6th grade reading level and were based upon theories of patient activation, adult learning, and cognitive dissonance. The visually appealing brochure repeatedly emphasizes that patients should not make any medication changes without first consulting their health care provider.

As we did in our pilot study, we will adapt the brochures to tailor the presentation to a Veteran population and to align with current VA initiatives. We will change images and names to be more representative of Veterans to promote relatability. Importantly, to mirror efforts of the Whole Health initiative, we will add the following two questions to prompt reflection by the Veteran: 1) "How does staying on (medication name) help me reach my personal health goals?" and 2) "How does stopping (medication name) help me reach my personal health goals?"

This proposed intervention will not directly deprescribe medications; we will not be randomizing patients to medication discontinuation. Instead, we are testing an intervention to prompt consideration of a clinical decision, analogous to a clinical reminder in the electronic health record prompting the provider to consider appropriate care. We propose an innovative approach to promote medication use review that starts by contacting the patient, not the clinician, yet the ultimate decision remains with the patient-provider dyad.

Study Aim

The study primary aim is to examine the impact of a patient-centered intervention to change provider prescribing (the primary outcome), as determined by the frequency with which medications are either deprescribed or de-escalated. Our primary outcome will be the composite of deprescribing and de-escalation of target medications, identified in pharmacy dispensing records of the Corporate Data Warehouse (CDW).

Hypothesis

The hypothesis is deprescribing will be greater for Veterans receiving the intervention brochure than for those in the historical control group.

Study sites

We will target Veterans at three primary care sites who meet eligibility criteria and are prescribed the target medication at the time of their scheduled primary care visit (in-person, video technology-based, or telephone clinics). These sites were selected based upon ability to recruit adequate samples, geographic variability, and patient population. We will include all PCPs at VA Medical Centers (VAMCs) and Community Based Outpatient Clinics (CBOCs), except for resident clinicians, as these trainees are likely to turn over during the intervention.

Randomization

Previous research, including our pilot study, revealed differences in deprescribing tendencies across providers. Thus, although our intervention intends to engage patients, our study design prioritizes comparisons of patients within the same provider to maximize power. At each intervention site, individual PCPs will be randomized to the sequence of medication cohorts. We will randomize PCPs to one of the three medication groups at the beginning of the first (month 1) and second (month 7) window and assigned them to their

remaining medication group at the start of the third (month 13) window. Our primary comparisons are between "brochure-intervention" patients and "baseline" patients (matched in terms of eligibility) from the same provider. Each patient will only have one opportunity to receive a brochure, even if they subsequently meet eligibility criteria for receipt of a second, different brochure. This allows equal exposure to the intervention for all Veterans since the impact of a second brochure might be influenced by the first brochure.

Although our primary comparison is between patients of the same provider pre- and post-intervention, we will also collect data at non-equivalent control sites matched by geography who will not receive the intervention; all data on control patients will be from the Corporate Data Warehouse (CDW). Including additional control sites will allow us to address potential temporal trends in deprescribing over the timeframe of our study that are not due to our intervention. The use of separate control sites (rather than randomizing some PCPs at each intervention site to control conditions) was preferred due to concerns about potential contamination across intervention and control conditions within sites. For both the control sites and the pre-intervention baseline period, we will identify patients who would have been eligible for the study; patients meeting criteria for multiple cohorts will be randomly allocated to only one.

Study Cohorts

The intervention cohort will consist of eligible patients in one of the three medication groups with an upcoming PCP appointment during the study enrollment period. We will create a comparison historical control cohorts comprising eligible patients in each medication group who were seen by the same PCPs at the same sites as our intervention cohort eighteen months to one year before our intervention cohort window to allow for comparable follow-up time before the intervention commenced. Patients in the intervention cohorts will be excluded from the historical control cohorts.

Medication Groups

To be enrolled in the study intervention or control cohort, patients needed to meet eligibility criteria for one of three medication-based groups. We have selected three medication-based patient groups based upon variations in 1) type of potentially inappropriate use, 2) medication factors (potential benefit and harms of continued use), and 3) anticipated interest in deprescribing by patients and providers.

1. Proton Pump Inhibitor Cohort (PPI)

The PPI cohort will be defined as patients with prescriptions for any PPI at any dose for 90 consecutive days in patients of any age.

2. Diabetes – Hypoglycemia Risk (DM-HR)

To create diabetes cohorts, we identify overly-controlled patients with diabetes based upon International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) diagnosis codes, most recent HbA1c <7%, as well as one or more of the following criteria: 1) age 65 or older, 2) renal insufficiency defined as creatinine >2 mg/dL, or 3) cognitive impairment defined by a diagnosis of cognitive impairment and/or prescription for an acetylcholinesterase inhibitor (e.g., donepezil). Patients in the DM-HR group needed to have a current prescription for either insulin or sulfonylurea with at least 90 consecutive days on the medication in the prior year.

