DEPRESCRIBING IN SPECIAL POPULATIONS AT RISK OF MEDICATION OVERLOAD

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Table of contents

Thesis Abstract

Background

Medically complex patients are often prescribed multiple medications (polypharmacy). Many of these may be potentially inappropriate medications (PIMs), risking adverse drug events, defined as harm caused by a medication. A patient prescribed ≥1 PIMs can be said to have medication overload. It is distinct from polypharmacy, as the latter only describes a medication count and not appropriateness. Deprescribing reduces PIM burden, but is often laborious and mostly studied among older adults. Other special populations at high risk of polypharmacy, thus medication overload, could also benefit from it, such as residents of long-term care homes (LTCHs), patients on dialysis, and people with HIV (PWH).

Objectives

My thesis objectives were to 1) measure the proportion of patients with polypharmacy and medication overload in three special populations; 2) determine the efficacy of an electronic deprescribing decision support intervention among i) residents of a LTCH and ii) patients on dialysis. My thesis consists of 3 studies and 4 manuscripts, each manuscript presented in the style of the journal published, as per McGill thesis policy.

Methods

I used an existing Canadian-made electronic deprescribing decision support tool, MedSafer, for each study's special population (LTCH, dialysis, PWH). Age, sex and medical data (comorbidities,

medications, and select laboratory values) were extracted from electronic medical records (EMR), input into the MedSafer web-based portal, then cross-referenced for each patient with evidence-based deprescribing guidance from the Beers', Screening Tool of Older People's Prescriptions (STOPP), and Choosing Wisely Criteria. MedSafer generated individual deprescribing reports providing a list of PIMs, deprescribing instructions and patient information links.

Clinicians received reports in the before-and-after quality improvement study during Quarterly Medication Reviews (QMR) in the LTCH in Ontario, Canada (manuscript 1), and in the multimodal deprescribing quality improvement project in dialysis (the protocol is found in manuscript 2, and results are found in manuscript 3). In the third study, descriptive results were reported of the retrospective cohort study among 100 older PWH aged ≥50 years and followed at the McGill University Health Centre's Chronic Viral Illness Service (manuscript 4). People with HIV aged ≥50 were included as they are biologically similar to seronegative older adults aged ≥65.

Results

My first study was in a LTCH. All residents (55/55) had polypharmacy (defined as ≥5 prescribed medications); 96.4% (53/55) had medication overload (defined as ≥1 PIMs). The number of medications deprescribed per resident was significantly higher at the MedSafer QMR (aRD 0.5; SD 1.1; p=0.02).

In my second study in hemodialysis (manuscript 3), 97.6% (124/127) on the control unit and 98.5% (67/68) on the intervention unit had polypharmacy; 96% (122/127) of patients on the control unit and 97% (66/68) on the intervention unit had medication overload. The proportion of patients with ≥1 PIMs deprescribed was significantly higher on the intervention unit (aRD=36.6%; 95% CI=24.5-48.6; p<0.0001; NNT=3).

In my final study, 89% (89/100) of older PWH had polypharmacy, and 58% (58/100) had medication overload. Calcium supplements (19%), antidiabetics (including insulin) with a hemoglobin A1C of <7.5%, and sedative hypnotics (16%) were the most common PIMs.

Conclusion

I introduced and furthered the distinction between polypharmacy and medication overload, both common among the three special populations studied. Electronic decision support such as MedSafer can increase deprescribing in LTCHs, and outpatient hemodialysis clinics by providing deprescribing support to clinicians. Further research should investigate such tools integrated in the EMR in larger cohorts (such as PWH), controlled trials, and in non-academic clinical settings to measure efficacy, durability, and scalability.

Résumé de la thèse (French Abstract)

Contexte

Les patients médicalement complexes se font souvent prescrire plusieurs médicaments (polypharmacie), dont plusieurs peuvent être potentiellement inappropriés (MPI), risquant des événements indésirables médicamenteux, définis comme un préjudice causé par un médicament. Un patient recevant ≥1 MPI aurait donc une surmédication ; un terme distinct de la polypharmacie, car cette dernière décrit un décompte de médicaments et non une pertinence. La déprescription réduit le fardeau des MPI, mais elle est souvent laborieuse et étudiée chez les personnes âgées ; d'autres populations spéciales à risque de polypharmacie, et donc de surmédication, pourraient aussi en bénéficier, comme les résidents des centres d'hébergement et de soins de longue durée (CHSLD), les patients dialysés et les personnes âgées vivant avec le VIH (PAVVIH).

Objectifs

Les objectifs de ma thèse étaient de 1) mesurer la proportion de patients avec une polypharmacie et une surmédication dans trois populations spéciales ; et 2) déterminer l'efficacité d'un soutien à la déprescription électronique chez les i) résidents d'un CHSLD et ii) patients dialysés. Ma thèse comprend 3 études et 4 manuscrits, chacun présenté dans le style de la revue publiée, selon la politique de McGill.

Méthodes

J'ai utilisé un outil électronique de soutien à la décision canadien, MedSécure, pour déprescrire

chez chaque population spéciale étudiée (CHSLD, dialyse, PAVVIH). L'âge, le sexe et les données médicales (comorbidités, médicaments et données paracliniques sélectionnées) ont été extraits des dossiers médicaux électroniques (DMÉ), saisis dans le portail web de MedSécure, et croisés avec des recommandations de déprescription des critères Beers, Screening Tool of Older People's Prescriptions (STOPP) et Choisir avec soin. MedSécure a généré des rapports individuels de déprescription incluant la liste de MPI, les instructions de déprescription et des liens informatifs pour les patients. Les cliniciens ont reçu ces rapports dans deux études d'amélioration de la qualité 1) de format avant-après lors des Revues de médicaments trimestrielles (RMT) dans un CHSLD en Ontario, Canada (manuscrit 1), et 2) de format multimodal en dialyse (le manuscrit 2 comprend le protocole, le manuscrit 3, les résultats). La 3e étude (manuscrit 4) comprend les résultats de l'étude de cohorte rétrospective parmi 100 PAVVIH âgés de ≥50 ans et suivis au Service des Maladies Virales Chroniques du Centre universitaire de santé McGill. Les PAVVIH de ≥50 ans étaient incluses car elles sont biologiquement similaires aux adultes séronégatifs de ≥65 ans.

Résultats

Dans ma 1re étude en CHSLD, tous les résidents (55/55) avaient une polypharmacie (≥5 médicaments prescrits) ; 96,4% (53/55) avaient une surmédication (≥1 MPI). Le nombre de médicaments déprescrits par résident était plus élevé lors de la RMT MedSécure (RD 0,5 ; é.-t. 1,1 ; p=0,02). Dans ma 2e étude en hémodialyse (manuscrit 3), 97,6% (124/127) de l'unité témoin et 98,5% (67/68) de l'unité d'intervention avaient une polypharmacie ; 96% (122/127) des patients de l'unité témoin et 97% (66/68) de l'unité d'intervention avaient une

surmédication. La proportion de patients ayant ≥1 MPI déprescrits était plus élevée dans l'unité d'intervention (RD=36,6% ; IC 95%=24,5-48,6 ; p<0,0001 ; NNT=3). Dans ma 3e étude, 89% (89/100) des PAVVIH avaient une polypharmacie, et 58% (58/100) avaient une surmédication. Les suppléments de calcium (19%), les antidiabétiques (y compris l'insuline) avec une hémoglobine A1C<7,5%, et les hypnotiques sédatifs (16%) étaient les MPI les plus courants.

Conclusion

J'ai introduit et approfondi la distinction entre la polypharmacie et la surmédication, toutes deux courantes parmi les trois populations spéciales étudiées. Un soutien à la décision électronique comme MedSécure peut augmenter la déprescription dans les CHSLD et les cliniques de dialyse ambulatoires en fournissant un soutien à la déprescription aux cliniciens.

Acknowledgements

When I was told to chemically sedate a resident confined to a wheelchair before wheeling her in front of a wall until lunch as a nursing student, I told myself I would do everything in my power to make sure that was the last time I'd do such a thing. I did my best to stand true to my promise and do exactly that, but this was not achieved alone. Words cannot express my gratitude to Dr. Emily McDonald and Dr. Todd Lee, my PhD supervisors, for their guidance, support, and mentorship throughout my degree. This thesis would not have been possible without them, and I will forever be indebted to them for their investment of their time into my success in research. I would like to express my sincerest appreciation for Dr. Anne-Marie Lauzon, chair of the Graduate Program in Clinical and Translational Research, and Dr. Nandini Dendukuri, my academic advisor, for their invaluable patience, feedback, guidance, and mentorship. I naturally could not have undertaken this journey without my thesis committee. Dr. Lisa McCarthy has helped me in words I cannot describe to grow as a researcher and healthcare professional; Dr. Robyn Tamblyn showed me the power of nurses in deprescribing research; Dr. William Archambault taught me how to thoughtfully engage listeners of my work, and to trust the research process to spark change; Dr. Antony Robert provided generous time, knowledge, and expertise in guiding me during my PhD. I am incredibly grateful for Dr. Kate Rice for her incredible contribution in helping shape both the person and researcher I am today. Merci, du fond du cœur, au Bureau de coopération interuniversitaire pour leur soutien financier des infirmières cliniciennes doctorantes.

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the past three years of my life, for helping me walk across the broken glass of ceilings you've shattered, to show me just how limitless my dreams can be.

Contribution to Original Knowledge

My thesis will further the distinction between polypharmacy and medication overload, two concepts that are often used interchangeably, but can lead to different interventions and outcomes. Medication overload is also potentially a more accessible term to the public. This original distinction will allow for future research to concentrate efforts on reducing the burden of medication overload and addressing the prescription and deprescribing of potentially inappropriate medications (PIMs). Furthermore, while deprescribing currently includes processes such as discontinuation, tapering, dose reduction and switching medications to a safer class, my PhD will introduce the concept of medication regimen simplification, defined as the deprescribing of multiple dosing of a medication when fewer doses can be administered of noninferior or superior efficacy. One of the goals of deprescribing is to reduce the overall pill burden of patient, and the introduction of medication regimen simplification aims to do so, as a form of deprescribing. Finally, while the field of polypharmacy and deprescribing has focused in recent decades on studying their prevalence and impact among older adults, my PhD thesis will further the idea that older adults are studied because they have several chronic illnesses that require multiple medications, but these premises do not uniquely affect this population. In fact, several other populations also have several chronic illnesses that require polypharmacy, such as residents of long-term care homes, patients on dialysis and older people with HIV. The software that I use, MedSafer, to identify PIMs has already been proven to be safe and effective at deprescribing in a cluster randomized controlled trial among hospitalized older adults; now, its implementation in clinical practice must be studied, to translate its use from bench to bedside, among these special populations at risk of medication overload.

List of Figures and Tables

        - Supplemental Figure 3: Subgroup analyses – stratified by age (younger vs. older than 65)
        - Supplemental Figure 4: Example of a deprescribing EMPOWER brochure
        - Supplemental Figure 5: Example of a MedSafer deprescribing report
        - Supplemental Manuscript 1: Use of MedSafer Electronic Decision Support for Deprescribing in Patients on Hemodialysis: A Qualitative Study
    - Chapter 3
        - None

List of Abbreviations

ACE: angiotensin converting enzyme

ADE: Adverse drug event

ADR: Adverse drug reaction

ADWE: Adverse drug withdrawal event

AIDS: Acquired immunodeficiency virus syndrome

ARB: angiotensin receptor blocker

aRD: absolute Risk Difference

ARMS: Adherence to Refills and Medications Scale

ART: Antiretroviral therapy

CHEDSS: Changes in Health, End-Stage Disease and Signs and Symptoms Scale

CI: Confidence interval

COPD: Chronic obstructive pulmonary disease

COVID-19: Coronavirus 2019

CWC: Choosing Wisely Canada

EMR: Electronic Medical Record

ESKD: End-stage kidney disease

GIB: gastrointestinal bleed

HIV: Human Immunodeficiency Virus

INSTI: Integrase strand inhibitor

IQR: Interquartile range

JAMA: Journal of the American Medical Association

LESS-CHRON: List of Evidence-Based Deprescribing for Chronic Patients criteria

LTCHs: Long-term care homes

MAI: Medication Appropriateness Index

MedRec: Medication Reconciliation

MUHC: McGill University Health Centre

NNRTI: Non-nucleotide reverse transcriptase inhibitor

NNT: Number Needed to Treat

OPUS-AP: Optimiser les pratiques, les usages, les soins et les services – Antipsychotiques

OR: Odds ratio

PDSA: Plan Do Study Act

PEPS: Programme d'évaluation de la personnalisation des soins

PI: protease inhibitor

PIM: Potentially inappropriate medication

PIMDINAC: PIM (potentially inappropriate medication) + DI (drug interactions) + NAC (non-adherence to treatment component)

PWH: People with HIV

PPI: Proton pump inhibitor

PRN: Pro re nata

QMR: Quarterly medication review

RAI-MDS: Resident Assessment Inventory Minimum Data Set

RCT: randomized controlled trial

REB: Research Ethics Board

RISQ: Réseau informatique du SIDA du Québec

SD: Standard deviation

SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

SQUIRE: Revised Standard for Quality Improvement Reporting Standards

STOPP: Screening Tool of Older Persons' Prescriptions

STOPP/START: Screening Tool of Older Persons' Prescriptions / Screening Tool to Alert to Right Treatment

Introduction

Background and Rationale

Advancements in medicine have allowed patients to live longer than ever before, while managing multiple, oftentimes severe, chronic comorbidities. Diseases previously associated with a poor prognosis are now considered chronic, and people can live with them for many years: cardiovascular risk is readily modifiable with statins, end-stage kidney disease can be managed through hemodialysis,[1] and HIV is now considered a chronic illness.[2] However, living with chronic comorbidities is often synonymous with a need for multiple drugs to manage each condition separately, sometimes in isolation from each other. Guidelines addressing treatment of each separate condition (as opposed to the person as a whole) have contributed to polypharmacy,[3] a globally recognized contributor to medication-related harm.[4] In the past 20 years in the United States, the prevalence of polypharmacy increased by 300%.[5]

Canadian estimates suggest that polypharmacy is experienced by around 50% of community dwelling older adults and up to 90% of those in long-term care homes (LTCHs) with costs of the related harm estimated to be upwards of $419 million per year in Canada.[6] Yet, there is no universally agreed upon definition of polypharmacy. It is generally defined through a count-based approach, wherein a patient is prescribed multiple medications. In fact, the World Health Organization defines polypharmacy as the “concurrent use of multiple medications”.[4] The King’s Fund, an independent think tank in England, defined it in a report as the “concurrent use of multiple medications by one individual”.[7] Recent systematic reviews proposed defining polypharmacy through a cut-off, for research purposes, as taking 5 or more medications.[8-10] All

of these reviews warned that the lack of a standardized definition of polypharmacy could lead to a mis-capture of outcomes, and eventually lead to inadequate policy development.

Among older adults, polypharmacy can often be indicated and beneficial to manage their comorbidities.[8, 11-13] However, certain medications may be potentially inappropriate, and in this case the term *medication overload* has been proposed, originally coined by a working group of the Lown Institute on polypharmacy.[14] Medication overload can be said to be present when a patient is prescribed one or more potentially inappropriate medications (PIMs)[15-18]. A PIM is a medication that is 1) high risk and almost never necessary (the harms almost always outweigh the benefits), e.g., opioids for chronic non cancer pain; or 2) intermediate risk and may be indicated (depending on the balance of harms and benefits), e.g., long term proton-pump inhibitors (PPIs) or are no longer necessary, e.g., dual anticoagulant therapy beyond six months post-cardiac stent insertion; or 3) low risk and simply increases a patient's pill burden, e.g., docusate or vitamin E (Table 1).[14, 18, 19]

Table 1: Potentially Inappropriate Medications According to Their Risk Category

Risk Classification	High Risk	Intermediate Risk	Low Risk
Definition	Medications are almost never necessary	Medications may be indicated, depending on the balance of harms and benefits	No longer necessary or simply increase a patient's pill burden
Examples	• Opioids for chronic non cancer pain[20] • Sleeping pills[21] • Insulin prescribed when a patient has a glycated hemoglobin of <7.5%[22]	• Proton-pump inhibitors[23] • Dual anticoagulation beyond 6 months post-stent insertion[24] • Gabapentinoids[25] • Non-insulin	• Docusate[27] • Vitamin E[28] • Non-statin lipid-lowering drugs[29]

		antidiabetics with a glycated hemoglobin of 7.5%[26]	

Both polypharmacy and medication overload increase the risk of developing adverse drug events (ADEs), or harm caused by a medication[30, 31] such as falls,[32] fractures,[33, 34] cognitive impairment,[35] decline in autonomy,[36] emergency room visits,[37] hospital admissions and readmissions, and premature death (Figure 1).[34, 37, 38]

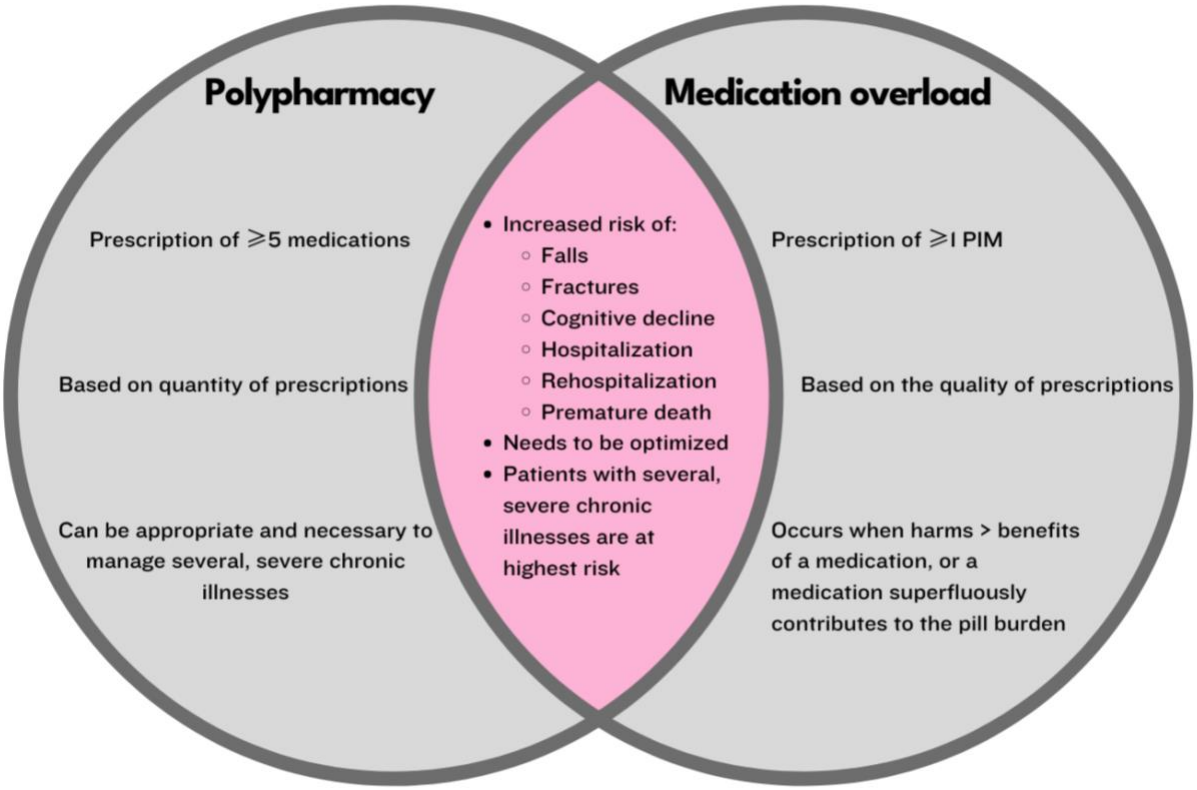

Figure 1: Distinction Between Polypharmacy and Medication Overload

Polypharmacy is not inherently problematic; the prescription of multiple medications can be necessary to manage multiple comorbidities. However, a count-based definition of polypharmacy does not distinguish between necessary medications and PIMs, whereas these clearly don't have the same risk to benefit profiles. Distinguishing medication overload from polypharmacy highlights the differences between the appropriateness of a medication versus the pure count of medications.

Most studies on polypharmacy are conducted among older adults because they are known to have multiple chronic illnesses requiring the prescription of several medications. However, the presence of multiple comorbidities and polypharmacy does not uniquely affect older adults. In fact, there are other patient populations that are at risk of polypharmacy and therefore medication overload at younger ages because of the severity and number of chronic illnesses with which they live. Two examples are patients with end-stage kidney disease (ESKD) on hemodialysis,[17] and older people with HIV (PWH).[13] There is a lack of data describing the extent of medication overload in these populations, their impact on health outcomes, and solutions such as deprescribing, regardless of age.

Deprescribing is a proposed solution to polypharmacy defined as the process of stopping, dose reduction, tapering, or changing an inappropriate medication to a safer alternative.[39] The process may be initiated by the patient,[21] but generally is supervised by a healthcare provider with the goal of managing polypharmacy and improving outcomes through shared decision making.[39] Deprescribing is effective at reducing a patient's pill burden, sustainably optimizing

their medication therapy, potentially improving their quality of life, and in some studies, reducing ADEs.[3, 40]

MedSafer is an electronic deprescribing clinical decision support tool that, in clinical trials, has been shown to increase deprescribing for hospitalized older adults.[17, 18, 36] MedSafer identifies deprescribing opportunities by electronically cross-referencing a person's usual medication list and medical comorbidities, with a curated ruleset of evidence-informed deprescribing guidelines (based on indications from the American Geriatrics Society,[41] Screening Tool of Older Persons' Prescriptions (STOPP),[42] and Choosing Wisely[43]). An 11-center cluster randomized controlled trial showed the MedSafer software safely increased deprescribing among hospitalized older adults with polypharmacy by absolute adjusted risk difference of 22% (95% CI = [16.9%-27.4%]),[18] without increasing ADEs (aRD = −0.8%; 95% CI = −2.9%-1.3%) or adverse drug withdrawal events (ADWEs) (aRD = −0.1%; 95% CI = −1.2%-1.0%), defined as a set of symptoms related to the discontinuation of a medication.[44]

Objectives

The aims of my PhD were two-fold. The first was to determine, through quality improvement studies, the efficacy of MedSafer in increasing deprescribing in two special populations when integrated in the workflow of clinicians caring for i) older adults in LTCHs (manuscript 1) and ii) patients on dialysis (manuscripts 2 and 3). Older adults in LTCHs and patients on dialysis are special populations at risk of polypharmacy and thus medication overload, and there is currently a lack of effective interventions to address this. While the MedSafer tool has been shown to be effective in a randomized controlled trial of hospitalized older adults,[18] the implementation of

this solution, or other electronic deprescribing interventions, in the workflow of clinicians in LTCHs and for patients on dialysis is understudied.

The second aim of my PhD was to describe the prevalence of polypharmacy and medication overload among older PWH (manuscript 4), to inform the design of future deprescribing trials in this population. Among older PWH, there are a lack of studies that describe the prevalence of polypharmacy and medication overload as well as the frequency and types of deprescribing opportunities, so I aimed to address this gap through my second aim.

A Comprehensive Review of the Relevant Literature

History of the Definition of Polypharmacy

As described in the Introduction, there are different definitions for polypharmacy.[4 7 10, 39, 45 8, 46] Moreover, several studies qualify polypharmacy using terms such as minor, major, simultaneous, cumulative, continuous, appropriate, inappropriate, mega-, hyper-, or excessive polypharmacy, etc., to nuance the implications.[8] The definitions of these qualifiers change between studies, making the terms even more confusing for readers (megapolypharmacy, for example, may be defined by the prescription 10,[17] 15,[47] or 20[48] medications, depending on the study). Consequently, although there is an interdisciplinary pool of researchers, clinicians, policymakers, and patients who are all working towards a common goal of reducing polypharmacy, the understanding of the nature and severity of the problem varies, depending on study definitions. This can make it challenging for researchers to have a harmonized scientific approach and makes it harder to study a consistent population when the definition of polypharmacy is a moving target.

To align with current recommendations from multiple systematic reviews [8-11, 38, 39, 49]and calls for a universal definition, I have defined polypharmacy in my thesis as the prescription of five or more medications,[45] including in this count any regular, over the counter, and as-needed medications (also known as pro re nata or PRN medications). It is commonplace for patients with multiple, severe, chronic illnesses to be prescribed five or more medications, and thus polypharmacy. This does not necessarily imply danger for a patient. In fact, polypharmacy can often be indicated and beneficial to manage their comorbidities, such as triple immunosuppressive therapy for patients with transplanted organs,[50] antidiabetics for patients with diabetes,[51, 52] anticoagulants and antihypertensives for patients with vascular risk factors, etc.[8, 11-13, 31, 53, 54]

Distinguishing Medication Overload from Polypharmacy

While studies have found an association between increasing medication counts and the risk of falls,[33] hospitalizations,[55, 56] and premature death,[5, 33, 38, 45, 56-61] one important confounder worth discussing is frailty, defined as a patient's increased vulnerability to and reduced capacity to resist stressors due to a depleted physiologic reserve.[62] Frailty is strongly associated with polypharmacy;[58] patients with frailty are more likely to have multiple medications to manage their medical conditions, which themselves contribute to frailty.[57] In turn, certain medications can increase frailty, such as sedative-hypnotics, anticholinergics, and antipsychotics.[63] Both polypharmacy and frailty are associated with cognitive impairment,[34] increased risk of falls,[33] delirium, increased risk of adverse drug events (ADEs)[64]. Thus, controlling for frailty as a confounder is important when measuring the clinical impacts of polypharmacy. Although frailty was not adjusted for throughout my thesis, it is reassuring to note that in the 2022 MedSafer

study that I coauthored,[18] the proportion of patients with one or more PIMs deprescribed did not significantly change after having adjusted for several confounders, including frailty (ARR 22.8%; 95% CI = 17.6%-28.0%); frailty thus did not significantly bias the primary outcome results. Future randomized controlled trials (RCTs) should control for frailty to determine if it biases the outcome results. Additionally, because appropriate polypharmacy is more and more commonplace among patients with several, severe chronic illnesses, research in the field of safer prescribing is moving towards studying not just how *many* medications are prescribed, but what *types* of medications are prescribed to patients with several comorbidities.

While research needs to identify an empirically based threshold to define polypharmacy, studies need to also look beyond a count of medications and include a measurement of the appropriateness of the medications the patients are receiving. When conceptualizing polypharmacy and its appropriateness, it can often be viewed as a balance scale, where one plate holds the benefits of a medication, and the other holds its harms (Figure 2).[18]

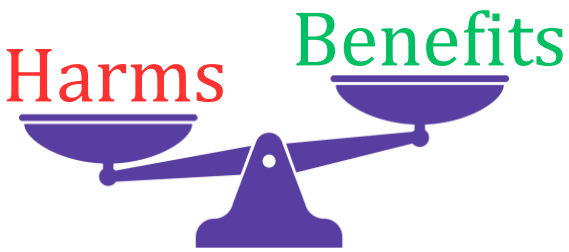

Figure 2: Illustrative Concept of Medication Overload

When the benefits of medications hold more weight or are of more importance than the associated risks and harms of the totality of medications a person is taking, polypharmacy might be considered appropriate. Instances may include, for example, a kidney transplant recipient

that may be appropriately prescribed ramipril, tacrolimus, mycophenolate mofetil, prednisone, and magnesium. Contrastingly, when the harms outweigh the benefits of one or more medications, this is referred to as potentially inappropriate polypharmacy or medication overload.[30] Medication overload is a term that has previously been proposed by the Lown Institute, and while not extensively used, I have introduced it and reinforced it as related but distinct to polypharmacy, throughout my thesis.[14]

However, it is important to note that a medication is potentially inappropriate for one patient, but may not be inappropriate for another. The medication alone may not be inherently inappropriate. The inappropriateness often depends on a patient's health, their concurrent medical conditions, their frailty, their prognosis, and their values.[12] For example, a patient experiencing a first episode of psychosis may require quetiapine, an antipsychotic, to manage their illness. However, the prescription of quetiapine for sleep for an older adult living in a LTCH would be potentially inappropriate because this medication has marginal benefits for improving sleep quality and quantity, while increasing the risk of ADEs, especially in a frail older adult. Therefore, even though the same drug is at play, the older adult in this scenario would be considered to have medication overload; the younger patient would not be. Overall, medication overload and the identification of PIMs need to be individualized and based on each patient's state of health.

A Knowledge Gap in the Field of Medication Overload and Polypharmacy

The majority of studies on polypharmacy are conducted among older adults because they are known to have multiple chronic illnesses requiring the prescription of several medications and, in several instances, are prescribed medications that lead to medication overload. These two

premises – 1) that this patient population is known to have multiple, severe chronic illnesses, and 2) their illnesses require the prescription of several medications – do not uniquely affect older adults. In fact, there are other patient populations at risk of medication overload at younger ages because of the severity and number of medical conditions with which they live. Examples are patients with ESKD receiving hemodialysis,[17] older PWH[65], patients with migraine[66] or chronic pain,[67] solid organ transplant recipients,[68] patients living with cancer,[69] etc. There is a lack of data describing the extent of medication overload in these populations, their impact on health outcomes, and solutions to address it among young and middle-aged adults with complex medical conditions and medication overload and/or polypharmacy, such as deprescribing.

The Definition of Deprescribing

As previously described in the introduction, deprescribing aims to manage polypharmacy and improve patient outcomes. The process involves either stopping, dose reduction, tapering, or switching an inappropriate medication to a safer alternative.[39] I would argue that the concept of medication regimen simplification, aimed at decreasing a patient's pill burden, is also a form of deprescribing.[70]

Switching an inappropriate medication to a safer alternative, or starting a new medication to replace an inappropriate one, is a form of deprescribing, yet is met with substantial controversy. This was recently highlighted in an article by Thompson et al., whereby authors reported 32% of deprescribing trials paradoxically involved the start of a new medication.[71] Authors in this short communication described the studies that made use of the potential prescribing omission algorithm part of the safer prescribing tool Screening Tool of Older Persons

Prescriptions/Screening Tool to Alert to the Right Treatment (STOPP/START; START portion). However, the use of the START portion of the STOPP/START is different from switching an inappropriate medication to a safer alternative that involves the prescription of a new medication. The START criteria, which will be described later, seeks to add new medications to correct underprescribing of certain medications, whereas a deprescribing switch seeks to reduce the harms associated with an already prescribed inappropriate medication.[72] Therefore, the initiation of a new medication can be done in a deprescribing context if it seeks to minimize the harm and/or pill burden associated with a currently prescribed medication; in any other context than this, adding a new medication would not be considered as a form of deprescribing.

Tools Used to Deprescribe

The first step to the deprescribing process is identifying PIMs. There are two ways to complete this step, using either implicit or explicit interventions. Implicit interventions aim to leverage the clinical judgement of the prescriber and the patient's individual circumstances, and addresses the entire list of medications, whereas explicit interventions make use of criteria-based deprescribing tools, such as the American Geriatrics' Criteria or the STOPP/START criteria.[73] An example of a tool that makes use of the implicit interventions is the Medication Appropriateness Index (MAI).

The Medication Appropriateness Index (MAI): Creation, Definition, Strengths and Limitations

The MAI's development was inspired by previous work done by Naranjo et al. on clinically adjudicating ADEs.[74] The adjudication of ADEs is defined as the process of determining the probability that an adverse event is attributable to a medication or not.[30] Prior to Naranjo et al.,

and even in several studies conducted today, adjudication of ADEs was purely based on clinical judgment. However, this gives rise to large inter and intra-rater reliability.[75] In clinical research, this lack of standardized method can increase the study's risk of non-reproducibility. As such, Naranjo et al. developed a method for clinically adjudicating ADEs in 1988.[75] It relies on clinical judgment but standardizes the process to increase reliability and precision.

Inspired by this implicit approach that is heavily informed by clinical judgment, in the United States, Hanlon et al. gathered a team comprised of clinician prescribers, a sociologist, a biostatistician, and a psychologist to develop the Medication Appropriateness Index in 1992.[74, 76] The ultimate goal of the MAI was to serve as a tool to improve the quality of prescribed medications. It was used as part of a clinical pharmacist intervention within a randomized controlled trial that was eventually published in 1996.[77] The MAI requires clinicians to assess the appropriateness of every single medication that a patient is prescribed through a 10-question assessment tool. Unlike explicit PIM identification tools like the Beers' Criteria and the STOPP/START criteria that we will address shortly, the MAI requires clinicians to assess each medication's effectiveness, administration instructions, potential duplication, and cost.[78] In essence, the higher the MAI score, the higher the risk a patient has of being prescribed inappropriate medications. The creators of the MAI published two reviews on research conducted on deprescribing in 2014[76] and 2022,[78] showing improving inter-rater and intra-rater reliability (kappa >0.40 for all studies in the 2014 review, and 0.75-0.94 in the 2022 review).

In clinical trials, the MAI is a useful tool to measure the appropriateness of a patient's medication as it requires the prescriber to assess drug-drug and drug-disease interactions,

which other explicit tools lack; however, its largest limitation is its time-consuming nature. In fact, a literature review and a recent doctoral project of a nurse practitioner found that it took a prescriber an average of 10 minutes per medication to complete the MAI.[79] When the MAI was created, the prevalence of polypharmacy among older adults was around 8.5%, so implementing the MAI was potentially more feasible then.[80] Today, the prevalence of polypharmacy, using the definition of ≥5 medications, ranges from 16.1% to 85%.[81] At a minimum, if clinicians wished to conduct a medication review using the MAI among patients with polypharmacy, this would take at least 50 minutes (5 medications × 10 minutes per medication). This is over double the average consult time in primary care in Montreal, Canada, which can last up to 22.8 minutes on average.[82]

The MAI is an example of implicit criteria to deprescribe. Another type of deprescribing tool makes use of explicit criteria, whereby lists of PIMs are provided to support the clinician in the medication review process. We subsequently explore two commonly used explicit tools: the criteria from the Beers' Criteria and the STOPP/START Criteria.

