**Adverse Drug Events Related to Polypharmacy in Older Adults:**

**Defining Outcomes and Identifying Opportunities for Safer Prescribing**

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August 2020

A thesis submitted to McGill University in partial fulfillment of the requirements of the degree of *Master of Science*

**Abstract**

**Background:** Polypharmacy, or the concurrent use of multiple medications, is prevalent in adults aged 65 years and older. These patients are vulnerable to adverse drug events (ADEs), due to age-related physiologic changes, the co-prescription of multiple medications, and the use of potentially inappropriate medications (PIMs). Deprescribing is a proposed solution for managing polypharmacy and reducing ADEs. The primary outcome of interest is to reduce ADEs, without a concurrent increase in adverse drug withdrawal events (ADWE). Currently, there is no universally accepted gold standard adjudication method for use in clinical trials of deprescribing, to measure this outcome, nor a method specifically designed to capture ADWEs.

**Objectives:** The primary goal of my thesis was to familiarize myself with polypharmacy and the challenges faced when deprescribing in a clinical setting. I sought to perform a thorough literature review to identify, compare, and contrast existing approaches for the adjudication of ADEs. Secondly, based on extensive research, I took the initial steps to craft a new method in order to allow researchers to easily and more accurately capture rates of ADEs (including ADWEs) in deprescribing interventions. A third objective of my research was to apply the principles of safer prescribing to special populations including; patients on risky medications, patients with chronic illnesses, and patients with COVID-19.

**Methods and Results:** Objective #1- *Methods to Adjudicate Adverse Drug Events,* I performed a systematic review of the literature, compared and contrasted the identified adjudication methods. I identified 10 unique ADE adjudication methods. Objective #2- *New Method of ADE Adjudication,* I made recommendations for an updated methodology. This new method is easy to use, applicable in a variety of settings, has an ADWE component. Objective #3- COVID-SAFER, I theoretically exposed a cohort of patients 65 years and older enrolled in a deprescribing study to hydroxychloroquine. The cohort contained a total of 1,001 unique patients, of which, 590 (58.9%) had one or more home medications that could potentially interact with hydroxychloroquine, and of these 255 (43.2%) were flagged as potentially inappropriate by the MedSafer tool.

**Discussion:** The primary aim of my thesis was to critically analyse the literature. I identified ADE adjudication methods, compared and contrasted their strengths and limitations, and

made recommendations for a new method. Secondly, based on these recommendations I proposed a new method of ADE adjudication to be used in deprescribing trials. This new method is designed to be intuitive for clinicians to use, capturing all potential ADEs more accurately, and being standardized across all studies and settings contributing to an overall safer prescribing environment for older adults. The third objective of my thesis was to apply deprescribing to special populations. I identified a risky medication which places older adults at risk of harm, two populations for which deprescribing may need to be considered at a younger age due to chronic illness, and how polypharmacy may affect older adults with COVID-19. This work throughout my thesis contributes uniquely to the research field while providing the groundwork for future studies.

**Résumé**

**Informations Générales:** La Polypharmacie, ou l'usage concomitant de plusieurs médicaments, est répandue chez les adultes de 65 ans et plus. Ces patients sont vulnérables aux effets indésirables liés aux médicaments dû aux changements physiologiques relatifs à l'âge, la co-prescription de multiples médicaments, et l'utilisation des médicaments potentiellement inappropriés (MPI). La déprescription est une solution proposée pour gérer la polypharmacie et réduire les effets indésirables. Il y a plusieurs résultats importants qui sont étudiés dans les essais cliniques de déprescription, tels que la réduction du nombre de médicaments et de MPI, sans une augmentation simultanée d'évènements indésirables liés au retrait de médicaments. Actuellement, il n'existe pas de méthode d'arbitrage universellement acceptée dans les essais cliniques de déprescription ni de méthode désignée pour capturer les évènements indésirables liés au retrait de médicaments.

**Objectifs:** Le principal objectif de ma thèse de recherche était de me familiariser avec la polypharmacie et les défis rencontrés lors de la déprescription de médicaments dans un contexte clinique. Ayant établi les connaissances de base, j'ai effectué une revue de la littérature pour identifier, comparer et contraster les approches existantes à l'arbitrage des effets indésirables. Deuxièmement, basé sur une vaste recherche, j'ai pris l'initiative d'établir une nouvelle méthode qui permettrait aux chercheurs à capturer plus facilement et précisément les effets indésirables (incluant les évènements indésirables liés au retrait de médicaments) dans les interventions de déprescription. Un troisième objectif de ma recherche était d'appliquer les principes de prescription sécuritaire à une population particulière incluant; les patients prenant des médicaments à haut risque, les patients avec des maladies chroniques et les patients avec le COVID-19.

**Méthodes et Résultats:** Objectif #1- Revue et Synthèse de la Littérature, J'ai effectué une revue systématique de la littérature, comparé et contrasté les méthodes d'arbitrage identifiées. J'ai identifié 10 méthodes différentes pour statuer les effets indésirables. Objectif #2- Nouvelle Méthode D'arbitrage pour les Effets Indésirables, basé sur les résultats de la revue littéraire, j'ai fait des recommandations pour une nouvelle méthodologie. Cette nouvelle méthode est facile à utiliser, s'applique dans plusieurs circonstances, a une composante qui s'adresse aux

évènements indésirables liés au retrait des médicaments et devrait augmenter le taux de réussite. Objectif #3- COVID-SAFER, J'ai théoriquement exposé une cohorte de patients 65 ans et plus inscrits dans une étude de déprescription, à l'hydroxychloroquine. La cohorte comprenait un total de 1,001 patients, desquels 590 (58.9%) recevaient un ou plus de médicaments qui pourraient potentiellement interagir avec l'hydroxychloroquine. De ceux-ci, 255 (43.2%) ont été identifiés comme étant potentiellement inappropriés par l'outil de Medsafer.

**Discussion:** Le but principal de ma thèse de recherche était l'analyse critique de la littérature. J'ai identifié des méthodes d'arbitrage des effets indésirables, j'ai comparé et contrasté leurs forces et faiblesses et j'ai formulé des recommandations pour une nouvelle méthode. Deuxièmement, basé sur les recommandations j'ai proposé une nouvelle méthode d'arbitrage des effets indésirables à être utilisée dans les essais cliniques de déprescription. Cette nouvelle méthode est conçue pour être intuitive pour les cliniciens à utiliser tout en capturant plus précisément les effets indésirables potentiels. Elle est standardisée à travers toutes les études et contribue à un environnement de prescription plus sécuritaire pour les adultes âgés. Le troisième objectif de ma thèse était d'appliquer la déprescription à une population particulière. J'ai identifié un médicament à haut niveau de risque pour les patients plus âgés, deux populations pour lesquels la déprescription devrait débuter plus tôt dû aux maladies chroniques et comment la polypharmacie peut affecter les adultes âgés atteints de COVID-19. Ma thèse contribue à la recherche dans ce domaine tout en fournissant des idées pour des projets futurs.

**Acknowledgments**

I would like to extend my deepest and most sincere gratitude to my thesis supervisor, Dr. Emily McDonald for all of her support and supervision throughout my studies. I very much appreciate her taking me on as a graduate student, guiding my training and research, and providing me with opportunities to grow as an academic and as a person. I would also like to thank my co-supervisor Dr. Todd C. Lee for all of his contributions, guidance, and advice through the years. My success is greatly due to both of their contributions and encouragement, so for that, I thank them.

I would also like to extend a special thank you to the members of my thesis committee; Dr. Peter Wu, Dr. Robyn Tamblyn and Louise Papillon-Ferland. Each and every one of them provided me with valuable input throughout the drafting of my manuscripts, and at each committee meeting, contributing greatly to the work in my thesis.

Financial support for the first year of my studies was provided by my supervisors Dr. McDonald and Dr. Lee. In the second year I received support from the Research Institute of the McGill University Health Centre (RI-MUHC) Studentship Award and the Canadian Institute of Health Research (CIHR), Canada Graduate Scholarships-Master's (CGS M) Award.

Finally, I wish to thank my family, friends and everyone else who helped and supported me during my master's degree in Experimental Medicine. I therefore would like to dedicate my thesis to everyone who helped me out in some capacity along the way.

**Contribution of Authors**

My contribution to the thesis was to design the studies, generate the research hypotheses, review the literature, develop the study protocols and methods, interpret the findings, and write all of the contents of this thesis including the two manuscripts, with the guidance of my supervisors, my thesis committee members, and all co-authors.

**Chapter 1 (Introduction):** I conducted the background research and wrote the introduction, my supervisors Dr. McDonald and Dr. Lee aided in the review and editing process.

**Chapter 2 (Manuscript 1):** I designed the study, conducted the literature search, chose inclusion articles with the assistance of Anika Antique, described all methods of adjudication, and drafted the manuscript. My supervisors Dr. McDonald and Dr. Lee, and my committee members Dr. Tamblyn, Dr. Wu and Louise Papillon-Ferland, edited the manuscript, provided suggestions for improvement and signed off on the final content. I submitted it to the journal and made any other suggested revisions.

*Ross, S. B., Wu, P. E., Atique, A., Papillon-Ferland, L., Tamblyn, R., Lee, T. C., McDonald, E. G. (2020). Adverse Drug Events in Older Adults: Review of Adjudication Methods in Deprescribing Studies. J Am Geriatr Soc. doi:10.1111/jgs.16382*

**Chapter 3 (Manuscript 2):** Dr. McDonald, Dr. Lee and I, contributed to the study concept. I designed and drafted the manuscript with the guidance of Dr. McDonald. Dr. McDonald, Dr. Lee and Dr. Wilson conducted the data analysis. I, Dr. Wilson, Dr. McDonald, Dr. Lee, Louise Papillon-Ferland, Sarah Elsayed, Dr. Wu, Kiran Battu, Sandra Porter, Dr. Rashidi, Dr. Tamblyn, Dr. Pilote, Dr. Downar, Andre Bonnici, and Dr. Huang, revised and approved the manuscript.

*Ross, S. B., Wilson, M. G., Papillon-Ferland, L., Elsayed, S., Wu, P. E., Battu, K., Porter, S., Rashidi, B., Tamblyn, R., Pilote, L., Downar, J., Bonnici, A., Huang, A., Lee, T. C., McDonald, E. G. (2020). COVID-SAFER: Deprescribing Guidance for Hydroxychloroquine Drug Interactions in Older Adults. J Am Geriatr Soc. doi:10.1111/jgs.16623*

**Chapter 4 (Discussion):** I developed, designed and wrote the content of the discussion. Dr. McDonald and Dr. Lee reviewed this section and provided suggestions for improvement.

**Appendices:** I also designed and developed all the content of the appendices. Dr. McDonald and Dr. Lee also provided suggested revisions.

**Abbreviations**

AE=adverse event

ADEs=adverse drug events

ADRs=adverse drug reactions

ADWEs=adverse drug withdrawal events

PIMs=potentially inappropriate medication

PMH=past medical history

HIV=human immunodeficiency virus

HD=hemodialysis

SARS-CoV-2=severe acute respiratory syndrome coronavirus 2

COVID-19=coronavirus disease 2019

AHFS=American hospital formulary service

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## Chapter 1. Introduction

### *General Context*

Polypharmacy, or the concurrent use of multiple medications, is increasingly common in adults aged 65 years and older.[1] Frequently, older adults present with multimorbidity, which is the co-existence of two or more chronic health conditions.[2] The presence of multiple chronic conditions results in an increasingly complex course of therapeutic management for both the patients and the healthcare professionals.[3] Polypharmacy is therefore common in older adults with multimorbidity.[4] In this age group, physiologic interactions between aging and disease can increase the risk of adverse drug events (ADEs), which are especially common in patients taking multiple medications.[5-7] While multiple medications may be necessary for the treatment of chronic medical conditions, over time, the balance of harms and benefits may shift, especially for medications taken for prevention, those with weaker overall evidence of benefit, and prescriptions known to negatively impact on cognition.[8,9] In patients with multimorbidity, each additional potentially inappropriate medication (PIM) places them at an increased risk of ADE.[1,8,10] PIMs are drugs taken in an individual where the risks out weight the benefits, they are commonly seen in old age having little added value (contributing to the pill burden) and/or increasing the risk of drug-drug and/or drug-disease interactions.[11,12] ADEs are increasingly common and there is no single driver responsible for this current epidemic; rather, it is a complex issue with several contributors: a culture of prescribing; gaps in information and knowledge; and a highly fragmented system of health care.[13]

### *Health and Economic Cost*

As many as 56.7% of community-dwelling North Americans over the age of 65 are taking 5 or more regular medications.[13,14] This issue not only impacts the health of the affected individuals but has contributed to a major economic burden and heavy societal costs.[13,15] Patients hospitalized with an ADE have an increased length of hospital stay[16,17], higher costs[17-20], an increased risk of in-hospital death[17,21], and risk of re-admission.[15,21] Using data for 2013

from the National Prescription Drug Utilization Information System database, Morgan et al. found that $419 million CAD was spent on inappropriate medications identified by the Beer's list[22], averaging $75 per older Canadian adult.[23] This contributed to an estimated $1.4 billion CAD spent in indirect costs attributable to PIMs.[23] Additionally, preventable ADEs related to medication errors cost an estimated $2.6 billion CAD a year, with each hospitalized patient costing an estimated $6,750 CAD.[24,25] In the USA, a 2018 study by the Lown Institute, estimated 5 million outpatient visits for ADEs and 280,000 hospitalizations, costing $3.8 billion USD.[13] Older adults in the United States make up 56% of all ADE hospitalizations despite only accounting for 14% of the population.[26] Furthermore, it is estimated that less than half of patients experiencing an ADE seek treatment and therefore the occurrence and cost are likely greatly underestimated.[27] Reducing the use of PIMs in older adults will lead to a reduction in ADEs and in North America alone, a saving of billions of dollars annually for the healthcare system.[28]

*Nuances surrounding the term "polypharmacy"*

Polypharmacy is a driver of this high health and economic burden on society. The term polypharmacy was originally coined to refer to the use of multiple medications, issues related to multiple drug consumption, and excessive drug use.[29] Over time it has evolved to refer to either a numerical cut off or be associated with measures of appropriateness. [30] While there is no definite cut- off for the number of medications required to be considered polypharmacy, the most common definition used is 5 or more medications daily.[1] However, there is a wide range of numerical definitions ranging from 2 to 11 medications used to define polypharmacy in studies.[1] Polypharmacy is associated with adverse outcomes which include, ADEs, adverse drug reactions (ADRs), falls, and mortality.[31,32] Each additional medication increases the risk of an ADE due to drug-drug interactions (DDI), ADRs, drug-disease interactions, as well as other causes on ADEs in older adults.[33,34] That being said, polypharmacy is not always deleterious; and thus the Lown Institute identified the need to differentiate between appropriate and inappropriate polypharmacy.[13] The Lown Institute put together an international working group on polypharmacy composed of clinicians, stakeholders, patient representatives, public health experts and policy makers. They are a not for profit organization that seeks to optimize care for

Americans and place a heavy focus on high value care in addition to accesses to affordable care. They coined the term "medication overload", as an alternative to describe harmful polypharmacy. They defined medication overload as the use of multiple medications for which the harm to the patient outweighs the benefit. This alternate term to polypharmacy has no strict cut-off for the number of daily medications considered harmful, instead medication overload is contingent upon the prescription of *non-necessary* medications; when the side effects from indicated medications outweigh the potential benefits, when a patient is prescribed a medication for longer than needed, and when a patient takes unnecessary over the counter medications.[13] Indicated and beneficial polypharmacy is when patients can benefit from multiple medications provided that prescribing is evidence based, reflects patients' clinical conditions, and considers all potential drug interactions.[35] Although, even if all the medications are indicated there still needs to be consideration that more medications can increase the risk of ADEs. A good example of appropriate polypharmacy would be a patient with a solid organ transplant or who is living with HIV, as these individuals may take multiple daily medications, all of which may be medically necessary and life-saving. In our research, we often use a cut-off of 5 or more medications as a simple means to reproducibly identify polypharmacy and then examine the medications to see which are potentially inappropriate and medically unnecessary for the individual older adult. There is evidence around the number of 5 medications in terms of increased risk of certain harms as well as likelihood that they are taking a PIM.

*Distinguishing Between Adverse Drug Events, Adverse Drug Reactions and Adverse Drug Withdrawal Events*

One of the most harmful consequences of polypharmacy is related to drug induced injury, and therefore it is important to understand the different classifications that are presented in the literature and the varying definitions for this type of adverse consequence.