3. Gabapentin (Gaba)

The gabapentin cohort will include patients prescribed a total daily dose of gabapentin >1800mg for a minimum of 90 days.

Subject Exclusion Criteria

We will not exclude women or minorities, but children will not be eligible for participation.

1. Proton Pump Inhibitor Cohort (PPI)

In response to feedback from our pilot study, we will exclude diagnoses for which PPI continuation would be appropriate (e.g., Barrett's esophagus, or those prescribed chronic glucocorticoids or NSAIDs).

2. Diabetes – Hypoglycemia Risk (DM-HR)
No exclusion criteria.

3. Gabapentin Cohort (Gaba)
We will exclude patients with recommended indications for gabapentin, including documented neuropathic pain using established criteria, those with seizure disorders, documented neuropathic pain, and cancer-related pain.

Recruitment

As we did for our IRB approved pilot study, we are requesting a waiver of informed consent and a waiver of HIPAA authorization to identify eligible Veterans to whom we will mail brochures.

Note about Patients with Cognitive Impairment – Due to the eligibility criteria for the Diabetes cohort, it is possible that patients with cognitive impairment will be recruited. Veterans with cognitive impairment represent a population at potentially increased risk for worsened outcomes associated with overtreatment of diabetes, especially for hypoglycemia (low blood sugar). Thus, it is important to understand the effect of promoting deprescribing on this vulnerable population. Veterans with mild cognitive impairment may still comprehend the brochure well enough to ask their primary care provider about the need for diabetes medication. Veterans with more severe cognitive impairment may not interact with the brochure, but a caregiver may on their behalf. Veterans with cognitive impairment significant enough to not interact with the brochure are likely at *greater* risk of harm from potentially inappropriate medication use and subsequent risk for hypoglycemia than they are from hyperglycemia should they decide to stop taking their medication prior to discussing with their PCP.

Data Collection/ Study Measures

Data collection procedures

Before starting the trial and mailing medication-specific brochures, using material similar to that in our pilot study, we will inform clinicians (attending physicians, nurse practitioners, physician assistants, and clinical pharmacy specialists) and staff via either Outlook or Enterprise Feedback Management (Verint)-managed email about the project, describe an overview of deprescribing, and provide them with deprescribing algorithms and guidelines available online. The intention is to prepare providers to respond to a patient engaged by the medication-specific brochure, as the patient is the focus of the proposed intervention. When the patient cohort changes, prescribers will receive "refresher" emails, for a total of three points of contact during the intervention.

Chart review – We will conduct chart reviews on a sample of subjects; this activity will assess the concordance of the medication dispensing data obtained from CDW with that of both electronic health record documentation.

Study Measures

We will query CDW for 6 months following the date of each scheduled primary care visit to assess our primary outcome of deprescribing. Based upon findings in our pilot study, medication orders may not be discontinued in electronic health records even if discussions occur in the clinic visit (e.g., the PCP tells the patient to deprescribe but does not change the order). Notably, because our primary objective is to improve safe prescribing and reduce PIMs, pharmacy dispensing data best reflects our deprescribing outcome. As per our definition, either complete cessation or dose reduction will be fulfillment of our primary outcome.

Modeling our approach after the methods of Steinman, Sussman, and Martin, we will use non-refill of the medication in the 6 months following the primary care appointment as our a priori definition of cessation, based upon dispensing dates. [4,5] Per VA Pharmacy policy, medications are only refilled upon request, and therefore, non-refill of a medication can indicate that it was discontinued, it expired (typically one year after it was ordered), or the patient did not refill it. If the medication continues to be dispensed, we will determine any reduction in the total daily dose, indicating de-escalation (one component of our deprescribing definition). An

exception to the de-escalation rule will be for insulin, where only complete cessation will qualify since dose changes are less likely to be reflected in the order compared to oral medications.

Consistent with our conceptual framework, we will also assess patient and provider factors that may influence deprescribing. Patient factors will be obtained from CDW, and will include age, race, sex, Elixhauser comorbidities in the two years prior to the scheduled primary care visit. Provider factors include sex, discipline, age, and site.

To assess potential ADWEs, we will ascertain if the deprescribed medication is subsequently restarted or returns to original dosing. We will then query CDW for diagnoses of GI bleeding for the PPI cohort, diabetic ketoacidosis or hyperosmolar hyperglycemic state for the DM cohort, and seizure for the gabapentin cohort in the year following the index visit. Note, we consider substitution to a lower potency medication (e.g., histamine-2 receptor antagonist for a PPI) to be a neutral or desirable event and not an ADWE.