The Beers' Criteria: Creation, Definition, Strengths, and Limitations

The Beers' Criteria were first created in 1991 by Dr. Mark Beers, a geriatrician in the United States that had initially ran a cohort study among 850 older adults living in nursing homes to describe the pattern of prescription of psychotropic medications, given the growing knowledge that psychotropics could be harmful to older adults.[83] He published the findings in 1988; more than half of residents in his study were prescribed at least one psychotropic medication.[83] This was one of the first studies to develop the term "appropriateness" of medications among older

adults, defined by the balance of harms and benefits of a medication for a given older adult.[83] After publishing these findings, Dr. Beers gathered thirteen experts in the field of geriatrics, including physicians, nurses, pharmacists, etc. to develop explicit criteria identifying the first set of potentially inappropriate medications among older adults.[84] A total of 30 indications were developed in the first edition of the Beers' criteria and published in the Archives of Internal Medicine, known today as JAMA Internal Medicine, in 1991.[84]

The Beers' Criteria are currently updated every 3 years,[85] with the most recent version, at time of writing my thesis, published in 2023.[41] This list of PIMs identifies mostly psychotropic medication and provides rationale and recommendations for each indication. The tool serves to inform the clinician of the potential of a medication to be inappropriate and, ultimately, the final decision to adjudicate it as such relies on the clinical expertise of the prescriber.

There are limitations to this tool. The criteria are very focused on the deprescription of high-risk medication, whereas there are several medications that are often superfluous, such as calcium, vitamin D, docusate, etc., but are not found in this list as potentially inappropriate medications, despite their contribution to increasing the pill burden and drug costs. The criteria also do not provide clinical decision support for the shared decision-making process with the patient, which may prove imperative in the deprescribing process.[86] Finally, the Beers' criteria were designed in the United States, with the American drug formulary in mind. In fact, up to 50% of PIMs listed are not available in the European drug formulary.[87] This can limit the generalizability of the Beers' Criteria in international clinical settings. This later limitation is largely why the STOPP/START criteria were developed.

The STOPP/START Criteria: Creation, Definition, Strengths, and Limitations

After the Beers' Criteria update in 2003,[88] two important European studies were published measuring the proportion of older adults with one or more PIMs prescribed using the Beers' Criteria 2003.[87, 89] Both found the prevalence of PIMs was significantly lower in the European countries compared to the United States,[87, 89] likely due to the Beers' Criteria not being adapted to the European drug formulary or prescribing indications.[90]

Consequently, in 2008, the STOPP/START criteria were developed by Gallagher et al. in Ireland,[90] gathering experts in geriatric pharmacotherapy, using a modified Delphi panel; 65 criteria were developed for the STOPP portion and 22 for the START portion of the tool.[90] The STOPP portion provides opportunities to identify and deprescribe PIMs, and the START criteria provides opportunities to identify potential prescribing omissions (PPOs) to correct situations where patients are being underprescribed certain medications.

In deprescribing research, however, the STOPP criteria are most often applied, as the field explores the ways of deprescribing PIMs, not how to add medications based. Potential prescribing omissions remain nonetheless important in the field of safer prescribing, but these fall outside of the scope of my thesis. The STOPP criteria are often combined with the Beers Criteria to provide a more complete, but still not exhaustive, evaluation process of PIMs.[91] The tools complete each other; while the Beers Criteria do not specifically tackle ADEs, this is something that is addressed in the STOPP criteria.[92] Studies have shown that the medications listed in the STOPP criteria are associated with ADEs.[92] Another study found that, when STOPP was applied within 72 hours of a hospital admission, the length of stay and frequency of ADEs

decreased.[93] In this same study, authors, who were accessorily the inventors of the STOPP criteria, found that STOPP criteria detected avoidable ADEs 2.8 times more often than the Beers Criteria.[93]

A second version of STOPP/START was created in 2015, again using the modified Delphi panel after having conducted a literature review of evidence (randomized controlled trials or reviews.[42] A total of 27 new indications were added in this second version. A third version was created in 2023 using the Delphi panel again.[72] A total of 76 new indications were created, for a total of 190 indications for STOPP/START v3. Overall, this consistent process of reviewing and creating criterion has been maintained, which can increase the tool's validity.[42, 72, 90] However, this latest version of the STOPP/START has been met with some criticism.[94] A Quebec team of pharmacists wrote a letter to the editor of European Geriatric Medicine, where the 3rd version of STOPP/START was published, addressing the methodology in the literature review that informed the questionnaires of the Delphi process; the literature review was not systematic, it was never registered in a database such as PROSPERO, and authors did not clarify the selection criteria during the screening process of the articles.[94] Furthermore, and this is the case for all of the STOPP/START indications, there are no levels of certainty accompanying each indication. Finally, the STOPP/START tool currently has 190 criteria; its increasing length may make its use in clinical practice difficult for prescribers.

The Choosing Wisely Canada Initiative: Creation, Definition, Strengths and Limitations

In 2009, the National Physicians Alliance in the United States created a list of medical interventions that clinicians should "question", in an effort to reduce overuse and waste in

healthcare, but always based on evidence.[95] In 2011, an official campaign was launched aimed for specialist physician associations to join the Choosing Wisely movement.[95] Since then, Choosing Wisely initiatives around the world were created; notably, the Choosing Wisely Canada[96] and Choisir avec soin Québec[97] movements. The overarching goal is to reduce medical waste through creating guidelines that were evidence-based; Choosing Wisely Canada (CWC) includes a strong component on limiting the prescription of harmful medications such as sleeping pills and antipsychotics in long-term care, but it also does substantial work on superfluous pills, such as docusate. Choosing Wisely Canada is constantly creating new guidelines and has a strong patient engagement component to raise awareness around wasted medical interventions, notably through advertising and slogans that are easy to remember, such as "Bye-Bye PPI"[98] to assess the overuse of proton-pump inhibitors. However, this tool does have limitations; today, Choosing Wisely Canada has 62 different specialties that contain guidelines to reduce medical futility and harm. While all guidelines can be downloaded at once, doing so creates a 205-paged file for a clinician to screen to identify indications on deprescribing.[43]

Other Less Commonly Used Tools: The PIMDINAC, LESS-CHRON, PRISCUS, and Marc Criteria

While the MAI, American Geriatrics Society, STOPP, and Choosing Wisely criteria are the most widely available tools/criteria, several others, though less commonly used in research on deprescribing and medication safety, also exist to identify PIMs. A first example are the PIMDINAC criteria [PIM (potentially inappropriate medications) + DI (drug interactions) + NAC (non-adherence treatment components)].From a scoping review,[99] this tool is used infrequently.

It is split into three components: the PIM section used the STOPP criteria;[90] drug interactions (DI) were defined by the Liverpool HIV Drug Interactions Database;[100] non-adherence to treatment components (NAC) were measured through the Adherence to Refills and Medications Scale (ARMS).[101] Each of these tools have been validated; however, the use of the PIMDINAC tool to flag potential PIMs has not been validated, and it seems to be used specifically in Spain among older adults with HIV. The List of Evidence-Based Deprescribing for Chronic Patients (LESS-CHRON) is a second tool based on a series of criteria created in 2017 to identify PIMs among patients with multimorbidity.[102] This tool was found in two systematic reviews and meta-analyses to be effective to identify and deprescribe PIMs among patients with chronic illnesses.[103, 104] However, in its validation study from 2019, it was found to have lower interrater reliability (kappa 0.46), [102] and it has not yet been extensively testing among a large cohort of patients, or in randomized controlled trials. Two other tools include the PRISCUS (Latin for old and venerable)[105] criteria, uncommonly used deprescribing tool due to its low sensitivity in detecting PIMs,[106] and the Marc criteria, a list of medications at high risk of medication errors among older adults, but that does not contain deprescribing instructions.[107]

Barriers to Deprescribing

The existence of several barriers to deprescribing likely partially explains why there are so many tools attempting to identify and intervene on polypharmacy. In fact, a recent systematic review and meta-analysis found 95 different deprescribing tools in the literature.[108] One of the key barriers addressed by guidance documents is a lack of standardized knowledge among healthcare providers. However, other barriers exist as well.

Just like the Beers' Criteria, STOPP/START Criteria are paper-based, and clinicians that wish to use the tool have to do so manually, which is often incompatible with the pressures of clinical duties and the limited time available for clinicians to deprescribe.[109-111] In fact, the patients have more and more comorbidities that each require medications, and this has significantly increased within the past 15 years, according to a recent study[55] in JAMA Internal Medicine measuring patient complexity across time from 2001 to 2017. Patients in 2017 were more likely than in 2001 to be admitted to the emergency department, they had an increased number of comorbidities, polypharmacy, and were more likely to receive treatment for 5 or more acute medical issues. Coupled with the severe lack of time that clinicians have with patients, expecting clinicians to perform an exhaustive review of medications and use both the Beers' Criteria and the STOPP/START criteria to deprescribe is incompatible with current clinical practice.

Other barriers were explored in a systematic review and meta-analysis in 2020,[110] at the individual, interpersonal, organizational and cultural levels. Individual, or patient levels, include lack of knowledge related to deprescribing from both the patient and the clinician; interpersonal levels include clinicians' fear of impeding on another clinician's expertise by deprescribing medications that were prescribed by someone else; organizational issues include fragmentation of care; and cultural levels include such as clinical inertia, or the willingness to maintain the status quo and not "rock the boat" by initiating a deprescribing trial.[110]

Electronic clinical decision support tools to deprescribe have been described as a potential solution to the time-consuming and complex nature of the deprescribing process, especially due to the need to deprescribe medications among patients that have several medications required

to manage multiple comorbidities. In 2020, a narrative review was conducted on the types of tools used to deprescribe; a brief section discussed the types of electronic clinical decision support tools for deprescribing. I have described the available ones below, both informed by this narrative review and a brief literature search conducted on each of the tools. I have detailed in this table if the electronic clinical decision support tool has an application programming interface (API) which is a software that interconnects people, applications, and systems.[112] For the purposes of electronic deprescribing tools, APIs allow for medical data to be extracted from the electronic medical record and input into the electronic deprescribing tool to automate data entry.[36] This decreases the time necessary for clinicians to conduct a deprescribing process; instead of time taken to collect patient data, they can focus on the analysis portion of the deprescribing process.[113]

Table 1: Examples of electronic clinical decision support tools used for deprescribing

	MedSafer	MediQuit	TaperMD	G-MEDSS	MedStopper
Research stage	Implemented in long-term care homes in Ontario and in Point Click Care electronic medical records. Patient-facing version available for a fee	Pilot testing[114]	Being studied in an RCT[115]	Studied in an RCT (shown not superior to usual care to improve drug-burden index)[116]	Never studied
Location of software's development	Canada (Quebec)	Germany	Canada (Ontario)	Australia	Canada (British Columbia)
Application programming interface (API)	Yes	No	Yes	Yes	No
Largest number of patients studied in their trial/study	5698[18] in a cluster RCT	41 in an uncontrolled observational study[114]	360 (RCT in progress)[117]	201 in a cluster RCT[116]	N/A
Deprescribing tools used	• Choosing Wisely[43] • STOPP[42] • Beers Criteria[41]	• Clinical expertise	• Clinical expertise • Underpinnings from the Chronic Care Model[118]	• Drug Burden index calculator[119] • Revised patients' attitudes towards	• Clinical expertise • Beers[88] • STOPP[42]

				deprescribing goals of care management tools[120]	
Strengths	• Automated deprescribing support • 22.2% efficacy compared to routine medication reconciliation • Individualized deprescribing report • Uses existing, validated deprescribing tools • Adapted to Canadian formulary	• Multidisciplinary team to build this tool • Clinical expertise is valued • Electronic tool	• Clinical expertise combined with validated deprescribing tools. • API • RCT planned to end in December 2024 • Canadian software adapted to Canadian drug formulary.	• Use of several tools to build this software • Incorporation of patient and family wishes into the report through the rPATD • Clinical evaluation by a pharmacist and a physician are part of the initial assessment.	• Interactive tool • Available free of charge • For patients and clinicians alike • Accessible language • Tangible report either online or printable • Tool has been validated in a clinical trial
Challenges	• If there is no integration with in the electronic medical record, data entry is manual. • Fee for integration	• No validated, explicit deprescribing tools are used. • Would require translation from German to English. • Few participants in the pilot testing	• Unclear how much time needed to conduct thorough medication review. • Guideline; no formal data input	• Time-consuming: requires an hour-long interview with a pharmacist and 30 minutes with a physician • Few patients have participated in studies to date	• Not a tool for deprescribing, only for withdrawal • No API • Based solely on clinical experience • No deprescribing tools used • Time-consuming: manual data entry • Not user-friendly

Gaps in the Literature and Research on Deprescribing Among Special Populations at Risk of Medication Overload

No where is it more apparent that tools to overcome deprescribing barriers are needed than in some of the special populations studied in my thesis. While some tools exist, the study of their implementation is lacking.

Among Residents of Long-Term Care Homes

In LTCHs, up to 90% of residents have polypharmacy,[45] but it's difficult to assess the proportion of patients that have medication overload because studies use incomplete sets of tools to identify potential PIMs. In fact, a recent systematic review measured the prevalence of PIM prescriptions in nursing homes, also known as long-term care homes, using the Screening Tool for Older Persons Potentially inappropriate prescriptions (STOPP), and found a high prevalence between 67.8%-87.7%.[121] A "simple" solution would be to deprescribe the PIMs of residents, but several studies have determined at least partly why this is much easier said than done. Palagyi et al.[122] conducted a qualitative study on barriers to deprescribing in nursing homes. They found several barriers to deprescribing, including the fragmentation of care, whereby a single resident can have multiple different healthcare providers, each treating a different illness. As a result, physicians are hesitant to deprescribe the medication of another prescriber due to fear of overstepping their clinical responsibilities. Long-term care homes also have reduced staffing and high turnover, whether they be personal care workers, nurses, or physicians, leading to time constraints, so deprescribing never becomes a priority. Furthermore, because

residents of long-term care homes do not have acute medical issues, and that their comorbidities are relatively stable, clinicians adopt an attitude unwilling to challenge the status quo and not willing to be responsible for "rocking the boat".[122] In summary, various long-term care homes and their clinicians adopt the policy of "if it ain't broke, don't fix it", as Palagyi noted in their qualitative study. Authors did note the potential to support prescribers in the deprescribing process could help them trigger a decision to deprescribe. As I have noted earlier in my literature review, this is difficult when using paper-based tools.

This is why I set out to study an electronic deprescribing decision-support tool in a long-term care home, through a quality improvement study, to approximate a real-world experiment on deprescribing in this clinical setting.

In 2022, not long after my quality improvement study in long-term care was accepted for publication (Chapter 1), Desai et al. published a scoping review[123] on the state of research in deprescribing, and first coined the term deprescribing in "special populations". The first populations studied in the field of deprescribing were conducted among older adults because this population was first identified as being at risk of receiving PIMs, as Dr. Beers' noted when he first developed the Beers' Criteria.[83] However, in their scoping review, Desai et al. found that patients in palliative care, patients with psychiatric illnesses and patients on hemodialysis were also receiving deprescribing interventions. Based on this information, as there were already several studies being conducted on deprescribing in palliative care and the fact that only a case report had been conducted on deprescribing in a patient with a psychiatric illness, I decided to pursue the study of deprescribing among patients on hemodialysis.

Among Patients on Hemodialysis

Between 4.9 to 7.1 million people in the world have end-stage kidney disease requiring renal replacement therapy, otherwise known as dialysis; moreover, the worldwide prevalence of end-stage kidney disease (ESKD) is around 13.4%.[124] The most common causes of ESKD are diabetes and hypertension.[125] In addition to requiring dialysis, patients also require treatment for the underlying causes of their kidney disease, and potentially additional comorbidities, so much so that patients on hemodialysis are considered to have the highest pill burden of all chronically ill populations.[126] Up to 90% of patients on hemodialysis have polypharmacy,[127] and are most exposed to mega polypharmacy, or the prescription of ≥10 medications.[128] After the MedSafer Study was published in JAMA Internal Medicine in 2022, I co-authored a secondary analysis of this cluster RCT focusing on deprescribing among older patients on hemodialysis; 79.3% of patients had mega polypharmacy.[17]

As was the case with older adults in LTCHs, the proportion of patients with any type of medication overload (i.e., with ≥1 PIMs from any screening tool) was not known prior to this secondary analysis. The MedSafer secondary analysis showed that 93.6% of patients enrolled in the cluster RCT were prescribed PIMs;[17] this is a very similar, if not greater prevalence of PIM prescription compared to residents of long-term care homes.

After having conducted a search of the literature through MedLine and CINAHL in October 2023 to identify studies conducted on deprescribing in hemodialysis, only two studies were identified. The most recent one was an uncontrolled deprescribing study published in 2021,[129] where authors developed their own deprescribing algorithms for patients on dialysis based on expert

opinion, without referencing the supporting evidence, and previously pilot tested them among an unpublished study of patients on an outpatient hemodialysis unit. Authors measured the number of medications prescribed before and after the deprescribing intervention in this same unit.[129] The median number of medications had decreased 12 weeks following the deprescribing intervention, from 11 median medications to 7. The results were statistically significant, although a control group was absent.

In 2017, McIntyre et al. published a deprescribing quality improvement study targeting 5 select classes of medications among patients on hemodialysis: quinine, diuretics, alpha-1 blockers, PPIs, and statins.[130] They crafted deprescribing algorithms specifically for outpatient hemodialysis patients.[131] Quinine was selected as a PIM because it is often prescribed to dialysis patients for leg cramps, but carries a significant risk of ADEs such as dizziness, nausea and vomiting, and shows limited efficacy to relieve symptoms.[130, 132] Quinine even includes a Black Box warning due to a lack of evidence of efficacy and convincing evidence of life-threatening harms.[133] Diuretics were selected for anuric patients: those who do not urinate will not clinically benefit from being prescribed a diuretic because they are already not excreting urine.[130, 134] Also for the anuric patient, alpha-1 blockers used for increasing urinary flow will not have any clinical benefit to increase urine output if the patient is not producing urine; its use is therefore superfluous.[135] Alpha-1 blockers used as antihypertensives have also been associated with increased cardiovascular risk in the general population and, in hemodialysis patients, its use has never been studied in randomized controlled trials, as opposed to angiotensin converting enzymes (angiotensin converting enzyme, or ACE, inhibitors), angiotensin receptor blockers (ARBs), etc.[130, 136, 137] Proton-pump inhibitors were selected because their clinical necessity is

rarely reassessed; however, specifically relating to ESKD, PPIs have been associated with increased vascular calcification and decreased efficacy of calcium-based phosphate binders with prolonged PPI use.[130, 138] Finally, primary prevention statins were selected because there is a lack of evidence that they prevent cardiovascular events in this population.[130, 139]

After this quality improvement study took place, and after the MedSafer Study had finished but was not yet published, in 2020, Lefebvre et al. published the validation study of their five deprescribing algorithms.[131] These indications were not integrated in the MedSafer software at the time of the original MedSafer Study.[18] In the secondary analysis that I coauthored; we did indeed find that a greater proportion of PIMs were deprescribed (28.8% vs 19.3%; absolute increase 9.4%; 95% CI 1.3%-17.6%), but the proportion of patients with one or more PIMs deprescribed was not significantly different compared to placebo.[17] One of the hypotheses elicited to explain these finding was the lack of deprescribing algorithms designed specifically for patients on dialysis. Both previous studies on deprescribing among patients on dialysis had tested deprescribing algorithms specific to patients on dialysis. The efficacy of an exhaustive tool to deprescribe in this special population had not been previously tested. Additionally, the MedSafer Study was run amongst admitted patients and not tailored to dialysis. I aimed to tailor a deprescribing intervention to dialysis and execute it in the outpatient dialysis unit, before hospitalization. These reasons, the lack of testing of exhaustive deprescribing in this special population and the need to tailor of a deprescribing intervention *before* hospitalization, motivated the conduct of the second study of my PhD, the deprescribing quality improvement study in outpatient hemodialysis patients.

During the data analysis phase of this study, I noted that several patients on dialysis were also diagnosed with HIV, and they had a high number of medications prescribed. The dialysis population proved to be a fruitful group for deprescribing, so I aimed to identify a different special population who were community dwelling and at high risk of polypharmacy and medication overload, one of which was older PWH. I thus decided to undertake a retrospective study on the prevalence of polypharmacy and medication overload among older PWH.

Among Older People With HIV

In 2022, the Lancet HIV and the Lancet Healthy Longevity published a series on Aging with HIV.[140] Authors from various studies included in this series discussed how clinicians and researchers are only beginning to discover how people with HIV (PWH) are aging with the virus. Largely thanks to the efficacy of antiretroviral treatment (ART), the life expectancy of PWH in high-income countries approaches that of seronegative patients.[141] While the chronological age of PWH may be similar to seronegative patients, the biological age of PWH could be vastly different. Several studies have documented how HIV induces an accelerated aging process,[142] and ART increases the risk of developing chronic illnesses such as diabetes, hypertension, dyslipidemia, etc., to the effect that PWH aged 50 and older are biologically similar to seronegative adults aged 65 and older, and have a similar number of comorbidities. As a result, the proposed cut-off for defining older adulthood in PWH is 50 years or older. Additionally, the AIDS Therapy Evaluation in the Netherlands (ATHENA) national cohort study that took place in 2018 predicted that, by 2030, 84% of older PWH will have at least one additional comorbidity and 28% will have at least three, compared to 19% of the seronegative population;[143] naturally, these comorbidities will require medication to manage. An additional complexity among PWH is

the inclusion of antiretroviral therapy (ART) in their pharmacotherapy. While they are incredibly beneficial to manage HIV, they are not without risks. As I detail the third chapter of my thesis, each ART drug class carries its own risks of adverse drug events,[65, 144] and can even lead to the development of chronic illnesses, such as dyslipidemia, hypertension, insulin resistance, etc.[65] Consequently, ART and drugs to treat the adverse effects of ART are needed for the older PWH.

Interestingly, Back et al. measured the prevalence of polypharmacy among PWH to be between 15-94%.[65] Although this was never discussed in their original paper, this significant gap can be attributed to the inclusion or exclusion of ART in the medication count.[145] Some researchers choose not to include ART in the medication count because these are necessary medications that patients cannot live without and because ART already requires at least 3 medications; therefore, with the addition of two or more medications in addition to ART, patients would "unjustly" have polypharmacy.[146] However, excluding ART from the medication count is inconsistent with current count-based methods measuring polypharmacy in special populations. For example, dual anticoagulated patients require these medications for to reduce cardiovascular events post-angioplasty with stenting. This population is also at risk of gastrointestinal bleeding. They often are prescribed proton-pump inhibitors to prevent this. It would thus be illogical to exclude anticoagulants in the medication count of post-angioplasty patients because patients would require these medications to survive. All medications, including ART, carry a risk of harm. They all contribute to a patient's medication count and pill burden. Although a study published in the International Journal of the International AIDS Society in 2020 made a call to include ART medications in the medication count to measure polypharmacy,[65]

because of these diverging schools of thought, I chose to measure polypharmacy both including and excluding ART in the medication count in my retrospective study.

Medication overload is another issue affecting older PWH, the prevalence ranging from 29%-63.3% in previous studies.[13, 107, 147-155] Of these 11 published studies (grey literature excluded), two main issues in the methodology led to a significant gap in evidence warranting the conduct of my retrospective study. The first issue with the methodology is the selection of the age group to measure PIMs. In fact, 8/11 (73%) studies measured the prevalence of PIMs among older PWH aged only 65 or older.[107, 149-155] One study measured it among those aged 60 or older,[147] and only one Canadian study measured it among PWH aged 50 and older,[13] which is the recommended cut-off to define older adulthood among PWH. Next, no study exhaustively screens for all PIMs. A total of 6/11 (54.5%) studies[107, 149, 150, 152-154] used multiple tools to identify PIMs. Of these, three used a combination of the STOPP/START and Beers' Criteria,[149, 150, 152] and three used uncommonly used tools that I previously described: the PIMDINAC were used in combination with the STOPP/START criteria in Diaz-Acedo's study,[153] Vinuesa-Hernando et al. used the STOPP and LESS-CHRON criteria,[154] and Garcia-Lloret et al.[107] used a combination of the PRISCUS, Marc and STOPP criteria.

Clinicians and scientists working with older PWH evidently use a variety of different tools to identify PIMs in their studies. This gives rise to heterogenous measurement of medication overload across studies among older PWH. Furthermore, there is no study that has measured medication overload exhaustively among older PWH ≥50 years of age. Therefore, a retrospective cohort study is warranted to map the prevalence of medication overload and

polypharmacy, both including and excluding ART. This study must make use of electronic clinical decision support, such as MedSafer, that screens for PIMs as exhaustively as possible through the use of multiple deprescribing tools.

The literature review conducted on deprescribing research among older adults in long-term care, patients on hemodialysis, and older PWH demonstrates the lack of a "gold standard" approach to identifying PIMs and deprescribing them. Just as for any chronic illness, gold standard tests and treatments are established to detect the illness and treat it in the most precise and accurate fashion to ultimately reduce the risks of complications of the illness.[156] When a patient develops medication overload, which is very similar to a medical syndrome, a "gold standard" approach needs to be applied to reduce its risks of complications. In this case, however, the test and treatment need to be seamlessly integrated because, historically, identifying PIM and reaching a deprescribing plan is time consuming,[3] especially in cases of polypharmacy and mega polypharmacy. If the tests to detect medication overload are incompatible with the obligations of prescribers that need to administer the PIM identification "treatment", deprescribing will not be done.

The scope of my PhD is focusing on an intervention at the individual level to influence change at the interpersonal, organizational and cultural levels. New evidence is showing that, given the increasing adoption of EMRs, software could be integrated within them to help clinicians deprescribe, and provide electronic clinical decision support.[157, 158] MedSafer is an electronic decision support tool that, in clinical trials, has been shown to increase deprescribing for hospitalized older adults and for people residing in long-term care.[18, 36, 159] MedSafer identifies

deprescribing opportunities by electronically cross-referencing a person's usual medication list and medical comorbidities, with a curated ruleset of evidence-informed deprescribing guidelines (based on criteria from the Beers Criteria of the American Geriatrics Society,[41] STOPP[42] and Choosing Wisely[43]). A cluster randomized controlled trial showed the MedSafer software safely increased deprescribing by 22% (95% CI = [16.9%-27.4%]).[18]

Aims of My Thesis

Following demonstration of efficacy of MedSafer in a large randomized controlled trial of hospitalized older adults, I became interested in the applicability of the software in other clinical settings in special populations. The aims of my PhD were thus two-fold. The first was to determine, through two quality improvement studies, the effectiveness of MedSafer integrated in the workflow of clinicians caring for i) older adults in LTCHs and ii) people with ESKD. As discussed, older adults and people with ESKD on dialysis are typical populations at risk of medication overload, and there is currently a lack of effective interventions to address this. While the MedSafer tool has been shown to be effective in a randomized controlled trial of hospitalized older adults, the implementation of this solution in the clinical practice clinicians in LTCHs and people with ESKD on dialysis had not been studied.

The second aim of my PhD was to describe the prevalence of polypharmacy and medication overload among older PWH, to inform the design of future deprescribing trials measuring the effectiveness of MedSafer in this population. For PWH, there are a lack of studies that describe the prevalence of polypharmacy and medication overload as well as the frequency and types of deprescribing opportunities, so I aimed to address this gap through my second aim.

The proportion of patients with one or more PIMs deprescribed will remain a consistent outcome across the studies of my thesis because it measures the population effect of deprescribing, an important factor to determine the benefits of it at the patient, clinician and healthcare levels.[109]

Chapter 1: MedSafer to Support Deprescribing for Residents of Long-Term Care: A Mixed-Methods Study

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Abstract

Background

Polypharmacy is prevalent in long-term care homes (LTCH) and increases the risk of adverse drug events. Feasible and effective deprescribing interventions applicable in the LTCH environment are needed.

Methods

We performed a mixed methods study to evaluate the feasibility, applicability, and effectiveness of an electronic deprescribing tool, MedSafer, to facilitate quarterly medication reviews (QMRs) on two pilot units in an academic long-term care home (LTCH). Chart reviews collected resident health data. The prevalence of deprescribing at a standard QMR was compared with a QMR conducted three months later with MedSafer. Feedback from physicians on their experience with MedSafer was obtained through semi-structured interviews.

Results

Physicians found MedSafer helpful in guiding deprescribing decisions and suggested software improvements to increase the feasibility in LTCH. The average number of medications deprescribed per resident was significantly higher at the Med-Safer QMR (mean reduction = 1.1 medications, SD = 1.3) compared to the standard QMR (mean reduction = 0.5, SD = 0.9) (absolute difference of 0.5; SD 1.1; p = .02).

Conclusion

MedSafer has the potential to increase deprescribing in LTCHs by flagging potentially inappropriate medications. Integration in the electronic medical record might increase uptake in LTCHs. Further research should investigate the generalizability of MedSafer in a larger population and in non-academic LTCHs.

Key words

Polypharmacy, Deprescribing, Long-Term Care, Clinical Decision Support System, Medication Review

Introduction

Polypharmacy broadly refers to the use of multiple medications for comorbid conditions and often a cut-off of five or more regular medications is applied.[1,2] Polypharmacy is inappropriate when it is causes more harm to the patient than actual or future clinical benefits.[3] In long-term care homes (LTCHs), polypharmacy is a growing challenge, with a prevalence as high as 85–90% of residents, compared to 27–59% of community-dwelling older adults.[1] In addition to an increase in drug–drug and drug–condition interactions observed with polypharmacy, age-related decline in organ function and altered metabolism can affect medication clearance in older adults, which further increases their risk of ADEs.[4] Adverse drug events associated with inappropriate polypharmacy can range in severity from changes in cognition and falls to hospitalization and death.[2,5]

Deprescribing aims to address polypharmacy by identifying and discontinuing medications that are potentially inappropriate or no longer necessary, to maximize medication efficacy and safety, all the while contextualizing an individual's current level of functioning, life expectancy, values and preferences.[6] However, deprescribing can be challenging due to a number of factors.[7] Some medications may have been prescribed by a different physician, the original indication might not be clear, and there is also the possibility of re-emergence of symptoms that can occur when tapering or discontinuing potentially inappropriate medications (PIMs). This is especially true for medications that have been taken long-term, which can include medications such as psychotropics and opioids.[8] More specifically, in the long-term care setting, clinician preferences, clinical inertia, and lack of time and training are some of the many barriers that are observed.[2,9]

MedSafer is a deprescribing software that cross-references patient demographic information, medical history, and medication data with evidence-based deprescribing guidelines to identify opportunities for deprescribing and facilitate safer prescribing.[10] MedSafer is effective at reducing polypharmacy in acute care hospital settings;[11] however, there is a clear lack of research into the applicability of deprescribing softwares in LTCHs, where patient populations and clinical presentations are notably different. MedSafer provides an exhaustive deprescribing report based on the analysis of data input into the software. Patient preferences are accounted for upon review of the report (which provides prompts for the incorporation of patient values), and upon discussion of the report by the clinician with the patient and their loved ones.[11]

In Ontario, Canada, quarterly medication reviews (QMRs) are government-mandated for residents of LTCHs. The QMR involves a pharmacist who completes a medication review (MedsCheck LTC),[12] and makes recommendations for medication changes that are subsequently reviewed by the physician. There is no standardized process to incorporate deprescribing, but the QMR presents an excellent opportunity to reassess and reduce medication burden.[12] We identified the QMR as a potentially useful work process to pair with an electronic deprescribing intervention. The purpose of this study was to investigate the feasibility, applicability, and effectiveness of MedSafer during a regularly scheduled QMR and compare this to usual care.

Methods

Design and Setting

A mixed-methods study design was used to investigate MedSafer during a QMR on two pilot LTCH units at Baycrest Health Sciences (Baycrest), an academic geriatric centre of care in Toronto, Ontario. At Baycrest, a pharmacist, nurse, and physician meet every quarter to review residents' medications during the provincially mandated QMR. We collected and analyzed qualitative and quantitative data to assess feasibility, applicability, and effectiveness of the software in the LTCH. Feasibility was assessed quantitatively through retention rates (the proportion of QMRs during the intervention process to which physicians applied the tool), and qualitatively via semi-structured interviews with subjective questions that related to facilitators and barriers identified while using the software, including how easily the software was incorporated into the usual workflow and whether it led to additional time requirements when performing the QMRs. Applicability was assessed through interviews with physicians, using questions to determine the extent to which the software application was likely to impact their future practice and whether or not deprescribing recommendations were applicable to their specific patient population. Efficacy was assessed by the uptake of the deprescribing opportunities on physician practice during the QMR by comparing the number of medications deprescribed at the MedSafer QMRs to a standard QMRs conducted three months prior on the same pilot units. The research protocol was approved by the Baycrest Research Ethics Board (REB #18-31).

Intervention

MedSafer was incorporated into regularly scheduled QMRs for two pilot units to identify opportunities for deprescribing and support clinical decision-making. To generate MedSafer recommendations, the study team conducted a chart review and manually entered resident

data (medications and medical conditions) in the MedSafer web-based portal. MedSafer cross-references resident data with evidence- based deprescribing recommendations[36, 160] and identifies opportunities for deprescribing PIMs. The clinical team reviewed the individualized reports generated during the QMR (January 17, 2019, for Unit 1 and November 28, 2018, for Unit 2) for appropriateness of deprescribing during the intervention phase. Reports were generated by the research team, printed out and provided to the QMR team for review.

Data Collection & Measures

Physician experience with reviewing the deprescribing opportunities during the QMR was assessed using semi-structured interviews.

Physicians were interviewed for the study as they were the primary decision-makers at the QMR. Interviews were approximately 30-minutes in length and were conducted in-person by a research assistant using a semi-structured inter- view guide developed by the study team. Physicians were asked open-ended questions about the impact of reviewing the deprescribing opportunities on their practice during the QMR, integration into the workflow, whether they agreed or disagreed with the deprescribing opportunities (were the recommendations applicable to their patient population), and if any facilitators or barriers were identified with using MedSafer (feasibility). Questions from the interview guide can be found in Appendix A.