An adverse event (AE) is defined as an unintended injury caused by medical management, rather than the underlying disease, resulting in a prolonged hospital stay and/or leading to death.[36] Medications are the most common cause of adverse events, resulting in adverse drug events (ADEs).[37,38] An ADE is defined as an injury resulting from medical intervention related to

a drug.[39] A portion of medication errors will result in potential ADEs, preventable ADEs, and ameliorable ADEs. A potential ADE is a medication error which has the potential to cause harm, but either due to circumstances or chance, it does not result in an injury.[40] A preventable ADE is an injury resulting from a medication error, while an ameliorable ADE is when the severity or duration of the injury could have been minimized if different actions were taken.[40] The most common cause of an ADE is due to the use of inappropriate medications.[40] The term ADE encompasses all injuries resulting from the use of medications, including the subcategory adverse drug reactions (ADRs).[40] An ADR is a subset of ADEs, which is defined as the response to a drug which is noxious and unintended given a normal dose of the medication.[41]

In the literature the terms ADE and ADR are commonly used interchangeably, creating some confusion. While both terms encapsulate an injury resulting from the use of a medication, they have very important distinguishing factors that need to be considered. In order for an injury resulting from the use of medication to be considered an ADR, there needs to be *a causal relationship between the medication and the event established*. All ADRs are an ADE, but not all ADEs are ADRs. Thus, ADRs are a subset within ADEs evaluating if the drug was the causal factor in the ADE, not if an ADE has occurred or not. This direct causal relationship can only be identified through rigorous criteria whereas ADEs can have more of an implied causal relationship using expert knowledge on pharmacological and disease interactions. An example of an ADE that is not an ADR, is a patient who is newly started on trazodone for sleep at hospital discharge and then returns to the hospital 1-2 weeks later with a fall and bleeding in the head. The brain bleed is not due to a pharmacological reaction of the medication but rather attributed to the fall, which is a known potential side effect of medications with sedating properties prescribed for sleep. ADRs are subclassified into A through F, where subclasses A and B are the two main types, A are common predictable side effects with low mortality and B are unrelated to the pharmacologic action of the drug (e.g. penicillin hypersensitivity). Type C ADRs relate to long term side effects, Type D is uncommon and dose-related, type E is related to side effects from the withdrawal of a drug, and type F is from drug-drug interactions.[42] An important component of our research involves differentiating between ADEs and ADRs in order to clarify

outcome measures, and in particular how this can affect the adjudication of the primary outcome in clinical trials of deprescribing interventions.

I further wish to distinguish another subcategory of ADEs, adverse drug withdrawal events (ADWEs). ADWEs are a particular subset of ADEs that are related to the potentially serious consequence of the discontinuation of a medication, defined as a clinically significant set of signs and symptoms caused by the removal of a drug.[43] Drug removal could be due to the accidental stopping of medications by either the patient or practitioner, the deliberate stopping and/or non-renewal of a drug, and deprescribing (with or without tapering). The clinical manifestations of ADWEs usually present in 4 categories; 1) physiological withdrawal reactions, e.g. rebound hypertension or tachycardia after beta-blocker cessation; 2) morbidity related resurgence of initial treated condition, e.g. increased risk of stroke after stopping a beta-blocker due to high blood pressure; 3) a new set of symptoms, e.g. weakness and nausea after stopping chronic long-term therapy with oral corticosteroids for obstructive lung disease[43] or 4) a pharmacologic consequence caused by changes in metabolism of the remaining drugs[44]. In a deprescribing setting, it is important to be able to distinguish between ADEs and ADWEs in order to monitor for harm from deprescribing as a counter-balancing measure. In a clinical study setting, it is imperative to be able to identify the cause of the adverse event in order to take the necessary steps to mitigate harm and improve the outcomes for future patients and studies. Ideally, through the safe and conscientious deprescribing of inappropriate medications, we can mitigate ADWEs, by providing tapering instructions for medications at high risk of causing ADWEs or medications known to be associated with withdrawal symptoms (e.g. benzodiazepines for sleep) and by anticipating any drug interactions. While ADWEs may still occur, taking these steps in future studies could improve outcomes. Unfortunately, very few ADE adjudication methods have a robust means of distinguishing between ADWEs and ADEs that can be easily applied in a research setting. In my manuscript 1; *Adverse Drug Events in Older Adults: Review of Adjudication Methods in Deprescribing Studies,* I highlight the importance of identifying and distinguishing ADWEs (chapter 2), and this factors into my new methodology of adjudicating ADEs presented (in chapter 4) of my thesis.

*A Solution to Polypharmacy is Deprescribing*

So far, I have introduced the concepts of polypharmacy, PIMs, and the complications they may cause, including various forms of ADEs. A potential solution that has been proposed to address inappropriate prescribing of medications and polypharmacy as a way to reduce the risk of ADEs is deprescribing.[45] A popular definition from Reeve et al. is "the process of withdrawal of an inappropriate medication, supervised by a healthcare professional with the goal of managing polypharmacy and improving outcomes".[46] Stopping medications which are no longer required will reduce the risk of medication-related harm, while a reduction in the total number of medications will reduce the potential harms associated with polypharmacy.[47,48] Appropriate prescribing from the outset reduces some need for deprescribing, but there are still medications that are medically appropriate at some ages (e.g. cardiovascular primary prevention medications) that are no longer beneficial later in life when the harms and benefits may shift due to life expectancy or competing risks from other illnesses (e.g. advanced cancer). For a frail older adult in their 90s who has never had a cardiovascular event, aspirin may cause bleeding and lead to recurrent side effects that are bothersome (e.g. bruising) and/or dangerous (e.g. gastrointestinal bleeding), but this medication is no longer vital to prevent a myocardial infraction and could be considered for deprescribing. As life circumstances change, deprescribing is an important component of a good prescribing continuum. Deprescribing is a good example of a patient-centered intervention, as it utilizes shared decision making, informed patient consent, and involves the close monitoring of drug effects.[45] The process of deprescribing usually begins with a medication review by a healthcare professional, to identify PIMs and opportunities to deprescribe in order to improve health outcomes for the individual. All older adults with polypharmacy should undergo medication reviews as a standard of care.[13] Yet, due to a variety of factors including time constraints, fragmented care among multiple prescribers, incomplete information, and uncertainty towards the benefits and harms of continuing vs. discontinuing a specific drug, many healthcare providers are not comfortable with taking on this task.[49,50] Also, many physicians (especially subspecialists) may prescribe medications based on recommendations from disease-specific guidelines, but these are less

likely to apply to older adults with multimorbidity and polypharmacy.[51,52] Therefore, a safe and appropriate medication regimen in older adults with multimorbidity is extremely complex and often requires expert knowledge in order to achieve.

With this in mind Scott et al.[45] developed recommendations outlining a 5-step process for the manual deprescribing of medications. There are also deprescribing software tools that help to partly automate the process by using existing electronic healthcare data[53]. In my manuscript 2 "*COVID-SAFER: Deprescribing Guidance for Hydroxychloroquine Drug Interactions in Older Adults"*, for example, I used an automated tool called MedSafer which electronically cross references medications and medical conditions to provide prioritized recommendations for deprescribing.[54] More information on this tool will be presented in the COVID-SAFER paper (chapter 3).

*Thesis Objectives & Aims*

Taking into consideration the health and economic cost of PIMs, the inconsistency around the labelling of ADEs and ADRs, and the potential opportunities surrounding the promising solution of deprescribing, I conducted several interconnected projects throughout my master's in order to advance research in this essential field.

My research goal was to define outcomes and identify opportunities for safer prescribing in older adults. In my manuscript 1 (chapter 2 of my thesis) my aim was to critically evaluate the literature regarding deprescribing and safer prescribing in older adults, identify gaps in the research, and make recommendations for future research studies. An important component of ADE reporting is utilizing an accurate and consistent method of adjudication across studies in order to properly measure the impact of the intervention. I identified a significant gap in the literature with regards to the adjudication and reporting of ADEs. I described and critically analyzed multiple ADR and ADE causality tools and evaluated their discretionary capacity to identify ADWEs. I also sought to address the issues regarding the presented methods, and I provided recommendations for a modified adjudication method to be used in future studies, which I will present and go into greater detail in the discussion section of my thesis (chapter 4).

Furthermore, I also identified other smaller projects and opportunities for research to be conducted with regards to polypharmacy and ADEs. While older adults are considered to be at the highest risk for polypharmacy and ADEs, it became apparent to me that it may be important to broaden the concepts of deprescribing to other populations or subgroups who may be at high risk from a disproportionate use of certain medication classes or due to chronic illness that may also place them at an equally increased risk for ADEs, outside of the usual age confines that we typically refer to in polypharmacy and geriatrics. Certain drug categories may pose an increased risk in middle age adults in addition to older adults, including; analgesics, combinations of anticoagulants, antihypertensives with off-target effects, high risk hypoglycemic drugs, off-label use of psychoactive drugs, and anticonvulsant medications.[55] Many of these classes of medications also required a concerted effort and patient engagement to effectively deprescribe and avoid restarts over the long term. In my work I focused on Gabapentinoids as an opportunity to inform and educate older adults on their risk and provide them with the tools necessary in order to engage them in the deprescribing process and to help make an informed decision about deprescribing (Appendix B).

I also deemed it important to consider how certain chronic medical conditions may play a role in a patient's disease course and pharmacologic treatment plan. In my thesis I present two study protocols (Appendix C), which are designed to critically analyze both an HIV and hemodialysis population in order to describe their special and individual needs in regard to deprescribing, wherein we applied less restrictive inclusion criteria for age (inclusion of adults 50 years and older as opposed to 60-65 years and up). Such patients are likely to have both beneficial and unnecessary polypharmacy with increasing pill counts also contributing to challenges with adherence. While I did work on several smaller projects related to deprescribing, such as the creation of the patient empowerment brochure and I engaged in background research on polypharmacy in younger adults with chronic diseases, these should be considered complementary projects that I pursued. Due to the COVID-19 pandemic and the halt of non-essential research I was unable carry out these projects, but they have both received ethics approval and present an opportunity for future research in the field.

With the current COVID-19 pandemic I, like many researchers, had to pivot and find opportunities to continue to conduct relevant research in spite of many restrictions that were put in place. I identified an opportunity to conduct an adjacent study examining how deprescribing interfaces with the global health crisis and what important lessons can be learned in order to decrease overprescribing and polypharmacy in the future (chapter 3).

*The main objective in this manuscript style thesis is to demonstrate that I have contributed substantively to the field of deprescribing research*. My principal aim is to provide *clarity on a need for stringent outcome definitions in deprescribing trials*. I hope to have accomplished this by providing an in-depth review of the strengths and weaknesses of available methodologies for capturing ADEs as the primary outcome of interventional studies. *Based on this work, I have outlined a new method that addresses prior limitations we identified.* With the COVID-19 pandemic, I hope to have made *a clear case for the importance of continuing work and research in deprescribing* through the manuscript COVID-SAFER and have proposed studies where we could look at the concepts of polypharmacy and appropriate prescribing outside of the older adult demographic. Ideally this work contributes uniquely to the deprescribing research field while providing the groundwork for future studies to be conducted.

## Chapter 2. Adverse Drug Events in Older Adults: Review of Adjudication Methods in Deprescribing Studies

### Preamble to manuscript 1

I began my research by conducting a review of the current literature regarding ADE adjudication methodologies. The aim of this manuscript was to report my findings with regard to adjudication methods, critically evaluate the limitations of the current methods, provide recommendations for a new method and lay the foundation for future studies in the field. This publication is the foundation of the rest of my thesis, and all of my additional research ties back to it. This manuscript was published in the Journal of the American Geriatric Society (JAGS) on March 6th, 2020.[56]

I initially performed a systemic literature review, by developing a search strategy for Medline, and Cochrane, but while publishing the manuscript the reviewers asked us to change it to a narrative review. I therefore published as a narrative review but used systematic methods and the PRISMA-P checklist in my research. For my literature search I also only included articles which looked at deprescribing trials, which I defined as a clinical trial wherein the intervention was deprescribing and the outcome included some form of assessment of ADEs. While my primary interest is in deprescribing in clinical trials my work can translate to individual patients undergoing deprescribing in in a primary care setting.

Finally, by conducting this literature review I was able to identify important areas of research in regard to adjudication and make recommendations that contribute to the design of my new methodology as part of the discussion of the thesis.

**Title Page:**

**Adverse Drug Events in Older Adults: Review of Adjudication Methods in Deprescribing Studies**

*Running title*: Methods for adverse drug event adjudication

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This work was accepted for presentation in abstract form at the International Preventing Overdiagnosis Conference in Sydney, Australia, December 2019. The work was completed with funding from *the Centre for Ageing and Brain Health Innovation* and *the Fonds de Recherche Santé- Québec.*

**Abstract:**

**Background** Polypharmacy is common in older adults and is associated with adverse drug events (ADEs). Several methods exist to help correlate ADE causation in studies.
**Objective** We performed a narrative review to identify methods for ADE adjudication. We compared their strengths and limitations to assess their applicability to deprescribing studies (of which clinical trials are a subset), and to encourage the use of a standardized method in future studies.
**Methods** A review of original articles was employed (1946-2019), using the MEDLINE (Ovid) and Cochrane databases. We also conducted a manual reference search of review articles. Abstracts were screened for relevance. Adjudication methods were compared for advantages and limitations including validity, ease of use, and applicability to clinical trials with deprescribing as the primary intervention.
**Results** The search yielded 1,881 articles of which 175 articles were included for full-text review. Following in-depth review, 135 were excluded: 79 had no ADE outcome data; 35 were not specific to older adults; 9 were not relevant; 6 were review articles; 5 contained duplicate data; and 1 was not written in French or English. This left 40 articles for analysis, from which we identified 10 unique ADE adjudication methods. No method was originally developed for use in a deprescribing setting.
**Conclusion** A standard method to identify ADEs is important to reliably capture the outcome in deprescribing studies. All methods we identified had limitations in terms of capturing adverse events from the withdrawal of medications. Future work should focus on refining adjudication methods for capturing ADEs related not only to medication continuation, new drug starts but also to deprescribing and drug discontinuation.

**Key words:** polypharmacy; deprescribing; adverse drug events (ADEs); adverse drug withdrawal events (ADWEs); Adjudication

**Introduction**

Polypharmacy, or the concurrent use of multiple medications, is common in adults aged 65-years and older.[1] Due to age and disease-related physiologic changes, older adults are particularly vulnerable to adverse drug events (ADEs)[2], which may present as a new health problem, worsening of an existing problem, or death. Even though individual drugs may be indicated for the treatment of chronic diseases, polypharmacy increases the risk of ADEs.[3] While sometimes risks are justifiable in the context of evidence-based therapy for important comorbidities, older adults are also increasingly exposed to potentially inappropriate medications (PIMs), which may confer little benefit to offset the risks.[1,4-7] Avoiding ADEs is an important goal for the individual and for the healthcare system. Patient's hospitalized due to an ADE have longer hospital stays, higher costs per hospitalization, and an increased risk of in-hospital death.[7-10] It is predicted that in the absence of any intervention, ADEs will cost the US healthcare system $62 billion over the next 10 years.[11]

One solution to polypharmacy is deprescribing, which is the intentional tapering or cessation of a medication.[12,13] Deprescribing is often geared towards older adults with polypharmacy, where the risk of some medications outweigh the benefits.[13] While several clinical trials have evaluated the impact of deprescribing on process measures such as drug count, number of PIMs, or costs, it is increasingly recognized that studies designed to demonstrate an impact on ADEs are needed.[14] Deprescribing clinical trials that demonstrate a neutral or even positive impact on ADEs will help to better quantify the potential harms and benefits of such interventions.[15] A reliable and reproducible method of capturing ADE outcomes is essential for this process to be successful and to facilitate meaningful comparisons between studies.

There are already several existing adjudication methods to identify and classify ADEs and adverse drug reactions (ADRs), which are a subset of ADEs, resulting in a noxious or unintended consequence of a drug being given at its normal dose.[16-18] There are significant limitations to most methods, some of which are particularly relevant to deprescribing. For example, many tools are designed to address whether a specific drug was the single casual

factor responsible for an ADE, but not whether a drug-comorbidity or drug-drug combination was contributory. In addition, there is no universal approach for classifying ADEs in deprescribing studies and current methods may not capture ADEs that arise as a result of discontinuation of a medication, or "adverse drug withdrawal events" (ADWEs). Detecting an ADWE that arises as a result of a specific decision to taper or stop a medication needs to consider both the anticipated physiological withdrawal effects but also any consequences resulting from the resurgence of the initially treated pathology.