Statistical Analysis Plan (see attached statistical analysis plan for greater detail)

Our Aim 1 primary quantitative outcome will be binary: deprescribing versus not, assessed via pharmacy dispensing data. To investigate the impact of the medication-specific brochure on deprescribing, we will use Hierarchical Generalized Linear Modeling (HGLM) to account for the nesting of patients within providers. This approach will provide information not just about the average effectiveness of the intervention, but also about how much variation there is in the intervention impact across providers. In all models, Level 1 (patient-level) intercepts and slopes will be treated as random effects, and parameters will be estimated with robust standard errors. We will conduct all analyses using SAS software.

Using this approach of nesting patients within providers, for our primary analysis, we will compare the likelihood of deprescribing among patients in the pre-intervention period to that for patients in the intervention periods for providers at the intervention sites only. We predict that intervention patients will be significantly more likely to have deprescribing than patients in the pre-intervention period with the same eligibility criteria. We will then examine whether the intervention effectiveness is moderated by the target medication. We do not expect a discontinuation rate of 100%, as many patients could still have an indication to remain on the medication.

Provider Effects – Although our intervention is designed to target and engage patients, it is possible that the intervention may be more effective with certain PCPs. If we find significant variance in the average effectiveness of the intervention across PCPs in our primary analyses, we will use HGLM to explore how provider characteristics by accessing CDW data (e.g., age, race, discipline) impact intervention effectiveness.

Patient-Level Effects – We will again use HGLM analyses to assess the extent to which patient factors collected from CDW (e.g., age, race, sex, comorbidities) are associated with deprescribing among patients who receive the intervention.

Ethical Issues

Risks

Risk of the intervention – It is important to note that the decision to deprescribe or not remains in the purview of the patient-provider dyad; we are not randomizing patients to have medications withdrawn. The primary intervention is distribution of information directly to patients. As such, this study involves a low level of risk to all human subjects.

It is possible that Veterans could feel discomfort receiving information about their medications, expressing their beliefs and perspectives, or have concerns that their subsequent health care services will be affected. Bringing the issue of potential medication overuse to Veterans' attention may also lead them to worry that they are taking too many medicines or that the targeted medications (PPIs, diabetes medications, or gabapentin) may have caused them harm.

The intervention could lead to the actual discontinuation of unnecessary medications as intended; nonetheless, there is a slight possibility that the intervention could unintentionally lead to discontinuation of medications that are necessary or that the discontinuation of medications perceived as unnecessary could actually result in adverse drug withdrawal events. It is also possible that patients will stop a medication after receiving the brochure but without consulting their primary care provider.

The risks of deprescribing medications include, but are not limited to, adverse drug withdrawal reactions and return of a medical condition. Adverse drug withdrawal reactions are rare, especially in comparison to adverse drug events. It is more common for patients to experience a return of symptoms for which the medication was initially prescribed. Serious adverse events resulting from inappropriately discontinuing a medication include upper gastrointestinal bleeding for the PPI cohort, diabetic ketoacidosis or hyperosmolar hyperglycemic state for the DM cohort, and seizure for the gabapentin cohort.

Risk from breach of confidentiality – The risk to participants includes potential compromise of confidential information; however, the use of VA data in research analyses similar to those proposed is standard practice and there are no viable alternatives to obtain this quantity and quality of data. We will take all actions required to protect the security and integrity of confidential and personal health information.

Procedures to Minimize Risk

Veterans receiving the intervention (brochure) and survey – Exclusion criteria have been carefully incorporated to help minimize Veteran risk prior to enrollment. Further, as noted, we are not randomizing patients to have medications withdrawn. The primary intervention is distribution of information directly to patients. It is important to note that the decision to deprescribe or not remains in the purview of the patient-provider dyad. We will provide a brief cover letter when sending the medication-specific brochure to patients, and the medication-specific brochure states multiple times to not decrease or discontinue a medication without first consulting with a clinician. We are also mailing the brochures two weeks prior to a primary care visit, so if patients decide they want to stop a medication, they will already have an appointment scheduled. Taken together with the fact that patients and providers already have the ability to make deprescribing decisions, the risk of this study is not greater than current standard practice.