Two physicians on the pilot units were eligible to participate in the study. The research assistant obtained written informed consent from the physicians. Interviews were audio- recorded and manually transcribed by the study team. The research assistant provided the physicians with the

MedSafer recommendations such that training with the software was not required. Neither physician had any prior experience with using MedSafer.

A chart review collected demographics, comorbidities, medications, and recent lab values (electrolytes and creatinine), as well as hemoglobin A1C for residents living with diabetes. Residents' medication lists were collected at four time points: pre- and post-standard QMR and pre- and post-MedSafer QMR, to compare medication changes made during the intervention with historical changes that occurred in the review that took place in the prior quarter. Deprescribing rates were calculated for each QMR by calculating the average decrease in the number of medications per resident pre- vs. post-QMR.

Resident health outcomes were collected from the Resident Assessment Inventory Minimum Data Set (RAI-MDS) 2.0, which is administered every quarter in Ontario LTCHs. RAI-MDS outcome scales collected before and after the MedSafer QMR included the Aggressive Behaviour Scale; Activities of Daily Living; Changes in Health, End-Stage Disease and Signs and Symptoms Scale; Cognitive Performance Scale; and Depression Rating Scale.[12]

Data Analysis

Interviews were transcribed and coded using Microsoft Excel by two raters for agreement and inter-rater reliability. Qualitative coding was both inductive (based on observed patterns) and deductive (based on the study purpose). Interview data were grouped into prevalent themes, and categorized under the headings of feasibility, applicability, and efficacy of MedSafer to augment the usual processes of the QMR. No formal means was used to reach data saturation during the interview process. Descriptive statistics reported resident characteristics, medication orders, and

deprescribing outcomes. Changes in resident health outcomes pre-post MedSafer QMR were assessed using chi-square or Fisher's exact tests. Paired *t*-tests assessed deprescribing by comparing the number of medications before and after the standard and MedSafer QMRs. Deprescribing rates, or the mean reduction in medications at the standard and MedSafer QMRs, were compared using the independent *t*-test. Effect sizes are reported as standardized response means using the ratio of the mean difference and the standard deviation of the mean difference. Effect size values: 0.20, 0.50, and 0.80+ were interpreted as small, medium, and large effects.[13]

Results

Qualitative Interviews with Physicians

Two physicians participated in the interviews—one from each pilot unit. The qualitative data were grouped into the following three prevalent categories: 1) feasibility of using MedSafer during the QMR, 2) applicability of MedSafer in the LTCH setting, and 3) effectiveness of MedSafer in identifying medication deprescribing opportunities.

Feasibility

In this study, physicians only reviewed the deprescribing opportunities at the time of the QMR session. The reports were easily integrated into the workflow, and the time to complete a QMR did not increase (on average a QMR took 20 minutes with or without MedSafer). Retention was high and all reports were reviewed for all residents. Although the software recommendations were prioritized into high, medium, and low-risk categories, physicians reported that they reviewed all the deprescribing opportunities to determine the applicability to the resident's clinical case. To allow for time to review the deprescribing opportunities, physicians suggested

reviewing the deprescribing opportunities in advance of the QMR and on an ongoing basis, between QMRs. Since resident data, including lab results, were manually entered in the software, physicians suggested integrating the lab portal's results with the software algorithm to increase the feasibility of using the software.

Applicability

Physicians felt that most recommendations from the reports were applicable to the LTCH population, but they identified information to incorporate from the electronic medical record (EMR) into MedSafer's algorithm such as medication administration instructions (i.e., crushed vs. whole tablets), additional lab results, and goals of care that would increase the applicability of the software to LTCH residents. In line with this, they reported that some deprescribing opportunities identified by MedSafer were not applicable due to the resident's goals of care, such as a resident's life expectancy being less than a year or palliative care provision. In considering medication deprescribing opportunities and resident goals of care, it was suggested that MedSafer include the Changes in Health, End-Stage Disease, Signs and Symptoms Scale scores to indicate the level of health instability, including end-stage disease, as well as a palliative care screening question including a note regarding high-risk medications used for comfort care and symptom management.

Effectiveness

Physicians noted that the software fulfilled its purpose of flagging potential drug interactions and high-risk medications which helped guide their decisions regarding medications to potentially deprescribe. Although physicians reported they were often familiar with the PIMs and risks that

MedSafer identified, due to their experience of medication management in LTCH, they commented that MedSafer was effective at increasing awareness and drawing their attention to PIMs that required regular and ongoing review. Physicians also highlighted the helpfulness of MedSafer as a decision-making tool for prescribers new to LTCH, when a clinical pharmacist cannot be consulted at the QMR, as a useful means to guide their reflections on deprescribing.

Resident Characteristics

Residents of the two pilot units (N = 55) had a mean age of 86.6 years (SD = 11.9) and 72.7% were female. Units were mostly similar in prevalence of common medical conditions, aside from dementia, which was more prevalent on Unit 2 (92.6%) than Unit 1 (46.4%). The median Aggressive Behaviour Scale score was 0 (IQR = 0.0, Q1, Q3 = 0), indicating an absence of aggressive behaviour. Over half of residents (50.9%) were “dependent” or “totally dependent” in their activities of daily living. The Changes in Health, End-Stage Disease, Signs and Symptoms Scale showed that 56.4% had “minimal” to “moderate” health instability. The median Cognitive Performance Scale score was 3 (IQR = 5.0, Q1 = 1.0, Q3 = 6.0), indicating “moderate” impairment, and 41.8% of residents had “moderate/severe” to “very severe” cognitive impairment (Table 1).

Deprescribing Intervention

MedSafer identified deprescribing opportunities for 53 out of the 55 residents across both units (96.4%; Table 2). Commonly flagged PIMs included psychotropics and opioid analgesics for chronic non-cancer pain. Nearly a third of residents (32.7%) had a PIM deprescribed at the MedSafer QMR. The reasons for deprescribing included: 1) MedSafer identified the PIM as potentially having little added benefit (5 deprescribed/25 identified or 20.0%), 2) reduced

resident life expectancy (4/16 or 25.0%), and 3) overly tight control of diabetes (6/14 or 42.9%). Overall, an average of 0.5 (SD = 0.9) medications per resident were deprescribed in the standard QMR and an average of 1.1 (SD = 1.3) medications per resident were deprescribed at the MedSafer QMR. In comparing deprescribing rates, there was an average of 0.5 (SD = 1.1) more medications deprescribed per resident at the MedSafer QMR than the standard QMR (p = .02 ES = 0.5 or medium effect size). On one study unit, the intervention was more effective and the MedSafer QMR resulted in a mean reduction of 1.6 (IQR = 1.0) medications per resident, while the standard QMR on that unit resulted to a mean reduction of 0.3 (IQR = 1.0) medications per resident. The mean difference of 1.4 (IQR = 1.0) more medications deprescribed at the MedSafer QMR compared to the standard QMR was significant (p < .001, ES = 1.3 or large effect size). Across the two units, there was also a larger reduction in average medication orders per resident observed at the MedSafer QMR (mean = -1.1, SD = 1.3, ES = -0.8 or large effect, IQR = 2.0) compared to the standard QMR (mean = -0.5, SD = 0.9; ES = 0.6 or moderate effect, IQR = 1.0).

Discussion

Deprescribing software has been identified as a sustainable intervention to assist in safer prescribing for older adults.[11] This study demonstrated that an electronic deprescribing tool was applicable to the LTCH population, feasible to incorporate into the workflow, and effective at increasing deprescribing. This was the case even in the presence of pharmacy support and on

an academic geriatric unit with expert knowledge in medication reviews. Elements to in- crease feasibility and applicability were identified through the interview process.

Physician feedback included recommendations to improve applicability of the software to LTCHs by incorporating additional lab results and goals of care within the software algorithm. Areas for improvement identified through this study have been subsequently addressed through software modifications. For example, MedSafer is now integrated in two Canadian EMRs (Point Click Care[14] and Med e-Care[15]) and is currently being evaluated in that setting. This addresses the need for manual data input which is no longer required. Physicians reported that the software fulfilled its purpose in flagging potential drug interactions and high-risk medications. In this study, one-third of residents had one or more PIMs deprescribed at the MedSafer QMR. The over- all deprescribing rate was lower than previous research in acute care, which in one study showed a deprescribing rate of 54.7% among patients in the intervention group.[16] Our study took place on an academic geriatric unit and therefore physicians had some baseline knowledge of deprescribing. This, along with the small sample size and the short follow-up time, could explain lower rates than might be observed in a non-academic LTCH, or with repeated software facilitated mediation reviews over time.

Furthermore, medication management differs between acute and long-term care for various reasons. Residents in LTCHs have chronic, multiple comorbidities and are generally medically stable compared with patients in acute care.[17-19] Workflow, lengths of stay, and barriers to deprescribing are impacted differently in each of these settings.[19-21] Given the prevalence of comorbidities in this population, the indication for medications can sometimes be unclear, and

drugs could have been initiated and maintained by another clinician.[7] Finally, an important barrier resides in deprescribing in LTCHs: there is a known culture of maintenance of status quo for residents, which can dissuade physicians in initiating a deprescribing attempt.[22] The above factors and the short study duration could explain, in part, why the deprescribing rates were statistically significant, but not as high as those reported in acute care settings.

There were several limitations in this single-site pilot study. Although the present study benefited from the involvement of a pharmacist, physician, and nurse in completing the QMR, it should be noted that these resources are not always available in all LTCHs. The applicability of a deprescribing software facilitated QMR without the involvement of pharmacy or nursing still requires further study. As mentioned previously, this study took place on an academic geriatric unit and so study outside of this setting would increase the generalizability of the intervention. We only evaluated the software during a single QMR on two pilot units, with a focus on the feasibility and applicability of software, rather than proving efficacy, which would require a larger sample size, a longer study duration, and a different study design. Feedback on the MedSafer recommendations was only obtained from two physicians involved in the QMR, and the views of pharmacists, nurses, residents, and families, who are also heavily implicated in deprescribing process, were not captured. Finally, the software was not integrated in the EMR; therefore, physicians reviewed reports on paper and had to log into the EMR in order to deprescribe. Now that the software is integrated into the EMR,[14,15] future research will need to include a larger study population, longitudinal evaluations, and assessment of the impact on important resident and family-reported health outcomes. One strength of our study was that, to the authors' knowledge, there have been few studies evaluating the implementation of

deprescribing softwares in LTC, let alone one that addresses all possible classes of PIMs, as opposed to just a targeted class of medications (e.g., sedative hypnotics or antipsychotics). Most studies of deprescribing in long-term care have been limited to a single drug class or a few harmful medications.[7,23]

Conclusion

When using MedSafer electronic deprescribing software at the QMR, deprescribing events were increased and the number of medications per resident was reduced on two units of an academic LTCH. Software augmented QMRs are likely effective for deprescribing in this setting given a higher observed deprescribing rate when electronically generated deprescribing opportunities were paired with the QMR. Future research is needed to determine the feasibility and applicability in non-academic LTCHs and for larger populations over time. Integration with EMRs could make this a scalable intervention to support physicians in LTCH medication management.

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Conflict of Interest Disclosures

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Table 1: Resident Demographics and Clinical Characteristics

Variable	Unit 1 (n=28)	Unit 2 (n=27)	Overall (N=55)
Age in years, mean (SD)	86.1 (10.8)	87.1 (13.1)	86.6 (11.9)
Sex: Female, n (%)	17 (60.7)	23 (85.2)	40 (72.7)
Code Status: DNR, n (%)	18 (64.3)	18 (66.7)	36 (65.5)
Length of Stay in Months			
Admission to standard QMR, mean (SD)	40.1 (47.7)	46.6 (46.8)	43.3 (46.9)
Admission to MedSafer QMR, mean (SD)	43.5 (47.6)	47.8 (46.8)	45.6 (46.8)
Resident Assessment Inventory Minimum Data Set 2.0			
Aggressive Behaviour Scale			
No behaviours, n (%)	28 (100.0)	17 (63.0)	45 (81.8)
Mild/moderate to severe/very severe behaviours, n (%)	0 (0.0)	10 (37.0)	10 (18.2)
Activities of Daily Living Self-Performance Hierarchy			
Independent to limited impairment, n (%)	5 (17.9)	0 (0.0)	5 (9.1)
Extensive assistance, n (%)	13 (46.4)	9 (33.3)	22 (40.0)
Dependent to total dependence, n (%)	10 (35.7)	18 (66.7)	28 (50.9)

Changes in Health, End-Stage Disease and Signs & Symptoms			
No health instability, n (%)	11 (39.3)	13 (48.2)	24 (43.6)
Minimal to low/moderate health instability, n (%)	17 (60.7)	14 (51.9)	31 (56.4)
Cognitive Performance Scale			
Intact/borderline intact to mild/moderate impairment, n (%)	28 (100.0)	4 (14.8)	32 (58.2)
Moderate/severe to very severe impairment, n (%)	0 (0.0)	23 (85.2)	23 (41.8)
Depression Rating Scale			
No depressive symptoms, n (%)	19 (67.9)	17 (63.0)	36 (65.5)
Some depressive symptoms to possible depressive disorder, n (%)	9 (32.1)	10 (37.0)	19 (34.5)
Palliative Performance Scale version 2[a]			
≤30% level, n (%)	---	13 (48.1)	---
> 30% level, n (%)	---	14 (51.9)	---
Prevalent Comorbidities[b]			
Dementia	13 (46.4)	25 (92.6)	38 (69.1)
Hypertension	15 (53.6)	14 (51.9)	29 (52.7)
Depression	10 (35.7)	12 (44.4)	22 (40.0)
Comorbidity Category Prevalence[b]			

Neurologic, n (%)	20 (71.4)	26 (96.3)	46 (83.6)
Endocrine/ metabolic, n (%)	17 (60.7)	16 (59.3)	33 (60.0)
Psychiatric, n (%)	17 (60.7)	13 (48.2)	30 (54.6)

[a] Not available for Unit 1.

[b] Residents had combinations of comorbidities.

Table 2: MedSafer Outcomes

Outcomes	***Unit 1***	***Unit 2***	***Overall***
Medication Orders*			
Total number of medication orders before the MedSafer QMR	447	374	821
Medications orders per resident, mean (SD)	16.0 (5.5)	13.9 (4.5)	14.9 (5.1)
Medications with MedSafer deprescribing opportunities, n (%)	128 (28.6)	110 (29.4)	238 (29.0)
Deprescribing Opportunities			
Total number of deprescribing opportunities†	118	90	208
Residents with one or more deprescribing opportunities, n (%)	26 (92.9)	27 (100.0)	53 (96.4)
Deprescribing opportunities per resident, mean (SD)	4.2 (3.3)	3.3 (2.0)	3.8 (2.8)
Deprescribing opportunities implemented during the	13 (11.0)	13 (14.4)	26 (12.5)

MedSafer QMR, n (%)			
Deprescribing opportunities not implemented during the QMR, n (%)‡	105 (89.0)	77 (85.6)	182 (87.5)
Categories of deprescribing opportunities			
Risk for adverse drug event			
High risk, n (%)	69 (58.5)	45 (50.0)	114 (54.8)
Intermediate risk, n (%)	38 (32.2)	31 (34.4)	69 (33.2)
Lower risk but of potentially little benefit or value, n (%)	11 (9.3)	14 (15.6)	25 (12.0)
Cause for deprescribing opportunity			
Medical condition, n (%)	70 (59.3)	37 (41.1)	107 (51.4)
Drug interaction, n (%)	4 (3.4)	8 (8.9)	12 (5.8)
Reduced life expectancy, n (%)§	---	16 (17.8)	16 (7.7)
Other causes, n (%)‖	44 (37.3)	29 (32.2)	73 (35.1)
Medication class			
Psychotropics, n (%)	24 (20.3)	31 (34.4)	55 (26.4)
Analgesics, n (%)	32 (27.1)	15 (16.7)	47 (22.6)
Bone Health, n (%)	8 (6.8)	15 (16.7)	23 (11.1)
Gastrointestinal, n (%)	14 (11.9)	9 (10.0)	23 (11.1)
Diabetes, n (%)	8 (6.8)	6 (6.7)	14 (6.7)
Other, n (%)	32 (27.1)	14 (15.6)	46 (22.1)

No. of residents with a low-medium risk PIM deprescribed at the MedSafer QMR, n (%)	12 (42.9)	24 (88.9)	36 (65.5)
No. of residents with a high-risk PIM deprescribed at the MedSafer QMR, n (%)	8 (28.6)	10 (37.0)	18 (32.7)

Note: Unit 1 = 28 residents, Unit 2 = 27 residents, Overall = 55 residents

* Certain medications had multiple orders (e.g., separate orders for PRN vs. scheduled) or had multiple deprescribing opportunities with different causes

† Excludes opportunities for a certain medication that had inconsistencies between the electronic health record and MedSafer

‡ Changes may have been made at a later date after the MedSafer QMR

§ Other causes for deprescribing opportunities included potentially inappropriate medications flagged due to reduced life expectancy may offer little benefit or potentially be of harm to the resident. Reduced life expectancy was calculated using a Palliative Performance Scale cut-off score of 30%. Palliative Performance Scale data was only available for Unit 2 residents.

‖ Some medications were always flagged as potentially inappropriate medications regardless of resident health status (e.g. psychotropic medications and

Bridging Text 1: From Long-Term Care Homes to Outpatient Hemodialysis

As we submitted our manuscript on deprescribing among residents of a LTCH, the MedSafer study was published in JAMA Internal Medicine- a 5698-patient cluster randomized controlled trial on deprescribing.[18] As previously mentioned, this study demonstrated that MedSafer increased deprescribing without having a detrimental impact on ADEs or adverse drug withdrawal events. After this study was published, I coauthored a secondary analysis of this initial study with Dr. Joseph Moryousef, medical student and now resident physician in urology, on the rate of deprescribing among patients on hemodialysis.[17] The results of this study on the prevalence of polypharmacy and medication overload were very important: 90% of participants had polypharmacy and 93.6% had medication overload. Additionally, 79.3% had mega polypharmacy, defined as the prescription of 10 medications or more. However, in this subpopulation, while MedSafer did significantly increase the proportion of PIMs deprescribed, the effect was not as strong as in the general MedSafer population. As I will detail in my publications below, one of the hypotheses elicited to explain this finding was the lack of deprescribing algorithms designed specifically for the hemodialysis population. At the time, there were no deprescribing algorithms specifically for patients on hemodialysis. However, since the study was published, Lefebvre et al. validated and published a series of deprescribing algorithms for the dialysis population.[131] The algorithms were face and construct validated. Face validity is defined as the end-user's evaluation of a tool's clarity, comprehensibility and appropriateness.[161] Construct validity refers to the extent to which a tool is representative of its intended concepts.[162] Following this validation, I set out to integrate these deprescribing

algorithms into the MedSafer software and to conduct a controlled quality improvement study on deprescribing in two outpatient hemodialysis clinics at the McGill University Health Centre. To integrate these algorithms into MedSafer, I worked with the computer scientist working on MedSafer to translate them into binary rules that MedSafer would be able to "understand" and interpret to emit a deprescribing indication, if it recognized a medication as a PIM. Below is the second project of my PhD, the controlled, quality improvement MedSafer deprescribing study in hemodialysis.[163] There are three parts to this study. First, given the complexity of the planned intervention, I published a protocol of the study in the Canadian Journal of Kidney Health and Disease detailing the entirety of the interventions taking place. Second, the quantitative portion of the results are published in the journal Kidney Medicine. Third, the qualitative portion of the study (the results of the interviews with physicians on their experience participating in the intervention), is under review at the Health Literacy and Communications Open and can be found in the Appendix of my thesis.

Chapter 2: Medication Deprescribing in Patients on Hemodialysis: A Prospective, Controlled, Quality Improvement Study

Section 2.1: Electronic Decision Support for Deprescribing in Patients on Hemodialysis: Clinical Research Protocol for a Prospective, Controlled, Quality Improvement Study

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Abstract

Background

Patients on dialysis are commonly prescribed multiple medications (polypharmacy), many of which are potentially inappropriate medications (PIMs). PIMs are associated with an increased risk of falls, fractures, and hospitalization. MedSafer is an electronic tool that generates individualized, prioritized reports with deprescribing opportunities by cross-referencing patient health data and medications with guidelines for deprescribing.

Objectives

Our primary aim is to increase deprescribing, as compared to usual care (medication reconciliation or MedRecs), for outpatients receiving maintenance hemodialysis, through the provision of MedSafer deprescribing opportunity reports to the treating team and patient empowerment deprescribing brochures provided directly to the patients themselves.

Design

This controlled, prospective, quality improvement study with a contemporary control builds on existing policy at the outpatient hemodialysis centres where biannual medication reconciliations (MedRecs) are performed by the treating nephrologist and nursing team.

Setting

The study takes place on two of the three outpatient hemodialysis units of the McGill University Health Centre in Montreal, Quebec, Canada. The intervention unit is the Lachine Hospital, and the control unit is the Montreal General Hospital.

Patients

A closed cohort of outpatient hemodialysis patients visit multiple times per week one hemodialysis centre for their hemodialysis treatment. The initial cohort of the intervention unit includes 85 patients, whereas the control unit has 132 patients. Patients that are transplanted, hospitalized during their scheduled MedRec, or die before or during the MedRec will be excluded from the study.

Measurements

We will compare rates of deprescribing between the control and intervention units following a single MedRec. On the intervention unit, MedRecs will be paired with MedSafer reports (the intervention) and on the control unit, MedRecs will take place without MedSafer reports (usual care). On the intervention unit, patients will also receive deprescribing patient empowerment brochures for select medication classes (gabapentinoids, proton-pump inhibitors and sedative hypnotics). Physicians on the intervention unit will be interviewed post-MedRec to determine implementation barriers and facilitators.

Methods

The primary outcome will be the proportion of patients with 1 or more PIMs deprescribed on the intervention unit, as compared to the control unit, following a biannual MedRec. This study will build on existing policies aimed at optimizing medication therapy in patients undergoing maintenance hemodialysis. The electronic deprescribing decision support tool, MedSafer, will be tested in a dialysis setting, where nephrologists are regularly in contact with patients. MedRecs are an interdisciplinary clinical activity performed biannually on the hemodialysis units

(in the Spring and Fall), and within one week following discharge from the hospitalization. This study will take place in the Fall of 2022. Semi-structured interviews will be conducted among physicians on the intervention unit to determine barriers and facilitators to implementation of the MedSafer-supplemented MedRec process and analyzed according to grounded theory in qualitative research.

Limitations

Deprescribing can be limited due to nephrologists' time constraints, cognitive impairment of the hemodialyzed patient stemming from their illness and complex medication regimens, and lack of sufficient patient resources to learn about the medications they are taking and their potential harms.

Conclusions

Electronic decision support can facilitate deprescribing for the clinical team by providing a nudge reminder, decreasing the time it takes to review and effectuate guideline recommendations, and by lowering the barrier of when and how to taper. Guidelines for deprescribing in the dialysis population have recently been published and incorporated into the MedSafer software. To our knowledge, this will be the first study to examine the efficacy of pairing these guidelines with MedRecs by leveraging electronic decision support in the outpatient dialysis population.

Trial registration

This study was registered on Clinicaltrials.gov on October 2nd, 2022, prior to the enrolment of the first participant on October 3rd, 2022. The registration number is pending at the time of protocol submission.

Keywords

hemodialysis, dialysis, polypharmacy, deprescribing, end stage kidney disease

Introduction

Background and Rationale

Patients with end-stage kidney disease (ESKD) who require dialysis are prescribed an average of 10 to 12 daily medications, often by 4 to 5 different clinicians, amounting to as many as 19 pills per day.[1-4] The dialysis patient population has one of the heaviest pill burdens of all chronic conditions due to concurrent treatment of co-existing conditions such as hypertension, vascular disease, and diabetes,[4] as well as treatment of complications of ESKD itself (eg, increased propensity for bleeding, bone mineral metabolism disorders, pruritus, pain, and insomnia).

More than 90% of dialysis patients take 5 or more medications (polypharmacy),[2,5] contributing to medication overload.[6,7] Furthermore, more than 90% are prescribed 1 or more potentially inappropriate medications (PIMs)[1,4,8]; PIMs are associated with an increased risk of harm (often through adverse drug events, ADEs) or they have a relatively low chance for benefit and merely contribute to a patient's pill burden.[2,4,7] Adverse drug events such as falls, fractures, and cognitive impairment can occur as a direct result of PIMs, or due to drug-drug interactions, both of which are more common with polypharmacy.[9,10] Polypharmacy and ADEs contribute to emergency room visits, hospital admissions, loss of autonomy, and premature death.[11-13] There is, therefore, a pressing need for pragmatic, scalable interventions to address polypharmacy in dialysis patients.[3,14,15]

We previously demonstrated that MedSafer, an electronic decision support tool, can increase deprescribing for hospitalized older adults and for people residing in long-term care homes.[16,17] MedSafer identifies deprescribing opportunities by electronically cross-referencing a person's usual medication list and medical comorbidities, with a curated ruleset containing evidence-

based deprescribing guidelines (based on criteria from the American Geriatrics Society,[18] STOPP,[19] and Choosing Wisely[20]).[17] MedSafer stratifies deprescribing opportunities into high-risk, intermediate-risk, or little added value categories. High risk implies there is an elevated risk of developing ADEs; intermediate risk implies that the harms must be weighed against the benefits of the drug; and drugs of little added value simply increase the pill burden of a patient or have evidence demonstrating no effect. Examples of a typical deprescribing report and of different drugs that fall into the 3 categories can be found in the Supplement of the MedSafer Study.[16] Our large cluster randomized clinical trial of older adults hospitalized in the acute care setting (N = 5698) included 140 patients receiving maintenance hemodialysis. The net deprescribing rate among dialysis patients was 9.4% (95% confidence interval [CI] = 1.3%-17.6%) higher in the intervention period compared with the control period. While effective, the general population in the study benefited from a much higher rate of deprescribing (absolute increase of 22.2%, 95% CI = 16.9%-27.4%).[16] At that time, no dialysis-specific rules were integrated into the MedSafer software, and patients were enrolled during a time of acute illness.

Since then, McIntyre et al[15] have developed deprescribing algorithms specifically for hemodialysis patients in a quality improvement study.[4,8] However, like most guidelines, there are barriers to implementation and uptake. Guidelines for deprescribing contain long lists of rules that preclude memorization; some may contain conflicting recommendations for patients taking 10 to 15 medications; and not all guidelines explain how to deprescribe (e.g., when and how to taper and what rebound symptoms to watch out for).[2,21-23] We therefore integrated the dialysis-specific deprescribing recommendations into the MedSafer ruleset, coupled them with

links to patient deprescribing empowerment brochures, and added instructions for tapering where required.

Objectives

Our primary aim in this study is to increase deprescribing, as compared with usual care (medication reconciliation or MedRec), for outpatients receiving maintenance hemodialysis, through the provision of MedSafer deprescribing opportunity reports to the treating team and patient empowerment deprescribing brochures provided directly to the patients.

Study Design

This is a controlled, prospective, quality improvement study, with a contemporary control. Publication of the study will follow the SQUIRE 2.0 reporting guideline: Revised Standard for Quality Improvement Reporting Standards.[24] Relevant elements of SQUIRE 2.0 have been addressed in this protocol (Supplemental Appendix). This protocol follows the SPIRIT[25] checklist (Standard Protocol Items: Recommendations for Interventional Trials) and is ordered according to the *Trials* Journal Structured Study Protocol Template.[26]

Methods : Participants, Intervention, and Outcomes

Study Setting

The study takes place on the 2 largest (of 3) outpatient hemodialysis units at the McGill University Health Centre in Montreal, Quebec, Canada. The intervention unit is the Lachine Hospital dialysis unit, and the control unit is the Montreal General Hospital dialysis unit. This assignment was random.

Eligibility Criteria

Inclusion criteria

Outpatients receiving maintenance hemodialysis on one of the two participating units.

Aged 18 years and over.

One or more PIMs identified.

Exclusion criteria

Patient is currently hospitalized or is planned to undergo a transplant during the time of the MedRec.

New patient initiating maintenance hemodialysis.

Who Will Take Informed Consent?

Not applicable (a waiver of consent was obtained for this quality improvement project; medication reviews are considered best practice in our institution for patients on dialysis).[1]

Additional Consent Provisions for Collection and Use of Participant Data and Biological Specimens

No biological specimens will be collected as part of this trial.

Interventions

Explanation of the choice of comparators

We are comparing the intervention on 2 of 3 outpatient hemodialysis units within the same hospital center. Although there are some differences between the patients on each unit, they are similar. The third unit is smaller and treats more medically complex patients, including those with active cancer and solid organ transplant. We selected our control and intervention units as they resemble typical community dialysis units to increase the external validity of our findings.

Intervention description

This study will build on existing policies aimed at optimizing medication therapy in patients undergoing maintenance hemodialysis. The electronic deprescribing decision support tool, MedSafer, now includes dialysis-specific deprescribing indications. For example, if a dialysis patient is receiving aspirin for primary prevention, MedSafer will generate a dialysis-specific deprescribing opportunity for the clinician stating the following: "The use of aspirin in dialysis patients increases the risk of bleeding. Also, there is little benefit of using aspirin in dialysis patients for primary prevention." Patients who are receiving aspirin for secondary prevention will have this rule suppressed. In this way, deprescribing reports are individualized. The aspirin deprescribing opportunity is an example of a high-risk alert; a flag where the harms outweigh the benefits in most patients. Other categories include intermediate risk (harms and benefits need to be balanced and assessed by the clinician) and medications of little added value (no demonstrated value or evidence of no effect). Where relevant, tapering schedules are provided if the drug must be gradually discontinued and opportunities are linked to patient deprescribing empowerment brochures from the Canadian Medication Appropriateness and Deprescribing Network.[27,28]

The use of MedSafer reports during MedRecs will be tested in the dialysis setting, where nephrologists are regularly in contact with patients. MedRecs are an interdisciplinary clinical activity performed biannually on the hemodialysis units (in the Spring and Fall), and within 1 week following discharge from any hospitalization that occurs. This study will take place in the Fall of 2022.

The usual MedRec process occurs as follows: a dialysis nurse first validates with the patient their list of usual home medications and correlates this with the medication list provided by the pharmacy. Discrepancies between the patient's medication list and the pharmacy's medication list are resolved through discussion with the patient and pharmacy. Afterward, the treating nephrologist and the nurse review the patient's list of medications and perform any necessary adjustments. The process is meant to avoid medication duplication, ensure appropriate dosing in the dialysis context, and avoid omissions. Deprescribing does not routinely take place as part of the MedRec process despite this being an opportune time to re-evaluate the ongoing necessity, harms, and benefits of PIMs. Currently, whether deprescribing occurs is nephrologist dependent.

Next, for the purpose of the study, the study lead (É.B.-C.) will enter the best medication history (described above), medications, and select laboratory values (hemoglobin A1c and serum creatinine) into MedSafer and generate reports for all patients in the study. The intervention unit (Lachine Hospital) will perform one of their usual biannual MedRecs paired with MedSafer deprescribing reports, including dialysis-specific deprescribing opportunities (the intervention).

Reports will be pre-generated and provided to the interdisciplinary team, along with patient deprescribing empowerment brochures.

One of the deprescribing brochures will be a fact sheet on the topic of deprescribing, and others are given for select classes of medications (sedative-hypnotic drugs,[29] gabapentinoids,[30] proton-pump inhibitors [PPIs],[31] and opioids for chronic non-cancer pain[32]). The control hemodialysis unit (Montreal General Hospital) will, concurrently, perform their usual biannual MedRec, in the absence of deprescribing reports or patient empowerment brochures.

MedSafer contains deprescribing opportunities from several existing guidelines for safer prescribing in older adults.[18,19,33] As previously mentioned, the reports will be printed and placed in a study binder at the physician's desk on the intervention unit and organized alphabetically according to the first letter of the last name of each patient. If MedSafer does not emit any recommendations, a report stating "no deprescribing opportunities were identified at this time" will be generated and placed in the binder.

Physicians on the intervention unit will receive a university-affiliated email from the study lead 2 weeks before the first planned start of the study to explain the workflow of the MedSafer MedRec process. They will be provided with a checklist to follow while they are performing MedRecs with the MedSafer reports as a guide. Study contact information is also provided for any support with the project. This guide (Supplemental Appendix) will ensure standardization of the MedRec process on the intervention unit. This initial email will also contain an example of a MedSafer deprescribing report. The treating physicians on the intervention unit will meet the study lead at the intervention site in person the day before the planned start of the study to

review the MedSafer MedRec workflow and introduce them to the MedSafer reports and deprescribing brochures.

The patient deprescribing empowerment brochures (available in French and English) will be made available to the physician in the study binder, paired with the deprescribing reports. At the physician's discretion, these will be provided to the patient to increase the motivation to deprescribe and provide an active learning opportunity for patients regarding their pharmacotherapy. Each patient on the intervention unit will receive a deprescribing fact sheet available in a third-grade-level language (Supplemental Appendix).

Ultimately, the decision of whether to deprescribe is left to the clinical reasoning of the treating team, and shared decision making with the patient will be encouraged, as this is a pragmatic intervention to study the real-world efficacy of making the deprescribing reports and brochures available in hemodialysis units.

Criteria for discontinuing or modifying allocated interventions

There are no planned interim analyses, as this is a quality improvement intervention that is considered best practice. Medication reconciliation for patients receiving maintenance hemodialysis occurs as part of usual care.

Strategies to improve adherence to interventions

Efforts will be made in this study to facilitate the ease of access to MedSafer reports and to iteratively improve the MedRec workflow through weekly "plan, do, study, act" cycles. To begin with, an introductory email will be sent to the nephrologists attending on the intervention unit.

This email will contain an overview of the study, how it integrates with the existing workflow, and the expectations for the treating nephrologist (to review the MedSafer report at the time of performing a MedRec, perform any relevant deprescribing, provide the deprescribing brochures to the patient, and make a note in the electronic when the MedRec is complete). The study lead will generate sample MedSafer reports for the clinical team, so they can familiarize themselves with the report format prior to the intervention commencing. A physician nephrologist champion (T.P.) will be available to answer any questions or concerns.