For these reasons, we performed a narrative review of the literature to: 1) identify, compare, and contrast ADE adjudication methods in terms of validity, ease of use, and applicability for capturing this outcome in deprescribing studies (of which clinical trials are a subset) and 2) identify gaps in the literature with regards to the available methodologies for identifying ADWEs. We captured these outcomes by applying our expert knowledge to the evaluation of each method, understanding how each method works, their benefits and limitations, and the kappa score when available. Original articles where the tools were developed and validated were also included in the review. The results of this review are intended to inform future research with regards to standardizing and optimizing ADE outcome adjudication methods for future deprescribing studies.

## Methods

The reporting of this narrative review conforms to the Preferred Reporting Items for Systematic reviews and Meta-Analysis Protocols (PRISMA-P) 2015 statement.[19]

### *Search Strategy*

We performed a comprehensive computerized literature search using the Medline (Ovid) and Cochrane databases. The search criteria included articles from January 1, 1946, to March 27, 2019, restricted to English and French. The search strategy was developed in consultation with the McGill University Health Centre librarians. We defined a deprescribing study as a clinical trial wherein the intervention was deprescribing and the outcome included some form of assessment of ADEs. We used the Medical Subject

Heading (MESH) Terms adapted for each database in order to identify original research articles. The search strategy included the terms: drug-related side effects and adverse reactions, adverse drug reaction reporting systems, deprescribing, inappropriate prescribing and iatrogenic disease, using a combination of Boolean operator "AND" and "OR" functions (see supplement S2.1 for full search strategy). We hand-searched references from articles to identify any additional relevant abstracts not captured by the electronic search. We included all interventional and observational studies that had ADE outcome data and used clear methods for incident reporting of ADEs in adults 60-years and older, in all settings. We also included studies that specifically evaluated ADRs. We excluded studies with no outcome data, studies that only reported on process measures (for example potential inappropriate medication counts), case studies, review articles, belief/knowledge questionnaires, duplicates, and articles not written in English or French. Studies not specific to older adults were later removed because we were most interested in how these tools performed where the distinction between ADE, comorbid illness, and age/frailty is more challenging than in younger populations. However, we evaluated studies in all age groups to identify any additional adjudication methods not captured in studies limited to older adults. We excluded grey literature except for unpublished randomized control trials assessing deprescribing and ADEs, which were identified in our search.

*Study Selection*

Titles and abstracts from the original search were screened by two authors (SBR and AA) excluding all non-relevant studies and duplicates. Remaining articles were reviewed by full-text, also by the same two authors, to identify studies meeting our inclusion criteria. Discrepancies were settled by consensus.

Reviewers weren't blinded to the authors or journal titles.

*Data Extraction*

Study characteristics and relevant data were extracted and included: name of first author, year of publication, study country, type of study (prospective or retrospective), age

group, duration and setting (community-dwelling, residential care facility, emergency department, inpatient and post-hospital discharge), ADE definition and ADE adjudication methodology used. Where available, we extracted the kappa value for inter-observer reliability for each method whereby 0.41 to 0.59 was considered moderate, 0.6 to 0.8 substantia and greater than 0.8 excellent reliability.[20]

## Results

### *Included studies*

A total of 1,881 articles were reviewed for inclusion and 49 duplicates were removed. By title and/or abstract, 1,657 articles did not contain ADE reporting data, leaving 175 for full-text review. Of these, 79 had no ADE outcome data (including 20 that only analyzed PIMs as an outcome), 35 were not specific to older adults, 9 were not relevant, 6 were reviews, 5 contained duplicate data, and 1 was in a language other than English or French. The remaining 40 articles were included for analysis (Figure 2.1).

### *Synthesis of literature*

Table 2.1 provides a summary of the study characteristics from the included studies. An additional 35 studies not specific to older adults are included in Supplementary Table S2.2.

### *Description of Methodologies*

We identified 10 methods of adjudication in the included studies; Leape & Bates,[21,22] Naranjo algorithm,[16] Clinical Judgement,[23] WHO-UMC,[24] Computerized trigger tool,[25] French Method,[26] Karch and Lasagna,[18] Hallas,[27] Howard,[28] and Self-Reported.[29] A description of the adjudication methods, the benefits, the limitations, and the kappa value for inter-observer reliability (when reported) are reported in Table 2.2. Of note, no method that we evaluated was originally designed or validated in a deprescribing context.

The Leape & Bates method[21,22] developed in 1995 was designed to capture ADEs. It uses a 6-point Likert scale that ranges from 1- outcome definitely caused by the patient's disease to 6- outcome definitely caused by the patient's medication; scores of 5 (probably caused by the patient's medication) or 6 (definitely caused by the patient's medication) are considered an ADE. Between studies, kappa ranged from 0.63 to 0.88.[30-33]

Clinical judgement,[23] similar to Leape & Bates, assesses the relationship between the medication, comorbidities and the event, using an unstructured format.

The Naranjo algorithm[16] developed in 1981 uses an ADR probability scale questionnaire consisting of 10 questions. It walks the clinician through the process of determining drug causality with a list of specific questions (e.g. "was the drug detected in the blood in toxic levels?" and "was the reaction more severe when the dose was increased?"). Questions are answered with "yes", "no" or, "do not know," and are assigned point values (-1, 0, +1, or +2) for a total score ranging from -4 to +13; an ADR is considered definite if ≥ 9; probable 5 to 8; possible 1 to 4; and doubtful ≤ 0. Between studies, kappa ranged 0.7 to 0.92.[34,35]

The World Health Organization- Uppsala Monitoring Centre (WHO-UMC) method[24] developed as a practical tool for the assessment of case reports, takes into account the clinical-pharmacological aspects of the case. The goal was to develop a simple and broad use algorithm that was able to detect unknown and unexpected adverse reactions. It relies on causality determination through assessment criteria such as abnormal laboratory tests, the timing of drug administration, and the presenting pathology. An event's relationship to the drug is classified as either; unassessable/unclassifiable; conditional/unclassifiable; unlikely; possible; probable/likely; or certain. A classification of probable/likely or certain is considered an ADR. Inter-rater reliability was not reported in any included deprescribing studies.[4,36-38] It has previously been reported as 0.71.[39]

The computerized trigger tool[25] relies on a computerized ADE monitoring system that detect signals such as discontinuation of medications, decreases in dosage, ordering of known antidotes, or specific laboratory tests. Agreement between the computerized trigger tool and an independent adjudicator was not reported in any of the included studies.[40]

The French method[26] developed in 1977 is used almost exclusively in France. It is a 3-stage assessment combining chronologic criteria with clinical and laboratory findings. ADRs are classified as doubtful, possible or probable using a table combining chronologic and symptomatology scores. Kappa was not reported in the included studies.[41,42]

The Karch and Lasagna method[18] developed in 1975 assesses the cause-effect relationship by classifying ADRs as definite, probable, possible, conditional or doubtful. Classification within this method involves the evaluation of: the reasonable temporal sequence from administration of the drug; the known response pattern of the suspected drug; not being able to explain the response by any other known condition; and a de-challenge and re-challenge of the suspected drug. This method has been further modified to the Hallas[27] and Howard[28] criteria for causality, which use the same criteria in a slightly modified format. The Hallas[27] method associates each criteria seen in the Karch and Lasagna method[18] with a number from 1 to 5. If each criterion has been satisfied it is classified as a 'definite' ADR; if only numbers 1 to 4 are satisfied, the ADR is 'probable'; 1 to 3 is 'possible'; and any less is 'unlikely/unevaluable'. The Howard[28] method uses amended Hallas[27] criteria, wherein slightly different terminology are used to convey the same criteria. The fulfillment of all 5 criteria results in a 'definite' classification; any 4 criteria fulfilled results in a 'probable' classification; any 3 is 'possible'; and 2 or less is 'unlikely/unevaluable'. The kappa was not reported in the included studies that employed Karch and Lasagna or the Hallas method.[3,43-45] The Howard[28] criteria reports a Kappa ranging from 0.74 to 0.88.

Finally, the self-reported method[29] involves the patients themselves reporting if they had an ADE or not, in the absence of a guideline or any predefined criteria, solely based on their perception that a side-effect was caused by their medication.

**Discussion**

We performed a narrative review to identify studies in older adults that provided methodologic details regarding ADE adjudication as a study outcome. We identified a total of 10 unique methods, each with strengths and limitations. Unfortunately, only 4 of the 10

methods had a measure of inter-observer reliability reported in the included studies, despite this measure being possible to calculate with most methods. The most commonly used methods were the Naranjo algorithm and Leape and Bates. Practical examples of these can be found in the supplement S2.3.

Based on our experience, an ideal adjudication method should be intuitive for researchers to apply. Ideally, it should be: weighted towards clinical judgment, but not ambivalent to drug causality; not be overly burdensome or time-consuming; sensitive to ADEs and not just ADRs; applicable using a limited dataset that is relatively easy to collect; standardized, allowing for a measure of inter-observer reliability; and should specifically identify and label ADWEs related to deprescribing. In deprescribing studies, an adequate assessment of both ADEs and ADWEs is essential to balance the effect of continuing vs discontinuing medications and informs the benefits and risks of each strategy.

The first common limitation of many methods is the inability to capture a broad range of ADEs, but rather only ADRs (a subtype of ADEs), possibly rendering these methods less sensitive. ADE is an umbrella term for adverse events causing harm during drug therapy and includes inappropriate use, overdoses and ADRs. ADRs are a type of ADE whereby a reaction to a drug is noxious, unintended and the drug is considered causal. This is the case for the Naranjo algorithm, the WHO-UMC method, the French method, the Karch & Lasagna method and its derivatives, which we here on in refer to as “ADR causality methods”. Of note, many of these methods (including the French method,[26] Karch and Lasagna,[18] Hallas,[27] and Howard[28]) are also fairly complex and labor-intensive.

Second, none of the methods explicitly cues adjudicators to identify adverse events as a first step in the adjudication process. For example, these methods might not categorize a fall post-hospital discharge as an ADR as the processes do not begin by identifying that an adverse event occurred. ADR methods determine drug causality only *once an adverse event has already been identified* (for examples refer to the supplement S2.3). The heavy focus these methods place on cementing an association between an event and a suspect culprit drug unfortunately leads to many circumstances where ADR causality cannot be confirmed due to lack of information, leaving the score in the grey/undefined zone.

Third, while not essential for the use of ADR causality tools, these methods contain questions requiring specialized testing (such as drug levels). However, settings such as aged care facilities may not have the capacity to obtain timely serum concentrations of suspected drugs (e.g. digoxin levels) prompting the adjudicator to respond with "do not know" (see supplement S2.3 for applied examples) making these methods less sensitive.

Fourth, these methods, ideally suited for the assessment of a single drug, may miss ADEs that involve a combination of medications and conditions. ADEs in older adults with polypharmacy may present as geriatric syndromes such as falls, cognitive impairment, and functional decline, rather than as pure ADRs clearly attributable to a single medication. In the setting of polypharmacy, it may be more practical to use a broad method that captures a wide variety of ADEs, including deleterious effects due to the continuation of chronic drugs, initiation of a new medication, deprescribing ADWEs and/or medication errors/omissions. Adjudication methods that focus on a reaction from a single medication may be less likely to capture the global effects of age-related changes and polypharmacy.

From this respect, the Leape & Bates method has advantages; it is better suited to capture a broad range of ADEs, in a variety of settings, and accommodates when multiple medications may be implicated. By allowing the clinician the flexibility to consider several contributing factors such as falls and cognitive impairment, it is also useful for self-reported adverse events. For example, it can be applied in the setting of post-hospital discharge follow-up studies, where certain clinical details may be lacking, and multiple drugs may be implicated (see supplement S2.3 for an example where a patient reports being re-hospitalized with acute kidney injury).

While the Leape & Bates[21,22] method relies heavily on clinical judgment it has several other advantages. It allows the clinician to consider all medications as potential contributors to an ADE, including unintended omissions, prescribing errors, non-adherence, and PIMs. While it was not designed to assess withdrawal events due to the discontinuation of a medication, it could be modified to directly address this issue. Of note, despite some limitations, the Naranjo algorithm does in fact have a separate modified component called "ADR probability scale: drug withdrawal",[16,46] which follows the same steps as the ADR probability scale but addresses

questions related to medication discontinuation. The Naranjo algorithm also provides more specific guidance than the Leape & Bates method. In practice, the two have never been compared head to head.

The computerized trigger tool[25] is also an interesting option; it has the advantage of automated detection of ADEs, possibly increasing the rate of detection of certain ADEs, but in its current form, its use is limited to specific hospital settings. It requires an information technology infrastructure with linkage to source systems for structured clinical data (e.g. lab and pharmacy systems). As it was not designed to be used outside of the acute hospital setting, it is less useful for deprescribing trials with follow-up for ADE detection in the community. Finally, the self-reported method,[23] used in Brazil where self-medication with prescription drugs is common, allows patients to report their own symptoms. In theory, this could increase the sensitivity of detection, while potentially reducing specificity. However, sensitivity and specificity have not been formally measured.

No method evaluated in our literature review was designed or validated for deprescribing studies. As such, the majority do not intuitively capture adverse drug withdrawal events (ADWEs), defined as the "unintended consequence and balancing outcome caused by the removal of a drug," which are important outcomes to monitor following deprescribing (please refer to the supplement S2.3 for examples of ADWEs).[46] Most methods outlined in this review were originally designed to capture ADRs from the receipt of a single medication in a clinical drug trial. The modified Naranjo algorithm for drug withdrawal focuses on a single medication discontinuation, and may not capture all adverse events related to deprescribing (e.g. medication errors induced by a change in a patient's regimen by following a tapering schedule or altered effects from removal of a previously balanced drug interaction).

Our study has several limitations. Notably, we chose to focus on studies that only included older adults, but none of the methods we identified were specific to older adults. Our search strategy included all ages did not identify any additional ADE adjudication methods. Our review identified multiple methodologies which adopt a generalized approach to ADR and ADE detection. That said, organ-specific methods of causality have also been developed, such as the Roussel Uclaf Causality Assessment Method (RUCAM), used to assess drug-induced liver injury

and the Registry of Severe Cutaneous Adverse Reaction (RegiSCAR), for assessing drug reaction with eosinophilia and systemic symptoms, which were not used in any studies included in this review.[47,48] These methods may be less useful in a deprescribing context, considering events such as liver injury and severe skin reactions are unlikely to occur when stopping or reducing a medication, but is still an important factor to consider.[31,47] Adding in these organ-specific methods on a case by case basis could be one option to more specifically characterize some ADEs. The methods we identified in this review are specifically for determining outcomes in scientific trials and have not been studied in a clinical context. However, many of the methods could be used to follow individual patients after a medication has been deprescribed. Our original search strategy included EMBASE; however, including this database yielded thousands of articles that were not specific to our topic of interest and for feasibility we limited the final search to Medline and Cochrane, making this a narrative review. Finally, the MESH descriptor "deprescribing" was only created in 2016 in Medline, possibly making some studies related to the subject before this date more difficult to identify.

Based on the findings of this review, we propose that a revised method to adjudicate ADEs in the context of deprescribing trials is needed. One such approach would be to first examine whether any adverse event has occurred based on a set of predefined criteria. With increasing patient complexity and drug regimens, it may not always be feasible to determine if an adverse event is an ADE, however an adverse event is more straight forward to recognize and should still be captured as an important outcome. Once an adverse event is identified, greater focus can then be placed on determining if it represents an ADE or ADWE by adapting an existing framework to meet the needs identified in this review.

**Conclusion**

Standardizing the primary outcome across deprescribing studies is important in order to compare the effectiveness of interventions and summarize the literature. From a narrative review we identified several methods for adjudicating ADEs that were used variably across deprescribing studies. Many methods relied heavily on proving drug causality, which

may not be an ideal approach for capturing outcomes specifically in the context of deprescribing studies. While all methods had limitations, the Leape and Bates method offered the greatest flexibility and ease of use with a combination of clinical judgment and implied causality, though it was not perfectly suited to capture ADWEs. Future research into deprescribing interventions in older adults will require the refinement of existing methods for ADE adjudication in order to broadly capture all pertinent adverse events.