Risk from breach of confidentiality – In order to assure appropriate research subject selection and high-quality data collection, all study personnel will undergo training in the study protocols. We will take all necessary steps to ensure the protection of confidential information in accordance with VA regulations and other applicable laws. All identifiable data will be protected from improper use or disclosure. Only research team members will have access to data. We will enter survey data into an electronic database with a unique identifier, removing any Protected Health Information (PHI). We will store all electronic data entirely within the VA network, which is protected by firewalls. User identification codes limit access to specific directories and files. We will not include names on audio-recordings or transcriptions, and publications will not identify individual participants or the sites from which they were recruited. We will not disclose identifiable information to any other person or entity outside VA, except as required by law, for authorized oversight of this research study, or for approved use in another study by an IRB. We will store physical data in locked cabinets within the Section of General Internal Medicine and Center for Healthcare Organization and Implementation Research (CHOIR) offices at VA Boston

Potential Benefits

Veteran participants of the intervention may benefit from the attention focused on considering their medication regimens and potential discontinuation of medications that are unnecessary or place them at risk for harm. The concept of deprescribing is gaining increased recognition as an important component of standard clinical practice. The study intervention primarily provides the patient with an opportunity to learn more about their medication and encourages them to contemplate the role of medication within their overall health goals, and thus may lead to a more knowledgeable, activated patient. The proposed research, taken together with future research efforts, has the potential to reduce the prescribing of non-indicated medications and reduce associated adverse effects, improving the care and safety of Veterans nationally.

Analysis of Risks in Relation to Benefits

Given the high prevalence of adverse drug events, any successful reduction in the use of inappropriate, non-indicated, or unnecessary medications has the potential to reduce medication-related errors and associated adverse events. Further, within any system with constrained resources, reducing low-value care will enable resources to be focused more efficiently on those practices which are considered high-value. This study will determine the effectiveness of a low-tech patient-centered intervention on changing prescribing patterns. We will also understand the actions patients take after receiving this type of intervention, and how it enhances

ownership of their health care. The value of the knowledge gained outweighs the minimal risk to subjects of compromised patient or clinician data.

Stopping Rules

A participant may always withdraw their participation at any time.
The study has no stopping rules.

Safety Monitoring Plan

Per instructions of the VA HSR&D Program, the full Data Analysis Plan has been submitted to the Data Safety Monitoring Board (DSMB) using the Just-In-Time (JIT) document manager. Because the intervention described is an educational outreach to patients, there is minimal risk since clinical providers retain complete authority to deprescribe, de-escalate, and resume medications per their clinical judgement. However, it is possible that deprescribing could lead to adverse drug withdrawal. We expect these to be extremely rare occurrences, as we are identifying Veterans likely to be over-treated and further excluding populations for whom the medications are indicated. Thus, we will assess for serious adverse drug withdrawal events, specifically looking for emergency department and hospital visits for upper gastrointestinal bleeding for the PPI cohort, diabetic ketoacidosis or hyperosmolar hyperglycemic state for the DM cohort, and seizure for the gabapentin cohort on a quarterly basis for all recruited subjects.

Monitoring progress reports will be submitted to regulatory bodies (e.g., IRB) as requested and/or required. This will serve as a method for identifying systematic problems and allow the study team to identify and resolve problems and continuously maintain and improve data quality and Veteran safety. Additionally, we will schedule weekly team meetings to be led by the study PI and include all study personnel directly involved in enrollment, data collection, data entry and the intervention protocol. These team meetings will allow the study PIs to keep track of enrollment numbers, data integrity (e.g., reasons for missing data), and protocol implementation challenges that need to be addressed in a timely manner.

Adverse Event/Unanticipated Problems Reporting Plans

The Principal Investigator at VABHS will report Unanticipated Problems, Adverse Events, and safety monitors' reports to the IRB in accordance with VHA Handbook 1058.01 and VABHS IRB SOP. This is a multi-site study, but all procedures will be conducted at VABHS and thus oversight remains with the VABHS IRB.

References

1. Linsky AM, Kressin NR, Stolzmann K, et al. Direct-to-consumer strategies to promote deprescribing in primary care: a pilot study. *BMC Primary Care*. 2022/03/22 2022;23(1):53. doi:10.1186/s12875-022-01655-5
2. Tannenbaum C, Martin P, Tamblyn R, Benedetti A, Ahmed S. Reduction of Inappropriate Benzodiazepine Prescriptions Among Older Adults Through Direct Patient Education: The EMPOWER Cluster Randomized Trial. *JAMA Internal Medicine*. 2014;174(6):890-898. doi:10.1001/jamainternmed.2014.949
3. Canadian Medication Appropriateness and Deprescribing Network: Patient Handouts. (2023). https://www.deprescribingnetwork.ca/patient-handouts
4. Sussman JB, Kerr EA, Saini SD, et al. Rates of Deintensification of Blood Pressure and Glycemic Medication Treatment Based on Levels of Control and Life Expectancy in Older Patients With Diabetes Mellitus. *JAMA Intern Med*. Dec 2015;175(12):1942-9. doi:10.1001/jamainternmed.2015.5110
5. Lam KD, Miao Y, Steinman MA. Cumulative Changes in the Use of Long-Term Medications: A Measure of Prescribing Complexity. *JAMA Internal Medicine*. 2013;173(16):1546-1547. doi:10.1001/jamainternmed.2013.7060