Relevant Concomitant Care Permitted or Prohibited During the Trial

All usual care will be permitted, and no specific care is prohibited during the study.

Provisions for Post-trial Care

Patients in the study will continue to receive usual (usually thrice weekly) care in the hemodialysis unit, post-intervention.

Outcomes

The *primary outcome* will be the efficacy of MedSafer for deprescribing, based on the proportion of patients with 1 or more PIMs deprescribed, compared between the intervention and control units. This will be conditioned on patients with 1 or more PIMs at baseline. Deprescribing will be defined as any PIM that is identified by the MedSafer deprescribing algorithms, that is: stopped or deliberately reduced or tapered.

The key *secondary outcomes* will be the reduction in the mean number of prescribed drugs from baseline following a MedRec compared between the intervention and control units, and

implementation barriers and facilitators collected from qualitative, semi-structured interviews with nephrologists on the intervention unit. The number of gastrointestinal bleeds will be reported in total and by intervention status.

Sample Size

The sample size is fixed to the number of patients in each of the dialysis units (85 patients on the intervention unit and 153 on the control unit). A previous study of MedSafer in hemodialysis estimated ~90% of dialysis patients are prescribed 1 or more PIMs, which is the assumption we will make here as well (N = 214). In our acute care study, we found a baseline rate of PIM deprescribing in the hemodialysis subpopulation of 19.3%. However, in outpatients, deprescribing of sedative hypnotics is often as low as 5%.[27] Therefore, we will estimate a 10% baseline rate of deprescribing. With a 2-sided alpha of 0.05, 80% power, and approximately 1:2 allocation between intervention and control, we can show an increase of at least 15% in the proportion of patients with 1 or more PIMs deprescribed. The statistical code for this calculation is available in the Supplemental Appendix.

Recruitment

A waiver of consent was granted by the McGill University Health Centre Director of Professional Services for this Quality Improvement Intervention. For the purposes of analysis, only the initial closed cohort will be included in the study. New patients who are initiated on maintenance hemodialysis during the study will not be included. Patients who die or are transplanted prior to

a MedRec, or who are admitted to hospital and cannot have a MedRec performed, will be accounted for, described, but excluded from the final analysis.

Assignment of Interventions: Allocation and Blinding

Sequence generation, Concealment mechanism, Implementation of Allocation, are all not applicable to this study.

Who Will Be Blinded?

Clinicians at the control unit will not receive MedSafer reports but will carry out a biannual MedRec as part of usual care. Clinicians rounding on the intervention unit will be made aware of the intervention approximately 2 weeks prior to starting, to allow for familiarization of the MedSafer reports. Four nephrologists will round on the intervention unit during this time, and 3 different nephrologists will round on the control. There is no crossover between physician schedules. Therefore, there is little risk of contamination of the intervention and the control site.

The *Procedure for unblinding* is not applicable to this study.

Data Collection and Management

Plans for Assessment and Collection of Outcomes

Baseline demographic data, the best possible medication history data, the most recent glycated hemoglobin as a measure of diabetes control, and creatinine will be collected for both the control and intervention unit from the electronic medical record (EMR), called NephroCare.

These data will be input in the MedSafer web-based portal, and deprescribing reports will be generated for patients on the intervention unit.

Following a MedRec, medication changes will be captured from NephroCare and input into the MedSafer software for both the intervention and control units, permitting an analysis comparing deprescribing that took place on the 2 units.

At the time of MedRec, nephrologists will review the medication list of the patient (obtained from the EMR), validate the list with the patient, and then deprescribe when deemed appropriate (based on the MedSafer report). Medication changes will be faxed the same day to patient's pharmacy. During this process, if a patient advises the clinical team that they are no longer taking a prescribed drug, this medication will be removed from the patient's medication list in the EMR. If it is discovered that a patient has already discontinued a drug at the time of performing a MedRec, this will not be counted in the primary outcome of deprescribing.

At the end of the intervention, nephrologists who participated in MedRecs will be invited to participate in semi-structured interviews with the study lead to address their perceived facilitators and barriers related to deprescribing on the dialysis unit. Afterward, themes will be developed from the data collection, according to the grounded theory in qualitative research.[34]

Plans to Promote Participant Retention and Complete Follow-up

We do not expect significant loss to follow-up given the intensity that patients on outpatient hemodialysis are monitored and the short timeframe of the intervention.

Data Management

Manual baseline data entry for all patients will occur in the MedSafer web-based portal with data extracted from the NephroCare EMR by a trained study investigator. Any medication changes that occur are input into NephroCare at the time of performing the MedRec. When a MedRec occurs, the date is noted in the unit "task binder" located on site and accessible to all clinicians. MedRecs are considered up to date if they have been completed in the past 6 months and are only redone in the event a patient is hospitalized.

Before and after the MedRecs have been completed, each patient's medication and comorbidity data will be updated in MedSafer, and a pre- and post-intervention medication dataset (coded by study ID) will be extracted and stored on a secure server. Analysis will be conducted on these coded datasets to record medication changes and deprescribing.

Confidentiality

Only É.B.-C. will have access to the nominal MedSafer data, which has the identity data encrypted and password protected at the level of the user account. MedSafer patient reports generated by the system must be nominal such that they can be given to the correct patient. These will be printed within the hospital, hand delivered, and stored in a secured area in the dialysis unit until needed. Following completion of the study, the printed MedSafer reports will be securely destroyed.

Statistical Methods

Statistical methods for primary and secondary outcomes

Baseline demographics will be expressed as numbers and percentages for categorical variables and median (interquartile range [IQR]) for continuous variables. Differences between the intervention and control patients will be compared by χ^2 or rank sum as appropriate.

For the primary outcome, we will use a mixed-effects logistic regression model controlling for the unit of intervention. As we expect some baseline differences in patient complexity between the control and intervention units whereby patients on the control unit tend to be more medically complex, we will adjust for the Charlson comorbidity index,[35] median number of medications, and median number PIMs, as fixed effects. Adjusted risk differences will be estimated from the model parameter differences. A similar analysis will be conducted for the key secondary outcome. Analyses will be conducted in Stata Software Version 17 (StataCorp LP, Corpus Christi, USA).[36]

There are no planned *interim analyses*.

Methods for Additional Analyses

A planned subgroup analysis will be conducted by biologic sex and by age category (<65 vs >65). The analytic approach will be the same as that used for the primary outcome analysis.

Methods in Analysis to Handle Protocol Non-Adherence and Any Statistical Methods to Handle Missing Data

The study will be analyzed according to the intention to treat principle. Patients who are hospitalized, transplanted or who die prior to receiving a MedRec will be excluded from the final analysis. Missing data will not be imputed.

Plans to Give Access to the Full Protocol, Participant-Level Data, and Statistical Code (31c)

The full protocol will be published online, and the anonymous participant-level data required to replicate the final study manuscript will be made available within 3 months of publication.

Oversight and Monitoring

Composition of the data monitoring committee, its role, and reporting structure (5d and 21a)

Not applicable.

Adverse Event Reporting and Harms

MedSafer reports have been extensively tested on older adults with polypharmacy in the acute care setting (including patients receiving maintenance hemodialysis).[16] If a clinician suspects that a report contains an erroneous recommendation or that an adverse event has occurred secondary to the intervention, they will contact the study team to report it.

Frequency and Plans for Auditing Trial Conduct

Not applicable.

Plans for Communicating Important Protocol Amendments to Relevant Parties (eg, Trial Participants, Ethical Committees)

Not applicable.

Dissemination Plans

Study results will be made available through publication in a peer-reviewed indexed journal. Study results will be shared at a leading annual conference on nephrology and/or general internal medicine.

Discussion

This quality improvement study integrates electronic deprescribing decision support with the usual process of MedRec taking place on our dialysis units. To our knowledge, this is the first study to test the implementation of the new dialysis-specific deprescribing algorithms in a real-world setting. Potential implications of this quality improvement study include reducing the number of PIMs prescribed and decreasing pill burden by reducing the mean number of medications prescribed. This is a pragmatic study as it is built into the existing workflow for performing MedRec at our hospital center. As many dialysis units have similar MedRec procedures, we expect our findings would be scalable to other centers.

There are barriers to deprescribing during routine MedRec in hemodialysis. In fact, clinicians can lack sufficient time to complete a medication review and subsequently deprescribe; patient values and previous lived experiences with their medications, their perceived therapeutic effects, and potential adverse events are important factors to consider.[37] Because of their chronic renal disease and complex medication regimens, patients on dialysis can also experience cognitive impairment that may affect the clinician's ability to comprehensively perform medication reconciliation given already limited time constraints.[21] Patients may also lack sufficient resources to learn about the medications they are taking, including their potential harms. The therapeutic relationship between the patient and the clinician can also influence initiation of a deprescribing trial or affect readiness to attempt a drug deprescription.[38,39] This study aims to overcome these barriers through its methodology; we aim to address the lack of time by providing nephrologists with prepared deprescribing reports.

Whenever possible, patients should be involved in the deprescribing process. Patients may be reluctant to have certain drugs deprescribed because they have been taking them for a long time, and/or are wary of withdrawal or rebound side effects, such as acid reflux, inability or difficulty sleeping, or pain. This is a potential challenge that we hope our study methodology addresses by providing patients with deprescribing empowerment brochures for some relevant drug classes. The goal of the deprescribing brochures is to generate cognitive dissonance with an introductory quiz and increase motivation to deprescribe. We also aim to overcome the challenge of limited patient resources by providing patients with deprescribing brochures that use accessible language.

This study has several important limitations that need to be recognized. First, the study cohort is closed, so the sample size may, over the course of the study, decrease due to deaths, hospitalization, or transplant. We do not expect this to majorly affect the overall sample size as the duration of the intervention is short (taking place over 2 months). In this study, we do not currently have the resources to follow patients long term and are investigating the short-term impact of providing deprescribing reports on a single MedRec. The long-term impact on polypharmacy would need to be the subject of a further funded study. This study is also not powered to observe an effect on hard outcomes such as death, adverse drug events or hospitalization, especially in the short term. We will be reporting the number of gastrointestinal bleeds numerically, but we will not be powered to demonstrate a difference between intervention groups.[40] This is a single-center study, and to influence outcomes such as these likely requires more than 6000 patients (based on our previous study of MedSafer in the acute care setting). This study is also not randomized; we aim to minimize (but cannot eliminate),

through statistical adjustment, obvious baseline differences in comorbidities between the control and intervention units. Next, our study is not sufficiently powered to capture differences in rates of represcribing between the control and the intervention group. It should be noted that our study will capture prescribed/deprescribed drugs, and not *dispensed* drugs, or drugs actually taken by the patient. Another caveat is that our dialysis units do not have the support of a pharmacist, and so the MedRec process will be performed by the doctor and nurse on the unit. Finally, our study is taking place at an academic hospital center and so the patients may not resemble those treated in all dialysis centers. That said, the 2 units participating in the study tend to provide dialysis for general nephrology patients, and the intervention unit is attached to our community hospital site.

Ethics Approval and Consent to Participate

The McGill University Health Centre's Research Institute granted a waiver of consent for participants, given this study is a quality-improvement study.

Consent for Publication

Not required.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: E.G.M. and T.C.L. own the MedSafer intellectual property in conjunction with McGill University. E.G.M. and T.C.L. own the company MedSafer

Corp which licenses the MedSafer software for the purposes of eventual commercialization. Access to the software was provided free of charge for this quality improvement study.

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Abbreviations

ESKD: end-stage kidney disease

MedRec: Medication reconciliation

PIM: potentially inappropriate medication

PPI: proton pump inhibitors

EMR: electronic medical record

IQR: interquartile range

ADE: adverse drug event

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Author contributions

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Emilie Trinh (knowledge user): conceptualization, methodology, validation, investigation, writing - original draft, writing - review and editing, visualization, project administration

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Todd C. Lee (clinician-scientist): conceptualization, methodology, software, validation, formal analysis, investigation, resources, data curation management, writing - original draft, writing - review and editing, visualization, supervision, project administration, funding acquisition

Emily Gibson McDonald (senior author): conceptualization, methodology, software, validation, formal analysis, investigation, resources, data curation management, writing - original draft, writing - review and editing, visualization, supervision, project administration, funding acquisition

Availability of data and material

ÉBC, EGM and TCL will have access to the final data set.

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	Pre-Study Start September 2022		Study Dates October to November 2022		Post-study completion December 2022	
	Control	**Intervention**	**Control**	**Intervention**	**Control**	**Intervention**
Demographics	✓	✓			✓	✓
Usual home medications	✓	✓			✓	✓
Hemoglobin A1c	✓	✓			✓	✓
Identify PIMs	✓	✓			✓	✓
Usual Care			✓	✓		
Deprescribing brochures				✓		

MedSafer Report				✓		

Figure 1: Participant Timeline During the Study

Section 2.2: Medication Deprescribing in Patients on Hemodialysis: A Prospective, Controlled, Quality Improvement Study

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Abstract

Rationale

Patients on dialysis are commonly prescribed multiple medications (polypharmacy), including some potentially inappropriate medications (PIMs). PIMs are associated with an increased risk of medication harm (e.g., falls, fractures, hospitalization). Deprescribing is a solution that proposes to stop, reduce, or switch medications to a safer alternative. Although deprescribing pairs well with routine medications reviews, it can be complex and time consuming. Whether clinical decision support improves the process and increases deprescribing for patients on dialysis is unknown.

Objective

To test the efficacy of the clinical decision support software MedSafer at increasing deprescribing for patients on dialysis.

Study Design

Prospective controlled quality improvement study with a contemporaneous control.

Setting and Participants

Patients prescribed ≥5 medications on two outpatient dialysis units in Montréal, Canada.

Quality Improvement Activities

Patient health data from the electronic medical record was input into the MedSafer web-based portal to generate reports listing candidate PIMs for deprescribing. At the time of a planned biannual medication review (usual care), treating nephrologists on the intervention unit additionally received deprescribing reports and patients received EMPOWER brochures

containing safety information on PIMs they were prescribed. On the control unit, patients received usual care alone.

Analytical Approach

The proportion of patients with ≥1 PIMs deprescribed was compared between the intervention and control units following a planned medication review to determine the impact of using MedSafer. The absolute risk difference (aRD) with 95% confidence interval (CI) and number needed to treat (NNT) were calculated.

Results

195 patients were included (127 control unit; 68 intervention unit); the mean age was 64.8 (SD=15.9) and 36.9% were female. The proportion of patients with ≥1 PIMs deprescribed on the control unit was 3.1% (4/127) vs. 39.7% (27/68) on the intervention unit (aRD=36.6%, 95% CI=24.5-48.6; p<0.0001; NNT=3).

Limitations

This was a single center non-randomized study at risk of type 1 error. Deprescribing durability was not assessed, and the study was not powered to reduce ADEs.

Conclusions

Deprescribing clinical decision support and patient EMPOWER brochures provided during medication reviews could be an effective and scalable intervention to address PIMs in the dialysis population. A confirmatory randomized controlled trial is needed.

Registration

NCT05585268.

Key words

Polypharmacy; Chronic Renal Insufficiency, Deprescribing; Electronic Decision Support;

Hemodialysis

Introduction

The burden of polypharmacy (taking multiple medications) in patients who receive dialysis is substantial: more than 90% of patients take 5 or more medications.[1] The majority are important to modify cardiovascular risk and to assist in maintenance of calcium and phosphate balance. However, in addition to indicated and beneficial medications, many are also potentially inappropriate.[2,3] Potentially inappropriate medications (PIMs) may have limited benefit, can increase a patient's pill burden,[4] and are associated with an increased risk of adverse drug events (ADEs).[5,6] An ADE is an umbrella term for harm arising during medication therapy[7]; examples include falls,[8] fractures,[9] and cognitive impairment.[10] An ADE can occur from an individual PIM or through drug-drug or drug-condition interactions.[11] It is increasingly recognized that polypharmacy and ADEs are common, costly, and harmful to patients and the health care system, contributing to preventable emergency room visits, hospital admissions, premature loss of autonomy, and death.[9,12] Given that 93% of patients treated with dialysis are estimated to be receiving one or more PIMs,[1] pragmatic, scalable deprescribing interventions to reduce medication burden in this patient population are needed.[13,14,15]

Deprescribing is defined as the "process of withdrawal of an inappropriate medication, supervised by a health care professional, with the goal of managing polypharmacy and improving outcomes."[16] It has been shown to reduce the number of prescribed drugs and, in some studies, reduce the risk of falls, hospitalization, and mortality.[17] MedSafer is an electronic decision support tool for deprescribing that has been shown to increase deprescribing for hospitalized older adults and for people residing in long-term care.[1,11,18,19] In a cluster randomized controlled trial (RCT) of 5,698 hospitalized older adults, when compared to usual

care, paired receipt of deprescribing reports and relevant patient information EMPOWER brochures increased the proportion of patients with one or more PIMs deprescribed by 22.2% (95% confidence interval [CI], 16.9%-27.4%).[18] MedSafer is a Canadian-built software that cross references a person's usual medication list and their medical diagnoses with a curated ruleset of evidence-informed deprescribing guidelines (Box 1).[18,20,21,22] Reports generated through the software identify candidate PIMs for deprescribing, or so-called deprescribing opportunities, ordered by level of potential harm, along with tapering regimens for drugs considered at risk for withdrawal reactions.[20,21,22,23] This RCT included 140 patients who were receiving maintenance hemodialysis (~2.5% of the overall study population); in the dialysis subgroup, the proportion of patients with one or more PIMs deprescribed increased by 9.4% (95% CI, 1.3%-17.6%)[1] with the intervention, which was lower than the rate of 22.2% observed in the general study population.[18] We hypothesized that the lower rate of deprescribing was related to the complexity of medical admissions for patients receiving dialysis and, perhaps, due to a lack of dialysis-specific deprescribing rules.

After the RCT was published, Lefebvre et al[13] proposed additional dialysis-specific deprescribing algorithms as part of a quality improvement initiative. We set out to integrate these algorithms into the MedSafer software and to study the efficacy of clinical decision support for deprescribing in the outpatient dialysis unit setting.

Methods

Design and Setting

This prospective, controlled, quality improvement study is reported using the SQUIRE guidelines.[24] It was prospectively registered in ClinicalTrials.gov (NCT05585268).[25] The study

took place between September and December 2022 in the 2 largest (of 3) outpatient hemodialysis units at the McGill University Health Centre in Montreal, Quebec, Canada. The detailed protocol for this study was published previously.[26] The intervention unit was the Lachine Hospital dialysis unit, and the control unit was the Montreal General Hospital dialysis unit. The physician-champion randomly assigned these units. Because this was largely an educational quality improvement intervention directed at the treating nephrologists, randomizing at the level of the individual patient would not have been feasible because this would have contaminated the intervention.[27] The intervention unit dialyzes approximately 80-90 patients per week and the control unit approximately 150-155. Patients visit the units thrice weekly on average. Both units use the electronic medical record Renal Insight (Constellation Kidney Group, previously known as NephroCare)[28] to store clinical data. Renal Insight contains clinical data such as medical diagnoses, home medications, and laboratory values and is bidirectionally integrated with the hospital's main electronic medical record (OACIS, Telus Health).[29] Our a priori sample size calculation suggested we would have 80% power to demonstrate at least a 15% increase in the proportion of patients with 1 or more PIMs deprescribed.[26]

We paired the intervention as part of usual workflow known as "medication reconciliation."[30] This is an interdisciplinary clinical activity performed biannually in our hemodialysis units in the Spring and Fall and within 1 week following hospital discharge (Fig S1). The usual reconciliation process occurs as follows: a dialysis nurse reviews the list of usual home medications and compares this with the medication list provided by the community pharmacy, noting any discrepancies. Afterward, the treating nephrologist and nurse jointly review these data and

perform necessary adjustments. This process aims to confirm appropriate dosing and avoid duplications, omissions, or errors. There is no clinical pharmacist in either unit. Deprescribing may occur, but it is not protocolized and depends on the nephrologist's clinical judgment.

The Intervention

MedSafer stratifies deprescribing opportunities (eg, PIMs that have the potential to be deprescribed) into categories of high risk, intermediate risk, or medications of little added value, informed by indications based on patient comorbid conditions and past medical history.[18] High risk equates to an elevated risk of developing an ADE, intermediate risk medications have harms that must be weighed against the benefits, and drugs of little added value superfluously increase the pill burden of a patient or have evidence demonstrating no effect.[19] Examples of a typical deprescribing report can be found in the Supplementary Material. Patients also received deprescribing EMPOWER brochures for select classes of PIMs (eg, opioids, gabapentinoids, sedative hypnotics).[31] These brochures contain nonpharmacologic alternatives and information about the potential harms of the medication class (see Item S2 for an example). This multimodal approach (providing deprescribing reports to clinicians and brochures to patients) was successfully implemented in a prior large RCT with MedSafer.[18]

Planning the Intervention

Both units had a scheduled medication reconciliation planned for Fall 2022 (September-December 2022), during which time we implemented and studied this quality improvement intervention. The physicians taking part in the study attended solely in one of the 2 units and did not cross over between sites. The control unit performed medication reconciliation as usual

care, without the provision of deprescribing reports to nephrologists or brochures to patients. In the intervention unit, an introductory email was sent to the attending nephrologists containing the overview of the study and how the MedSafer reports and deprescribing brochures would integrate with the existing medication reconciliation workflow of 10-15 medication reconciliations per week. Nephrologists were also provided with a sample MedSafer report to familiarize themselves with the output. A nephrologist champion (TP), for our study purposes defined as a physician facilitating the change necessary to implement a new electronic health information technology,[32] was available to answer inquiries.

Reports were generated in advance before the patient's scheduled medication reconciliation and were alphabetically stored in a binder on the intervention unit to be used as part of the exercise. The nephrologist would notify the study team of upcoming medication reconciliations and they would be provided the patient's documentation package from the binder to review. Five sequential Plan-Do-Study-Act (PDSA) cycles were subsequently used as an implementation strategy to achieve the aims of the project in the intervention unit (Fig S2).[33,34] Each PDSA cycle was preceded by a system analysis that identified specific barriers inhibiting the success of the workflow.[33]

Outcomes

At the end of the intervention period for both units (December 2022), the medication reconciliation notes were reviewed to identify any deprescribing of PIMs (medications flagged by the MedSafer deprescribing report).

The primary outcome was a process measure: the proportion of patients with one or more PIMs deprescribed. Subgroup analyses by age category (<65 vs >65) were prespecified. Deprescribing was defined as any PIM that was either stopped, deliberately reduced, or tapered.[18,19]

Key secondary outcomes included the reduction in the mean number of prescribed drugs and PIMs from baseline. Although this study was not sufficiently powered to have an effect on ADEs (including adverse drug withdrawal events), we nonetheless collected 2 counterbalancing indicators of harm for descriptive purposes: gastrointestinal bleeds (GIBs) within 3 months following the intervention and death following the intervention (see Item S1). GIBs were selected as a counterbalancing measure (an approach used in quality improvement studies)[35] because a prior, uncontrolled, observational study of deprescribing proton pump inhibitors (PPIs) in patients receiving dialysis found that 2 of 29 patients (7%) had a GIB within 2-4 weeks of having the PPI deprescribed.[36] Implementation barriers and facilitators were collected from semistructured interviews with nephrologists (reported separately).

Recruitment of Patients

For the purposes of analysis, only the initial closed cohort was included in the study. This cohort was comprised patients receiving maintenance hemodialysis (>3 months). New patients initiated on maintenance hemodialysis during the study, transplanted patients, and those hospitalized, transferred to another dialysis unit, or who died before their regularly scheduled medication reconciliation were excluded from the final analysis.

Ethics

The McGill University Health Centre Director of Professional Services approved the plan for the quality improvement activity, granted access to medical charts, and provided a waiver of consent for the intervention.

Data Collection

From Renal Insight, the study lead extracted, for all patients in the study, medical conditions (diagnoses), usual home medications (from the best possible medication history informed by the community pharmacy's list and the electronic medical record's list of medications), and recent glycated hemoglobin. This data were input into the MedSafer web-based portal, and opportunities for deprescribing were assessed. Reports were only provided to nephrologists for patients in the intervention unit.

Data Analysis

Descriptive statistics were used to compare baseline health characteristics between patients. $\chi 2$ and Fisher exact tests were used to compare categorical differences. Wilcoxon rank-sum tests and t tests were used to compare medians and means between groups. For the primary outcome, we used a 2-sample test of proportions with 95% CIs. For the number of drugs before and after medication reconciliation, we used logistic regression, adjusting for the presence of the intervention and the number of baseline drugs. Covariates were selected a priori based on known potential confounders and pragmatically, based on the availability of data in the electronic medical record. All statistical comparisons used a 2-sided α of 0.05 as significant with no adjustment for multiplicity of testing.

Results

PDSA Iterations

In PDSA cycle 1, to improve efficiency, the study lead prepared and ordered packages for the intervention alphabetically (Fig S2). In PDSA cycle 2, to reduce the burden on the care team, we made it explicit that only patients with select PIMs deprescribed needed to receive EMPOWER brochures. During PDSA cycle 3, to facilitate data extraction, the keyword “MedSafer” was entered into their progress note to document the intervention had taken place. During PDSA cycle 4, to improve efficiency, the study lead emailed the attending nephrologist the list of patients who were due for medication reconciliation 1 business day before the start of their rotation. During PDSA cycle 5, to improve efficiency, the list of PIMs for each patient was provided to the nephrologist before rounding.

Population

Initially, 240 patients were assessed for eligibility (Fig 1), and 26 (10.8%) were excluded before beginning the study: 18 from the control unit and 8 from the intervention unit. Twelve died before the beginning of the intervention, 8 were transplanted before the start of the study, 3 were transferred to another facility, 2 changed mode of dialysis, and 1 patient had no PIMs identified. During the study, an additional 10 patients were excluded in the control unit and 9 in the intervention unit; these patients were enrolled in the study but did not receive any medication reconciliation because of these events (Fig 1).

Ultimately, 195 patients were included in the final analysis (127 in the control and 68 in the intervention unit). The mean age was 64.8 ± 15.9 (SD) and 36.9% were women (Table 1). The 3 most prevalent comorbid conditions were hypertension (n = 173, 88.7%), dyslipidemia (n = 124, 63.6%), and diabetes (n = 114, 58.5%). Intervention and control unit patients were similar with respect to common medical conditions, except for diabetic neuropathy, orthostatic hypotension, and gastroesophageal reflux disorder, which were more prevalent in the intervention unit (Table 1). Patients were prescribed a mean of 15.3 (5.3) medications in the control unit and 14.6 (4.7) medications in the intervention unit (P = 0.33) and a median of 4 PIMs (interquartile range, 3-6) in both the control and intervention units (P = 0.5).

Primary Outcome

The proportion of patients with one or more PIMs deprescribed in the control unit was 3.1% (4/127) compared with 39.7% (27/68) in the intervention unit for an absolute increase of 36.6% (95% CI, 24.5%-48.6%; P < 0.0001; Fig 2). The number needed to treat for deprescribing was 3. The subgroup analysis stratified by age showed efficacy in both patients above and below 65 years of age (Fig S3). Of the 45 PIMs deprescribed in both units, 5 (11.1%) were from patients in the control unit and 40 (88.9%) from patients in the intervention unit. From both units, 11 PIMs (24.4%) were high-risk (eg, a sedative hypnotic), 22 (48.8%) were intermediate-risk (eg, long-term use of a non–evidence-based PPI), and 12 (26.6%) were low-risk (eg, docusate).

Secondary Outcomes

Following medication reconciliation, the mean ± SD number of medications prescribed was 15.3 ± 5.3 in the control unit and 14.0 ± 4.6 in the intervention unit. The linear regression model (Table 2) showed that, after adjusting for the intervention status of the patients and their baseline number of medications, the difference in the mean number of medications prescribed after the intervention decreased by −0.54 medications per patient (95% CI, −0.69 to −0.39; P < 0.0001). In the intervention unit, 11 of 38 (29%) of the deprescribing opportunities related to the newly integrated dialysis-specific rules.

Counterbalancing outcomes

Following medication reconciliation, 2 patients died in the control unit and 1 patient died in the intervention unit. None of the deaths were related to deprescribing. Five patients in the control unit, and 2 in the intervention unit had a GIB (Table 3). None of the GIBs were related to PPI deprescribing. In the control unit, 4 of 5 patients had a GIB despite being on a PPI. In the intervention unit, at the time of the GIB, 1 patient was actively prescribed a PPI, and the other was never prescribed a PPI.

Discussion

This is one of the first trials to increase PIM deprescribing among patients on hemodialysis, which we accomplished with a number needed to treat of 3, compared with usual care. Patients on hemodialysis are prescribed multiple medications; in our study, patients took an average of 15 medications. Identifying PIMs in a list of over a dozen medications can be laborious and time-consuming for clinicians. We aimed to make the process more accessible for nephrologists by leveraging an existing workflow, medication reconciliation, as the opportunity for medication "rationalization," using electronic decision support. We noted higher rates of deprescribing in

this study compared with our RCT (number needed to treat of 4-5), possibly because of the addition of hemodialysis-specific deprescribing indications. Other reasons can be attributed to the single-center nature of this study versus the multicentered trial, to differences between the acute care setting and the dialysis unit, or to differences between nephrologists vs other subspecialists attending the inpatient units of the RCT.

The use of the MedSafer technology to generate a deprescribing report addressed 2 key barriers to deprescribing: patient medical complexity and the time-consuming nature of the process.[1,2,11,18,37,38,39,40,41,42,43] These barriers are addressed by leveraging technology, in this case the backend of the software, which contains hundreds of algorithms with opportunities for deprescribing. It further provides the clinical and scientific rationale for deprescribing, along with tapering instructions (when needed), at the point of care. The aforementioned barriers are particularly true for patients with end-stage kidney disease who have multiple coexisting medical conditions and are often treated with 12-15 medications.[1,18] To our knowledge, this is the first controlled study to test the newly developed dialysis-specific deprescribing guidelines by Lefebvre et al.[13] Our results align with 2 small noncomparative studies that previously evaluated the efficacy of providing dialysis-specific deprescribing recommendations15,44; one study of 5 dialysis-specific medication class recommendations deprescribed 78% of PIMs identified.[15] Another study implemented 8 dialysis-specific deprescribing algorithms and managed to deprescribe 35 of 59 (59.3%) PIMs, and 27 of 35 (77%) of these remained deprescribed at 16 weeks following the intervention.[44]

Our studies differed in our use of a contemporaneous control unit to observe differences with usual care. Furthermore, our reports contained both dialysis-specific and general deprescribing opportunities from multiple sources.[13,20,21,22] We also provided EMPOWER brochures to augment the intervention and engage patients. Of note, the opportunities we flagged often contained deprescribing opportunities typically geared toward older adults. However, in a prespecified subgroup analysis, the intervention was equally effective in both younger and older adults. Other strengths included leveraging Renal Insight, integrating with the existing medication reconciliation workflow, and use of a previously tested software to facilitate deprescribing decision support. We also deployed PDSA cycles to iteratively improve the process.

There are several limitations to this study worth discussing. First, we implemented 2 interventions simultaneously (eg, decision support and patient brochures); consequently, it was not possible to quantify the individual effect of each intervention. Both interventions have been shown to independently increase deprescribing, and we used the same approach in our multicentered RCT.[18,31] Second, this study only assessed early efficacy and not durability; reassuringly, in our RCT, 90% of medications remained deprescribed at 30 days.[18] In the 2 prior studies that deployed dialysis-specific deprescribing algorithms, durability was 85% at 6 months[15] and 77% at 16 months.[44] Third, although the assignment of units was random, this was a single-center study and was not an RCT. As such, there were slight imbalances in patient comorbid conditions between units. However, the intervention unit had a higher prevalence of some conditions that might have made deprescribing more challenging (eg, diabetic nephropathy, gastroesophageal reflux disorder, and orthostatic hypotension). If anything, we

think these imbalances would have biased the intervention toward the null. Fourth, knowledge of an ongoing intervention may have led to the Hawthorne effect.[45] Nonetheless, nonresearch deprescribing implementation efforts also benefit from clinical champions, as do audit and feedback interventions. Finally, this study was not powered to measure an effect on ADEs, emergency department visits, or hospitalization. We sought to first study whether the process was effective for deprescribing, before running a larger trial. Although deprescribing PIMs is a process measure, it still reduces pill burden for patients and decreases direct drug cost. Whether it also translates to improved outcomes and increased adherence in this population still needs to be demonstrated through a large RCT.

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Conclusion

Deprescribing through clinical decision support in the hemodialysis unit can be effective when paired with the usual medication reconciliation workflow. Future studies will need to evaluate the generalizability and scalability in multiple centers and other countries. Ideally, these studies will have large enough sample sizes to study the effect on ADEs and longer follow-up to evaluate the durability of the intervention.

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Deprescribing guidance

MedSafer identifies deprescribing opportunities by electronically cross-referencing a person's usual medication list and medical comorbidities, with a curated ruleset containing evidence-based deprescribing guidelines (based on criteria from the American Geriatrics Society, STOPP, and Choosing Wisely). MedSafer stratifies deprescribing opportunities into high risk, intermediate risk, or little added value categories. High risk implies there is an elevated risk of developing adverse drug events (ADEs), intermediate risk implies that the harms must be weighed against the benefits of the drug, and drugs of little added value simply increase the pill burden of a patient or have evidence demonstrating no effect.