**Figure 2.1.** PRISMA Flow Diagram

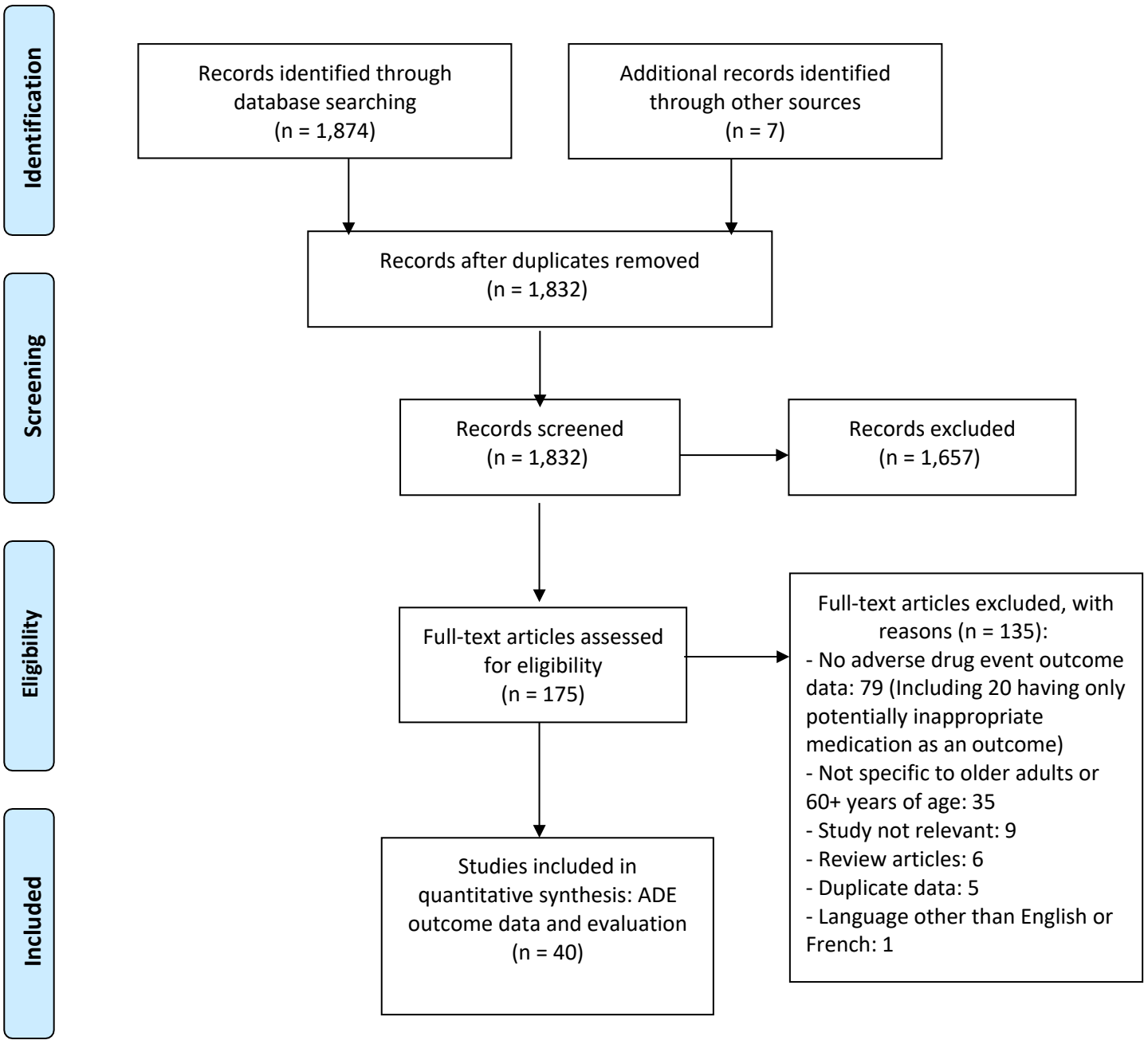

**Table 2.1.** Study Characteristics & ADE Adjudication Methods of Included Articles

| Author/Year | Location | Study | Age | F/U (mos) | Setting | Adjudication Method | ADE Definition |
|---|---|---|---|---|---|---|---|
| Ailabouni, N., et al., 2019[23] | NZ | P | ≥65 | 6 | RCF | Clinical Judgment | NR |
| Azad, N. et al., 2002[49] | Canada | P | ≥ 65 | 3 | H | Naranjo | AD |
| Baldoni Ade, O., et al., 2014[29] | Brazil | P | ≥ 60 | 6 | C | Self-Reported | NR |
| Boockvar, K., et al., 2004[50] | USA | P | ND | 2 | H | Naranjo + Leape & Bates | WHO |
| Cahir, C., et al., 2014[30] | Ireland | R | ≥ 70 | 6 | C | Leape & Bates | Parry |
| Chang, C. M., et al., 2005[51] | Taiwan | P | ≥ 65 | 5 | H | Naranjo | WHO |
| Chaye, H., et al., 2015[40] | France | R | ND | 24 | H | Trigger Tool | NR |
| Chrischilles, E. A. et al., 1992[52] | USA | P | ≥ 65 | 24 | C | Clinical Judgment | NR |
| Colt, H. G. et al., 1989[43] | USA | R | ≥ 65 | 1 | H | Karch & Lasagna | AD |
| Cullinan, S., et al., 2016[36] | Europe | P | ≥ 65 | 9 | H | WHO-UMC | WHO |
| Cunningham, G., et al., 1997[44] | Scotland | P | ≥ 65 | 17 | H | Hallas | AD |
| Dilles, T., et al., 2015[53] | Belgium | R | ND | 1 | RCF | Clinical Judgment | NR |
| Dormann, H., et al., 2013[37] | Germany | P | ND | 1 | ED | WHO-UMC | WHO |
| Farfel, J. M., et al., 2010[54] | Brazil | R | ≥ 60 | 6 | ED | Clinical Judgment | AD |
| Fradet, G., et al., 1996[41] | France | R | ≥ 65 | 12 | H | French Method | NR |
| Franceschi, M. et al., 2012[55] | Italy | P | ≥ 65 | 14 | H | Naranjo | Edwards Aronson |
| Galli, T. B., et al., 2016[56] | Brazil | R | ≥ 60 | 12 | H | Naranjo | NR |
| Hamilton, H. et al., 2011[4] | Ireland | P | ≥ 65 | 4 | H | WHO-UMC | WHO |
| Hedna, K., et al., 2015[3] | Sweden | R | ≥ 65 | 3 | C | Howard | WHO |
| Kanaan, A. O., et al., 2013[31] | USA | R | ≥ 65 | 4 | H | Leape & Bates | AD |
| Lindley, C. M., et al., 1992[57] | UK | P | ≥ 65 | 2.5 | H | Clinical Judgment | NR |
| Lund, Brian C et al., 2010[58] | USA | P | ≥ 65 | 3 | C | Clinical Judgment | AD |
| Matanovic, S. M.; et al., 2014[59] | Croatia | P | ≥ 65 | 7 | H | Naranjo | AD |
| McDonald, E. G., et al., 2019[32] | Canada | P | ≥ 65 | 24 | H | Leape & Bates | NR |
| Mergenhagen, K.; et al.,2012[34] | USA | P | ND | 3 | H | Naranjo | NR |
| Montastruc, F., et al., 2014[42] | France | P | ≥ 75 | 6 | C | French Method | NR |
| Ness, J., et al., 2006[60] | USA | P | ≥ 65 | 3 | C | Leape & Bates | AD |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| O'Connor, M., et al., 2012[38] | Ireland | P | ≥ 65 | 13 | H | WHO-UMC | WHO |
| Onda, M. et al., 2015[61] | Japan | R | ≥ 65 | 1 | C | Clinical Judgment | NR |
| Page, R. L., 2nd; et al., 2006[62] | USA | R | ≥ 75 | 18 | H | Naranjo | AD |
| Passarelli, M. C., et al., 2005[63] | Brazil | P | ≥ 60 | 21 | H | Naranjo | WHO |
| Saka, S. A., et al., 2018[64] | South Africa | R | ≥ 60 | 12 | H | Naranjo | WHO |
| Sakuma, M., et al., 2011[65] | Japan | P | ≥ 65 | 6 | H | Leape & Bates | NR |
| Schmader, K. et al., 2004[35] | USA | P | ≥ 65 | 41 | H | Naranjo | WHO |
| Segal, J. L. et al., 1979[45] | USA | R | ≥ 60 | N/A | C | Karch & Lasagna | Karch & Lasagna |
| Sevilla-Sanchez, D. et al., 2017[66] | Spain | P | ND | 10 | H | Naranjo | AD |
| Thomas, E. J., 2000[67] | USA | R | ≥ 65 | 12 | H | Leape & Bates | AD |
| Varallo, F. R. et al., 2011[68] | Brazil | P | ≥ 60 | 5 | H | Naranjo | WHO |
| Wallace, E., et al., 2017[33] | Ireland | P | ≥ 70 | 24 | C | Leape & Bates | NR |
| Wang-Hansen, M. et al., 2019[69] | Norway | R | ≥ 75 | 7 | H | Clinical Judgment | AD |

P: prospective; R: retrospective; ND: not defined/“older adults”; F/U: follow-up duration (months); RCF: Residential Care Facility; ED: emergency department; H: In-Hospital; C: Community; NR: Not Reported, AD: Author defined

**Table 2.2.** Adverse Drug Event Adjudication Algorithms

| Study Protocol | Method Description | Benefits | Limitations |
|---|---|---|---|
| **Naranjo et al.** | Adverse drug reaction (ADR) probability scale questionnaire | Causality of ADRs, validated & strong between-rater reliability; Kappa= 0.7 – 0.92[34,35] Modified version available for adverse drug withdrawal reaction assessment | Difficult to apply outside of an acute care setting as it requires specialized testing and/or resources which may not be available; Limited to ADRs |
| **Leape & Bates** | A six-point Likert scale | Uses a combination of clinical judgment and implied causality; Kappa= 0.63 – 0.88[30-33] | Relies on clinical expertise; not designed to measure adverse drug withdrawal events |
| **Clinical Judgment** | Identify relationship likelihood | ADE detection is performed by an expert | No structured, systematic, reproducible procedure; Kappa N/A in included studies |
| **WHO-UMC** | Assessment criteria questions | Applicable to drug-drug interactions, assesses the actor drug influencing the other drug; Kappa= 0.71[39] | Specifically tailored for ADRs, and only captures immediate pharmacological aspects; Kappa N/A in included studies |
| **Computerized Trigger Tool** | Computerized ADE monitoring system | Automated detection of ADEs increasing the rate of detection | Expensive and requires the hospital to have a customized software system; Kappa N/A in included studies |
| **French Causality Assessment** | Chronological criteria, clinical and biological findings, and symptomatologic assessments | Good sensitivity for detecting new ADRs | Complex- involving a 3-stage flow chart; Limited to ADRs; Kappa N/A in included studies |
| **Karch & Lasagna** | Clinical judgment and ADRs rubric | Combination of clinical judgment and pre-determined definitions | Not applicable to routine clinical practices; detailed and time consuming; Limited to ADRs; Kappa N/A in included studies |
| **Hallas** | Modified Karch & Lasagna + dose-related therapeutic failure | Incorporates ADR avoidability | Not applicable to routine clinical practices; detailed and time consuming; Limited to ADRs; Kappa N/A in included studies |
| **Howard** | Modified Hallas criteria | High inter-reviewer reliability; Kappa= 0.74 – 0.88[28] | Not applicable to routine clinical practices; detailed and time consuming; Limited to ADRs |
| **Self-Reported** | Patient-reported | Useful for community dwellings Patient Involvement | Not verified by an expert; Kappa N/A in included studies |

Kappa score between 0.41 – 0.59 moderate, 0.6 - 0.8 substantial, 0.8 and above excellent reliability.[20] ADE: adverse drug event; ADR: adverse drug reaction; N/A: no kappa reported

**See Appendix A. Additional Material for Manuscript 1 (Chapter 2)**

**Supplementary Table S2.1.** Cochrane Search Strategy

**Supplementary Table S2.2.** Subgroup of Studies Not Limited to Older Adults (includes all ages)

**Supplementary Text S2.3.** Examples of ADEs and ADWEs

**References Manuscript 1:**


1. Masnoon N, Shakib S, Kalisch-Ellett L, Caughey GE. What is polypharmacy? A systematic review of definitions. *BMC geriatrics.* 2017;17(1):230-230.
2. Spinewine A, Schmader KE, Barber N, et al. Appropriate prescribing in elderly people: how well can it be measured and optimised? *Lancet (London, England).* 2007;370(9582):173-184.
3. Hedna K, Hakkarainen KM, Gyllensten H, Jönsson AK, Petzold M, Hägg S. Potentially inappropriate prescribing and adverse drug reactions in the elderly: a population-based study. *Eur J Clin Pharmacol.* 2015;71(12):1525-1533.
4. Hamilton H, Gallagher P, Ryan C, Byrne S, O'Mahony D. Potentially Inappropriate Medications Defined by STOPP Criteria and the Risk of Adverse Drug Events in Older Hospitalized PatientsPIMs Defined by STOPP Criteria and Risk of ADEs. *Archives of Internal Medicine.* 2011;171(11):1013-1019.
5. Coupland CAC, Hill T, Dening T, Morriss R, Moore M, Hippisley-Cox J. Anticholinergic Drug Exposure and the Risk of Dementia: A Nested Case-Control Study. *JAMA Intern Med.* 2019.
6. Gingras MA, Lieu A, Papillon-Ferland L, Lee TC, McDonald EG. Retrospective Cohort Study of the Prevalence of Off-label Gabapentinoid Prescriptions in Hospitalized Medical Patients. *J Hosp Med.* 2019;14:E1-e4.
7. Gallagher P, Lang PO, Cherubini A, et al. Prevalence of potentially inappropriate prescribing in an acutely ill population of older patients admitted to six European hospitals. *Eur J Clin Pharmacol.* 2011;67(11):1175.
8. Poudel DR, Acharya P, Ghimire S, Dhital R, Bharati R. Burden of hospitalizations related to adverse drug events in the USA: a retrospective analysis from large inpatient database. *Pharmacoepidemiology and Drug Safety.* 2017;26(6):635-641.
9. Institute of Medicine Committee on Quality of Health Care in A. In: Kohn LT, Corrigan JM, Donaldson MS, eds. *To Err is Human: Building a Safer Health System.* Washington (DC): National Academies Press (US)

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10. Hamilton HJ, Gallagher PF, O'Mahony D. Inappropriate prescribing and adverse drug events in older people. *BMC geriatrics.* 2009;9:5-5.
11. *Medication Overload: America's Other Drug Problem; How the drive to prescribe is harming older Americans.* Lown Institute; April 2019.
12. Thompson W, Farrell B. Deprescribing: what is it and what does the evidence tell us? *Can J Hosp Pharm.* 2013;66(3):201-202.
13. Scott IA, Hilmer SN, Reeve E, et al. Reducing inappropriate polypharmacy: the process of deprescribing. *JAMA Intern Med.* 2015;175(5):827-834.
14. Ouslander JG SK. Editor's Note on the MedSafer Study. *Journal of American Geriatrics Society.* 2019;67(9):1850.
15. Thompson W, Reeve E, Moriarty F, et al. Deprescribing: Future directions for research. *Research in Social and Administrative Pharmacy.* 2018.

16. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther.* 1981;30(2):239-245.
17. Bates DW, Cullen DJ, Laird N, et al. Incidence of adverse drug events and potential adverse drug events. Implications for prevention. ADE Prevention Study Group. *JAMA.* 1995;274(1):29-34.
18. Karch FE, Lasagna L. Adverse drug reactions. A critical review. *Jama.* 1975;234(12):1236-1241.
19. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev.* 2015;4:1.
20. Cohen J. A coefficient of agreement for nominal scales. *Educational and Psychological Measurement.* 1960;20:37-46.
*21.* Leape LL, Bates DW, Cullen DJ, et al. Systems Analysis of Adverse Drug Events. *JAMA.* 1995;274(1):35-43.
22. Gandhi TK, Weingart SN, Borus J, et al. Adverse drug events in ambulatory care. *The New England journal of medicine.* 2003;348(16):1556-1564.
23. Ailabouni N, Mangin D, Nishtala PS. DEFEAT-polypharmacy: deprescribing anticholinergic and sedative medicines feasibility trial in residential aged care facilities. *International Journal of Clinical Pharmacy.* 2019;18:18.
24. WHO. WHO-UMC system for Standardised Case Causality Assessment. 2018.
25. Classen DC, Pestotnik SL, Evans RS, Burke JP. Computerized surveillance of adverse drug events in hospital patients. *Jama.* 1991;266(20):2847-2851.
26. Begaud B, Evreux JC, Jouglard J, Lagier G. [Imputation of the unexpected or toxic effects of drugs. Actualization of the method used in France]. *Therapie.* 1985;40(2):111-118.
27. HALLAS J, HARVALD B, GRAM LF, et al. Drug related hospital admissions: the role of definitions and intensity of data collection, and the possibility of prevention. *Journal of Internal Medicine.* 1990;228(2):83-90.
28. Howard RL, Avery AJ, Howard PD, Partridge M. Investigation into the reasons for preventable drug related admissions to a medical admissions unit: observational study. *Quality and Safety in Health Care.* 2003;12(4):280.
29. Baldoni Ade O, Ayres LR, Martinez EZ, Dewulf Nde L, Dos Santos V, Pereira LR. Factors associated with potentially inappropriate medications use by the elderly according to Beers criteria 2003 and 2012. *International Journal of Clinical Pharmacy.* 2014;36(2):316-324.
30. Cahir C, Bennett K, Teljeur C, Fahey T. Potentially inappropriate prescribing and adverse health outcomes in community dwelling older patients. *Br J Clin Pharmacol.* 2014;77(1):201-210.
31. Kanaan AO, Donovan JL, Duchin NP, et al. Adverse drug events after hospital discharge in older adults: types, severity, and involvement of Beers Criteria Medications. *J Am Geriatr Soc.* 2013;61(11):1894-1899.
32. McDonald EG, Wu PE, Rashidi B, et al. The MedSafer Study: A Controlled Trial of an Electronic Decision Support Tool for Deprescribing in Acute Care. *J Am Geriatr Soc.* 2019.
33. Wallace E, McDowell R, Bennett K, Fahey T, Smith SM. Impact of Potentially Inappropriate Prescribing on Adverse Drug Events, Health Related Quality of Life and

Emergency Hospital Attendance in Older People Attending General Practice: A Prospective Cohort Study. *J Gerontol A Biol Sci Med Sci.* 2017;72(2):271-277.
34. Mergenhagen KA, Blum SS, Kugler A, et al. Pharmacist- versus physician-initiated admission medication reconciliation: impact on adverse drug events. *Am J Geriatr Pharmacother.* 2012;10(4):242-250.
35. Schmader KE, Hanlon JT, Pieper CF, et al. Effects of geriatric evaluation and management on adverse drug reactions and suboptimal prescribing in the frail elderly. *Am J Med.* 2004;116(6):394-401.
36. Cullinan S, O'Mahony D, Byrne S. Application of the structured history taking of medication use tool to optimise prescribing for older patients and reduce adverse events. *International Journal of Clinical Pharmacy.* 2016;38(2):374-379.
37. Dormann H, Sonst A, Müller F, et al. Adverse drug events in older patients admitted as an emergency: the role of potentially inappropriate medication in elderly people (PRISCUS). *Dtsch Arztebl Int.* 2013;110(13):213-219.
38. Connor M, O'Sullivan D, Gallagher P, Byrne S, Eustace J, O'Mahony D. Prevention of adverse drug events in hospitalized older patients: A randomised controlled trial using STOPP/START criteria. *European Geriatric Medicine.* 2012;3:S132.
39. Thaker SJ, Sinha RS, Gogtay NJ, Thatte UM. Evaluation of inter-rater agreement between three causality assessment methods used in pharmacovigilance. *J Pharmacol Pharmacother.* 2016;7(1):31-33.
40. Chayé H, Bernard M, Tubéry M, et al. [Hospital readmission induced by adverse drug reaction: a pilot study in a post-emergency unit of a French university hospital]. *Rev Med Interne.* 2015;36(7):450-456.
41. Fradet G, Legac X, Charlois T, Ponge T, Cottin S. [Iatrogenic drug-induced diseases, requiring hospitalization, in patients over 65 years of age. 1-year retrospective study in an internal medicine department]. *Rev Med Interne.* 1996;17(6):456-460.
42. Montastruc F, Duguet C, Rousseau V, Bagheri H, Montastruc JL. Potentially inappropriate medications and adverse drug reactions in the elderly: a study in a PharmacoVigilance database. *Eur J Clin Pharmacol.* 2014;70(9):1123-1127.
43. Colt HG, Shapiro AP. Drug-induced illness as a cause for admission to a community hospital. *J Am Geriatr Soc.* 1989;37(4):323-326.
44. Cunningham G, Dodd TR, Grant DJ, McMurdo ME, Richards RM. Drug-related problems in elderly patients admitted to Tayside hospitals, methods for prevention and subsequent reassessment. *Age & Ageing.* 1997;26(5):375-382.
45. Segal JL, Thompson JF, Floyd RA. Drug utilization and prescribing patterns in a skilled nursing facility: the need for a rational approach to therapeutics. *Journal of the American Geriatrics Society.* 1979;27(3):117-122.
46. Graves T, Hanlon JT, Schmader KE, et al. Adverse events after discontinuing medications in elderly outpatients. *Arch Intern Med.* 1997;157(19):2205-2210.
47. Danan G, Teschke R. Drug-Induced Liver Injury: Why is the Roussel Uclaf Causality Assessment Method (RUCAM) Still Used 25 Years After Its Launch? *Drug Safety.* 2018;41(8):735-743.
48. Kardaun SH, Sekula P, Valeyrie-Allanore L, et al. Drug reaction with eosinophilia and systemic symptoms (DRESS): an original multisystem adverse drug reaction. Results

from the prospective RegiSCAR study. *British Journal of Dermatology.* 2013;169(5):1071-1080.
49. Azad N, Tierney M, Victor G, Kumar P. Adverse drug events in the elderly population admitted to a tertiary care hospital. *Journal of Healthcare Management.* 2002;47(5):295-305; discussion 305-296.
50. Boockvar K, Fishman E, Kyriacou CK, Monias A, Gavi S, Cortes T. Adverse events due to discontinuations in drug use and dose changes in patients transferred between acute and long-term care facilities. *Arch Intern Med.* 2004;164(5):545-550.
51. Chang CM, Liu PY, Yang YH, Yang YC, Wu CF, Lu FH. Use of the Beers criteria to predict adverse drug reactions among first-visit elderly outpatients. *Pharmacotherapy.* 2005;25(6):831-838.
52. Chrischilles EA, Segar ET, Wallace RB. Self-Reported Adverse Drug Reactions and Related Resource Use: A Study of Community-Dwelling Persons 65 Years of Age and Older. *Annals of Internal Medicine.* 1992;117(8):634-640.
53. Dilles T, Van Rompaey B, Van Bogaert P, Elseviers MM. Resident and nurse reports of potential adverse drug reactions. *Eur J Clin Pharmacol.* 2015;71(6):741-749.
54. Farfel JM, Accorsi TA, Franken M, et al. Adverse drug events leading to emergency department visits in elderly: the role of inappropriate prescription. *Einstein (Sao Paulo).* 2010;8(2):175-179.
55. Franceschi M, Scarcelli C, Niro V, et al. Prevalence, clinical features and avoidability of adverse drug reactions as cause of admission to a geriatric unit: a prospective study of 1756 patients. *Drug Saf.* 2008;31(6):545-556.
56. Galli TB, Reis WC, Andrzejevski VM. Potentially inappropriate prescribing andthe risk of adverse drug reactions in critically ill older adults. *Pharm Pract (Granada).* 2016;14(4):818-818.
57. Lindley CM, Tully MP, Paramsothy V, Tallis RC. Inappropriate medication is a major cause of adverse drug reactions in elderly patients. *Age Ageing.* 1992;21(4):294-300.
58. Lund BC, Carnahan RM, Egge JA, Chrischilles EA, Kaboli PJ. Inappropriate Prescribing Predicts Adverse Drug Events in Older Adults. 2010;44(6):957-963.
59. Matanović SM, Vlahović-Palčevski V. Potentially inappropriate prescribing to the elderly: comparison of new protocol to Beers criteria with relation to hospitalizations for ADRs. *Eur J Clin Pharmacol.* 2014;70(4):483-490.
60. Ness J, Hoth A, Barnett MJ, Shorr RI, Kaboli PJ. Anticholinergic medications in community-dwelling older veterans: prevalence of anticholinergic symptoms, symptom burden, and adverse drug events. *Am J Geriatr Pharmacother.* 2006;4(1):42-51.
61. Onda M, Imai H, Takada Y, Fujii S, Shono T, Nanaumi Y. Identification and prevalence of adverse drug events caused by potentially inappropriate medication in homebound elderly patients: a retrospective study using a nationwide survey in Japan. *BMJ Open.* 2015;5(8):e007581.
62. Page RL, 2nd, Ruscin JM. The risk of adverse drug events and hospital-related morbidity and mortality among older adults with potentially inappropriate medication use. *Am J Geriatr Pharmacother.* 2006;4(4):297-305.

63. Passarelli MC, Jacob-Filho W, Figueras A. Adverse drug reactions in an elderly hospitalised population: inappropriate prescription is a leading cause. *Drugs Aging.* 2005;22(9):767-777.
64. Saka SA, Nlooto M, Oosthuizen F. American Geriatrics Society-Beers Criteria and adverse drug reactions: a comparative cross-sectional study of Nigerian and South African older inpatients. *Clinical Interventions In Aging.* 2018;13:2375-2387.
65. Sakuma M, Morimoto T, Matsui K, et al. Epidemiology of potentially inappropriate medication use in elderly patients in Japanese acute care hospitals. *Pharmacoepidemiol Drug Saf.* 2011;20(4):386-392.
66. Sevilla-Sanchez D, Molist-Brunet N, Amblas-Novellas J, Roura-Poch P, Espaulella-Panicot J, Codina-Jane C. Adverse drug events in patients with advanced chronic conditions who have a prognosis of limited life expectancy at hospital admission. *European Journal of Clinical Pharmacology.* 2017;73(1):79-89.
67. Thomas EJ, Brennan TA. Incidence and types of preventable adverse events in elderly patients: population based review of medical records. *BMJ.* 2000;320(7237):741-744.
68. Varallo FR, Capucho HC, Planeta CS, Mastroianni Pde C. Safety assessment of potentially inappropriate medications use in older people and the factors associated with hospital admission. *Journal of Pharmacy & Pharmaceutical Sciences.* 2011;14(2):283-290.
69. Wang-Hansen MS, Wyller TB, Hvidsten LT, Kersten H. Can screening tools for potentially inappropriate prescriptions in older adults prevent serious adverse drug events? *Eur J Clin Pharmacol.* 2019;20:20.

## Chapter 3. COVID-SAFER: Deprescribing Guidance for Hydroxychloroquine Drug Interactions in Older Adults

### Preamble to manuscript 2

In March-April 2020, during the early stages of the COVID-19 pandemic while most daily activities in North America were abruptly halted, I identified an opportunity for COVID-19 research related to Polypharmacy and ADEs. Due to the nature and importance of this topic I had a very brief window of opportunity to conduct research and publish. I was successful in going from idea to an online publication in under 4 weeks. This manuscript was published in the Journal of the American Geriatric Society (JAGS) first online on May 22nd, 2020.[54]

At the time of conducting this study hydroxychloroquine was receiving a lot of attention and was emerging as a possible treatment for COVID-19. I therefore used hydroxychloroquine as a representative example for possible unforeseen consequences of polypharmacy in older adults during the COVID-19 era. The study which I conducted can be replicated using the same methodologies for other potential treatments that may emerge, but it is the fundamental concept of deprescribing to pre-emptively avoid drug-interactions with antiviral therapy which emerges as most novel.

This surprise additional project ties in well with the rest of the work completed to this point and contributes to the novelty and results of the thesis. No one knows how long we will be living in the COVID-19 era, and when a treatment will become available, and thus this work advocates for the importance of reducing polypharmacy and PIMs in older adults prior to it becoming an urgent or forced issue. Tying in with my work on ADE adjudication, if we are to proactively deprescribe medications in older adults, we need to have proper measurement tools to captures outcomes related to successful deprescribing and counter-balancing safety measures.

**Title Page:**

**COVID-SAFER: Deprescribing Guidance for Hydroxychloroquine Drug Interactions in Older Adults**

*Running title: COVID-SAFER*

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**Abstract:**

**Background** Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection causes high morbidity and mortality in older adults with chronic illnesses. Several trials are currently underway evaluating the antimalarial drug hydroxychloroquine as a potential treatment for acute infection. However, polypharmacy predisposes patients to increased risk of drug-drug interactions with hydroxychloroquine and may render many in this population ineligible to participate in trials.

**Objectives** We aimed to quantify the degree of polypharmacy and burden of potentially inappropriate medications (PIMs) that older hospitalized adults are taking which would interact with hydroxychloroquine.

**Methods** We reanalyzed data from the cohort of patients 65 years and older enrolled in the MedSafer pilot study. We first identified patients taking medications with potentially harmful drug-drug interactions with hydroxychloroquine that might exclude them from participation in a typical coronavirus disease 2019 (COVID-19) therapeutic trial. Next, we identified medications that were flagged by MedSafer as being potentially inappropriate and crafted guidance around medication management if contemplating the use of hydroxychloroquine.

**Results** The cohort contained a total of 1001 unique patients with complete data on their home medications at admission. Of these 1001 patients, 590 (58.9%) were receiving one or more home medications that could potentially interact with hydroxychloroquine, and of these 255 (43.2%) were flagged as potentially inappropriate by the MedSafer tool. Common classes of PIMs observed were antipsychotics, cardiac medications, and anti-diabetic agents.

**Conclusion** The COVID-19 pandemic highlights the importance of medication optimization and deprescribing PIMs in older adults. By acting now to reduce polypharmacy and use of PIMs, we can better prepare this vulnerable population for inclusion in trials and, if substantiated, pharmacologic treatment or prevention of COVID-19.

**Key Words:** polypharmacy; potentially inappropriate medications (PIMs); hydroxychloroquine; coronavirus disease 2019 (COVID-19); deprescribing

**Introduction**

The first cluster of cases of COVID-19 disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was reported to the World Health Organization on December 31st, 2019.[1,2] On March 11th, 2020 the World Health Organization declared COVID-19 a pandemic[3] and at the time of writing, greater than 4.3 million laboratory-confirmed cases have been documented globally, with greater than 290,000 related deaths.[4] In response, more than 600 interventional trials have been registered to investigate whether existing medications are safe and effective for the treatment of COVID-19 disease.[5]

One class of medications that has demonstrated therapeutic properties *in vitro* are the antimalarial agents chloroquine and hydroxychloroquine.[6] Following results from the early emerging literature, including several small clinical trials[7-10], an uncontrolled case series[11], and an open label non-randomized study from France[12], the U.S. Food and Drug Administration (FDA) granted an Emergency Use Authorization (EUA) for hydroxychloroquine for hospitalized patients with COVID-19 who are unable to participate in clinical trials.[13-15] These studies were heavily referenced in the media despite inconclusive data and trials for use as prophylaxis and treatment are ongoing. [12,16] More recently, an observational study on hydroxychloroquine was published showing no improvement in clinical outcomes in patients hospitalized with COVID-19.[17] At the present time, the FDA and the Infectious Disease Society of America (IDSA) recommend against its use outside of clinical trials.[18] The results of randomized controlled trials are forthcoming and the medication may still be prescribed outside of a trial, for lack of any alternative treatment.

One population in critical need of effective treatments for COVID-19 are older adults with comorbid conditions including diabetes, hypertension, and cardiac conditions. Studies suggest older adults are more susceptible to infection with COVID-19 and are at a higher risk of severe complications when compared to the general population.[19,20] Outbreaks in long-term care facilities resulting in death have emphasized the vulnerability of this population.[21] With increasing age, there are higher rates of medical conditions observed, leading to a higher prevalence of polypharmacy (taking multiple medications);[22,23] as many as 56.7% of community

dwelling North Americans over the age of 65 are taking five or more regular medications.[24,25] Polypharmacy is harmful, given the association with falls, fractures, and other adverse drug events.[26] However, we are now encountering another problem from taking multiple medications: a substantial risk of drug-drug interactions with potential therapies for COVID-19.[27] Many of these interacting medications are potentially inappropriate medications (PIMs), which themselves carry an increased risk for adverse drug events (ADEs), and could be deprescribed (stopped, tapered or switched to a safer alternative).[28-31]

We hypothesized that due to polypharmacy and clinically significant drug-drug interactions, many older adults with their current drug regimens will be ineligible for COVID-19 therapeutic trials and/or treatment with medications that are currently under investigation, including, but not limited to, the antimalarial hydroxychloroquine. This despite older adults being at an increased risk of complications as a result of COVID-19 and representing a population most likely to benefit from different therapeutic options. We postulated that many of these drug-drug interactions are due to PIMs which could be deprescribed proactively. In light of a recent FDA warning regarding risk of QTc prolongation, we examined hydroxychloroquine[14] (as a test case) to estimate the prevalence of prescribed medications with drug-drug interactions in a cohort of hospitalized older adults with polypharmacy. We aimed to better characterize the burden of PIMs that could be deprescribed with the impetus being the COVID-19 pandemic.