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Table 1: Baseline Patient Characteristics

No (%)			
Characteristic	**Control (n = 127)**	**Intervention (n = 68)**	**p-value**
Demographic information			
Age, mean (sd)	64.8 (16.9)	64.7 (13.8)	0.95
Female sex	50 (39.4)	22 (32.4)	0.42
Medications			
Number of medications, mean (sd)	15.3 (5.3)	14.6 (4.7)	0.33
Number of PIMs identified, median (IQR)	4 (3-6)	4 (3-6)	0.5
Comorbidity			
Diabetes	79 (62.2)	35 (51.5)	0.15
Diabetic neuropathy	64/79 (81.0)	35/35 (100)	**0.006**
Hypertension	112 (88.2)	61 (89.7)	0.75
Dyslipidemia	82 (64.6)	42 (61.8)	0.7
Ischemic heart disease	36 (28.3)	17 (25)	0.62

Heart failure	35 (27.6)	22 (32.4)	0.48
Atrial fibrillation	16 (12.6)	8 (11.8)	0.87
Valvular heart disease	11 (8.7)	8 (11.8)	0.49
History of ischemic stroke	11 (8.7)	9 (13.2)	0.32
History of venous thromboembolism	10 (7.9)	7 (10.3)	0.57
COPD	12 (9.4)	2 (2.9)	0.09
Asthma	9 (7.1)	5 (7.4)	0.95
Orthostatic hypotension	3 (2.4)	15 (22.1)	**< 0.001**
Gastroesophageal reflux disease	5 (3.9)	13 (19.1)	**< 0.001**
History of gastrointestinal bleed	11 (8.7)	7 (10.3)	0.71
Constipation	33 (26)	20 (29.4)	0.61
Solid organ cancer	23 (18.1)	20 (29.4)	0.07
Psychiatric disorder[a]	25 (19.7)	11 (16.2)	0.55
Parkinson's disease	3 (2.4)	0 (0)	0.20

[a] substance use disorder, major depressive disorder, bipolar affective disorder, schizophrenia.

Abbreviations: sd, standard deviation; IQR, interquartile range; COPD, chronic obstructive pulmonary disease.

Table 2: Outcomes

Characteristic	Control (N=127)	Intervention (N=68)	p-value
Number of patients with ≥1 PIMs deprescribed (n, %)	4 (3.1)	27 (39.7)	< 0.0001
Absolute risk difference (RD) of deprescribing	RD 36.6 (95% CI 24.5-48.6)		
Number Needed to Treat (NNT)	3		
Mean estimated change in total drugs (95% CI)	REF	-0.54 (95%CI -0.69 to -0.39)	<0.0001

Abbreviations: PIM=potentially inappropriate medication, CI=confidence interval, REF=referent comparison group

Table 3: Counterbalancing Measure of Harm: Gastrointestinal Bleeds

Bleeding episode[a]	Allocation	Did GIB lead to death?	Proton pump inhibitor status at time of GIB	Anticoagulants prescribed at time of GIB
Patient 1	Control	Yes	Active prescription	-
Patient 2	Control	No	-	-
Patient 3	Control	No	Active prescription	Aspirin 80 mg daily
Patient 4	Control	No	-	-
Patient 5	Control	No	-	-
Patient 6	Intervention	No	Active prescription	-
Patient 7	Intervention	No	Active prescription	Aspirin 80 mg daily

[a]During the study and for 3 months post intervention

Abbreviations: GIB=gastrointestinal bleed

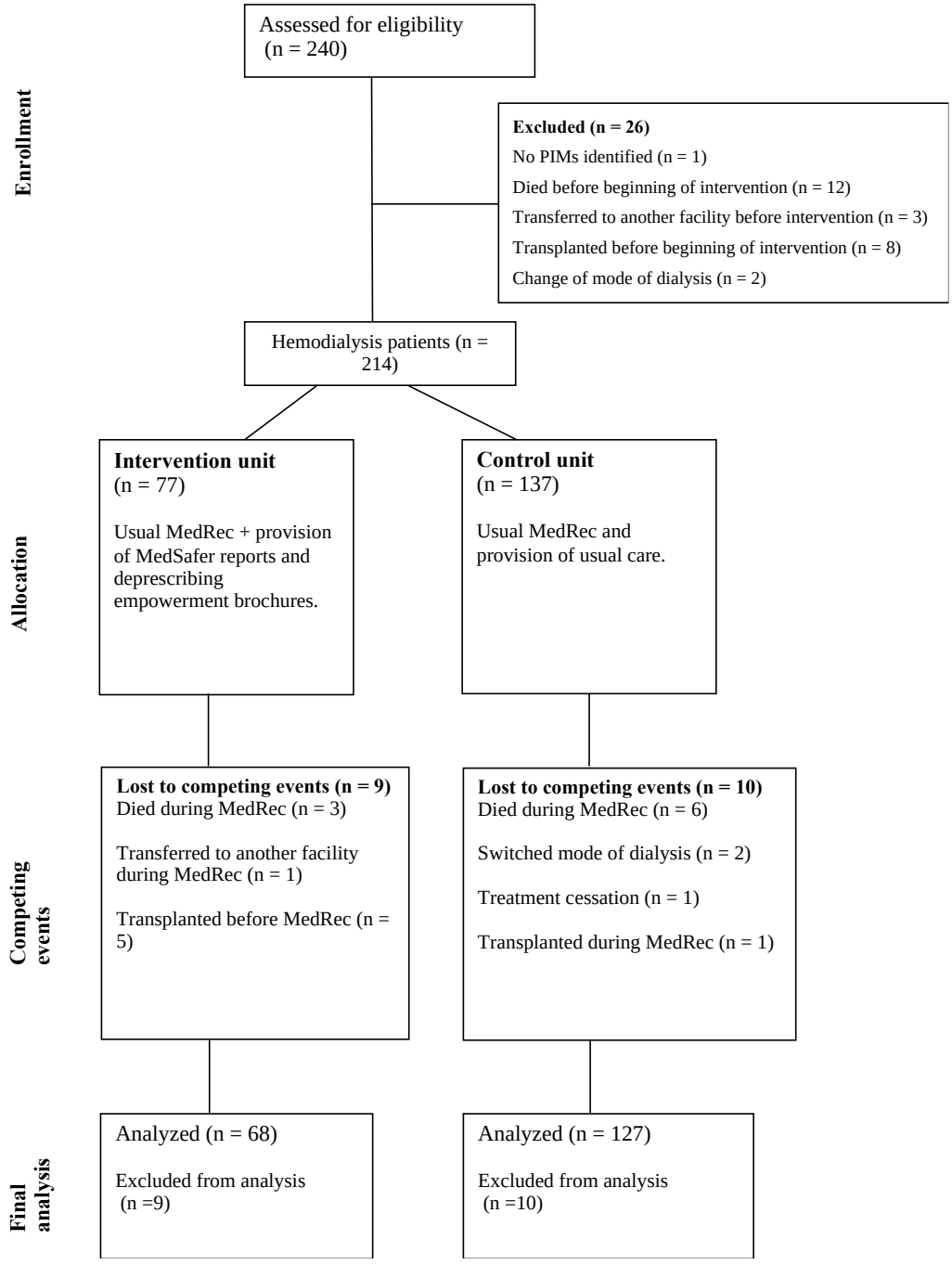

Figure 1: Consort Flow Diagram of Hemodialysis Patients Assessed for Study Inclusion

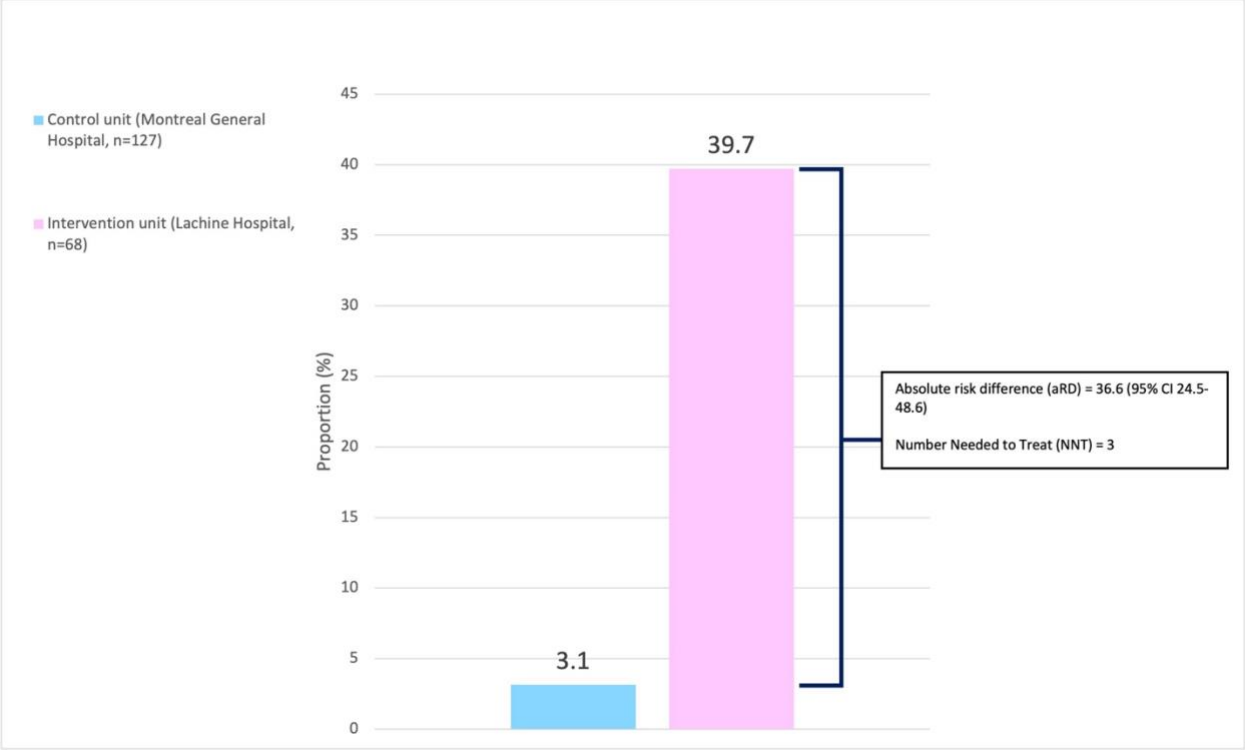

Figure 2: Proportion of Patients With 1 or More PIMs Deprescribed by Intervention Status

Bridging Text 2: From Outpatient Hemodialysis to Older People with HIV

During the data extraction phase of the outpatient hemodialysis study, I found that several patients on dialysis also had HIV. I also recognized that the benefit of deprescribing might be maximized in this special patient population, as a high proportion of PWH have both polypharmacy and medication overload.

After I finished my study on deprescribing in hemodialysis, I conducted a rapid review of the literature on polypharmacy among PWH and I discovered a Lancet Healthy Longevity and Lancet HIV journal collaboration series on HIV and aging.[164] In this series, they described how HIV is no longer considered a life-limiting illness, largely due to the improvements in antiretroviral therapy (ART).[140] People with HIV, if they have access to adequate treatment, now have a similar life expectancy to people that are seronegative.[164] Since the HIV epidemic in the 1980s, PWH are now aging with the virus; in the Lancet series, authors describe how HIV accelerates biological aging processes[142]. As such, PWH are considered older adults as of age 50 because they are biologically similar to seronegative people aged 65 and older with similar severe comorbidities.[140] However, few studies exist on the prevalence of polypharmacy and PIM prescriptions; most only evaluate PIM prescriptions as of age 65, which does not represent the full spectrum of older adulthood among older PWH, and others only use one tool to screen for PIMs. Furthermore, none distinguished between polypharmacy and medication overload. I thus decided to conduct a retrospective study addressing these gaps: I aimed to study and distinguish medication overload from polypharmacy, evaluate these syndromes among older PWH aged 50 and older, and I made use of MedSafer to screen for medication overload more

exhaustively. I drafted the Research Ethics Board (REB) protocol, amended it as per the REB's guidelines, and I obtained approval to conduct this retrospective study. I worked with the EMR and Réseau Informatique du SIDA du Québec (RISQ) administrator at the MUHC, Costa Pexos, to extract the list of older PWH that had at least one visit at the Chronic Viral Illness Service of the MUHC. I randomly sampled 10% of older PWH from this list to include in the final analysis. Below is the study manuscript of my final PhD project, the retrospective study of polypharmacy and medication overload among older PWH, which is currently under peer review at the BMC Infectious Diseases journal at the time of writing.

Chapter 3: Prevalence of Medication Overload Among Older Adults Living with HIV: A MedSafer Study

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Abstract

Background

Older people with HIV (PWH) are at risk of polypharmacy (taking multiple medications). Most medications may be necessary and indicated to manage HIV (e.g., antiretroviral therapy [ART]) and HIV-associated comorbidities. However, some are potentially inappropriate medications (PIMs), defined as causing greater harm than benefit, which leads to medication overload. The objective of this study was to characterize polypharmacy (taking multiple medications) and medication overload (prescription of ≥1 PIMs) among older PWH.

Methods

This retrospective study included older PWH (aged ≥50 years old) attending the tertiary care HIV clinic at the McGill University Health Centre (Montreal, Canada), from June 2022–June 2023. Patient characteristics, medications, and select laboratory values (e.g., CD4 count, hemoglobin A1C) were entered into the MedSafer software identifying PIMs and classifying them according to risk of adverse drug event. We measured the prevalence of polypharmacy (≥5 medications prescribed, both including and excluding ART) and medication overload (≥1 PIMs). Multivariable logistic regression identified factors associated with medication overload.

Results

The study included 100 patients, with a median age of 59 years (IQR = 54-63; range 50-82); 42% female. Polypharmacy affected 89% of patients when including antiretroviral therapy (ART) and 60% when excluding ART. Medication overload was present in 58% of patients, and 37.4% of

identified PIMs were classified as high-risk. Polypharmacy was the sole predictor of medication overload.

Conclusion

Older PWH are at significant risk of medication overload and receiving higher risk PIMs. Deprescribing PIMs in this population could improve medication appropriateness while reducing the risk of ADEs.

Introduction

Adult persons with HIV (PWH) appear to age prematurely due to the interaction between aging-related, comorbidity-related, and antiretroviral drug-related factors.[1] In fact, PWH aged 50 and older are considered physiologically similar to seronegative patients aged 65 and older with a similar prevalence of chronic conditions.[1-4] A Dutch study predicted that by 2030, 84% of older PWH will have at least one additional comorbidity and 28% will have at least three, compared to 19% of the seronegative population.[5]

Given both HIV and medical comorbidities both require pharmacologic treatment, PWH are more likely to experience polypharmacy[6] which is frequently defined as taking 5 or more medications.[7] A recent Canadian study found that typically older PWH are prescribed an average of 6 to 7 non-ART medications.[8] The prevalence of polypharmacy in PWH across all ages varies between 15-94%,[6] and can depend on whether antiretroviral therapy (ART) is included in the medication count.[6] Many medications taken by PWH are in fact indicated and expected to produce net clinical benefit; however, as the medication count rises, there is an increased challenge with adherence, a greater risk of known and unknown interactions, and the possibility that some medications will be inappropriate. Potentially inappropriate medications (PIMs) are medications that have limited benefit, superfluously increase a patient's pill burden, and/or may be associated with an increased risk of adverse drug events (ADEs).[9] Adverse drug events contribute to harms such as falls, fractures, cognitive impairment, functional decline, and premature death.[10] When a patient is prescribed one or more PIMs, they are said to have "medication overload," a term proposed to help differentiate from polypharmacy, which, in contrast, is based on medication count alone, and doesn't factor in appropriateness.[11]

Determining the prevalence of medication overload, defined as the prescription of ≥1 PIMs, can be achieved by cross referencing medications and medical conditions with evidence-based lists of drugs to avoid in older adults.[12-14] However, individual lists are not exhaustive, and the process can be time-consuming, particularly in cases of mega polypharmacy (15-20 or more medications).[9] While previous studies have quantified the prevalence of polypharmacy and medication overload among older PWH, they have several significant limitations that we aimed to address in this article. Notably, PWH in previous studies were ≥65 years old and not 50 years old as per guidelines to cutoff older adulthood in this population; only one or two PIM identification tools were used, leading to an incomplete assessment of any potential PIMs, and several studies lacked the stratification of polypharmacy based on inclusion and exclusion of ART.

We therefore set out to use MedSafer,[15] a Canadian electronic deprescribing software that cross-references a patient's medication list and medical diagnoses to identify PIMs and provide an individualized list of deprescribing opportunities, triaged according to the potential for harm. The levels of harm are stratified as high risk, meaning where the harms almost always outweigh the benefits of the medication (such as sleeping pills and sulfonylureas); intermediate risk, where the risks and benefits need to be weighed (such as proton pump inhibitors, antidiabetics with a most recent glycated hemoglobin lower than 7.5% (58 mmol/mol equivalent), or antidepressants);[16] low risk, where the medication has no added benefit and superfluously adds to the patient's pill burden (such as docusate). MedSafer only identifies potentially inappropriate medications; on a case-by-case basis, the clinician still needs to evaluate if the harms of a medication outweigh its benefits. In some cases, for example, it may be entirely

appropriate to maintain tighter diabetes control; however, it would not be appropriate to allow hypoglycemic episodes to occur. Medications prescribed without clinical indication (e.g., dual oral anticoagulant therapy with a stent placed beyond 6 months prior), and medications that were inappropriately dosed (e.g., antipsychotic prescribed at a dose to function as a sleeping pill, or first-generation antihistamines prescribed at high doses leading to sedation) were also flagged as PIMs. MedSafer was initially designed for older adults, as it was first developed using criteria from the American Geriatrics Society,[12] Screening Tool Of Older People's Prescriptions (STOPP),[13] and Choosing Wisely[14] to identify PIMs. Since then, it has been updated to include deprescribing indications for patients on hemodialysis.[17] While the majority of rules are for older adults, older adulthood for PWH begins at a younger biological age; thus, we felt the majority of the rules apply to this population. There were no target values set for cholesterol profiles based on a recent randomized controlled trial where statins were recommended to all PWH aged 40 and older, given their beneficial effects on inflammation.[18]

In this study, we aimed to describe the prevalence of medication overload, polypharmacy (both including and excluding ART), and describe the types of PIMs encountered among older PWH, to better understand the population's medication related risks and to inform future deprescribing interventions. Future work based on this prevalence study will be to add HIV-specific recommendations to MedSafer, as was done for dialysis patients.

Methods

This retrospective study followed STROBE[19] reporting guidelines. We defined older PWH as those 50 years and older. The study population was randomly sampled from patients with HIV attending the McGill University Health Centre's tertiary care Chronic Viral Illness Service

(Montréal, Canada) between June 2022 and June 2023. We obtained data from both the electronic medical record (EMR; Oacis) and the Réseau Informatique du SIDA du Québec (RISQ), a database containing demographic and clinical data for HIV-related research across HIV clinics in Québec, Canada.

Patients were included if they: (1) had at least one outpatient clinic visit between June 15th, 2022, and June 15th, 2023; (2) were aged 50 years and older; (3) had a diagnosis of HIV (regardless of viral load); (4) had a complete "best possible medication history"[20] completed by a pharmacist and documented in their file; and (5) had health data in both of the data sources to ensure completeness and accuracy of the data.

Lists of medical diagnoses, select laboratory values (most recent glycated hemoglobin, creatinine, CD4 count, and viral load), duration since HIV diagnosis, and the best possible medication list (including active ART, as well as low-dose ritonavir and cobicistat) were extracted from RISQ and validated manually with the EMR. This data was entered into the web-based MedSafer portal using coded identifiers and analyzed to determine both the prevalence and type of PIMs present. All PWH are screened for sexually transmitted and blood-borne infections (STBBIs), including hepatitis C upon their first visit. Any medication received for these infections were included in the medication count. For brand-name ART combinations, each individual medication was entered separately to obtain a drug count (as opposed to a pill count).

As the study was descriptive, non-interventional, and reliant on manual chart review and data entry, we randomly selected approximately 10% of the clinic population that was over the age

of 50, until we obtained 100 patients who met our eligibility criteria. Since the COVID-19 pandemic, the clinic's demographics have changed; there are more female PWH that are asylum seekers, and there are now younger PWH with fewer comorbidities. The clinic's population described in a previous study is similar to that of our study's sample.[21]

Outcomes

The coprimary outcomes were the proportion of older PWH with 1) polypharmacy (with and without the inclusion of ART) defined as taking 5 or more medications, including medications taken as needed (natural health products or over-the-counter medications were only included if they were explicitly listed in the medical record or in the pharmacist's best possible medication history, and 2) medication overload, defined as the presence of one or more PIMs. Defining polypharmacy both with and without ART aimed to capture medication usage comprehensively, and allow comparisons with prior literature.

Statistical methods

All statistical analysis was conducted using R version 4.3.1.[18] The random sample of 100 patients was generated in R from the list of patients who had files in both the RISQ and Oacis, using the dplyr package.[19] Comparisons used a two-sided alpha of 0.05 as significant. Categorical variables were compared using Chi-square or Fisher's exact tests. Non-categorical variables were compared using t-tests. Non-normal distributions were compared using the Wilcoxon rank-sum tests as appropriate. When analyzing the types of PIMs prescribed, similar medications within a class were combined to facilitate interpretation of results (e.g., proton-pump inhibitors included pantoprazole, lansoprazole, omeprazole, and dexlansoprazole; sleeping pills included

benzodiazepines, "z-drugs".[20] Quetiapine[21] and trazodone were included as sleeping pills if they were prescribed at doses of 100mg or less prescribed at bedtime, in the absence of an alternative indication (e.g., major depressive disorder).

Multivariable logistic regression

To determine potential factors associated with medication overload, we performed multivariable logistic regression. We identified a priori clinically significant covariates based on previous studies on medication overload among older adults,[15, 22, 23] and research on polypharmacy among PWH[8, 24-26]: age as a continuous variable, sex, duration of diagnosed HIV infection in years, exposure to polypharmacy as a binary variable (≥5 versus <5 medications), and CD4 count. Two logistic regressions were conducted, both with and without including ART in the definition of polypharmacy. Odds ratios were reported with 95% confidence intervals.

Efforts to Address Bias

Given the retrospective nature of this cohort study, efforts were made to minimize information bias. Patients were randomly selected and replaced if data could not be validated through the two available data sources until the total sample size was achieved.

Ethics

The McGill University Health Centre's Research Ethics Board granted a waiver of consent (HIV-Safer / 2024-9854) for participants, given the retrospective nature of this study and the use of existing data sources.

Results

From 947 patients followed in the clinic, patients were randomly selected until a sample size of 100 was reached. The median age was 59 (IQR = 54-63) and 42% were female. Aside from HIV, the three most prevalent comorbidities were hypertension (n=38, 38%), dyslipidemia (n=26, 26%), and type 2 diabetes (n=23, 23%). Patients were prescribed a median of 9 (IQR 6-13) medications including ART, and a median of 5.5 (IQR 3-10) medications excluding ART. The median number of PIMs identified was 1 (IQR = 0-2). There was no significant difference in the number of PIMs prescribed after stratifying patients that were older versus younger than 65 years of age (Table 1).

Overall, the proportion of older PWH with polypharmacy was 89% (89/100) including ART and 60% (60/100) without ART. The proportion of patients with medication overload with one or more PIMs prescribed was 58% (58/100) (no ART was classified as a PIM). In total, 155 PIMs were identified (Figure 1): 58 (37.4%) were classified as high-risk (e.g., sedative-hypnotics), 58 (37.4%) were intermediate-risk (e.g., long-term use of a proton-pump inhibitor without an evidence-based indication), and 39 (25.2%) were low-risk, low benefit (e.g., docusate, which in randomized controlled trials is no better than placebo). Patients were commonly prescribed the following PIMs, regardless of risk category: calcium supplements31 (19%); antidiabetics (including insulin) (17%) with a hemoglobin A1C below 7.5% (equivalent to 58 mmol/mol), documented hypoglycemia, or the use of a high-risk sulfonylurea like glyburide; and sleeping pills (16/100, 16%). The three most common high-risk categories of PIMs prescribed to the cohort were sleeping pills (12% of the population), antidiabetics (including insulin) in the

presence of an A1C less than 7.5% (less than 58 mmol/mol) (10%), and opioids for chronic non-cancer pain (7%).

Multivariate Logistic Regression

Two analyses were performed to evaluate the association of risk factors with medication overload (Table 2). Only the presence of polypharmacy was independently associated with medication overload, adjusted OR = 6.1 (95% CI = 1.2-32.0, p=0.03) including ART and adjusted OR = 11.4 (95% CI = 3.9-33.5, p < 0.0001) excluding ART. Sex was not significantly associated with medication overload.

Discussion

This is the first exhaustive evaluation of PIMs and medication overload among older PWH aged 50 and older conducted using an electronic clinical decision support tool. In this contemporary cohort of older PWH, we describe a substantial burden of both polypharmacy, both including (89%) and excluding (60%) ART and of medication overload (58%). This degree of polypharmacy approximates what has been observed in prior studies of older PWH.[6]

Naturally, prior studies that excluded ART found a lower prevalence of polypharmacy. One argument in favour of excluding ART from the medication count is that most ART is comprised of 3 medications and a definition of polypharmacy only requires 5.[28] In our study, we opted to evaluate polypharmacy both with and without ART in the medication count.

We wish to highlight three reasons why it may be reasonable to include ART in the pill count when evaluating medication appropriateness in the HIV population. First, ART drugs themselves can cause ADEs which contribute to prescribing cascades.[6] For example, non-nucleotide reverse

transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) can contribute to the metabolic syndrome leading to prescriptions for dyslipidemia or diabetes.[29] Tenofovir disoproxil can decrease bone mineral density potentially predisposing to fracture and leading to the addition of calcium[27] and vitamin D supplements[30] (which may or may not reduce the risk of fracture, but do add to pill burden) and bisphosphonates (which may lead to gastroesophageal reflux and proton pump inhibitor use).[29] Integrase strand inhibitors (INSTIs) can increase the risk of dizziness or insomnia in older adults (which may lead to use of sedative hypnotics) and contribute to weight gain (which may lead to the addition of weight loss drugs).[29] Taken together, the inclusion of ART in any contextual analysis of medication appropriateness seems relevant.

Second, due to advancements of ART, HIV is no longer life-limiting if adherence to ART is maintained.[31] We evaluated the medications used to treat HIV, in order to measure the prevalence of polypharmacy (by medication count) and compared this to the prevalence of medication overload (one or more PIMs). In other patient populations with chronic illnesses, such as patients with chronic pain,[32] transplant recipients,[9] and those with chronic renal insufficiency,[33] medications used to treat the condition are also included in medication counts. This allows clinicians and researchers to compare and contrast rates of polypharmacy and medication overload between different chronic disease states and to identify and share opportunities and challenges in medication appropriateness interventions.

Third, a recent Lancet review identified that higher pill counts, paired with neurocognitive decline associated with HIV and aging, may impair older PWH's understanding of their

medication regimens.[34] This in turn can lead to an increase in ADEs from, for example, accidental duplications or omissions.[6] Overall, our study showed that, regardless of the type of exposure to polypharmacy (including or excluding ART in the medication count), polypharmacy was the sole predictor of medication overload. Like many disease states, the more medications a person takes, the more likely one or more is potentially inappropriate and can be intervened on (deprescribed).

Several recent studies, such as Kosana et al.,[35] and Fernandez-Fradejas et al.,[36] have measured the prevalence of PIM prescription in older PWH using an age cut off of 65 and above, thereby limiting our understanding of the extent of medication overload among all older PWH. A strength of our study was to follow the proposed age cut off of 50 and above to define older adulthood among PWH, providing a more comprehensive understanding of medication overload in this population. Another strength of our study was to leverage a clinical decision support tool that references multiple guidelines to identify PIMs. Some studies only reference one guideline, thereby potentially omitting some PIMs. It follows that the proportion of PWH with one or more PIMs in the literature has quite a large range (from 14.5%-81%[8, 24-26, 36-40]), which is likely partly explained by which set of rules was used to identify PIMs. Finally, we also characterized PIMs according to perceived risk categories, which can be useful in planning a deprescribing intervention, in order to set priorities for which PIMs to address and in what order, and to power a study for potential reductions in ADEs.

Our study had several limitations worth discussing. First, this study had no control group, which could have given rise to a selection bias; however, we aimed to address this limitation by taking

a random sample of 100 patients at the Chronic Viral Illnesses Service clinic to describe the prevalence of medication overload and polypharmacy. Second, any criteria used to identify PIMs have not been validated in older PWH, particularly those below 65 years old. Recently, specific deprescribing guidelines were developed for patients on hemodialysis.[45] We suggest that professional societies involved in the care of older PWH similarly develop criteria to identify PIMs specific to the HIV population, and that better meet their needs. For example, the role of primary prevention statins may be beneficial in this population[41] whereas the value of statins may be less so for patients with a limited life expectancy, where deprescribing has even been associated with an improved quality of life.[18, 46] Other HIV-specific recommendations could be important to consider, such as the simplification of ART regimens when possible, factoring cost and access, to limit pill burden. Second, because our retrospective data was derived from the electronic health record, we were unable to identify a measure of frailty in the patient population (frailty equating to a more marked vulnerability to adverse health outcomes).[47] A previous study found that frailty was associated with non-ART polypharmacy and chronic pain in older PWH.[48] It has been observed that PWH have a higher rate of opioid prescriptions for chronic non-cancer pain despite an association with an increased risk of falls and fractures.[49] In our study, the proportion of patients with an opioid prescription for chronic non-cancer pain was only 7%, compared with 16.3% in our previous randomized controlled trial on deprescribing among hospitalized older adults (the majority without HIV).[15] This lower proportion may have been due to chance, or because the population had access to continuous medical care in a specialized clinic. Third, the medication list was derived retrospectively from the electronic medical record, following a pharmacist conducted best possible medication history. As with any

retrospective study, data may have changed following the date of assessment and the date of data entry. We therefore tried to minimize errors and increase the accuracy in the medication list by cross verifying the medication lists from the pharmacist's best possible medication history in the electronic medical record, with medications listed in the HIV database, to approximate the most recent and accurate list of medications. Fourth, we did not capture medication-related harm in this study, the study was non-interventional, and it was a single Canadian center. Finally, our study had a relatively small sample size (100 patients) which could limit the generalizability of the findings, but we aimed to mitigate this through a random sample of eligible patients. Future studies should evaluate similar outcomes from larger databases, as well as the feasibility and efficacy of deprescribing interventions in older PWH with medication overload. For interventional studies, we suggest the primary outcome be the proportion of patients with one or more PIMs deprescribed, for better comparison with other deprescribing trials in conducted in people without HIV.[50] Reduction in ADEs, cost savings, and the impact on quality of life are also critical secondary outcomes to capture.

Conclusion

In our cohort, older PWH were clearly at an elevated risk of experiencing polypharmacy and medication overload, regardless of whether ART was included in the medication count. In our study, a majority of older PWH were taking at least one medication where the harms might outweigh the benefits or that was simply adding to their pill burden, and high risk medications were not uncommon. Future studies should help define PIMs specific to the HIV population and also assess the desirability and impact of deprescribing interventions.