**Methods**

The MedSafer Pilot study[32] was a large controlled before and after deprescribing trial that took place between September 2016 and May 2017 on 4 Canadian academic internal medicine clinical teaching units. The trial was designed to assess whether a computer-assisted medication review tool augmented the deprescribing of PIMs at discharge in a population of hospitalized older adults with polypharmacy. The software's algorithm identified PIMs and provided deprescribing recommendations for each individual patient by applying rules derived from widely available consensus documents for safer prescribing in older adults.[30,31,33]

Details of the trial are described elsewhere.[32] Briefly, patients were identified on admission via the emergency room to one of the designated units after discussion with the treating team to see if the met they broad inclusion criteria of 65-years and older and taking five or more medications. Patient data concerning medical conditions, validated medications and some lab results were collected and entered into the MedSafer deprescribing electronic decision support software which identified PIMs through drug-disease combinations; drug-drug interactions; or those that should be avoided or used with caution in older adults. The MedSafer system generated a report of the PIM, included a level of harm (high risk, intermediate risk, or low risk but little added value), the rationale for deprescribing and, when appropriate, a tapering protocol.

For the present study, we re-analyzed the MedSafer data as a representative sample of vulnerable older adults with polypharmacy. We first searched the literature for medications with known drug-drug interactions with hydroxychloroquine by examining the product monograph[34], referring to drug-drug interaction websites[35,36], and reviewing the exclusion criteria for a currently enrolling FDA and Health Canada approved hydroxychloroquine trial for COVID-19 (NCT04308668).[5,37,38] Medications with known interactions with hydroxychloroquine were grouped according to the American Hospital Formulary Service (AHFS) classification[39] (Table 3.1) and divided into two categories: chronic medications and medications typically prescribed for a short course such as antibiotics. We analyzed all patients in the MedSafer study who consented to participate in the deprescribing trial and who had a complete medication reconciliation performed on admission. We theoretically 'exposed' this patient cohort to treatment with hydroxychloroquine (minimum 5-days at a minimum dose of 600mg daily as in NCT04308668) and identified possible drug interactions, as well as potential harmful outcomes such as increased toxicity of hydroxychloroquine, risk of QTc prolongation or malignant cardiac arrhythmia, or risk of other adverse drug events requiring closer monitoring during therapy such as severe hypoglycemia (Table 3.2). From all interacting medications we ran the MedSafer algorithms to determine the proportion of medications that were PIMs and that could be deprescribed. We also identified the triggering condition associated with each PIM (e.g. atrial fibrillation, heart failure, dementia, delirium or renal failure).

Finally, we developed recommendations for how to manage potential drug interactions, including the option of not receiving hydroxychloroquine. Recommendations were based on the literature and expert consensus generated by the authors [experts in infectious diseases (TCL), general internal medicine (TCL, EGM, JD, BR, PEW), clinical pharmacy (RW, KB, SP, LPF), geriatrics (AH, LPF) and clinical pharmacology/toxicology (PEW)]. Ideally PIMs would be deprescribed proactively, prior to infection with COVID-19, but logistically this may not always be feasible and thus, we have made recommendations for these patients. Examples of recommendations included: medications that can be safely and abruptly held during treatment, those that require monitoring if there is to be ongoing use, and medications that likely cannot be stopped due to risk of an adverse drug withdrawal event.

**Results**

The MedSafer[32] cohort contained 1001 patients with complete data on their home medications. The median age of the cohort was 80 years and approximately 50% were women. More than half had hypertension, approximately 40% had diabetes, and close to 50% were moderately to severely frail as defined by the Clinical Frailty Scale.[40] All patients were hospitalized in a tertiary care hospital and were admitted to one of four general medical wards in one of 3 Canadian academic centres in Montreal, Ottawa, and Toronto.

We analyzed 1001 participants and found that 590 (58.9%) were prescribed one or more usual home medications that could potentially interact with hydroxychloroquine. The most commonly prescribed drug classes with known interactions were anti-diabetic medications (330/1001, 33%), the selective serotonin/norepinephrine reuptake inhibitors (SSRIs/SNRIs) (173/1001, 17.3%), antipsychotics (typical and atypical) (136/1001, 13.6%), and anti-arrhythmics, such as digoxin and amiodarone, (64/1001, 6.4%) (Table 3.3). The most common classes of antidiabetics were insulin 138/1001 (13.8%) and sulfonylureas 90/1001 (9.0%) (Table 3.3). The most serious interaction identified was a risk of QTc prolongation, torsade de pointes, and sudden death. A common but less severe interaction was a risk of hypoglycemia requiring

increased monitoring. Lowering of the seizure threshold and pharmacokinetic interactions leading to increased hydroxychloroquine levels was uncommon.

We then determined how many PIMs (as identified by the MedSafer tool) with known interactions with hydroxychloroquine presented an opportunity to be proactively deprescribed. Of the 590/1001 (58.9%) of participants who were prescribed a medication that could interact with hydroxychloroquine, 255 patients had the respective medication identified as a PIM, representing 43.2% of all patients with an interacting medication. Some common deprescribing opportunities that were identified included: 1) too high a dose of digoxin for a patient's renal function, 2) antipsychotic use in patients with a known history of delirium or neurocognitive disorder (risk of stroke, falls, confusion), and 3) insulin and sulfonylureas in patients with a history of hypoglycemia and/or tight glycemic control (HgbA1C <7.5%) (Table 3.4).

We prepared recommendations for the management of interacting medications in patients with COVID-19 who may want to receive treatment with hydroxychloroquine if found to be effective. Examples include holding low doses of antipsychotics or antidepressants during therapy, QTc monitoring and electrolyte optimization with continued use of QTc prolonging agents, and glucose monitoring with concurrent diabetes medications. We also highlight medications, such as amiodarone, that cannot be stopped on short notice for inclusion in clinical trials, due to prolonged half-life (Table 3.2).

**Discussion**

We re-analyzed data from the MedSafer pilot and found that 1 in 2 older adults with polypharmacy in our cohort have a chronically prescribed medication that could potentially interact with hydroxychloroquine, half of which were PIMs that could be deprescribed. The number of medical conditions and associated polypharmacy of the cohort places them at high risk of complications from COVID-19, but also potentially at risk of harm from treatments. We identified several common drug classes, many of which are also PIMs, that would preclude many older adults from enrolling in a trial. A main finding was that many older adults were taking medications that carry a known risk of prolonging the QTc. This finding should caution

against routine prescribing of QTc prolonging COVID-19 treatments outside of a clinical study, as there is real potential for harm. Importantly, more than 50% of interacting drugs were identified as a PIM that could be proactively deprescribed, rendering the person more likely to be eligible for a trial, and increasing the generalizability of study findings to this population.

In this analysis, we chose to focus on a specific drug, hydroxychloroquine. Of note, there is ongoing debate regarding the safety of hydroxychloroquine for treatment of COVID-19 and studies into efficacy are still ongoing. The risks associated with a medication such as hydroxychloroquine are likely higher for older adults with polypharmacy, especially given how common co-administration of QTc prolonging medications is and the prevalence of underlying cardiac conditions.[41] Many patients in our cohort were also overprescribed oral hypoglycemic agents (a1c <7.5% or a history of hypoglycemia), which when co-prescribed with hydroxychloroquine, could increase the risk of hypoglycemia. Older adults may have decreased oral intake as a result of COVID-19 infection and subsequent dehydration, electrolyte disturbances, nausea, and GI upset, which are also common adverse effects of hydroxychloroquine and may further exacerbate severe cardiac dysrhythmias.[42]

We have identified medications that may interact with study drugs that could be deprescribed proactively or at the time of treatment (e.g. off-label low dose quetiapine for sleep and agitation). Others, if stopped abruptly, could lead to serious adverse drug withdrawal events or uncomfortable withdrawal symptoms (e.g. methadone or higher doses of SSRIs).[43] Finally, some medications have long half-lives that require weeks to months to safely discontinue in order to avoid interactions, in this case, it may not be possible to stop the medication in time for treatment and thus the risk of interaction will not be reduced (e.g. azithromycin[44], fluoxetine, and amiodarone). Of note, while there is a risk of potential interactions between medications, this does not necessarily mean there will be any clinical manifestations.

Currently, the use of antimalarials for the treatment or prevention of COVID-19 has extremely limited evidence.[27] If robust evidence demonstrating efficacy in the treatment of COVID-19 is established, some clinicians might opt to continue certain medications that cannot be stopped abruptly, or where symptoms of withdrawal are thought to be significant. In most

cases, this would involve judicious monitoring of the QTc and minimizing other risk factors (electrolyte abnormalities, bradycardia). While cardiac monitoring is generally available for hospitalized patients, and perhaps at select nursing homes, this is likely not the case for most outpatients. Finally, it is important to take into consideration the half-life of the treatment medication to know how long symptoms should be monitored for and when it is safe to re-start medications (hydroxychloroquine, range: 20-120 days; mean: 40 days).[45-47] The risk of QTc prolongation may persist beyond the treatment period and remain clinically relevant for an unclear duration. Of note, the optimal effective does of hydroxychloroquine is not known. While our referenced study uses a daily dose of 600mg, in practice doses are variable, and some jurisdictions may prescribe lower doses of 400 mg daily, and this may have an impact on the risk of drug interactions and of side effects. The above considerations aside, for medications that are PIMs, their interactions with possible COVID-19 therapies are yet another reason to evaluate these medications for safe deprescribing immediately.[48] Any concern for abrupt discontinuation can be avoided by deprescribing in advance of acute illness.[48]

While we used hydroxychloroquine as a test case, this should not be interpreted as an endorsement of the medication. The clinical scenario described herein is not limited to hydroxychloroquine. Other treatments including but not limited to lopinavir-ritonavir, colchicine, and dapsone have also been proposed. These treatments similarly do not have significant evidence to support their use presently, but also carry risks of serious drug-drug interactions.[49,50] Clinicians may be tempted and indeed are prescribing medications out of desperation to provide patients with some form of treatment for COVID-19, but caution and a rigorous review of possible interactions is warranted, especially in older adults with polypharmacy. Notably, this population will often be underrepresented in clinical trials and even if proven effective, harms may still outweigh benefits for some therapies and an individualized approach should always be taken. Presently, while some medications have shown promise, such as hydroxychloroquine and more recently remdesivir[49], no medication for the treatment of COVID-19 has been proven to be effective and so we would suggest that outside of a clinical trial, the potential harms of off-label prescribing likely outweigh benefits. In

the meantime, it is important that we reduce the number of PIMs patients are taking, as it may facilitate more treatment options once clinical evidence is established.

Strengths of this study include a large cohort of older adults from a multi-site trial with polypharmacy, a thorough review of the literature to outline potential drug interactions, and clear instructions for medication management in the setting of drug interactions. This cohort also reflects the latest FDA recommendation that hydroxychloroquine should not be used outside of a clinical trial or a hospitalized setting.[14] Yet, our study has several limitations. As they were all hospitalized, the patients in this study likely represent those that are most likely to experience harm as a result of widespread prescribing of hydroxychloroquine. Future work should focus on finding safe and effective treatments in long-term care facilities where the burden of polypharmacy is high, there is an increased risk for COVID-19 exposure and effective treatments may decrease the risk of hospitalization. We chose to focus on hydroxychloroquine as a test case in order to provide realistic examples of harm that could result from widespread prescribing; reviewing all potential therapies and their subsequent drug-drug interactions was beyond the scope of this paper. However, similar recommendations could be generated for other potential treatments and may be more complex. For example, interactions with the lopinavir-ritonavir are more extensive than we have outlined for hydroxychloroquine. Additionally, the clinical significance of the interactions identified vary with; cardiac complications, with sudden death being the most severe, whereas absolute risks of seizure or hypoglycemia are less well defined. All patients in our cohort were on at least five medications. This is the case for approximately 50% of older Americans.[24,25] For those on fewer medications, the risk of drug-drug interactions is less. On the other hand, this study only looked at interactions with home medications. Patients who are hospitalized may have an even higher risk of interactions as they receive additional treatments (e.g. concurrent antibiotics that prolong the QTc, antipsychotics for the management of delirium, insulin etc.). Finally, while the population of patients we analyzed is Canadian, the problem of polypharmacy has been widely described in the United States and countries across the world, so the principles outlined in the discussion can be extrapolated to other jurisdictions.

**Conclusion**

Polypharmacy has many unpredictable consequences. There are well described harms (e.g. falls, fractures and cognitive impairment)[23] but we describe an emerging concern in the era of COVID-19. Patients may not be eligible for COVID-19 trials to study the effectiveness and safety of the medications under investigation. Others may be subject to harm as a result of off-label prescribing due to the risk of drug-drug interactions. Now more than ever, we should examine the medication lists of older adults with a focus on medication optimization and stopping PIMs, particularly those which may interact with potential COVID-19 therapies.

**Table 3.1.** Medications with Potential Drug-Drug Interactions with Hydroxychloroquine

| AHFS Drug Class | Drug Name | PIM* (Y/N) | Potential Interaction with Hydroxychloroquine |
|---|---|---|---|
| **Chronic Medications** | | | |
| *Cardiac medications (risk of QTc prolongation)* | | | Rare but serious and potentially life-threatening side effects may occur. Can result in an increase of irregular heart rhythm, QTc prolongation and malignant arrythmia. Increased risk with underlying cardiac conditions or congenital/pre-existing long QTc. |
| 24040404 | Procainamide | Y | |
| 24040412 | Flecainide | | |
| | Propafenone | | |
| 24040420 | Amiodarone | | |
| | Ibutilide | | |
| | Dofetilide | | |
| 242400 | Sotalol | | |
| *Medications acting on the CNS (risk of QTc prolongation)* | | | |
| 28160416 | Venlafaxine | Y | |
| 28160420 | Citalopram | | |
| | Escitalopram | | |
| | FLUoxetine | | |
| | Sertraline | | |
| 28160428 | Amitriptyline | Y | |
| | Desipramine | | |
| | Imipramine | | |
| | Doxepin | | |
| 28160808 | Typical antipsychotics (e.g. haloperidol) | Y | |
| 28160824 | | | |
| 28160804 | Atypical antipsychotics (e.g. quetiapine) | Y | |
| 28160424 | Trazodone | Y | |
| 282492 | Droperidol | N | |
| 2828 | Lithium | N | |
| 404 | Promethazine | Y | |
| 404 | Hydroxyzine | Y | |
| 1204 | Donepezil | Y | |
| 122004 | Cyclobenzaprine | Y | |
| *Gastrointestinal/miscellaneous (risk of QTc prolongation)* | | | |
| 563200 | Domperidone | Y | |
| 562220 | Ondansetron | N | |
| 861204 | Solifenacine | Y | |
| *Other drug classes requiring increased monitoring or dose adjustment* | | | |
| 81692 | Dapsone | N | Concomitant use of HCQ with antimalarial agents may increase the risk of hemolytic reactions. Concomitant use may increase the risk of nerve damage with longer term use (months/years). May require dose adjustment or more frequent monitoring. |

| | | | |
|---|---|---|---|
| 240408 | Digoxin | Y | Concomitant use may result in increased serum digoxin levels. Serum digoxin levels should be closely monitored in patients receiving combined therapy. |
| 681612 | Tamoxifen | N | Increased risk of retinal toxicity when used in combination with HCQ; greater risk with longer therapy (months/years) |
| *Medications for diabetes*** | | | |
| 682005 | DPP-4 inhibitors | Y | Risk of hypoglycemia |
| 682006 | GLP-1 receptor agonist | Y | |
| 682008 | Insulin | Y | |
| 682016 | Meglitinides | Y | |
| 682018 | SGLT2 inhibitors | Y | |
| 682020 | Sulfonylureas | Y | |
| 602028 | Thiazolidinedione | Y | |
| **Short-Term Use Medications** | | | |
| 8121204 | Erythromycin | N | Rare but serious and potentially life-threatening side effects may occur. Can result in an increase of irregular heart rhythm, QTc prolongation and malignant arrythmia. Increased risk with underlying cardiac conditions or congenital/pre-existing long QTc. |
| 8121292 | Azithromycin (Exception: Sometimes used Chronically) | N | |
| | Clarithromycin | | |
| 81218 | levoFLOXacin | N | |
| | Ciprofloxacin | | |
| | Moxifloxacin | | |
| 81408 | Ketoconazole | N | |
| | Itraconazole | | |
| 83092 | Chloroquine | N | |
| 280808 | Methadone | Y | |
| 83092 | Artemether | N | Co-administration may increase the toxic effect of antimalarials |
| | Lumefantrine | | |
| 83092 | Mefloquine | N | Co-administration of HCQ and mefloquine may increase the risk of seizure; avoid concurrent use (contraindicated) |
| 283228 | Sumatriptan | N | Rare but serious and potentially life-threatening side effects may occur. Can result in an increase of irregular heart rhythm, QTc prolongation and malignant arrythmia. Increased risk with underlying cardiac conditions or congenital/pre-existing long QTc. |
| | Zolmitriptan | | |

*Many of these medications are potentially inappropriate only under certain clinical circumstances (please refer to Table 2 for potential triggering conditions)
**Metformin was not considered to be at risk of causing hypoglycemia for the purposes of this analysis
PIM= potentially inappropriate medication; CNS= central nervous system; HCQ=hydroxychloroquine

**Table 3.2.** Medication Management for Potentially Inappropriate Medications with Hydroxychloroquine Interaction*

| AHFS Drug Class | Drug Name | Triggering condition: | General rationale for deprescribing: | Suggested Medication management for Hydroxychloroquine interaction IF unable to deprescribe in advance: |
|---|---|---|---|---|
| 24040404<br>24040412<br>24040420<br>24040412<br>242400 | Procainamide<br>Flecainide<br>Dofetilide<br>Sotalol<br>Propafenone | Atrial fibrillation | Data suggest that rate control yields better balance of benefits and harms than pharmacological rhythm control for most older adults. | If unable to deprescribe or hold during co-administration, use likely precludes HCQ given known risk of TdP for all medications listed apart from propafenone (conditional risk of TdP). Risk of sudden death. |
| 24040420 | Amiodarone | Atrial fibrillation | Amiodarone is associated with multiple toxicities, including thyroid disease, pulmonary disorders, and QT- interval prolongation. Consider a safer alternative. | The half-life of amiodarone is 60-142 days for long term oral maintenance therapy. If unable to deprescribe well in advance (weeks); likely precludes use of HCQ given known risk of TdP and risk of sudden death. |
| 240408 | Digoxin | Heart failure; chronic kidney disease; atrial fibrillation | Higher dosages of digoxin are not associated with any additional benefit and may increase risk of toxicity, especially in the presence of renal insufficiency. | If low dose (<125 mcg daily) may consider holding during co-administration. Consider alternate means of rate control. If given for HF: consider holding or reducing dose during HCQ treatment. Monitor for arrhythmia, monitor electrolytes (Na, K, Mg). Monitor digoxin level if available (co-administration may increase digoxin levels). |
| 280808 | Methadone | Triggered for all patients (unless active cancer or palliative treatment) | Do not initiate or maintain opioids long-term for chronic pain until there has been a trial of non-pharmacologic treatment and of non-opioid medications. | Chronic methadone therapy likely precludes use of HCQ given known risk of TdP, sudden death and risk of withdrawal syndrome from holding methadone therapy. |
| 28160416<br>28160420 | Venlafaxine<br>Citalopram | HypoNa Recurrent | SSRIs/SNRIs increase the risk of hyponatremia and also increase the | If low dose, consider holding during therapy and monitor for |

| | | | | |
|---|---|---|---|---|
| 28160420<br>28160420<br>28160420 | Escitalopram<br>FLUoxetine*<br>Sertraline | falls | risk of recurrent falls in older adults. | early withdrawal symptoms: dizziness, GI upset, flu-like symptoms, paresthesias, insomnia and psychiatric problems. For higher doses, suggest avoiding HCQ with (es)citalopram given known risk of TdP and sudden death. Possible risk of TdP for venlafaxine and conditional risk for fluoxetine and sertraline (co-administration requires careful electrolyte and QTc monitoring) |
| 28160424 | Trazodone | Flagged for all older adults | Do not use trazodone for sleep disorders or as first choice for behavioural symptoms unless agitation is severe and non-pharmacological interventions have failed. Increased risk of falls, daytime drowsiness, and impaired cognition. | If low dose, consider holding during therapy and monitor for withdrawal symptoms. For higher doses, may consider reducing dose with careful QTc monitoring, or avoiding HCQ altogether given possible risk of TdP. |
| 28160428<br>28160428<br>28160428<br>28160428 | Tricyclic anti-depressants;<br>Desipramine<br>Imipramine<br>Doxepin | Dementia; urinary retention; BPH; delirium; interactions with anti-cholinergics; | Alone or in combination may precipitate or worsen delirium, urinary retention, constipation, glaucoma, urinary retention and adverse CNS effects through anticholinergic effects. | If low dose, consider holding during therapy and monitor for early withdrawal symptoms: dizziness, muscular pain, GI upset, headache, malaise, trouble sleeping, irritability, hyperthermia, mania. For higher doses, suggest avoiding HCQ. If used concurrently, would require QTc and electrolyte monitoring. Amitriptyline and doxepin have a conditional risk of TdP. Nortriptyline and desipramine have a possible risk of TdP. |
| 28160804<br>28160804<br>28160808<br>28160824 | Typical and atypical antipsychotics | Triggered for all patients unless history of schizo-phrenia or bipolar disorder | Do not use antipsychotics for sleep disorders or as first choice for behavioural symptoms unless agitation is severe and non-pharmacological interventions have failed. Antipsychotics increase risk of stroke, falls, confusion, extra-pyramidal side effects, aspiration, | If low dose, consider holding during HCQ co-administration and monitoring closely for emergence of behavioural symptoms. For higher doses, may consider reducing dose with careful QTc monitoring, or alternatively, avoiding HCQ |

| | | | | |
|---|---|---|---|---|
| | | | and death. | altogether (haloperidol has a known risk of TdP and sudden death). Quetiapine, risperidone and olanzapine have a conditional risk of TdP. |
| 1204 | Donepezil | Flagged in combination with beta-blockers; history of falls; orthostatic hypotension | In combination with beta blockers can lead to bradycardia; on its own, can increase the risk of falls | Hold medication during co-administration with HCQ but monitor for changes in behaviour and development of confusion/delirium; may consider reducing dose with careful QTc monitoring, or alternatively, avoiding HCQ altogether due to known risk of TdP and sudden death. |
| 404 | Promethazine Hydroxyzine | Flagged for all older adults | Highly anticholinergic | Hold medications during co-administration with HCQ due to possible risk of TdP. |
| 122004 | Cyclo-benzaprine | Flagged for all older adults | Most muscle relaxants are poorly tolerated by older adults because of anticholinergic adverse effects, sedation, risk of fracture; effectiveness at dosages tolerated by older adults is questionable. Side effects are even more likely in patients with dementia or delerium. | Taper ahead of time to avoid symptoms of withdrawal. If low dose, consider holding during HCQ co-administration and monitoring closely for behavioural symptoms. For higher doses, may consider reducing dose with careful QTc monitoring given possible QTc prolongation. |
| 861204 | Solifenacine | Flagged for most older adults | Medications for overactive bladder symptoms may add to pill burden, contribute to adverse events from anticholinergic side effects, and the benefits rarely outweigh the harms | Hold medication during co-administration with HCQ or monitor QTc and electrolytes due to conditional risk of QTc prolongation. |
| 563200 | Domperidone | Parkinson's disease | Increased risk of sudden death in Parkinson's | Hold medication during co-administration with hydroxychloroquine due to known risk of QTc prolongation and risk of sudden death. |
| 682005<br>682006<br>682008 | DPP-4 inhibitors<br>GLP-1 receptor | Diabetes; Hypo-glycemia; | Consider decreasing if your patient had a recent hemoglobin A1c measurement of less than 7.5%. | Consider holding medications as per sick day protocol and monitoring glycemias closely. |

| | | | | |
|---|---|---|---|---|
| 682016<br>682018<br>862020<br>682028 | agonist<br>Insulin<br>Meglitinides<br>SGLT2 inhibitors<br>Sulfonylureas<br>Thiazolidinedione | Heart failure (for thiazolidine-diones) | Avoid using medications known to cause hypoglycemia. In many adults aged 65 and older who are frail or with a reduced life expectancy, moderate control (A1c 8-8.5%) is reasonable. Consider decreasing or stopping this medication. | |

AHFS=America hospital formulary service; TdP= torsade de pointes; Mg=magnesium; Na=sodium; K=potassium; HF=heart failure; HCQ=hydroxychloroquine; BPH=benign prostatic hypertrophy

*Risk of QTc prolongation and TdP is classified according to the following:

**Known risk of TdP** (substantial evidence and clear risk); **Possible risk of TdP** (substantial evidence for QTc prolongation but insufficient evidence that the drug causes TdP); **Conditional risk of TdP** (substantial evidence of QTc prolongation and but risk of TdP only under certain conditions such as hypokalemia, excessive dosing, congenital long QTc syndrome or through drug-drug interactions such as with HCQ) as per crediblemeds.org.

**Fluoxetine has a prolonged half-life of deprescribing needs to take place well in advance (4-6 weeks) of combining with hydroxychloroquine

**Table 3.3.** Drug interactions with hypothetical hydroxychloroquine on Admission

| AHFS | Generic medication name | N (%); (N = 1001) |
|---|---|---|
| *Cardiac Medications* | | |
| 240408 | Digoxin | 42 (4.2%) |
| 24040420 | Amiodarone | 17 (1.7%) |
| 242400 | Sotalol | 2 (0.2%) |
| 24040412 | Flecainide | 2 (0.2%) |
| 24040420 | Ibutilide | 1 (0.1%) |
| 24040420 | Dofetilide | 0 (0%) |
| 24040412 | Propafenone | 0 (0%) |
| 24040404 | Procainamide | 0 (0%) |
| *Medications acting on the CNS* | | |
| 28160804 | Atypical antipsychotics | 128 (12.8%) |
| 28160420 | Citalopram | 87 (8.7%) |
| 28160424 | Trazodone | 56 (5.6%) |
| 28160428 | Tricyclic antidepressants | 38 (3.8%) |
| 1204 | Donepezil | 37 (3.7%) |
| 28160416 | Venlafaxine | 29 (2.9%) |
| 28160420 | Sertraline | 27 (2.7%) |
| 28160420 | Escitalopram | 24 (2.4%) |
| 404 | Hydroxyzine | 22 (2.2%) |
| 280808 | Methadone | 8 (0.8%) |
| 28160808 | Haloperidol | 8 (0.8%) |
| 28160420 | FLUoxetine | 6 (0.6%) |
| 122004 | Cyclobenzaprine | 3 (3.0%) |
| 2828 | Lithium | 3 (0.3%) |
| 404 | Promethazine | 0 (0%) |
| 28160824 | Thioridazine | 0 (0%) |
| 282492 | Droperidol | 0 (0%) |
| *Gastrointestinal/miscellaneous medications* | | |
| 563200 | Domperidone | 19 (1.9%) |
| 861204 | Solifenacine | 14 (1.4%) |
| 8121292 | Azithromycin | 13 (1.3%) |
| 562220 | Ondansetron | 9 (0.9%) |
| 81692 | Dapsone | 3 (0.3%) |
| 681612 | Tamoxifen | 3 (0.3%) |
| *Medications for diabetes* | | |
| 682008 | Insulin | 138 (13.8%) |
| 682020 | Sulfonylureas | 90 (9.0%) |
| 682005 | DPP-4 inhibitors | 77 (7.7%) |
| 682016 | Meglitinides | 12 (1.2%) |
| 682018 | SGLT2 inhibitors | 6 (0.6%) |
| 682028 | Thiazolidinedione | 4 (0.4%) |
| 682006 | GLP-1 receptor agonist | 3 (0.3%) |

**Table 3.4.** Proportion of Potentially Inappropriate Medications that Interact with Hydroxychloroquine According to MedSafer

| Drug Class or drug name | Rule (shortened)- drug with triggering condition | N (%) (Total N= by class) |
|---|---|---|
| *Agents acting on the Central Nervous System* | | |
| Atypical Antipsychotics (N=128 patients) | High risk of urinary retention | 17 (13.3%) |
| | Risk of extra-pyramidal symptoms in patients with parkinsonism | 9 (7.0%) |
| | Risk of stroke, falls, confusion, and extra-pyramidal symptoms in patients with delirium or dementia | 40 (31.3%) |
| Haloperidol (N=8 patients) | Risk of extra-pyramidal symptoms in parkinsonism | 1 (12.5%) |
| | Should be avoided in patients with delirium or dementia | 4 (50.0%) |
| Citalopram<br>Escitalopram<br>FLUoxetine<br>Sertraline<br>(N=144 patients) | May contribute to additional fall risk | 6 (4.2%) |
| | Risk of exacerbating or precipitating hyponatremia | 9 (6.3%) |
| Tricyclic Antidepressants (N=38 patients) | May lead to or worsen urinary retention or delirium in patients with delirium or dementia | 5 (13.2%) |
| Trazodone (N=56 patients) | Risk of falls and impaired cognition | 56 (100%) |
| Donepezil (N=37 patients) | Risk of falls and of heart block in combination with beta blockers | 22 (59.5%) |
| Hydroxyzine (N=22 patients) | Risk of falls and impaired cognition | 22 (100%) |
| Cyclobenzaprine (N=3 patients) | Anticholinergic; sedating; risk of falls and fracture | 3 (100%) |
| Solifenacine (N=14 patients) | Highly anticholinergic | 12 (85.7%) |
| Methadone (N=8 patients) | Consider risks with patient before prescribing opioid analgesics as long-term therapy to treat chronic non-cancer pain. | 3 (37.5%) |
| Domperidone (N=19 patients) | Increased risk of sudden death in Parkinson's | 1 (5.1%) |
| *Cardiac Medications* | | |
| Digoxin (N=42 patients) | Higher dosages of digoxin may increase toxicity without additional benefit, particularly in heart failure and renal failure. | 39 (92.9%) |
| Amiodarone (N=17 patients) | Rate control yields better balance of benefits and harms than rhythm control for most older adults | 12 (72.2%) |
| | Associated with thyroid and pulmonary toxicity and QT prolongation | 10 (61.1%) |

| | | |
|---|---|---|
| Class 1c Antiarrhythmics (e.g. Flecainide, Propafenone) (N=2 patients) | Rate control yields better balance of benefits and harms than rhythm control for most older adults | 2 (100%) |
| Sotalol (N=2 patients) | Rate control yields better balance of benefits and harms than rhythm control for most older adults | 1 (50.0%) |
| *Diabetic Agents* | | |
| Sulfonylureas (N=90 patients) | High risk of hypoglycemia (esp. Glyburide)<br><br>And/or<br><br>Consider decreasing or stopping in patients with HbA1c* <7.5%. Moderate control (8-8.5%) is acceptable in patients who are frail or have reduced life expectancy. | 32 (35.6%) |
| Insulin (N=138 patients) | | 39 (28.3%) |
| DPP-4 inhibitors (N=77 patients) | | 8 (10.4%) |
| Meglitinides (N=12 patients) | | 4 (33.3%) |
| SGLT2 inhibitors (N=6 patients) | | 4 (66.7%) |
| GLP-1 receptor agonist (N=3 patients) | | 2 (66.7%) |
| Thiazolidinedione (N=4 patients) | | 1 (25.0%) |
| Thiazolidinedione (N=4 patients) | Potential to promote fluid retention and exacerbate heart failure | 1 (25.0%) |

No patients were on the following medication: Thioridazine, Procainamide, Promethazine

No patients had the following medication(s) flagged as potentially inappropriate: Venlafaxine