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Table 1: Baseline Patient Characteristics

Characteristics	All older PWH	Age ≥65	Age <65	p-value
Demographic information	**N=100**	N=22	N=78	NA
Age, median (IQR)	59.0 (54.0-63.3)	67.0 (66-70.5)	57.0 (53.3-60.0)	NA
Female sex (%)	42 (42)	5 (22.7)	37 (47.4)	**0.038***
CD4 count, median (IQR) (cells/mm^3)	594.00 (364.75-772.75)	524.00 (382.25 776.50)	612.5.00 (370.25-766.50)	0.61
CD4 count, n (%)				
≥500 cells/ mm^3, n (%)	60 (60)	12 (54.5)	48 (61.5)	NA
500 – 200 cells/mm^3, n (%)	33 (33)	9 (40.9)	24 (30.8)	0.37
<200 cells/ mm^3, n (%)	7 (7)	1 (4.5)	6 (7.7)	1
HIV RNA viral load				

Detectable (>50 copies/ml), n (%)	21 (21)	5 (22.7)	16 (20.5)	NA
Undetectable (<50 copies/ml), n (%)	79 (79)	17 (77.3)	62 (79.5)	0.78
HIV RNA viral load, log_{10} copies/mL, mean (sd)	0.42 (0.96)	0.36 (0.68)	0.45 (1.03)	1
Number of years since HIV diagnosis, mean (sd)	21.3 (9.8)	26.7 (9.5)	19.8 (9.4)	**0.0045***
ARV therapy type, n (%)				
Integrase inhibitor	90 (90)	21 (95.5)	69 (88.5)	0.45
Non nucleoside reverse transcriptase inhibitor (NNRTI)	30 (30)	6 (27.3)	24 (30.8)	1
Tenofovir (disoproxil or alafenamide)	71 (71)	14 (63.6)	57 (73.1)	0.43
Abacavir	9 (9)	3 (13.6)	6 (7.7)	0.41
Medications				

Number of medications, median (IQR), including ARV	9.00 (6.00-13.00)	9.50 (7.00-14.75)	9.00 (6.00-11.75)	0.33
Number of medications, median (IQR), excluding ARV	5.5 (3.0-10.0)	6.5 (3.25-11.75)	5 (3-9)	0.23
Number of PIMs, median (IQR)	1 (0-2)	1 (0-3)	1 (0-2)	0.63
Comorbidity, n (%)				
Hypertension	38 (38)	13 (59.1)	25 (32.1)	**0.021***
Dyslipidemia	26 (26)	10 (45.5)	16 (20.5)	**0.019***
Valvular heart disease	2 (2)	1 (4.5)	1 (1.3)	0.39
Ischemic heart disease	4 (4)	2 (9.1)	2 (2.6)	0.21
Atrial fibrillation	1 (1)	1 (4.5)	0 (0)	0.22
History of ischemic stroke	2 (2)	2 (9.1)	0 (0)	**0.047***
History of venous thromboembolism	4 (4)	3 (13.6)	1 (1.3)	**0.033***
History of gastrointestinal bleed	4 (4)	2 (9.1)	2 (2.6)	0.21

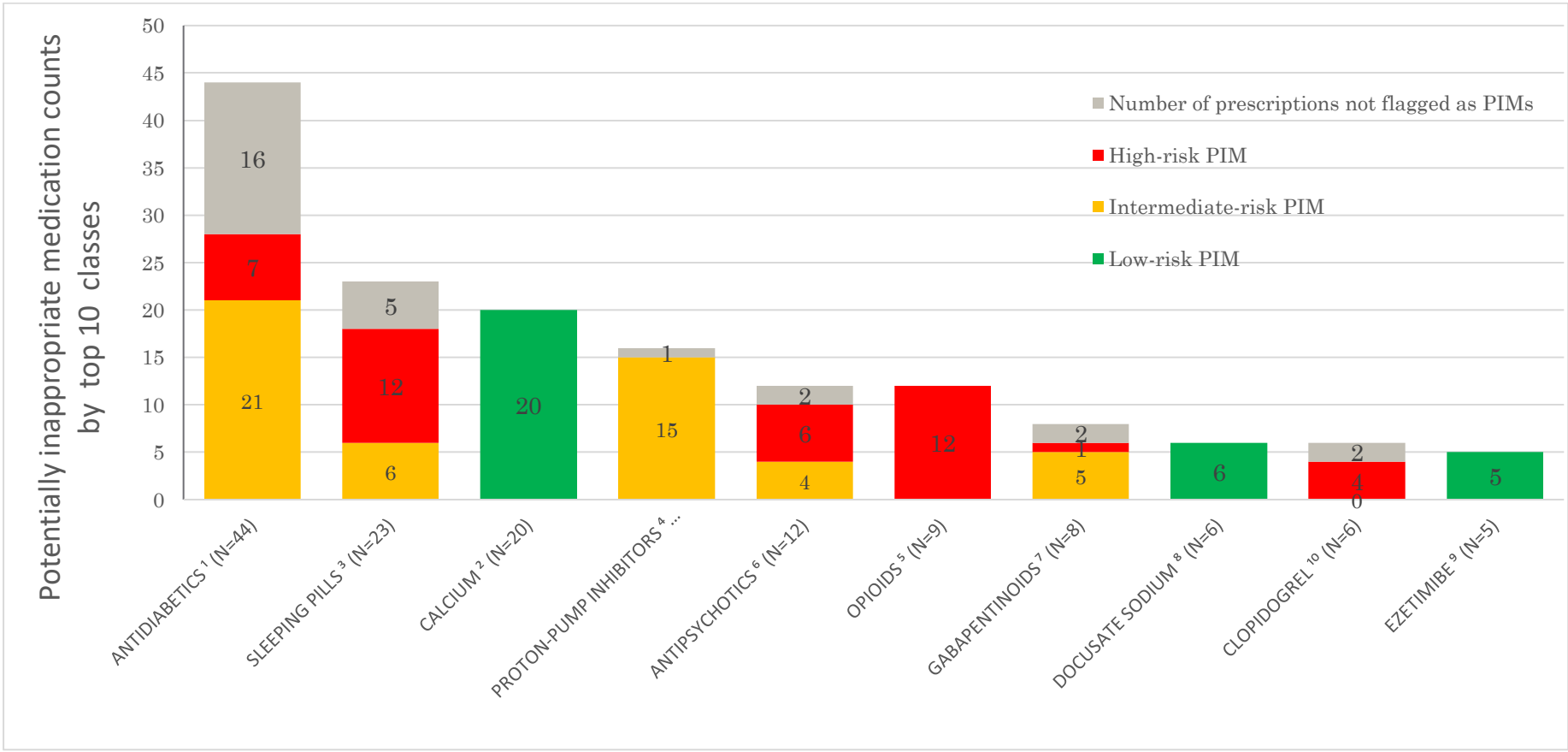
Gastroesophageal reflux disease	10 (10)	3 (13.4)	7 (9.0)	0.69
Hepatitis B co-infection	12 (12)	1 (4.5)	8 (10.3)	0.68
Hepatitis C co-infection	12 (12)	5 (22.7)	4 (5.1)	**0.023***
Diabetes	23 (23)	4 (18.2)	19 (24.4)	0.54
Chronic kidney disease	4 (4)	2 (9.1)	2 (2.6)	0.21
Asthma	10 (10)	1 (4.5)	9 (11.5)	0.45
COPD	7 (7)	3 (13.6)	4 (5.1)	0.18
Cancer (solid organ or hematological, total)	11 (11)	4 (18.2)	7 (9.0)	0.25
Cancer (solid organ or hematological, current)	7 (7)	2 (9.1)	5 (6.4)	0.65
Cancer (solid organ or hematological, in remission)	4 (4)	2 (9.1)	2 (2.6)	0.21
Osteoporosis	8 (8)	2 (9.1)	6 (7.7)	1.0
Major depressive disorder	21 (21)	5 (22.7)	16 (20.5)	0.78
Generalized anxiety disorder	9 (9)	2 (9.1)	7 (9.0)	1.0

Substance use disorder	8 (8)	2 (9.1)	6 (7.7)	1.0

Table 2: Multivariate Logistic Regression of Medication Overload

Variables	Polypharmacy including ART	p-value	Non-ART Polypharmacy	p-value
Unadjusted OR (95% CI)	7.1 (1.7-53.5)*	0.007	11.5 (4.6-31.6)*	p<0.0001
Adjusted OR (95% CI)	6.1 (1.2-32.0)	0.031	11.4 (3.9-33.5)*	p<0.0001
Covariates				
Age (years)	1.0 (0.9-1.0)	0.81	1.0 (0.9-1.1)	0.86
CD4 count (cells/mm^3)	1.0 (1.0-1.0)	0.16	1.0 (1.0-1.0)	0.94
Sex (male = 1)	1.4 (0.6-3.5)	0.46	1.0 (0.4-2.8)	0.98
HIV infection duration (years)	0.03 (0.0004-2.3)	0.13	1.0 (1.0-1.1)	0.66

*p<0.05



1. ANTIDIABETICS: Flagged if a patient had an A1C lower than 7.5% and was at risk of hypoglycemia, or if medication increases hypoglycemic risk.
2. CALCIUM: Flagged if the patient is taking multiple daily doses of calcium, and because of the lack of demonstrated efficacy of calcium to prevent fractures
3. SLEEPING PILLS: Benzodiazepines, Z-drugs, trazodone (<100 mg) and quetiapine (<100 mg) in the absence of a documented psychiatric condition.
4. PROTON-PUMP INHIBITORS: Flagged in the absence of dual anticoagulation, severe esophagitis, or prior upper gastrointestinal bleed.
5. OPIOIDS: Flagged due to serious adverse effects and limited effectiveness in relieving chronic non-cancer pain

6. ANTIPSYCHOTICS: Quetiapine (>100mg), risperidone, paliperidone, prochlorperazine, etc. flagged if there was an absence of indication for prescription of this medication (e.g., antipsychotic monotherapy for depression, off-label use)
7. GABAPENTINOIDS: Flagged in patients without a known history of epilepsy for risk of CNS depression, cognitive impairment, peripheral edema, etc.
8. DOCUSATE: Flagged due to nonsuperiority to placebo
9. EZETIMIBE: Limited evidence for the use of non-statin lipid-lowering drugs in preventing patient relevant cardiovascular outcomes, and potential for non-CYP-mediated drug-drug interactions.
10. CLOPIDOGREL: Flagged in combination with aspirin or another anticoagulant in the absence of a recent cardiac stent or recent cardiovascular or cerebrovascular event.

Figure 1 : Top 10 PIMs Identified by MedSafer and Proportion Potentially Inappropriate Within the Medication Class

A Comprehensive Scholarly Discussion of All the Findings

Polypharmacy, Medication Overload and its Potential Harms

Polypharmacy is practically inevitable in special populations that have several, significant chronic illnesses each requiring their own medications to treat. However, not all the medications within a patient's polypharmacy may be appropriate. My research has shown that polypharmacy can be appropriate, as we commonly see among older adults in long-term care, patients on hemodialysis, and older PWH. While the number of medications is related to the risk of having medication overload, the two terms are clinically distinct. Polypharmacy was present in all of these populations – more importantly was the prescription of PIMs and the incidence of medication overload which, in the LTCH and dialysis contexts, could be managed through deprescribing. Aging with HIV is a new frontier worthy of exploring because of the findings from my retrospective cohort study of a high burden analogous to the previous quality improvement studies which have been successful.

While the prevalence of PIMs distinguishes polypharmacy from medication overload, measuring harm, the other deciding factor distinguishing these two syndromes, is far more complex. Patients with polypharmacy (and potentially medication overload) have multiple illnesses, and multiple medications that can all interact between each other, leading to adverse effects with several potential causes. It may be very difficult to attribute a symptom as a pure consequence of an illness or a medication; the medical complexities of patients with multiple, severe, chronic illnesses that take multiple medications make the adjudication of ADEs challenging. There were

several tools between the 1970s and 1990s to adjudicate medication harm developed, such as the Naranjo algorithm[75] or the Leape and Bates method.[165] Randomized controlled trials of deprescribing that used these tools have not consistently demonstrated an improvement in the incidence of ADEs following deprescribing. This is likely due to several reasons, three of which I will describe below.

First, current tools have likely been adjudicating ADEs incorrectly because the methods used are outdated. These ADE adjudication tools, such as the Naranjo algorithm, the Leape and Bates, or the French method were all developed between the 1970s and the 1990s, a time when polypharmacy was nowhere near as prevalent as it is today. A study in Ontario, Canada, found that the rate of prescribing medications among outpatient older adults increased by 214% between 1997 and 2006, and the proportion of patients with mega polypharmacy increased by 188% between these same years.[166] Throughout my doctoral studies, I have been working with the previous master's student in our laboratory, Dr. Sydney Ross, on the development of a novel methodology to clinically adjudicate ADEs adapted for instances of polypharmacy and medication overload. It is my hope that the work I have been conducting with Dr. Ross will be published to allow for a secondary analysis of the ADEs in the initial MedSafer Study to adjudicate these events more accurately because this is one of the few studies published on deprescribing that has the statistical power to demonstrate a significant effect of deprescribing on ADEs.

Second, as a previous literature review found on adjudication methods of ADEs, these adjudication tools also only capture adverse drug reactions (ADRs), which are a subtype of

ADEs.[30] Adverse drug events are a broad term defined as harm caused by any medication, including ADRs, inappropriate use, and overdosing; they may be preventable or not.[30] However, the tools currently used only capture ADRs, limiting their sensitivity to detect all potential ADEs. Furthermore, these tools are not developed to capture ADWEs, or ADEs that arise due to the discontinuation, tapering, or deprescription of a medication. This is an important subcategory to ADEs to capture because it can indicate a measure of harm due to deprescribing. Dr. Ross' tool has incorporated the full spectrum of ADEs, including ADRs and ADWEs,[167] and accounts for situations of polypharmacy and medication overload, where the interactions between medications, and interactions between medications and the patient's environment and/or illness may occur more frequently. This tool will hopefully be the subject of a future secondary analysis of sufficiently powered randomized controlled trials to measure harm as an outcome during deprescribing.

Third, over 3000 participants would need to participate in a deprescribing randomized controlled trial to achieve the statistical power necessary to demonstrate a change in ADE incidence. In the MedSafer Study that included 5698 patients, the ADE incidence outcome was measured up until 30 days post-deprescribing; any change in this outcome beyond this timeframe was not captured. Thirty days may not be long enough to see the harms of medication overload or the benefits of deprescribing. This is similar to many deprescribing randomized controlled trials where the ADE incidences outcome is measured within a very short time frame.[168] Running randomized controlled trials for an extended period of time is very expensive and resource intensive; measuring ADE incidence for several months or more among over 3000 patients would be even more costly. Few deprescribing trials study their effect on

adverse drug events. In fact, a systematic review and meta-analysis published in 2022 by Omuya et al. evaluated the outcomes of deprescribing randomized controlled trials, and found that only one study had measured adverse drug event incidences.[40] This study was conducted by Lenander et al. and took place among 290 patients over 12 months, which is far from the necessary number of participants to achieve statistical power.[169] It found a non-significant decrease in the rate of adverse drug events in the intervention group (-0.12 ADEs per patient) compared to the control group (-0.03 ADEs per patient).

However, several studies did measure rates of falls, fractures and hospitalizations as measures for harm, and found that deprescribing did not demonstrably worsen these outcomes for patients compared to standard of care. Thompson et al. published an article in 2019 describing how this *no change* outcome can serve to demonstrate noninferiority of deprescribing.[158]

Given the above limitations of deprescribing studies capturing ADEs, for a future project in the field, I aim to apply Dr. Ross' adjudication tool and reanalyze all the events that occurred in the MedSafer Study published in JAMA Internal Medicine. Afterwards, I would like to use the results from this study to train an open-source machine learning algorithm adjudication of these events, and meta analyze all the ADEs from randomized controlled trials on deprescribing.

I have demonstrated throughout my thesis that three special populations at risk of medication overload can likely benefit from deprescribing. My work can serve as supporting evidence to inform the design of future, large randomized controlled trials that measure the effects of deprescribing on patient centered outcomes, hard outcomes (such as ADEs caused by polypharmacy and medication overload), and avoided costs on the healthcare system.

Peripheral Projects That Took Place During My Doctoral Studies

During my doctoral studies, I conducted a qualitative study on the nephrologists' perspectives using the MedSafer tool to deprescribe following the hemodialysis quality improvement study I had conducted. During peer review of the quality improvement study's protocol at the Canadian Journal of Kidney Health and Disease, a reviewer suggested we conduct qualitative interviews with participating nephrologists on their experience engaging in this quality improvement project. After completion of the project, I conducted qualitative interviews with physicians, adapting the questionnaire used in my first study (MedSafer in Long-Term Care) to the outpatient hemodialysis clinic's context. I have included the interview questions used in the MedSafer in Long-Term Care study in the Appendix of my thesis (Supplemental Manuscript 1, Figure 1). While only four physicians participated in the intervention portion of the study, these prescribers all cared for 68 patients during their rotation attending on the unit. The qualitative study evaluated the barriers and facilitators of implementing an electronic clinical decision support system to deprescribe in hemodialysis has never been previously studied. Overall, we found that while all physicians agreed that deprescribing was important, setting realistic goals, leveraging existing clinicians such as nurses and a clinical pharmacist, the latter that was lacking on the unit, can improve the workflow of medication reconciliation and deprescribing for the nephrologists. One of the coauthors of the study, Dr. Marisa Battistella, who helped develop the deprescribing algorithms in hemodialysis, is designing a randomized controlled trial on deprescribing in outpatient hemodialysis patients and will be using the results of this qualitative study to hopefully create an intervention that will be useful for both physicians and patients.

Following this hemodialysis qualitative study, I began data extraction from the electronic medical records of the participating older PWH for the retrospective study on medication overload among older PWH. I found that several PWH were being prescribed daily vitamin D, while others were being prescribed weekly vitamin D. Vitamin D in the end of life can be a superfluous PIM, but otherwise, although having failed to demonstrate clinically significant benefits,[170] vitamin D supplementation is not considered a PIM. Therefore, I became interested in determining if there was a way to simplify the medication regimen of daily vitamin D by switching it to weekly vitamin D. By doing so, patients would have 6 fewer pills to take during the week, which could be considered as a form of deprescribing. Pill burdens decrease adherence to treatment,[171] so efforts must be made to make the patient's medications the safest and simplest possible. However, before potentially considering daily vitamin D as an exacerbator of pill burdens, I needed to conduct a systematic review and meta-analysis of the efficacy of daily versus weekly vitamin D to correct hypovitaminosis D, otherwise known as vitamin D deficiency. While this article is still under peer review, according to my meta-analysis, weekly vitamin D is as effective as daily vitamin D to replete patients with a vitamin D deficiency. Based on this, I hope to integrate a rule in the MedSafer software to flag daily vitamin D as a superfluous PIM and recommend switching to weekly vitamin D prescription.

Future Directions for Research

After I had presented the initial results of the quantitative portion of the outpatient hemodialysis project at the Infectious Diseases, Immunity, and Global Health (IDIGH) Annual Research Day in 2023, I was approached by Dr. Tchervenkov, a transplant surgeon at the McGill University Health Centre. He noticed that several of his patients have polypharmacy, and likely

medication overload, based on the prevalences measured in my hemodialysis study. He was looking to implement a deprescribing quality improvement project for patients living with a transplanted organ. This is yet another special population that has justifiable and appropriate polypharmacy;[68, 172, 173] similarly to patients on hemodialysis and older PWH, this polypharmacy increases their risk of developing medication overload.

There is a scarce amount of research on the topic of polypharmacy among transplant recipients. In a study conducted in 2023 by Sridharan et al.,[172] the median number of medications prescribed in this population was 23 (range 6-55). A Japanese study found that 41% of patients had mega polypharmacy.[68] While I did not have the opportunity during my PhD to design a study in this population, I remain committed to study deprescribing in this population in the future. Quasi-systemic polypharmacy is complexifying the clinicians' tasks to navigate paper-based tools to not only identify PIMs but also how to deprescribe them. Based on the studies in my thesis that show that MedSafer is an effective tool to increase deprescribing, its use in more special populations can provide clinicians with the opportunity to assess the appropriateness of a patient's entire list of medications. The time commitment is a dissuasion to deprescribe,[110] so having an electronic clinical decision support tool to deprescribe can facilitate the process and make it more accessible.[157]

Several other special populations are also at risk of medication overload that would benefit from deprescribing studies in the future. Other populations include patients with migraine,[66] patients with epilepsy,[174, 175] and patients with cancer.[176] Patients with migraine would be an important population to study because of the use of several combination medications to

achieve pain relief, the risk of medication overuse headache, and the risk of prescribing cascades arising from the use of treatments to relieve the migraine crises.[66]

I have consistently observed across my studies the benefit of having a clinical pharmacist to provide expertise on medication safety and create opportunities within the healthcare team to deprescribe. Due to the fragmentation of care, physicians may not be aware of the full list of medications that a patient was prescribed in their previous appointments, but clinical pharmacists are key in providing continuity of care for patients with severe comorbidities that require polypharmacy. Pharmacists are on the receiving end of prescriptions from specialists, are optimally positioned to assess them in their entirety and decide the best path forward to ensure the safest medications are prescribed to patients.

Research on the benefits of having a clinical pharmacist involved in the deprescribing process has been shown to increase medication adherence, decrease the incidence of polypharmacy, and reduce the pill burden of patients. The D-PRESCRIBE trial published in JAMA in 2018 by Martin et al.[177] studied the discontinuation rate of PIMs following the pharmacist's distribution of educational deprescribing brochures to patients, and an evidence-based pharmaceutical opinion to recommend deprescribing to the physician in Quebec, Canada. Benzodiazepines, sedative-hypnotic Z-rugs (zolpidem and zopiclone), first-generation antihistamines, glyburide and non-steroid anti-inflammatory drugs (NSAIDs) were included as PIMs in this study. Authors found that this intervention led to a mean increase in the number of PIMs deprescribed (complete cessation) of 31% (95% CI 23-28%), and a relative risk of discontinuing the PIM of 3.55 (95% CI = 2.45-5.15). Ultimately, this study leveraged the central role of pharmacists in the

deprescribing process, and the channel of communication that pharmacists have to communicate with patients and clinicians effectively.

Throughout my research, I have learned that special populations that have several chronic illnesses are at risk of medication overload, but the causes of this risk are multifactorial. Studies have continuously documented how a healthcare system continuously expecting clinicians to accomplish more and more, with fewer and fewer resources, to the effect that in Canada, our current healthcare system can only be effective once a patient has a life-threatening illness or syndrome.[178] This comes to the detriment of patients and clinicians who no longer have the time or ability to receive or administer care respectively, the way they are supposed to. The core foundations of our healthcare system are being pushed to their limits, while policymakers and local governments continuously and chronically find ways to strip these structures down to their bare bones, even when it was not thought possible, to the effect that it has become vastly easier to prescribe a pill to a patient than it would be to address the underlying, social determinant, and broader contributors to illness.[179] Yet, no concrete or measurable action is taken by local governments and policymakers to reform healthcare and shift care from a reactionary one to a preventative one.[180]

Clinicians no longer have adequate time to assess patients' medications, identify potential PIMs, and propose a deprescribing plan. This is one of the limitations of my studies throughout my studies, and many of the studies published on deprescribing: data entry to evaluate which medications are potentially inappropriate is not done by clinicians working within a healthcare institution. Research assistants and clinicians are hired as part of a research project to draft a

deprescribing plan and study its effects once the plan is handed to the clinicians that routinely care for the studied patient sample. Deprescribing is rarely part of routine, clinical care. Research studies are temporary, and there is always the question of biasing results of deprescribing research away from the null because there were study personnel hired to complete tasks that the regular clinicians do not have time for, due to the pressures they face to do more and more, in less and less time, and with fewer and fewer resources.

For the MedSafer project in long-term care, MedSafer in hemodialysis, and MedSafer in older PWH, deprescribing reports were generated by research assistants (I was the research assistant in the last two studies). The true effect of deprescribing would likely have been smaller, had the prescribers regularly practicing in these clinical settings been responsible for generating the reports. More broadly, clinicians would have healthier patients and better patient outcomes if they had enough time and resources to complete, properly, the clinical tasks they are responsible for. In the past few years of my thesis, I have identified not only special populations that are at risk of medication overload, but also the need for sustainable deprescribing interventions. Studies in the field have consistently shown the need for deprescribing to ensure medication safety, but future research needs to shift towards a paradigm of studying ways to make deprescribing sustainable and regular, and ways to change a habit of overlooking the medication safety profile of a patient.

Advocacy work through international deprescribing networks has finally begun creating awareness among patients, providers, and government around deprescribing, medication overload, and polypharmacy.[181] I have seen in my own work by presenting deprescribing in the

community, at conferences and during presentations that deprescribing is becoming a term that stakeholders have at least heard of. When they do know more beyond the term "deprescribing", they often speak about sleeping pills, benzodiazepines and antipsychotics in long-term care homes. Deprescribing is so much more than stopping sleeping pills and antipsychotics; it is a continuous engagement between the prescriber and the patient to ensure maximal benefits from their medication therapy and a minimization of associated harms; it ensures that medication regimens are simple, easy to follow,[182] and that patients only take medications at the smallest doses of the shortest duration necessary to achieve the desired clinical benefits.

Governments have started to create their own deprescribing programs in response to the realization that medication overload harms patients; programs in Quebec such as the Programme d'évaluation de la personnalisation des soins (PEPS)[183] and Optimisation des pratiques, des usages, des soins et des services – Antipsychotiques (OPUS-Antipsychotics)[184] are province-wide, and aim to deprescribe benzodiazepines and antipsychotics in long-term care homes. While the intentions behind these initiatives should be rightfully applauded, there are potential limitations to implementing such programs with limited classes of medications that are subject to government policy. In Australia, when the national government created a policy to stop the use alprazolam, a benzodiazepine, the rates of prescribing alprazolam did in fact decrease, but the rates of prescribing different benzodiazepines increased.[185] In Canada, in a study that I am a coauthor on that is currently under peer review, the rates of patient exposure to opioids and benzodiazepines have in fact decreased in the past ten years by 13.5% and 37.7% respectively, but the rate of patient exposure to gabapentinoids, a medication class that at

particular dosages can mimic the effects sought after in benzodiazepines and opioids, increased by 83.7%.[186] It is possible to learn from the Australian prescribing program and the behaviours of prescribers to still seek similar effects of medications by prescribing differently. Extrapolating these findings and recognizing that, without an exhaustive deprescribing approach tackling every possible PIM, the system will not change. The system cannot change until all patients, caregivers prescribers, clinicians, healthcare systems and policymakers are aware of the harms of medication overload and work together to create lasting change to improve medication safety.

Addressing Thesis Reviewers' Comments

Following the external review of my thesis, because the published manuscripts within my thesis cannot be edited, I have added the following small points of clarification. First, in my quality improvement study on deprescribing in a long-term care home, the questionnaire that was used had not been previously validated.

Second, in my quality improvement study on deprescribing among patients on hemodialysis, it should be clarified that patients were selected if they had been on maintenance hemodialysis for more than three months; therefore, all patients had ESKD. Third, when categorizing commonly prescribed PIMs, I considered benzodiazepines and Z-drugs as sleeping pills. Fourth, tapering was defined as any deliberate dose decrease in a PIM identified by MedSafer.

Fifth, with regards to the prevalence of HIV in my hemodialysis deprescribing study, a total of four (2%) patients, all in the control group, had HIV. In my descriptive study among older PWH, four patients (4%) had chronic kidney disease.

Conclusion and Summary

In conclusion, polypharmacy can be associated with adverse events such as falls, fractures, hospitalizations, and premature death. However, special populations with multiple, severe comorbidities often require the prescription of multiple medications. Therefore, they may benefit from a more precise measurement of (in)appropriateness to more accurately reflect the safety of their medication. I proposed in my thesis to distinguish these cases by referring to the presence of medication overload, not simply polypharmacy. Across all the special populations of my studies – older adults in LTCHs, patients on hemodialysis, or older adults with HIV – all were at risk of medication overload. Deprescribing using an electronic clinical decision support tool, MedSafer, increased the proportion of patients with one or more PIMs deprescribed, not only among hospitalized older adults, but among two additional special populations (people in LTCHs and people receiving dialysis). Including a measure of population benefit (i.e., measuring the proportion of patients with PIMs deprescribed) more accurately captures the populational effect of deprescribing, rather than only measuring the net number of medications deprescribed. Medication overload was described for the first time among older PWH, and several high-risk PIMs were found that would benefit from a deprescribing approach (namely opioids for chronic non cancer pain, sleeping pills, and insulin prescribed in the presence of a glycated hemoglobin of less than 7.5%; deprescribing interventions in this population can be the subject of future studies. Ultimately, deprescribing must be done with the primary dual aims of addressing a patient's values and preferences, and ideally increasing the appropriateness of prescriptions. Future studies should evaluate the effect of deprescribing interventions in other

special populations at risk of medication overload because of their increased prevalence of polypharmacy. Special populations can include patients living with a transplanted organ,[68] patients with migraine,[187] patients with epilepsy, as well as confluent populations, such as older adults that have cancer[188]. Larger studies stemming from the pilot quality improvement studies I conducted are needed to convince policy makers on the value, scalability, and thus the uptake of electronic deprescribing interventions.

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Appendices

Chapter 1

Supplementary Table 1[1]: Standard Quarterly Medication Review Outcomes[a]

	Unit 1	Unit 2	Overall
Total Number of Medication Orders			
Standard Quarterly Medication Review (QMR)			
Before	428	354	782
After	408	347	755
Absolute difference (% difference)	-20 (-4.7)	-7 (-2.0)	-27 (-3.5)
MedSafer-LTCFs QMR			
Before	447	374	821
After	434	332	766
Absolute difference (% difference)	-13 (-2.9)	-42 (-11.2)	-55 (-6.7)
Average Number of Medication Orders per Resident, mean (SD)			
Standard Quarterly Medication Review (QMR)			
Before	16.5 (5.6)	14.2 (4.4)	15.3 (5.2)
After	15.7 (5.1)	13.9 (4.4)	14.8 (4.8)
Mean Difference[b]	-0.8 (1.0)	-0.3 (0.7)	-0.5 (0.9)
MedSafer-LTCFs QMR			

[1] This is the supplementary table describing the number of medication orders during the course of the study.

Before	16.0 (5.5)	13.9 (4.5)	14.9 (5.1)
After	15.5 (5.8)	12.3 (4.3)	13.9 (5.3)
Mean Difference[c]	-0.5 (1.1)	-1.6 (1.3)	-1.1 (1.3)
Difference in number of deprescriptions at MedSafer-LTCH vs. Standard QMR, mean (SD)[d]	+0.3 (1.0)	+1.3 (1.0)	+0.6 (1.1)

[a]Four residents were excluded from the standard QMR comparisons because they either (1) had admission dates, (2) were transferred from a different unit after their standard QMR, or (3) were in acute care at the time of the standard QMR.

[b]Unit 1 unadj paired t-test $p < 0.001$, ES = -0.78; Unit 2 unadj paired t-test $p = 0.07$, ES = -0.38; Overall unadj paired t-test $p < 0.001$, ES = -0.59.

[c]Unit 1 unadj paired t-test $p < 0.030$, ES = -0.45; Unit 2 unadj paired t-test $p < 0.001$, ES = -1.19; Overall unadj paired t-test $p < 0.001$, ES = -0.77.

[d]Unit 1 unadj independent t-test $p = 0.35$, ES = 0.26 [CB3]; Unit 2 unadj independent t-test $p < 0.001$, ES = -1.32 [CB4]; Overall unadj independent t-test $p = 0.18$, ES = -0.48 [CB5]

Supplementary Method 1: Interview Guide[2]

MedSafer-LTC: Staff Interview

Hello and thank you for taking the time to talk about your standard practice for quarterly medication reviews and your experience using MedSafer-LTC. During this session, I will ask you some questions and take notes as you respond to them. To make sure nothing is missed, I will also be audio recording this interview. I would appreciate if you could answer all of the questions as best as you can and provide as much detail as possible. Please be assured that all information collected will be kept confidential. This interview will be transcribed with no identifying information and recordings will be destroyed following analysis. Reporting will be based on overall feedback and responses will not be traced back to a specific person or discipline. De-identified quotes will be used to help illustrate overall themes. Your participation in this study is voluntary and will not affect your employment at Baycrest. Before we begin, do you have any questions?

Interview Questions:

1. Could you please describe your standard practice for reviewing medications at quarterly medication reviews without using MedSafer-LTC?

   Probe: In your standard practice, what considerations do you take into account before having conversations about medication changes with the client or the Substitute Decision Maker?

[2] This is the interview guide that was used to conduct the semi-structured interviews with participating physicians in the Quarterly Medication Reviews with MedSafer

2. Could you please describe how you used MedSafer-LTC in your practice at the quarterly medication review?

   Probe: How would you compare your standard practice for reviewing medications with your experience using MedSafer-LTC?

3. What was the impact of the MedSafer-LTC recommendations on your practice at the quarterly medication review?

   Probe: Do you feel the MedSafer-LTC recommendations were helpful in improving your knowledge about deprescribing medications?

4. How often did you agree with the recommendations provided by MedSafer-LTC? What did you disagree with and why?

5. Were you surprised by any of the recommendations made by MedSafer-LTC? If so, what surprised you?

   Probe: Based on your knowledge of current deprescribing criteria and practices, did any recommendations surprise you?

   Probe: Based on your knowledge of residents' health status, did any recommendations surprise you?

6. Did you identify any facilitators or barriers with using MedSafer-LTC and its recommendations during the quarterly medication review? If yes, what kinds of facilitators or barriers did you identify?

7. Did you have any conversations with clients or Substitute Decision Makers about deprescribing medications?

   Probe: If so, what were some reasons that the client or Substitute Decision Maker identified for agreeing or disagreeing with your deprescription recommendations?

   Probe: Were any of the conversations based on MedSafer-LTC recommendations?

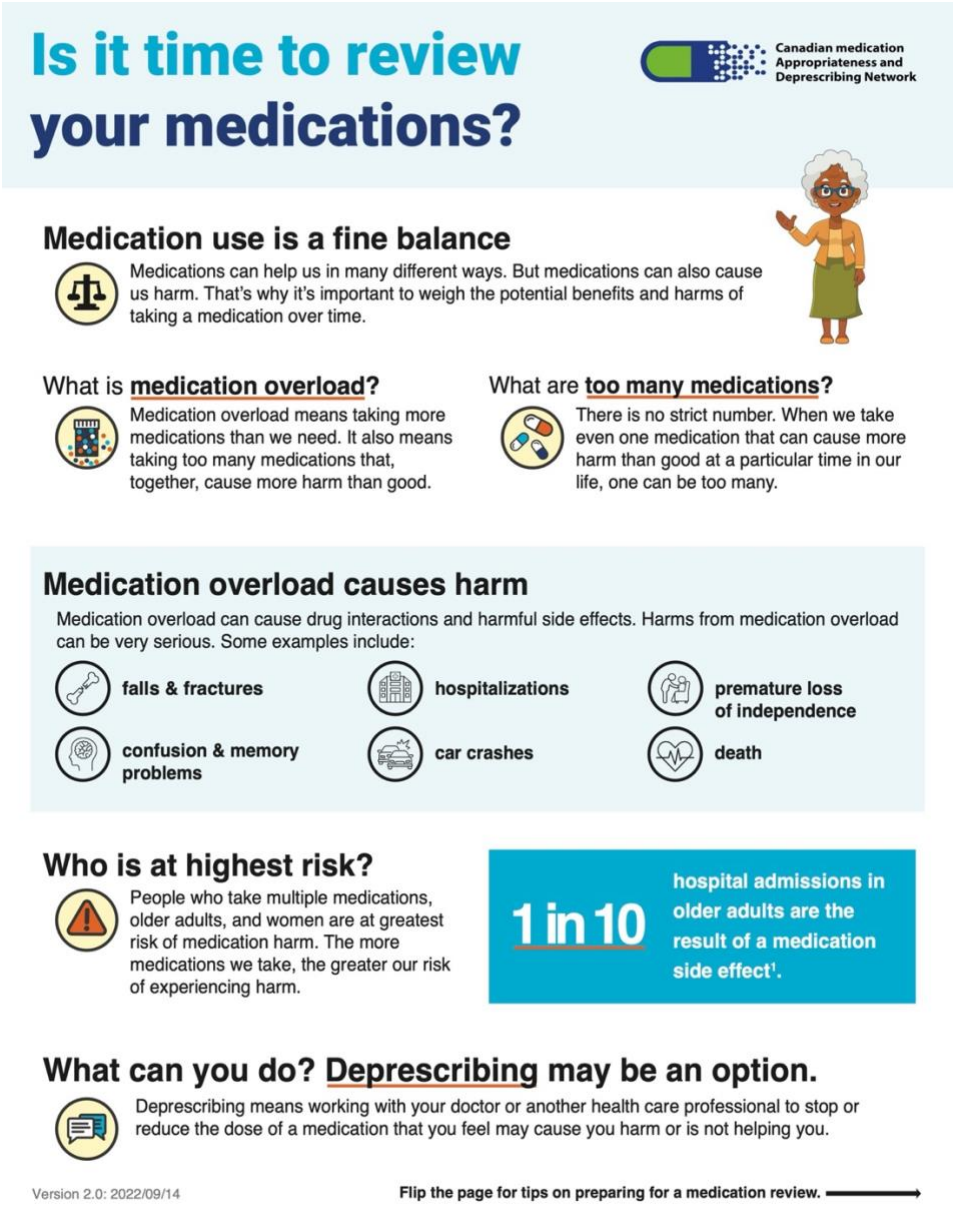
   Probe: How helpful was MedSafer in facilitating deprescribing conversations?

8. What was your comfort level with using MedSafer-LTC during the quarterly medication review? On a scale of 1 to 5, 1 being “very uncomfortable”, 3 being “neutral”, and 5 being “very comfortable”, how would rate your comfort level?

   Probe: Why do you feel that way?

9. Do you have any other comments about MedSafer-LTC you would like to share?

Supplementary Figure 1: General deprescribing fact sheet distributed to all hemodialysis patients on the intervention unit[3]



[3] This is the general deprescribing factsheet that was distributed to each patient from the intervention unit of the MedSafer in hemodialysis study.

Preparing for a medication review with your doctor, pharmacist or nurse

Canadian Deprescribing Network

1. **Book an appointment** with your doctor, pharmacist or nurse *specifically* to review your medications.

2. **Questions to ask yourself before your appointment:**

- How are my medications affecting me? Am I having any problems with them?
- If my doctor recommended that I stop taking one or more of my medications, would I be willing?

3. **Prepare your list of questions in advance!**

Here are 5 questions to ask your doctor, pharmacist or nurse when starting a new medication or reviewing one you are already taking:

1. **Why am I taking this medication?**
2. **What are the potential benefits and harms of this medication?**
3. **Can it affect my memory or cause me to fall?**
4. **Can I stop or reduce the dose of this medication (i.e. deprescribing)?**
5. **Who do I follow up with and when?**

Remember to write down any other questions you would like to ask about your medications, too.

4. **Bring an up-to-date medication list to your appointment.** Ask your pharmacist for a list of all your medications, or make your own (**visit DeprescribingNetwork.ca for a sample record**). Include over-the-counter medicines and supplements.

Learn more about deprescribing and medication safety at DeprescribingNetwork.ca

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Supplementary Figure 2: Statistical code in STATA[34] for the analyses[4]

```
power twoproportions 0.1 0.25, test(chi2) n(214) nratio(0.5)
nfractional

Study parameters:

        alpha =    0.0500
            N =  214.0000
           N1 =  142.6667
           N2 =   71.3333
        N2/N1 =    0.5000
        delta =    0.1500  (difference)
           p1 =    0.1000
           p2 =    0.2500

Estimated power:

        power =    0.8023
```

[4] This is the statistical code that was used to determine the necessary power to show a 15% change in the mean number of potentially inappropriate medications (PIMs) prescribed in this quality improvement study. N1 represents the control unit (the Montréal General Hospital) and N2 represents the intervention unit (the Lachine Hospital). Assuming an alpha of 0.05, and that the intervention unit cares for around half the number of patients on the control unit, a minimum of 214 patients would have to be included to have an 80% power to demonstrate a change (delta) of 15% in the number of prescribed PIMs.

Supplementary Figure 3: How to complete a MedSafer MedRec – Lachine Campus – for Physicians[5]

1. Gather the list of patients you will perform a MedRec on today
    a. We recommend doing 3-4 MedRecs per day, in a 5-day week on service.
    b. This week let's aim to do 17 MedRecs.
2. Identify the patients' MedSafer deprescribing reports in the binder called MEDSAFER REPORTS. The reports are sorted in alphabetical order, according to the patient's last name.
3. Review the MedSafer deprescribing report for one patient
    a. Review the deprescribing brochures attached for this patient and hand them to the patient
    b. Provide explanations on the topic of deprescribing and the benefits/risks of deprescription the proposed medication.
4. Document, in the NephroCare clinical note, the MedSafer MedRec completion, its date
5. In the clinical note, detail the changes implemented (to facilitate data collection for the study lead)
6. In NephroCare, adjust the MAR according to the MedRec changes
7. Document, on the MedRec sheet available on the clinical unit, that the "MedSafer MedRec done".
8. Once the MedSafer deprescribing report has been used, please attach it to the back of the MedRec sheet.
9. Repeat steps 3 to 8 for all patients you are doing MedRecs for.

If you have any questions, please contact the study lead, [redacted].

Email: [redacted]

Phone number: [redacted] (feel free to call/text this number)

[5] This was the instruction sheet that was provided to nephrologists on the intervention unit to complete a medication reconciliation using MedSafer, and documenting the process accordingly in each participant's electronic medical record.

The principal investigator of this study is [redacted] and [redacted] is the liaison between the research team and the hemodialysis team at the Lachine campus' outpatient hemodialysis clinic.

Supplementary Figure 4: Revised Standards for Quality Improvement Reporting Excellence (SQUIRE 2.0) September 15th, 2015 Checklist[6]

Revised Standards for Quality Improvement Reporting Excellence (SQUIRE 2.0) September 15th, 2015

Text section and item name	Section or item description
1. Title and abstract	Title
2. Abstract	Abstract
Introduction	Why did you start?
3. Problem description	Background and rationale
4. Available knowledge	Background and rationale
5. Rationale	Background and rationale
6. Specific aims	Objectives
Methods	What did you do?
7. Context	METHODS: Participants, Intervention and Outcomes (Study setting)
8. Interventions	Interventions (Explanation of the choice of comparators and Intervention description)
9. Study of the interventions	DATA COLLECTION AND METHODS
10. Measures	Plans for assessment and collection of outcomes Data management
11. Analysis	Statistical methods
12. Ethical considerations	Recruitment
Results	What did you find?
13. Results	N/A
Discussion	What does this mean?
14. Summary	DISCUSSION
15. Interpretation	DISCUSSION
16. Limitations	DISCUSSION
17. Conclusions	DISCUSSION
Other information	
18. Funding	Funding

[6] This was the checklist used to report the protocol for this quality improvement study on deprescribing among patients on hemodialysis using MedSafer.

Chapter 2.2

Supplementary Method 1: Method for Capturing Gastrointestinal Bleeds[7]

Based on a previous, uncontrolled, observational study,[189] there was suspicion that the deprescribing of a proton-pump inhibitor among patients on hemodialysis could increase their risk of developing a gastrointestinal bleed. Although the study we conducted was not sufficiently powered to capture a change in gastrointestinal bleed incidence, the counterbalancing measure for harm was reporting the gastrointestinal bleed occurrences in both the control and intervention units of our study.

The Clinical Informatics Specialist was asked to conduct a search in the electronic medical record's progress notes for the following criteria:

- From September 2022 – April 2023 (beginning of the deprescribing study until 3 months post study completion
- Any patient that had the following word listed in their progress notes during this time:
    - GI bleed ○ UGIB ○ LGIB
    - GIB
    - gastrointestinal bleed ○ red stool ○ black stool ○ hematochezia
    - Melena

From these results ÉBC manually extracted the list of patients that were included in the study (both intervention and control units) and reviewed each entry of these patients to determine an occurrence of a gastrointestinal bleed during the above specified timeframe. The study lead would then verify their list of medications and the date of prescription to determine if a proton-pump inhibitor had already been prescribed or not at the time of the gastrointestinal bleed.

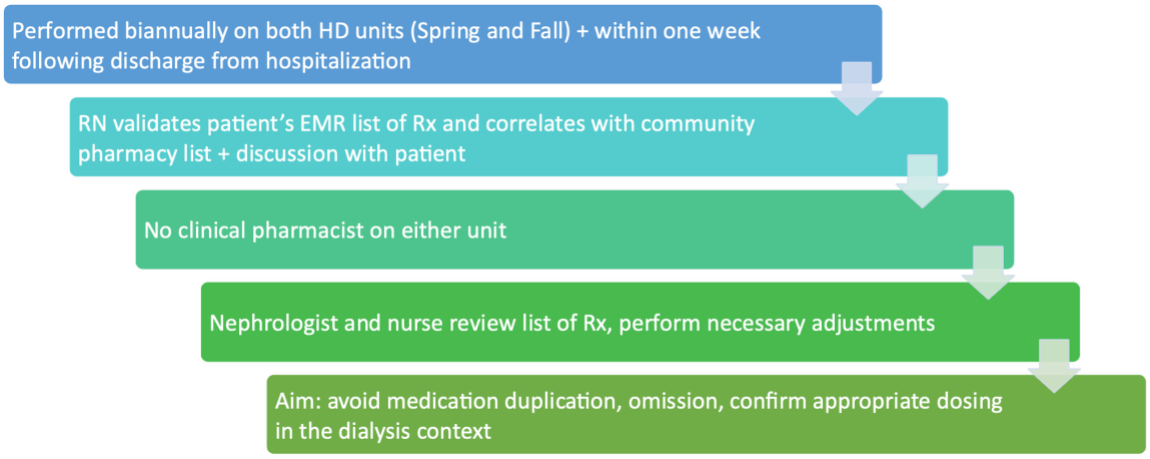
Supplemental Method 2: Method for Capturing Death[8]

From the initial list of patients given to the study lead (control and intervention units), at the end of the study, ÉBC manually conducted a search of each participant's progress notes to capture potential deaths that occurred during the same time frame specified for the reporting of the gastrointestinal bleeds.

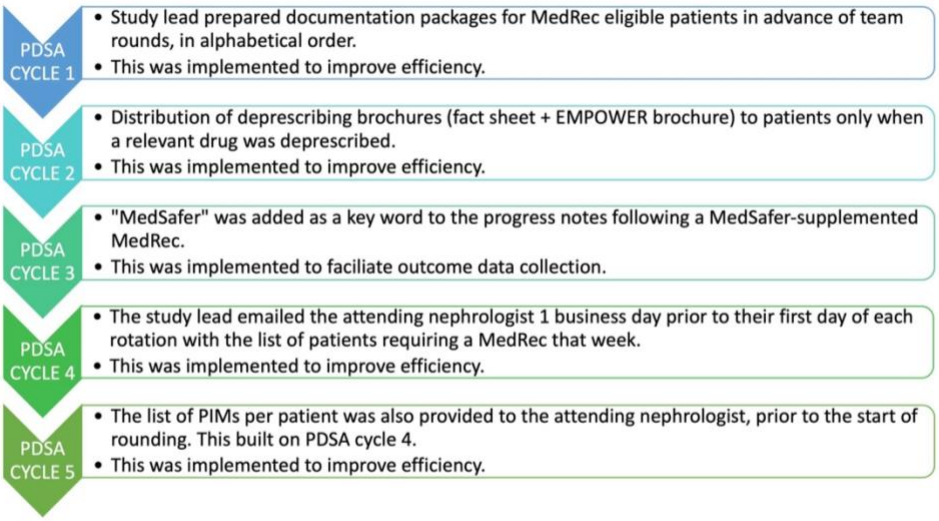
[7] This was the method used to screen and capture any possible gastrointestinal bleed that occurred during the study, and up to 3 months post-study completion.

[8] This was the method used to screen and capture any death that occurred during the study, and up to 3 months post-study completion.

Supplemental Figure 1: The Medication Reconciliation Process[9]



Supplemental Figure 2: Plan Do Study Act (PDSA) Cycles During the Quality Improvement Intervention[10]



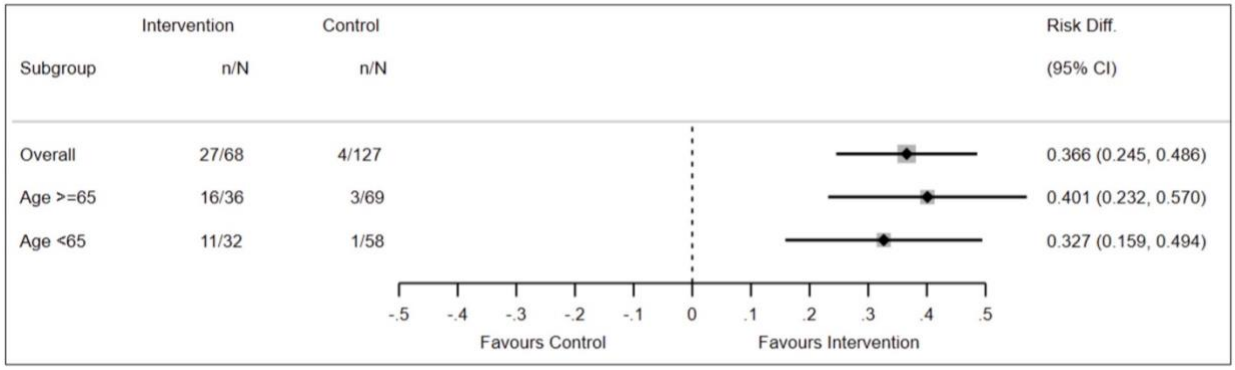
Abbreviations: PDSA=Plan, Do, Study, Act; MedRec=medication reconciliation; PIM=potentially inappropriate medication

---

[9] This figure describes the medication reconciliation process on the intervention unit of the deprescribing in hemodialysis project using MedSafer.

[10] This figure describes the five Plan, Do, Study, Act (PDSA) cycles that took place during the quality improvement study on the intervention unit. Each cycle aimed to facilitate the workflow of the deprescribing process during the medication reconciliation on the intervention unit.

Supplemental Figure 3: Subgroup Analyses – Stratified by Age (Younger vs. Older Than 65)[11]



[11] This figure reports the efficacy of usual medication reconciliation (control unit) versus usual medication reconciliation supplemented with MedSafer deprescribing (intervention unit), stratified by age (older vs. younger than 65 years old). This figure demonstrates that, irrespective of age, deprescribing reduced the number of potentially inappropriate medications prescribed to patients on dialysis on the intervention unit.

Supplementary Figure 4: Example of a Deprescribing Eliminating Medications Through Patient Ownership of End Results (EMPOWER) Brochure[12]

[12] This is an example of an Eliminating Medications Through Patient Ownership of End Results (EMPOWER) brochure that was provided to patients on the intervention unit of the quality improvement study on deprescribing using MedSafer. Types of deprescribing brochures provided during the study were specific to the following classes of medications: proton-pump inhibitors (PPIs), gabapentinoids, opioids for chronic non cancer pain and sedative-hypnotics. A patient received a brochure for every potentially inappropriate medication that was deprescribed and that belonged to one of those classes.


PPI
Rx Pharmacy
OMEPRAZOLE 20 MG
TAKE ONE CAPSULE BY MOUTH EVERY DAY
QTY: 60
MAY REFILL 6X BY
Date Filled: 12-01-2016
Do I still need this medication?
You are currently taking a proton pump inhibitor (PPI):
Dexlansoprazole (Dexilant®)
Esomeprazole (Nexium®)
Omeprazole (Losec®, Olex®)
Lansoprazole (Prevacid®, Prevacid Fast Tab®)
Pantoprazole sodium (Pantoloc®, Panto IV®)
Pantoprazole magnesium (Tecta®)
Rabeprazole (Pariet®)
* Generic brands often start with the words: APO, Novo, Pms, Ratio, Sanis, Teva
CIHR IRSC
iugm
Université de Montréal
La Chaire pharmaceutique Michel-Saucier en santé et vieillissement
Canadian Medication Appropriateness and Deprescribing Network

TEST YOUR KNOWLEDGE ABOUT THIS MEDICATION

QUIZ

Proton pump inhibitors (PPI)

1. PPIs are sometimes prescribed for heartburn and acid reflux. ◯ TRUE ◯ FALSE
2. More than half of all people taking PPIs probably do not need them. ◯ TRUE ◯ FALSE
3. There are no risks involved in taking PPIs for a long time. ◯ TRUE ◯ FALSE
4. PPIs are the best option to treat occasional heartburn. ◯ TRUE ◯ FALSE

ANSWERS

1. TRUE

Proton pump inhibitors (PPIs) are sometimes prescribed to treat heartburn and acid reflux. PPIs reduce the production of acid in the stomach. The stomach produces acid to help break down food, but sometimes the acid can reflux back up the throat and cause discomfort, pain or burning.

2. TRUE

To treat occasional heartburn, it is recommended to take Tums® or Rolaids® as needed. Should your condition require you to take a PPI, your physician should prescribe the lowest dose for the shortest amount of time possible. The next page lists reasons why PPIs should be continued or stopped.

3. FALSE

Taking a PPI for longer than 4 to 12 weeks has been linked to:

- A higher risk of hip fractures
- Pneumonia
- An infection with the bacteria *Clostridium difficile*, which can lead to severe diarrhea, fever, and in rare cases, death
- A higher risk of kidney problems
- Rare instances of vitamin B12 or magnesium deficiency

4. FALSE

PPIs are powerful drugs. If you have heartburn every now and then, you probably do not need a PPI. Over-the-counter antacids should be sufficient. You can ease heartburn without drugs. This brochure explains how.

Do I need to continue taking my PPI?

Check all that apply:

- ☐ Every day, I take medication that can irritate the stomach, such as anti-inflammatory medication (e.g. ibuprofen or corticosteroids).
- ☐ I had a major stomach bleed.

  If you tick this box, speak to your doctor about your specific circumstances.

I was referred to a gastroenterologist, who looked down my throat with a camera and diagnosed me with:

- ☐ Barrett's esophagitis.
- ☐ Severe erosive esophagitis.

If you checked any of these statements, then long-term use of PPIs is usually recommended.

If you don't know the answers, you should talk to your doctor before stopping your PPI.

When you need a PPI, you should take the lowest dose for the shortest amount of time possible.

Do I need to stop taking my PPI?

Check all that apply:

- ☐ I no longer have heartburn.
- ☐ My symptoms are infrequent.
- ☐ I have been taking my PPI for longer than 12 weeks and I did not check any of the statements on the previous page (page 6).

If you checked any of these statements, continue reading about how to stop your PPI.

Please consult your doctor, nurse or pharmacist before stopping any medication.

ALTERNATIVES

If you do not need to continue taking PPIs, speak to your doctor, nurse or pharmacist. You can make simple changes in your diet and lifestyle. To prevent heartburn, try these alternatives instead of taking a PPI:

- **Watch what you eat**. Try to figure out which food or beverage triggers your heartburn. You might want to avoid:
  - Alcohol
  - Fried food or junk food
  - Spicy food
  - Garlic and onions
  - Citrus fruits
  - Chocolate and peppermint
  - Food with lots of tomatoes
- **Eat smaller meals.**
- **Do not eat before going to bed.** You could also lie with your head raised up by using extra pillows.
- **Stop smoking.** Studies show that smoking increases your risk of heartburn and acid reflux.
- **Lose weight.** Studies show that just by dropping a few pounds, you could reduce heartburn and acid reflux.
- **Do not wear tight clothes.** The added pressure from tight-fitting clothes that constrict your abdomen can make heartburn worse.

MR. TREMBLAY'S STORY

He was taking a proton pump inhibitor (PPI) to relieve heartburn. He was taking Nexium®.

"I am 65 years old and had been taking Nexium® for at least two years to relieve heartburn. Recently, I was hospitalized for pneumonia. At my next medical visit, my doctor suggested I stop taking Nexium®, as new guidelines show that taking a PPI for more than eight weeks could be linked to pneumonia. Furthermore, my doctor told me it could also interfere with the osteoporosis drug I am now taking.

I took his advice. Now when I get heartburn every now and then, I take Tums® and it does the job.

I also made lifestyle changes. I stopped smoking and I lost a few pounds. Not only did my heartburn almost disappear, but these changes are having a very positive impact on my overall health.

When I know I will be having a big meal, I try to avoid foods that can cause heartburn. I do not drink coffee, I limit my consumption of alcohol and I go out for a walk after dinner.

I know PPIs, like Nexium®, are powerful drugs that have side effects. I trust my doctor to prescribe them only when appropriate and at the smallest dose possible."

TAPERING-OFF PROGRAM

If you have been taking PPIs for a while, your stomach is probably used to their effect. For some people, suddenly stopping PPIs can lead to rebound acidity and worsening symptoms for a couple of weeks. To minimise these symptoms, it is recommended to slowly taper PPIs over four weeks prior to stopping.

There are 3 approaches that are equally effective in preventing symptom return when you stop your PPI:

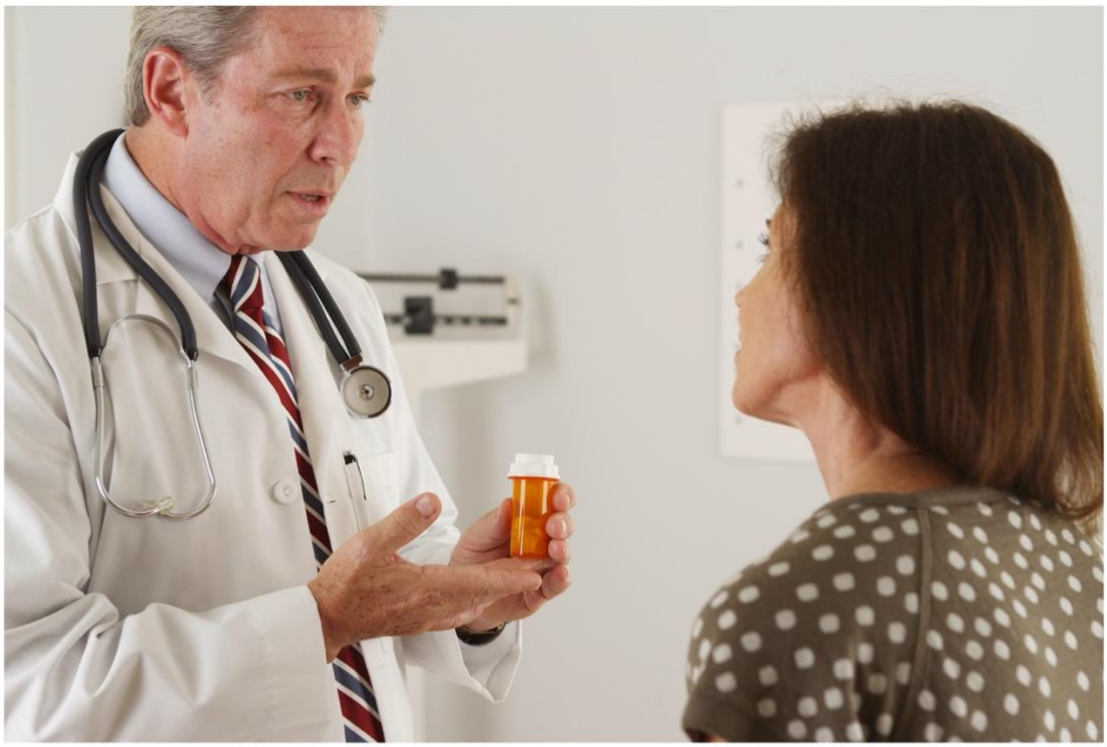
1. One approach is to ask your physician to write a new prescription for only half the dose and take this for four weeks, then stop.

2. Alternatively, you can simply skip a pill every second day for four weeks, then stop.

WEEKS	TAPERING SCHEDULE							✓
	MO	TU	WE	TH	FR	SA	SU	
1		●		●		●		
2	●		●		●		●	
3		●		●		●		
4	●		●		●		●	

3. Or, you can use your PPI or alternatives such as ranitidine (Zantac®) or antacids including Tums®, Rolaids® or Maalox® to keep control of your symptoms, only when needed.

In order to select the best option for you, make sure you discuss this with your doctor, nurse or pharmacist.



Most PPI tablets or capsules cannot be cut. Please talk with your phamacist before cutting your PPIs.

Make a special appointment to review your medications with your doctor, nurse or pharmacist.

Consult with a health care professional before deciding to taper off your PPIs. You may be on other medications (e.g. anti-inflammatory drugs or corticosteroids), which require you to stay on PPIs or switch to another stomach protective agent.

5 QUESTIONS TO ASK YOUR HEALTH CARE PROVIDER

1. Do I need to continue my medication?
2. How do I reduce my dose?
3. Is there an alternative treatment?
4. What symptoms should I look for when I stop my medication?
5. With whom do I follow up and when?

Questions I want to ask my health care provider about my medication

Use this space to write down questions you may want to ask:

This brochure can be found online at:

www.deprescribingnetwork.ca/useful-resources

Supplemental Figure 5: Example of a MedSafer Deprescribing Report[13]

2024-04-04 - Page 1 of 3

MedSafer
Working Towards Safer Prescribing

MedSafer Report - Deprescribing Opportunities
as of 2024-04-04

Mr. Potato Head Male 94yo - Private office

This document contains prioritized **opportunities** for a **reassessment** of the listed medications. Any decisions should take into context what you know about your patient and your clinical assessment of the **risks** and **benefits** of what has been presented.

If you have questions, suggestions, or you would like to report an error, please email support@medsafer.org with the subject line "MedSafer Report"

Tapering instructions or withdrawal concerns?

Please refer to the tapering instructions on last page.

Drugs considered high risk for adverse drug events

#	DRUG	CAUSE OF ALERT	WHY MIGHT THIS BE INAPPROPRIATE?	TAPERING INSTRUCTIONS
1	clopidogrel (clopidogrel bisulfate) (Plavix)	warfarin sodium (Coumadin)	Dual antithrombotic therapy increases the risk of major hemorrhage. Use of proton pump inhibitor reduces but does not eliminate GI bleeding risk. Dual therapy should be reevaluated for ongoing necessity.	No
2	insulin lispro (Admelog)	Diabetes	Your patient had a recent hemoglobin A1c measurement of less than 7.5%. Avoid using medications known to cause hypoglycemia. In many adults aged 65 and older, who are frail, or have a reduced life expectancy, moderate control (A1c 8-8.5%) is reasonable. Consider decreasing insulin dose.	Yes
3	hydromorphone hydrochloride (Hydromorph.ir)	General	Don't initiate or maintain opioids long-term for chronic pain until there has been a trial of non-pharmacologic treatment and of non-opioid medications. Non-pharmacologic modalities for chronic pain include exercise, weight loss, cognitive-behavioural therapy, massage and physical therapy. Depending on the pain mechanism and co-morbidities, non-opioid medications include: acetaminophen, NSAIDS and other molecules. An opioid trial should be guided by clear criteria for monitoring the success and a plan for stopping if criteria are not met. This message is adapted from Choosing Wisely Canada.	Yes
4	zopiclone (Zoclone)	General	Don't use benzodiazepines or other sedative-hypnotics in older adults as first choice for insomnia, agitation or delirium. For patient material related to this class of medications see link below.	Yes

Drugs considered intermediate risk for adverse drug event

#	DRUG	CAUSE OF ALERT	WHY MIGHT THIS BE INAPPROPRIATE?	TAPERING INSTRUCTIONS
1	candesartan cilexetil (Atacand)	Hyperkalemia	Risk of precipitating recurrent hyperkalemia, avoid combining with potassium sparing diuretics such as spironolactone if there is a history of hyperkalemia.	No

[13] This is an example of a MedSafer deprescribing report that was provided to nephrologists on the intervention unit. The report classifies a patient's potentially inappropriate medications (PIMs) according to risk. High risk means that the harms of the medication almost always outweigh the benefits; intermediate risk means that the risks and benefits need to be reevaluated, and low risk means that the medication is likely superfluous and contributes to the patient's pill burden. The last section of the report provides tapering instructions of PIMs, when necessary.

2	pantoprazole (pantoprazole sodium) (Panto-Byk)	General	Chronic PPI therapy should be reevaluated regularly. For patients aged 60 years and older along with two or more of the following, ongoing therapy may be beneficial: antiplatelet, NSAID, systemic steroids, anticoagulation, prior upper gastrointestinal bleed. Other scenarios requiring ongoing therapy include: hypersecretory conditions, dual antiplatelet therapy, variceal banding within 14 days, and H. Pylori treatment. For patient material related to this class of medications see link below.	Yes
3	warfarin sodium (Coumadin)	Dialysis	Consider deprescribing coumadin in patients with Atrial fibrillation and receiving hemodialysis. Apixaban could be a potential alternative, but this remains controversial. Studies are ongoing about the safety of replacing coumadin with apixaban. Prescriber must use clinical judgement in continuing coumadin. Please see guideline on Canadian Cardiovascular Society. Canadian Cardiovascular Society Guidelines for Atrial Fibrillation	Yes

Drugs of potentially little benefit or value

#	DRUG	CAUSE OF ALERT	WHY MIGHT THIS BE INAPPROPRIATE?	TAPERING INSTRUCTIONS
1	allopurinol (Alloprin)	Dialysis	If last gout attack was > 12 months ago AND absence of clinical manifestations of gout, initiate deprescribing trial of urate-lowering agent.	Yes
2	docusate calcium (Albert Docusate)	General	Don't use stool softeners to prevent or treat constipation. Controlled studies have shown that drugs such as docusate are ineffective at treating or preventing constipation.	No

Tapering Instructions

NOTE #	DRUG	INSTRUCTIONS
1	**ADMELOG INSULIN LISPRO**	No tapering required. Watch for rebound hyperglycemia.
1	**ALLOPRIN ALLOPURINOL**	No tapering required
1	**HYDROMORPH.IR HYDROMORPHONE HYDROCHLORIDE**	Withdrawal symptoms peak at 48-72 hours and resolve in days to weeks; psychological symptoms may last months. Initial signs: anxiety, sweating, lacrimation, yawning, rhinorrhea, piloerection, anorexia, irritability, mydriasis, cravings. Later signs: insomnia, gastrointestinal upset, tachycardia, hypertension, muscle spasms and pain. RECOMMENDATION: Withdraw gradually (empirical decrease by 10% every 5-7 days) and adjust depending on tolerance. For patient material on opioids/narcotics: http://www.criugm.qc.ca/fichier/pdf/OpioidsEN.pdf Opioid resources from the College of Family Physicians of Canada: https://www.cfpc.ca/chronic-non-cancer-pain-management-opioid-resources/
1	**ZOCLONE ZOPICLONE**	If used daily for more than 3 to 4 weeks, taper more slowly. Decrease by 10 to 25% every 2 weeks. Frequency of dose reductions may need to slow down at smaller doses (ex. 25% of original dose). Monitor every 1 to 2 weeks for duration of tapering. If intolerable symptoms of insomnia occur (usually 1 to 3 days after a dose change), go back to the previously tolerated dose until symptoms resolve, and plan for a more gradual taper. For patient material and a tapering regimen with patient/caregiver involvement, please see the following link on sedative-hypnotics: http://www.criugm.qc.ca/fichier/pdf/BENZOeng.pdf
1	**PANTO-BYK PANTOPRAZOLE (PANTOPRAZOLE SODIUM)**	Stopping a PPI abruptly may lead to rebound hyperacidity. Patients on long-term therapy (>3 months) or high dose may benefit from tapering over 2-4 weeks. As needed H2 blocker therapy may mitigate some symptoms of rebound hyperacidity. For patient material and a tapering regimen with patient/caregiver involvement, please see the following link on PPIs: http://www.criugm.qc.ca/fichier/pdf/PPI-EN-Men.pdf
1	**COUMADIN WARFARIN SODIUM**	No tapering required

Chapter 3

Supplemental Method 1: Sampling method[14]

```
filtered_patients <- anti_join(Oacis, RISQ, by = c("PatientID" =
"pt_mrn"))

sampled_pts <- filtered_patients %>% sample_n(100)

print(sampled_pts)
```

Supplementary Method 2: First Logistic Regression – Medication Overload, Using Polypharmacy Including Antiretroviral Therapy as a Covariate[15]

$$\begin{aligned} Medication\ overload \\ &= -3.05 - 0.081 * patient\ age + 0.38 * sex + 0.041 \\ &* duration\ of\ HIV\ infection + 1.84 \\ &* exposure\ to\ polypharmacy\ including\ ART + 0.0011 * CD4\ count \end{aligned}$$

[14] This was the sampling method used to randomly select 100 patients to be included in the retrospective study on medication overload among older adults with HIV.

[15] This was the final logistic regression equation determining the influence of polypharmacy, including antiretroviral therapy, on medication overload.

Supplementary Method 3: Second Logistic Regression – Medication Overload, Using Polypharmacy Excluding Antiretroviral Therapy as a Covariate[16]

$$Medication\ overload$$
$$= -1.23 + 0.23 * patient\ age - 0.043 * sex + 0.0079$$
$$* duration\ of\ HIV\ infection + 2.44 * exposure\ to\ non$$
$$- ART\ polypharmacy - (5.95 * 10 - 5) * CD4\ count$$

[16] This was the final logistic regression equation determining the influence of polypharmacy, excluding antiretroviral therapy, on medication overload.

Supplemental Chapter – Use of MedSafer Electronic Decision Support for Deprescribing in Patients on Hemodialysis: A Qualitative Study[17]

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[17] This was the study reporting on the qualitative interviews that were conducted among the nephrologists that participated in the intervention unit of the quality improvement study on deprescribing among patients on hemodialysis. This manuscript is currently under peer review at the Health Literacy and Communications Open Journal.

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H4A 3S9

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Number of tables and figures: 1 table

Abstract

Background

Patients on dialysis are commonly prescribed multiple medications (polypharmacy), many of which are potentially inappropriate medications (PIMs). PIMs are associated with an increased risk of falls, fractures, and hospitalization. Deprescribing is a promising intervention to reduce PIMs.

Methods

We previously conducted a prospective controlled trial whereby we provided deprescribing decision support to nephrologists in one of two tertiary care outpatient hemodialysis units in Montreal, Canada. We aimed to collect information on barriers and facilitators to implementing deprescribing decision support with an electronic tool (MedSafer) by conducting semi-structured interviews among the four nephrologists who participated in the intervention arm of the study, between February and April 2023, following completion of the study. The four nephrologists had conducted medication reviews for a total of 68 patients on the intervention unit during the study. Interviews with participating nephrologists were conducted and transcribed by the study lead. Afterwards, data was coded and analyzed thematically with a focus on their perspective on participating in a quality improvement project during their clinical practice. Two graduate students used a combination of deductive (Theoretical Domains Framework) and inductive coding to analyze each transcribed interview in duplicate. Each coder then created a mind map to visually interpret results and derive themes. A senior qualitative researcher oversaw the development of the final common themes from the interviews.

Results

Four themes were developed: 1) the importance of deprescribing for patients on hemodialysis, 2) barriers to the success of the deprescribing intervention (e.g., the lack of a clinical pharmacist on the unit), 3) resources that were needed during the intervention (e.g., multidisciplinary team members to facilitate medication reconciliation), and 4) resources that facilitated the intervention (e.g., the provision of deprescribing brochures to patients).

Conclusions

This was the first study to explore the perspectives of nephrologists participating in a quality improvement project on deprescribing for patients on hemodialysis. This study interviewed a limited number of prescribers, which could limit the contextualized understanding of the nephrologists' experiences. As a next step, some of the facilitators identified by the nephrologists should be implemented and studied in a larger clinical trial.

Trial registration: NCT05585268

Keywords (5)

Polypharmacy; dialysis; deprescribing; decision support; chronic renal insufficiency

Plain language summary

This study evaluated the feedback of nephrologists (kidney doctors) using a software to help them stop unnecessary or harmful medications that dialysis patients took. The study found that this tool was important, but there were some challenges to using it. For example, not having a pharmacist on the team led to more work for the nephrologists. The study also identified

helpful tools, like having a team of healthcare workers to check medication lists. It was also helpful to give patients information brochures about their medications. The study only interviewed a small number of doctors. The next step would be to test the software and the brochures in a larger study. This was the first study of its kind.

Introduction

Up to 90% of patients on hemodialysis have polypharmacy,[1] defined as taking five or more medications.[2] While the majority are important and beneficial, many are also potentially inappropriate.[3] Potentially inappropriate medications (PIMs) may have limited benefit, can increase a patient's pill burden, and can increase the risk of developing adverse drug events (ADEs), defined as harm caused by a medication.[4] Given that 93% of patients on dialysis are estimated to be receiving one or more PIMs,[1] pragmatic, scalable interventions to reduce medication burden in this patient population are needed. One promising intervention is deprescribing, defined as the process of stopping, dose reduction, tapering, or switching a medication to a safer alternative.[5] The process is supervised by a healthcare provider with the goal of managing polypharmacy and improving health outcomes, such as quality of life, risk of falls, or mortality.[6-8]

Despite a high prevalence of PIMs among patients on dialysis, deprescribing is poorly studied in this population. Deprescribing often takes the form of a healthcare professional with specialized medical expertise manually cross-referencing a patient's medications and their medical conditions with static PDF guidelines that contain lists of PIMs.[9,10] Qualitative research suggests that general practitioners and specialists are open to deprescribing initiatives, but view the

process as time-consuming and often incompatible with their work flow and competing clinical duties.[11,12] Electronic decision support is one proposed solution to overcome several barriers to deprescribing by shortening the time it takes to perform a medication review to identify PIMs, and by providing evidence and instructions for deprescribing at the point of care.[13-16] Electronic decision support is a promising solution to overcome several barriers to deprescribing. The process can shorten the time to perform a medication review and more readily identify PIMs at the point of care, coupled with evidence, and instructions for deprescribing. However, there are implementation challenges related to using these tools to deprescribe, such as manual data entry, the requirement for data linkage, data privacy and security, need for integration into numerous existing electronic medical records, and clinician alert fatigue.[16-18]

MedSafer is an electronic decision support tool that has previously been shown to increase deprescribing for hospitalized older adults[19] and for people residing in long-term care.[20] In September 2022, we conducted a quality improvement study with MedSafer in the outpatient hemodialysis setting. The primary aim of the previous quality improvement study was to compare the efficacy of MedSafer deprescribing decision support with usual care (medication reconciliation, a required activity for hospital accreditation in Canada) for patients receiving dialysis. The complete quantitative results of the study are published elsewhere; briefly, MedSafer increased the proportion of patients with one or more PIMs deprescribed by 36.6% (95% CI = 24.5-48.6; $p<0.0001$) compared to usual care.[21] Herein, we report the results of the paired qualitative study that sought to collect feedback on the barriers and facilitators to implementing deprescribing decision support with MedSafer by conducting semi-structured

interviews with nephrologists who participated in the intervention.

Methods

Design

We employed an exploratory approach to qualify the perspectives of four nephrologists who participated in the study. Interviews were conducted by the study lead to better understand how the nephrologists (hereafter referred to as the participants) experienced the implementation of deprescribing decision support on the dialysis unit and the influence this had on their practice. The information was not otherwise obtainable through survey methods. Ethics approval for the quality improvement patient-facing component of the study was waived for this study by the McGill University Health Centre Research Ethics Board (MUHC REB); for this qualitative component of the study, nephrologists provided verbal and written consent prior to the interview. Results are reported in accordance with the Consolidated Criteria for Reporting Qualitative Research (COREQ; checklist in the Appendix).[22]

Setting and participants

The study protocol for the intervention has been previously published.[3] Briefly, the study took place on two outpatient hemodialysis units at a large hospital centre in Montreal, Canada, from September to December 2022. During the intervention, each nephrologist attended on the unit for 7 days at a time. Nephrologists only conducted clinical rounds on the intervention unit to eliminate possible cross-contamination with the control site. Prior to the planned biannual medication reconciliation, patient health data from the electronic medical record (Renal Insight[23]) was input into MedSafer,[24] an electronic clinical decision support tool for deprescribing, to generate deprescribing reports for each patient. On the intervention unit, in

addition to usual medication reconciliation, treating nephrologists received the MedSafer reports, and patients received deprescribing EMPOWER[25] brochures for select classes of PIMs (sedative-hypnotic drugs,[26] gabapentinoids,[27] proton-pump inhibitors (PPIs)[28], and opioids for chronic non cancer pain[29]). The brochures aim to empower patients to act as drivers of safer prescribing practices.[30] They describe the risks and benefits of the medication class in patient friendly language, provide non-pharmacologic alternatives, and a proposed visual tapering schedule.[25] Four nephrologists on the intervention unit provided care for 68 patients over the course of the study. On the control unit, patients received usual medication reconciliation alone.

Between February and April 2023, following study completion, all four nephrologists attending on the intervention unit were invited by email and agreed to participate in qualitative interviews. The first author then conducted semi-structured interviews with each participant, using an encrypted teleconference software (Zoom[31]). Due to the limited number of prescribers that participated, all were selected to participate to maximize the amount of data extracted. All took part in the interviews, none dropped out or refused to participate. All four were clinicians (who were also either scientists or educators) working at the hospital centre.

Data collection

An interview guide is available in Appendix. It was previously tested by members of our team in a quality improvement study using MedSafer in a long-term care home; the guide was adapted for nephrologists attending on the outpatient hemodialysis unit. It was developed to focus on the usual medication reconciliation process, their experience taking part in the deprescribing

quality improvement study, and to explore barriers and facilitators that arose during the study. Questions were provided to the participants prior to the start of the interview.

Semi-structured interviews were conducted by a female nurse clinician (PhD candidate) with experience appraising qualitative health research through prior studies and graduate coursework. Interview dates (one per physician) were as follows: February 24th, March 2nd, March 14th, and April 20th. The interviews were conducted virtually using an encrypted teleconference software (Zoom[31]). Interviews generated a total of 60 minutes of data. No other researcher or non-participant(s) were present in the interviews. Participants were aware that the interviewer (ÉBC) was a nurse clinician and PhD candidate conducting her thesis on deprescribing in special populations. ÉBC had previously developed a collegial relationship with each participant during the study due to her presence on the unit while the study took place. Otherwise, no other characteristics were reported about her to them.

Audio recording from the teleconference platform was used to collect the data. One interview presented an audio dysfunction; in this case, the interviewer left the virtual meeting space and rejoined. The meeting recording was restarted later in the interview; the interviewer noted the answer of the nephrologist, performed a read-back with the nephrologist to validate their answer, and recorded it for data analysis. The interviewer also recorded and saved field notes with each transcript; neither were returned to participants for comment/correction because the interviewer summarized the contents of the response to the participant after each question answered during the interview. Moreover, participants were all busy healthcare professionals who lacked time in their schedules for a meeting to discuss our notes. Repeat interviews were

not conducted. Raw data (recordings, transcripts, field notes), coding schema, coded transcripts, and theme reports were filed by date to provide an audit trail. Each interview was then transcribed verbatim using artificial intelligence transcription software (OtterAI[32] and Happy Scribe[33]), then verified manually for accuracy against audio recordings. Transcripts were not deidentified for the first coder because she was the interviewer and recognized the identity of participants based on the recorded responses; however, transcripts were deidentified for the second coder and for subsequent researchers involved in the data analysis.

ÉBC coded interview transcripts along with a second coder, JJL (a female MSc student in digital health), who had prior experience with research in appropriate prescribing. Both coded independently. Supervisors were a female clinical pharmacist (PharmD) specialized in qualitative health research and a female researcher (PhD medical anthropology) expert in qualitative health research.

Data analysis

The transcripts were analyzed by ÉBC and JJL. The coding tree is provided in the Appendix. A mix of deductive and inductive coding was used.[34] The first author deductively used the 2nd version of the Theoretical Domains Framework[35] to code, line by line, the transcripts of each interview. The Theoretical Domains Framework was chosen for this exploratory study because of its use in understanding barriers and facilitators in healthcare quality improvement projects.[36] She found the topic of pertaining to the need for a clinical pharmacist on the unit was frequently raised in the transcripts, but no code from the Framework was able to capture this important feature from the transcripts. She thus added “Pharmacist” inductively to the coding of interviews.

Furthermore, she inductively added a code for each interview question number to analyze the contents of the interviews both in their entirety and separated by question. Her coding schema was applied manually using MAXQDA[37] in April 2023. To enhance credibility, throughout this period, ongoing coding review was done with the first coder and senior authors with expertise in qualitative health research (they received copies of the de-identified transcripts). This process allowed the research team to actively engage in recurrent observation and reflection with regards to the data. Several specific themes were drafted by the first coder, and excerpts from the transcripts supplemented them for validation. Afterwards, the first coder built a virtual mind map using SimpleMind[27] to visually situate and create links between these themes. This allowed a further refining of the initial themes.

After this was completed, the first coder provided the second coder with copies of the non-analyzed transcripts, the Theoretical Domains Framework (TDF), and readings on qualitative research to conduct prior to coding.36,38 She was instructed to use deductive, inductive, or a blend of both coding methods in her transcripts, to her discretion. She was also instructed to create a mind map of the contents of her findings from the interviews and to develop themes from these. Following these steps, both coders presented their mind maps to senior authors with expertise, to compare analyses and developed themes, and for derivation of the final four themes. Neither coder had prior access to the other coder's data or mind maps.

Results

We interviewed 4 nephrologist-participants (3 female; 1 male) that cared for a total of 68

patients from the primary study. We developed four themes from the qualitative data: 1) the importance of deprescribing for participants, 2) barriers to implementing the intervention, 3) resources needed to deprescribe during medication reconciliation, and 4) resources that facilitated the deprescribing intervention.

The importance of deprescribing for nephrologists

Participants were treating a wide variety of patients that each had their own sets of beliefs and values (TDF Beliefs about consequences – Beliefs). Interacting with their realities was both a facilitator and a barrier to deprescribing (Table 1: The importance of deprescribing for clinicians, Interacting with the realities of patients; TDF Person and environment interaction). All participants agreed on the importance of deprescribing in their practice. Patients on hemodialysis are regularly hospitalized, medications are often changed, added, reduced, and/or stopped. The dialysis nephrologist is often the physician the patient is most exposed to; they are the central point of contact for all their medical issues, often acting as a primary care provider. As a result, the nephrologists we interviewed felt a clinical duty to ensure medications were regularly reviewed for safety and effectiveness (TDF Professional role). The importance of deprescribing for participants was part of a broader context of ensuring they are providing the best care and striving for the best patient outcomes. Despite this general consensus, participants raised a number of barriers to deprescribing.

Barriers to implementing the intervention

We determined three main barriers to implementing the intervention: unpredictable timing of medication reconciliation, the organization of the workflow, and evidence to support

deprescribing opportunities.

Unpredictable timing of medication reconciliation

On the dialysis ward, it takes place biannually, if the patient requests it, and within one week following discharge from any hospitalization. However, when asked about the usual frequency of medication reconciliation, each participant gave a different answer (e.g., every 4-6 months, every 3-4 months, and another two said "regularly'). The lack of a fixed, predictable schedule to conduct medication reconciliation presented a possible barrier to implementing a deprescribing intervention (TDF Group norms).

Organization of the workflow

Participants further expressed that the organization of their workflow was a barrier to implementing the intervention (TDF Organizational culture/climate). In Quebec, Canada, the healthcare system is still heavily reliant on paper-based communication to members of the interprofessional healthcare team, such as pharmacists, and, most notably, through faxing. Three participants noted the time pressures and the difficulty allotting time outside their usual clinical duties to deprescribe were barriers to the success of the intervention (TDF Action planning): "It took an extra 10-15 minutes per patient. You have to talk to the patient, confirm the drug is being taken, which included discussing with the patient and reviewing previous medical records. Then, you need to take the medication that needed to be deprescribed, go in the EMR, discontinue the drug, print out the prescription to fax, sign the prescription, have it faxed (...)." (Table 1: Organization of the Workflow, point 1).

In addition, participants were asked to provide deprescribing brochures to patients for the classes of medications that were deprescribed. In practice, however, this was not systematically done. This was mainly due to a lack of time to provide both the brochure and education on its content (TDF Action planning).

This relates to an issue that three participants raised several times during their interviews: the lack of a clinical pharmacist on the unit. Unfortunately, the pharmacist recently retired and was never replaced. As a result, the responsibility of conducting the bulk of the medication reconciliation was on the shoulders of the nephrologists, (Table 1, Organization of the workflow, points 2, 3; TDF Cognitive overload). They found the workload related to the electronic deprescribing quality improvement project greater than their usual clinical duties.

Evidence to support deprescribing opportunities

MedSafer reports provide deprescribing opportunities along with a small paragraph summarizing the evidence and the rationale. However, two participants were not convinced by the evidence in the reports for certain medications: “I don't think [deprescribing] is widely accepted. I don't doubt that literature review and evidence [...]. But I don't think it's not widely accepted that aspirin shouldn't be prescribed for dialysis patients, or at least [that] there's no benefit. So [...] when my instinct or common sense, and the patient's common sense and instinct, did not agree with what was recommended, that made it difficult.” (Table 1, Evidence to support deprescribing opportunities, point 1, 2). One said the evidence for deprescribing was not readily available. Another highlighted a recent observational study on deprescribing proton pump inhibitors for patients on hemodialysis and expressed concern about gastrointestinal

bleeds.[39] Both participants said that more research is needed to validate that deprescribing will not harm patients (TDF Knowledge, including knowledge of condition/scientific rationale).

Resources needed to implement a deprescribing intervention

As one participant noted, for a deprescribing resource to be effectively implemented, electronic or not, it needs to include two factors: it must be readily available, and it must lead to deprescribing more efficiently. Three participants found that having a clinical pharmacist on the unit would enhance the intention of implementing of this electronic deprescribing intervention (TDF Implementation intention), would bring leadership to the interdisciplinary group (TDF Leadership), and allow for self-regulation of the medication reconciliation activities (Table 1: Resources needed to implement a deprescribing intervention, points 1 and 2; TDF Self-monitoring). The clinical pharmacist could support the workflow and workload of physicians, create opportunities to include patients in the deprescribing process through education, and help initiate the decision-making process to deprescribe. Given the clinical pharmacist's absence, one physician spoke of the importance of attributing a larger role to nurses during the medication reconciliation process because of their vast knowledge on medications and the medical field (Table 1: Facilitating Resources, point 1; TDF Professional role and Professional boundaries).

Leveraging the electronic medical record was identified as another resource to facilitate patient data entry on a web-based portal (TDF Resources/material resources). The MedSafer software has an application programming interface (API), which allows for integration into electronic medical records to generate reports by analyzing existing data in the medical record (removing any need for manual data entry). However, given this was a small pilot study, integration with

the medical record was not pursued. One participant did recommend MedSafer integration within the medical record for the future.

Finally, one participant spoke of goal setting to encourage and complete future medication reconciliations (TDF Goal/target setting): “If we ask everybody to review half a shift per week, this would imply reviewing seven, eight patients per week. I think everybody can do that. Even if time is limited, the resources are limited, and in three months, we will have done everybody, and they will wait three months, do nothing, and then start over again. But if we do not formally implement it, it risks getting a bit forgotten or delayed.” (Table 1: Resources needed, point 3).

Resources that facilitated deprescribing during medication reconciliation

Participants found that having the MedSafer deprescribing reports generally helped them deprescribe during the medication reconciliation activity (TDF Resources/material resources). Three participants reported feeling more confident deprescribing after having used MedSafer compared to previous experiences conducting medication reconciliation (TDF Professional confidence). One felt equally confident as before, although they said the tool helped them deprescribe.

Two participants again recommended making use of existing personnel during the medication reconciliation process. While the clinical pharmacist was not available on the unit, participants did highlight the role of nurses. A cursory medication review was performed by nursing staff and documented in the patient’s electronic progress notes, and the nephrologist subsequently reviewed the medications. This helped screen for potential omissions and duplications. (Table 1: Facilitating Resources, point 1).

The participants that provided the deprescribing EMPOWER brochures regularly or occasionally said they provided written knowledge, opportunity for patients to engage in the deprescribing process, and trigger a discussion on it (TDF Resources/material resources). They recommended that other members of the interdisciplinary team distribute and provide teaching on deprescribing, as participants had limited time, and an increased workload using MedSafer and conducting medication reconciliations.

Discussion

This qualitative study presents the experiences of nephrologists participating in paired deprescribing with medication reconciliation activities in the outpatient hemodialysis setting. These results show that for a deprescribing intervention to be successful, a structured, scheduled, and interdisciplinary program fitting seamlessly with the existing workflow needs to be implemented.

MedSafer has previously been shown to be effective for deprescribing in a large cluster randomized controlled trial; as such, the goal of this study was to examine barriers and facilitators to its implementation. The real-world application of deprescribing decision support is being studied in various clinical settings.[1,19,24] Efficacy was previously quantified in our quality improvement study,[21] with a number needed to treat of 3 (aRD 36.6%; 95% CI = 24.5-48.6; p<0.0001),[21] but potential barriers inhibiting the long-term success are ideally assessed qualitatively.[40,41] These factors are relevant for scalability; deprescribing is an ongoing continuous quality improvement process that ideally is not just conducted once.5 As nephrologists all stated in their interviews, medications often change among hemodialysis

patients through the evolution of their disease, from frequent hospitalizations and evolving goals of care. They are seen multiple times per week, for several hours at a time for hemodialysis treatments; they are extremely medically complex, are exposed to mega polypharmacy (10-15 daily medications), and have their own set of deprescribing indications.[42]

Consequently, there is both a need and opportunity to continuously review medications and consider deprescribing. Though these interviews were conducted post-study completion, we aimed to determine what works, what would work, and what will not work for nephrologists, so this intervention could become part of routine care and these results could be potentially sustained over time.

Our findings build on previous work studying the experiences of prescribers that deprescribed, but only two studies have explored this in the hemodialysis setting.[42,43] One gathered the perceptions of both patients and prescribers in hemodialysis following a pharmacist-led intervention of 8 deprescribing opportunities.[42] Interviewed providers found that protected time to review medications and deprescribe was needed and that workflow and workload were barriers to implementing a deprescribing intervention, similar to our study's findings.

Other studies conducted outside the hemodialysis context stress the importance of interdisciplinary collaboration, and the development of clear policies outlining the roles of each clinician within the care team during the medication reconciliation.[44] Having a pharmacist on the team can provide an environment conducive to reviewing medications.[44-47] Furthermore, they indicate the need to provide both clinicians and patients with resources to help them engage in the medication reconciliation and deprescribing processes,[48] which is what we aimed

to do in our quality improvement project by providing deprescribing reports for clinicians and brochures for patients. The EMPOWER brochures have been found to independently increase deprescribing in previous cluster randomized controlled trials.[30,49-51]

Our study has several strengths. First, to our knowledge, this is the first study to evaluate, through semi-structured interviews, the experiences of nephrologists using electronic decision support to deprescribe for patients on hemodialysis. Second, this is the first study to our knowledge that made use of the Theoretical Domains Framework to code interviews in this setting. This deductive framework allowed coders to develop themes through an implementation science lens based on how the intervention can be adapted in the future to ensure sustainability. The inductive and deductive coding blend created the opportunity to develop the "lack of a clinical pharmacist" concept, one that three nephrologists raised as a barrier to the success of the deprescribing intervention.

Our study has several limitations. First, only four nephrologists participated in the interviews, and patients were not interviewed in the study; this small sample may undermine the internal and external validity of our findings. However, these were all of the participants that took part in the deprescribing intervention. As a result, we recorded the experience of every single prescriber, capturing the broadest representation possible of their participation. Furthermore, both coders found substantial overlap between topics among nephrologists, indicating the interviews were exhaustive, collected a substantial amount of data, and increased the internal validity of the study. Second, the intervention was designed to be mainly delivered by a pharmacist, but there was none available on the unit (thankfully, after this study's completion, a

clinical pharmacist permanently joined the hemodialysis unit to provide expertise to the interdisciplinary teams and participate in medication reconciliation activities. We hope that the deprescribing intervention can therefore become a shared responsibility within the interprofessional team to ease the workload of nephrologists). However, there is research that suggests patients are more likely to accept deprescribing if their physician tells them that it is safe to do so.[52,53] Third, the patient-facing materials (brochures) were inconsistently used. This could have influenced patient understanding, shared decision-making and, ultimately, the efficacy of deprescribing in the quality improvement study. Fourth, the interviews generated a total of 60 minutes of data, which is not extensive. However, the highly specific study objective meant that a few brief questions were sufficient to generate the insights that we sought. Moreover, there was significant overlap in the responses provided between nephrologists. Finally, the study lead's multiple roles could have given rise to a Hawthorne effect,[54] given her presence on the unit during the intervention, as well as being the interviewer. The participants were also aware the interviewer was a healthcare professional herself; while prior studies have identified the potential challenges in having a clinician interview a fellow clinician,[55-57] the interviewer did not otherwise work on the dialysis unit and only spent a limited time interacting with nephrologists for the purposes of the study. Some research does show being interviewed by a clinician can, on the contrary, be an empowering process, and can lead to more honesty and vulnerability,[58] with a general appreciation that "at last", someone is listening to and is capable of understanding their concerns.

Conclusion

Among four nephrologists that used an electronic deprescribing decision support on the outpatient dialysis unit, deprescribing was seen as crucial to ensuring the best standard of care during usually performed medication reconciliation. All physicians felt equally or more competent deprescribing following the intervention. Providing deprescribing brochures to patients triggered a discussion on the topic and provided a learning opportunity for them. However, the lack of a clinical pharmacist and the lack of predictable timing of medication reconciliation were barriers to the success of the intervention. A future clinical trial is currently being designed to deprescribe in hemodialysis outpatient clinics by one of the coauthors aiming to address the barriers and facilitators developed in our study. Future studies should evaluate the sustainability of deprescribing following implementation of several of the solutions proposed by nephrologists in this study.

Declarations

Ethics approval and consent to participate

Ethics approval was waived for this study by the McGill University Health Centre Research Ethics Board (MUHC-REB). Informed consent was obtained from the nephrologists for recording and dissemination of interview results.

Availability of data and materials

Data will be made available upon written request to the corresponding author within 6 months of publication of this study.

Consent for publication

Not applicable.

Competing interests

EGM and TCL own the MedSafer intellectual property in conjunction with McGill University and licensed the MedSafer software free of charge for this quality improvement study. None of the other authors have any conflicts of interest to declare that are directly relevant to the manuscript.

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Authors' contributions (CRediT statement)

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Investigation: ÉBC

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Table 1: Quotes supporting themes derived from the interviews

Theme	Quote
The importance of deprescribing for clinicians	1. "It's important, first, because of potential side effects that this medication may have. Or second, some of the treatments are more important than others. So, you want the patient to take at least a few pills that are very important for their health. So, if you give too many, you risk that the patient will not take any of the pills you see?" 2. "It's very important. It gives the patients an opportunity to lessen their pill burden, sickness burden, to reappraise medications that were started that aren't necessary anymore." 3. "(...) I wouldn't say that deprescribing is critical. But a thorough and accurate review of medication on a regular basis is extremely important to ensure that the patients can be stopped from whatever medications they don't need, and then medications that they do need are given to them and that they're adherent to them. So, it's not just about deprescribing in my mind, it's about accurate medication prescription for an individual patient, and ensuring adherence to the appropriate medication without side effects. 4. Well, I think it is important because most of the patients have polypharmacy. There are numerous medications, and they are in and out of the hospital. Every time, something gets added and never reviewed back. So periodically reviewing and deprescribing what is not relevant or necessary is extremely important.
Interacting with the realities of patients	1. "We can prescribe and deprescribe and just fax everything to the pharmacy. But if the patient doesn't know and doesn't agree, then the whole work is wasted." Another physician said: "Some patients were a bit hesitant to stop taking something that they worked on for a long time." 2. "Some patients were a bit hesitant to stop taking something that they worked on for a long time. (...) But I think some of the patients received it very well also. They said: 'well, thank you for doing this. Thank you for looking into my file.' So, it depends on their personality also."

	3. "We deprescribe some of the [medication], but they asked for it back because the pain got worse, for example. So, although some are recommended for stopping, sometimes stopping doesn't work, because the patient seems to depend on it."
Barriers to implementing the intervention: Organization of the workflow	1. "It took an extra 10-15 minutes per patient. You have to talk to the patient, confirm the drug is being taken, which included discussing with the patient and reviewing previous medical records. Then, you need to take the medication that needed to be deprescribed, go in the EMR, discontinue the drug, print out the prescription to fax, sign the prescription, have it faxed (...)." 2. "We need a pharmacist. We used to have one who could talk to the patient, do [medication reconciliations], (...) explain to the patient why they need to take this medication, what the dose should be, why they should be stopping the medication, etc. We really lost that capacity. So, you know, a lot is on the shoulders of the physicians right now. And I think we really need an extra resource to do this in a more stable and reliable manner." 3. "[The pharmacist] retired a few years ago, and since then, we haven't found any replacement. And that's a problem. If we did have a pharmacist, I think that would facilitate the whole process a lot. The pharmacist could take over this initiative with the help of the physician, of course." 4. "So, the only way that [MedSafer-supplemented medication reconciliation] is going to work is that either we have a full-time pharmacist who is looking into this and putting the recommendations in front of our face, which is not going to happen anytime soon. Because you know, pharmacy resources are hard to come by. Or [...] an automatic alert goes to the physician [through the EMR]."
Barriers to implementing the intervention:	1. "[...] I think the literature is a bit controversial for some of those [deprescribing indications in MedSafer]. For PPIs, for example, I did read one study that was observational as well, but that stopping a PPI may have resulted in more adverse events in patients and so forth. So, I would like to see more solid data before uniformly doing these things [deprescribing using MedSafer indications]." 2. "I don't think [deprescribing] is widely accepted. I don't doubt that

Evidence presented in the MedSafer reports	literature review and evidence [...]. But I don't think it's not widely accepted that aspirin shouldn't be prescribed for dialysis patients, or at least [that] there's no benefit. So [...] when my instinct or common sense, and the patient's common sense and instinct, did not agree with what was recommended, that made it difficult."
Resources needed to implement a deprescribing intervention	1. "And I think we really need an extra resource [like a clinical pharmacist] to do this in a more stable and reliable manner. That interface with a patient is the hardest part." 2. Fortunately, [the absence of a clinical pharmacist] is something that, if it's fixed, then I think it will be very helpful for the patients, for patient safety, for us. And it will also be much more efficient as a practice because you can have the pharmacist and a tool like MedSafer and the physician, they are on a formal schedule, and then it will be perfect. You see." 3. "If we ask everybody to review half a shift per week, this would imply reviewing seven, eight patients per week. I think everybody can do that. Even if time is limited, the resources are limited, and in three months, we will have done everybody, and they will wait three months, do nothing, and then start over again. But if we do not formally implement it, it risks getting a bit forgotten or delayed."
Facilitating Resources	1. "[...]Nurses have a lot of medical knowledge. So, if they were actually taught on some of these deprescribing practices, then they could serve as alerts for the physicians as well. (...) I think that would actually enhance patient care a lot if the nurses were [more] involved."

Table 2: COREQ (COnsolidated criteria for REporting Qualitative research) Checklist

Topic	Item No.	Guide Questions/Description	Reported on Page No.
Domain 1: Research team and reflexivity			
Personal characteristics			
Interviewer/facilitator	1	Which author/s conducted the interview or focus group?	8
Credentials	2	What were the researcher's credentials? E.g. PhD, MD	8
Occupation	3	What was their occupation at the time of the study?	8
Gender	4	Was the researcher male or female?	8
Experience and training	5	What experience or training did the researcher have?	8
Relationship with participants			
Relationship established	6	Was a relationship established prior to study commencement?	8
Participant knowledge of the interviewer	7	What did the participants know about the researcher? e.g. personal goals, reasons for doing the research	8
Interviewer characteristics	8	What characteristics were reported about the inter viewer/facilitator? e.g. Bias, assumptions, reasons and interests in the research topic	8
Domain 2: Study design			
Theoretical framework			
Methodological orientation and Theory	9	What methodological orientation was stated to underpin the study? e.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis	10
Participant selection			
Sampling	10	How were participants selected? e.g. purposive, convenience, consecutive, snowball	7,8
Method of approach	11	How were participants approached? e.g. face-to-face, telephone, mail, email	7,8
Sample size	12	How many participants were in the study?	7,8
Non-participation	13	How many people refused to participate or dropped out? Reasons?	8
Setting			

Setting of data collection	14	Where was the data collected? e.g. home, clinic, workplace	8
Presence of non-participants	15	Was anyone else present besides the participants and researchers?	9
Description of sample	16	What are the important characteristics of the sample? e.g. demographic data, date	11
Data collection			
Interview guide	17	Were questions, prompts, guides provided by the authors? Was it pilot tested?	8
Repeat interviews	18	Were repeat inter views carried out? If yes, how many?	8,9
Audio/visual recording	19	Did the research use audio or visual recording to collect the data?	8,9
Field notes	20	Were field notes made during and/or after the inter view or focus group?	9
Duration	21	What was the duration of the inter views or focus group?	8
Data saturation	22	Was data saturation discussed?	19
Transcripts returned	23	Were transcripts returned to participants for comment and/or	9

Topic	Item No.	Guide Questions/Description	Reported on Page No.
		correction?	
Domain 3: analysis and findings			
Data analysis			
Number of data coders	24	How many data coders coded the data?	10
Description of the coding tree	25	Did authors provide a description of the coding tree?	10, Appendix
Derivation of themes	26	Were themes identified in advance or derived from the data?	10,11
Software	27	What software, if applicable, was used to manage the data?	10
Participant checking	28	Did participants provide feedback on the findings?	9
Reporting			
Quotations presented	29	Were participant quotations presented to illustrate the themes/findings? Was each quotation identified? e.g. participant number	Table 1
Data and findings consistent	30	Was there consistency between the data presented and the findings?	18, 19
Clarity of major themes	31	Were major themes clearly presented in the findings?	11
Clarity of minor themes	32	Is there a description of diverse cases or discussion of minor themes?	11-16

Developed from: Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *International Journal for Quality in Health Care*. 2007. Volume 19, Number 6: pp. 349 – 357

Figure 1: Qualitative interview questions

1. Before this study, what place did deprescribing have in your regular workflow?
2. How confident did you feel in deprescribing before participating in this study?
3. How did the MedSafer deprescribing process fit into your workflow on service at the hemodialysis clinic?
4. What were the facilitators of deprescribing in this study? What made the task easier to complete?
5. What were the challenges and obstacles you met deprescribing in this study?
6. How did MedSafer make deprescribing easier in your practice? If this is not the case, how did MedSafer make deprescribing more challenging?
7. What was your experience providing the deprescribing brochures to patients?
8. How confident do you now feel in deprescribing after completing this study?
9. What importance do you give to deprescribing in hemodialysis patients and why?
10. What will you retain in terms of deprescribing moving forward from this study?
11. What place will deprescribing have in your workflow moving forward?
12. Do you have anything you would like to add?

Figure 2 : Coding Tree Used, Based on the Theoretical Domains Framework

List of codes
Question 12
Question 11
Question 10
Question 9
Question 8
Question 7
Question 6
Question 5
Question 4
Question 3
Question 2
Question 1
INDUCTIVE CODES
Pharmacist
DEDUCTIVE CODES (From Theoretical Domains Framework)
Behavioural regulation
Action planning
Breaking habit

Self-monitoring
Beliefs about capabilities
Beliefs
Empowerment
Perceived behavioural control
Perceived confidence
Professional confidence
Self-confidence
Self-efficacy
Self-esteem
Beliefs about consequences
Anticipated regret
Beliefs
Characteristics of outcome expectancies
Consequents
Outcome expectancies
Emotion
Affect
Anxiety
Burn-out
Depression

Fear
Positive/negative effect
Stress
Environmental context and resources
Barriers and facilitators
Environmental stressors
Resources/material resources
Person x environment interaction
Organisational culture/climate
Salient events/critical incidents
Goals
Action planning
Goal priority
Goal/target setting
Goals (autonomous/controlled)
Goals (distal/proximal)
Implementation intention
Intentions
Stability of intentions
Stages of change model
Transtheoretical model and stages of change

Knowledge
Knowledge (including knowledge of condition/scientific rational
Knowledge of task environment
Procedural knowledge
Memory, attention and decision processes
Attention
Attention control
Cognitive overload/tiredness
Decision making
Memory
Optimism
Identity
Optimism
Pessimism
Unrealistic optimism
Reinforcement
Consequents
Contingencies
Incentives
Punishment
Reinforcement

Rewards (proximal/distal, valued/not valued, probable/improbable
Sanctions
Skills
Ability
Competence
Interpersonal skills
Practice
Skill assessment
Skills
Skills development
Social influences
Alienation
Group conformity
Group identity
Group norms
Intergroup conflict
Modelling
Power
Social comparisons
Social norms
Social pressure

Social support
Social/professional role and identity
Group identity
Identity
Leadership
Organisational commitment
Professional boundaries
Professional confidence
Professional identity
Professional role
Social identity