*HbA1c: Hemoglobin A1c

**References Manuscript 2:**


1. World Health Organization. Pneumonia of unknown cause - China. Janurary 5, 2020.
2. World Health Organization. Novel Coronavirus — China. Janurary 12, 2020.
3. World Health Organization. Rolling updates on coronavirus disease (COVID-19). March 11, 2020.
4. WorldOmeter. COVID-19 Coronavirus Pandemic. https://www.worldometers.info/coronavirus/. Accessed May 13, 2020.
5. NIH U.S. National Library of Medicine. https://clinicaltrials.gov/. Accessed April 29, 2020.
6. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res.* 2020;30(3):269-271.
7. Chen Z, Hu J, Zhang Z, et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. *medRxiv.* 2020:2020.2003.2022.20040758.
8. CHEN Jun LD, LIU Li,LIU Ping,XU Qingnian,XIA Lu,LING Yun,HUANG Dan,SONG Shuli,ZHANG Dandan,QIAN Zhiping,LI Tao,SHEN Yinzhong,LU Hongzhou. A pilot study of hydroxychloroquine in treatment of patients with common coronavirus disease-19 (COVID-19). *J Zhejiang Univ (Med Sci).* 2020;49(1):0-0.
9. Borba MGS, Val FFA, Sampaio VS, et al. Effect of High vs Low Doses of Chloroquine Diphosphate as Adjunctive Therapy for Patients Hospitalized With Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection: A Randomized Clinical Trial. *JAMA Network Open.* 2020;3(4.23):e208857-e208857.
10. Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *Biosci Trends.* 2020;14(1):72-73.
11. Gautret P, Lagier J-C, Parola P, et al. Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: A pilot observational study. *Travel Medicine and Infectious Disease.* 2020:101663.
12. Gautret P, Lagier J-C, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *International Journal of Antimicrobial Agents.* 2020:105949.
13. Bright R. Request for Emergency Use Authorization For Use of Chloroquine Phosphate or Hydroxychloroquine Sulfate Supplied From the Strategic National Stockpile for Treatment of 2019 Coronavirus Disease. In: (HHS) USDoHaHS, ed: U.S. Food & Drug Administration; 2020.
14. FDA cautions against use of hydroxychloroquine or chloroquine for COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems Close supervision is strongly recommended. In: Administration USFD, ed2020.
15. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19): A Review. *JAMA.* 2020.
16. Rowland C. FDA authorizes widespread use of unproven drugs to treat coronavirus, saying possible benefit outweighs risk. The Washington Post.

https://www.washingtonpost.com/business/2020/03/30/coronavirus-drugs-hydroxychloroquin-chloroquine/. Published March 30, 2020. Accessed April 15, 2020.
17. Geleris J, Sun Y, Platt J, et al. Observational Study of Hydroxychloroquine in Hospitalized Patients with Covid-19. *New England Journal of Medicine.* 2020.
18. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/. Accessed May 12, 2020.
19. McCreary EK, Pogue JM. Coronavirus Disease 2019 Treatment: A Review of Early and Emerging Options. *Open Forum Infect Dis.* 2020;7(4):ofaa105.
20. Grasselli G, Zangrillo A, Zanella A, et al. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. *JAMA.* 2020.
21. Applegate WB, Ouslander JG. COVID-19 Presents High Risk to Older Persons. *Journal of the American Geriatrics Society.* 2020;68(4):681-681.
22. Masnoon N, Shakib S, Kalisch-Ellett L, Caughey GE. What is polypharmacy? A systematic review of definitions. *BMC geriatrics.* 2017;17(1):230-230.
23. Maher RL, Hanlon J, Hajjar ER. Clinical consequences of polypharmacy in elderly. *Expert Opin Drug Saf.* 2014;13(1):57-65.
24. Ellenbogen MI, Wang P, Overton HN, et al. Frequency and Predictors of Polypharmacy in US Medicare Patients: A Cross-Sectional Analysis at the Patient and Physician Levels. *Drugs & Aging.* 2020;37(1):57-65.
25. *Medication Overload: America's Other Drug Problem; How the drive to prescribe is harming older Americans.* Lown Institute; April 2019.
26. Hamilton HJ, Gallagher PF, O'Mahony D. Inappropriate prescribing and adverse drug events in older people. *BMC geriatrics.* 2009;9:5-5.
27. Pastick KA, Okafor EC, Wang F, et al. Review: Hydroxychloroquine and Chloroquine for Treatment of SARS-CoV-2 (COVID-19). *Open Forum Infectious Diseases.* 2020.
28. Hamilton H, Gallagher P, Ryan C, Byrne S, O'Mahony D. Potentially Inappropriate Medications Defined by STOPP Criteria and the Risk of Adverse Drug Events in Older Hospitalized PatientsPIMs Defined by STOPP Criteria and Risk of ADEs. *Archives of Internal Medicine.* 2011;171(11):1013-1019.
29. Gallagher P, Lang PO, Cherubini A, et al. Prevalence of potentially inappropriate prescribing in an acutely ill population of older patients admitted to six European hospitals. *Eur J Clin Pharmacol.* 2011;67(11):1175.
30. American Geriatrics Society Beers Criteria Update Expert P. American Geriatrics Society 2019 Updated AGS Beers Criteria(R) for Potentially Inappropriate Medication Use in Older Adults. *J Am Geriatr Soc.* 2019;67(4):674-694.
31. Choosing Wisely Canada Recommendations. https://choosingwiselycanada.org/recommendations/. Accessed April, 15, 2020.
32. McDonald EG, Wu PE, Rashidi B, et al. The MedSafer Study: A Controlled Trial of an Electronic Decision Support Tool for Deprescribing in Acute Care. *J Am Geriatr Soc.* 2019.
33. O'Mahony D, O'Sullivan D, Byrne S, O'Connor MN, Ryan C, Gallagher P. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. *Age Ageing.* 2015;44(2):213-218.

34. Product Monograph Including Patient Medication Information Plaquenil. In: sanofi-aventis Canada Inc.; 2019.
35. Hydroxychloroquine Drug Interactions. https://www.drugs.com/drug-interactions/hydroxychloroquine-index.html. Accessed April 15, 2020.
36. Woosley R, Heise, CW and Romero, KA. QTdrug List. AZCERT. www.Crediblemeds.org. Accessed April, 27, 2020.
37. Fact sheet for health care providers emergency use authorization (EUA) of Hydroxychloroquine Sulfate supplied from the strategic National stockpile for treatment of COVID-19 in certian hospitilized patients. In: Administration USFaD, ed2020.
38. Fact sheet for health care providers emergency use authorization (EUA) of Chloroquine Phosphate supplied from the strategic National stockpile for treatment of COVID-19 in certian hospitilized patients. In: Administration USFaD, ed2020.
39. AHFS Pharmacologic-Therapeutic Classification System. https://www.oregon.gov/obnm/rules/AHFSClassificationwithDrugs.pdf. Accessed April 15, 2020.
40. Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. *CMAJ.* 2005;173(5):489-495.
41. Roden Dan M, Harrington Robert A, Poppas A, Russo Andrea M. Considerations for Drug Interactions on QTc in Exploratory COVID-19 (Coronavirus Disease 2019) Treatment. *Circulation.*0(0).
42. Malone MLH, T.M.; Perry, A.; Biese, K.; Bonner, A.; Pagel, P.; Unroe, K.T. COVID-19 in Older Adults: Key Points for Emergency Department Providers. *Journal of Geriatric Emergency Medicine* 2020;1(4).
43. Graves T, Hanlon JT, Schmader KE, et al. Adverse events after discontinuing medications in elderly outpatients. *Arch Intern Med.* 1997;157(19):2205-2210.
44. Przybyla H. Family of New York woman blames hydroxychloroquine combo for fatal heart attack. https://www.nbcnews.com/health/health-news/family-new-york-woman-blames-hydroxychloroquine-combo-fatal-heart-attack-n1185451. Published 2020. Accessed April 27, 2020.
45. Plaquenil Hydroxychloroquine Sulfate Tablets, USP. In: Administration USFaD, ed2020.
46. Fan H-W, Ma Z-X, Chen J, Yang X-Y, Cheng J-L, Li Y-B. Pharmacokinetics and Bioequivalence Study of Hydroxychloroquine Sulfate Tablets in Chinese Healthy Volunteers by LC-MS/MS. *Rheumatol Ther.* 2015;2(2):183-195.
47. Hydroxychloroquine: Drug information Lexicomp. https://www.uptodate.com/contents/hydroxychloroquine-drug-information. Published 1978-2020. Accessed April 28, 2020.
48. Optimizing Medication Management during the COVID-19 Pandemic: Implementation Guide for Post-Acute and Long-Term Care2020.
49. Grein J, Ohmagari N, Shin D, et al. Compassionate Use of Remdesivir for Patients with Severe Covid-19. *New England Journal of Medicine.* 2020.
50. Cao B, Wang Y, Wen D, et al. A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19. *New England Journal of Medicine.* 2020.

## Chapter 4: Discussion

In this chapter, I will lay out the structure of our proposed new method of adjudication, including a review of the current methods, our recommendations, important points of consideration involved in the design process, and future steps to be carried out.

### *Contribution of Previously Described Research Studies*

Throughout my research, I have identified gaps in the literature with regards to defining outcome measurements in deprescribing and adjudication of ADEs. First, I conducted a literature review where I identified that there is no adjudication methodology available which is consistently used across studies. I identified universal limitations seen in all of the methods and made recommendations for what to incorporate into any new or adapted method.[56] Out of the ten adjudication methodologies captured in my review of the literature, I identified that seven of them are designed to **only capture ADRs**, therefore they do not completely capture the full range of outcomes encompassed by ADEs. **No method explicitly cues the adjudicator to first identify an AE as the first step of the process**. All ADEs and ADRs are a sub-category within AEs, therefore logically an adjudication methodology should first prompt the adjudicator to identify if there was an AE, and if so, the cause of the event can then be determined. Deprescribing is also commonly conducted in a variety of research settings (e.g. in the clinic, in an acute care hospital, in long-term care and in the community) and thus **a methodology that functions well in all settings or that can be modified for each of these settings** would be beneficial. Many of the **current methods require specialized testing** and/or **re-exposure** to the offending drug and thus are only applicable in a hospital setting. Applicability in long term care and in the community can be impractical, resource-heavy and thus limited.

As discussed, deprescribing is most often performed for older adults, as a group at the highest risk for polypharmacy and ADEs, yet **no methodology is specifically designed with this age group in mind**. Older adults have specific needs to be taken into consideration, such as the type of medications they are taking, comorbidities that relate to the aging process, and the

physiological interactions between aging and disease, including frailty, changes in balance and cognition, and altered drug pharmacokinetics. All of these factors should be specifically considered when it comes to determining if an ADE occurred or not, and thus ideally need to be worked into the applied methodology. Finally, many of the methods **focus solely on reactions from (or to) a single drug**, and therefore may miss ADEs that occur due to a combination of medications and conditions. In the setting of polypharmacy, the adjudicator needs to be able to differentiate and identify a wide range of ADEs including **deleterious effects due to the continuation of chronic drugs**, **initiation of a new medication** (often easier/more intuitive to adjudicate), and **adverse drug withdrawal events** due to the removal of medication, including medication **errors/omissions** or secondary to deprescribing. Taking these limitations into consideration has allowed me to outline a new adjudication method that aims to maximize applicability, more accurately capture all types of ADEs including ADWEs and address the limitations I have identified with existing methods.

I also conducted further research within deprescribing (found in the appendices) in order to completely understand what challenges are being faced in the adjudication of ADEs in a complex aging population and how they may affect accurate outcome measurement. My work in identifying and deprescribing new and emerging risky medications (e.g. Gabapentinoids), and their role in the current epidemic of overprescribing in older adults, highlights the importance of medication knowledge in deprescribing. When adjudicating the occurrence of an ADE, it is important to be able to identify risky medications and understand the role they may have played in causing an ADE or ADWE. Often when a PIM is being deprescribed, an alternative medication may be prescribed in its place, and thus it is important for the adjudicator to have knowledge on the harmful effects of all the medications either being removed or added, and how they can contribute to complications in the patient's course of treatment.

My work on the gabapentinoid EMPOWER brochure (Appendix B.) has contributed to the design of the newly proposed methodology in two major ways. First, it allowed me to identify the need for a new method which allows the adjudicator the flexibility to consider the individual effect of each medication. An ADE can occur through a new prescription, through

deprescribing, or secondary to a chronic medication. Secondly, it demonstrated the need for the proper training and knowledge for adjudicators when it comes to understanding the complex interplay between medications and medical conditions in a deprescribing population. In order for a medication to be identified as causal to an ADE, a clinician needs expert knowledge in pharmacology; they must first be aware that drug X is a PIM, then they must evaluate its use in an individual patient based on harms and benefits, and in addition they must be aware of its potentially harmful side effects (e.g. in the case of gabapentinoids this includes a long list of side effects such as changes in cognition, balance, increased risk of fall/fractures, increased mortality in combination with opioids, fluid retention, etc.).

Next, my research into special populations (Appendix C) also contributed to the proposed design, as I identified a need to consider how certain chronic medical conditions play a role in a patient's care trajectory and treatment plan. Having a chronic illness may differentiate individuals from the general population and can require a tailored approach when it comes to deprescribing. For example, a patient on dialysis who has limited renal function has a baseline increased risk of bleeding compared to the general population (and compared to an older adult, of the same age, with normal renal function). They also have a more limited life expectancy. Balancing the risk and harms of anticoagulation in this population is nuanced and evidence to guide the clinical decision-making process may be lacking, as they are often underrepresented in clinical trials. This leaves the clinician with only expert knowledge to decide whether or not the benefits outweigh the harms. This can also leave the adjudicator questioning whether an ADE was preventable in the context of a chronic medication (such as a blood thinner) continuously prescribed over time.

I reviewed two special populations in more detail: the HIV and hemodialysis populations. These are but two examples of populations where there is an added element of complexity to deprescribing and defining outcomes, as they both have unique health factors to be taken into consideration above and beyond the general older adult population. However, there are many other special populations that are becoming more prevalent in aging populations, which will impact on deprescribing and ADEs. These include transplant patients, patients with aortic stenosis with transcutaneous valve implantation, the oncology population and others. These populations are increasingly represented among older adults and their

unique fragilities, organ pathologies, prognoses and resource utilization need to be factored into the adjudication of ADEs. **These factors add an element of complexity that was not present 15-20 years ago when many adjudication methods were designed and validated**, further highlighting the need for an updated methodology of adjudication. Similar to my deep dive into gabapentinoids (an exemplar of a new and emerging risky class of medications), my background research into special populations also highlights the importance of a method of adjudication which can be adapted for at-risk conditions and special populations when determining if an ADE or ADWE has occurred. It is paramount to understand the complex interplay between special populations, aging, and certain high-risk medications, and how these will affect a patient's course of treatment and their risk of ADEs.

Finally, my research during the time of COVID-19 examined an unforeseen consequence of polypharmacy: are older adults with polypharmacy at a disadvantage when it comes to a potential COVID-19 treatment? This work also contributed in the development of my newly proposed method of adjudication. The COVID-SAFER[54] study served as an example of the importance of proactively deprescribing PIMs in older adults during a pandemic, while all-the-while highlighting the complexity of the process. In this hypothetical clinical scenario, we explored how a clinician might approach a typical patient with polypharmacy when considering transiently adding a new potentially life-saving medication with multiple known medication interactions. In this scenario we described how the healthcare provider may need to hold some medications for a short period of time, or deprescribe completely, in order to safely expose a patient to a new medication for potentially treating COVID-19. In this case, there were many interacting medications and comorbidities at play. The complexity of the situation required, in theory, close monitoring of patients for development of both ADEs and ADWEs. It gave me immense insight into the complexity of certain drug-drug interactions (especially when they relate to QTc prolonging interacting drugs) and I realized that a methodology that is properly able to capture the outcome needs to be able to capture ADEs that may be subtle in their presentation and difficult to capture without invasive monitoring. The example in this case was hydroxychloroquine and need to monitor for cardiac arrhythmias and development of hypoglycemia. Thus, this further solidified my recommendation of a new method that factors in

a certain degree of clinical judgment and flexibility in adjudication of whether medications contributed to an adverse event, while providing expert knowledge and guiding the adjudicator through a systematic and easy to use adjudication process.

*Recommendations*

Based on my research I was able to begin to make recommendations as to what a new method for ADE adjudication should include. An adjudication methodology should be intuitive for researchers to apply while also being simple and easy to use, similar to the Naranjo algorithm. However, like the Leape & Bates method, it should be weighted towards clinical judgment, and sensitive towards ADEs (not just ADRs). It should also be standardized to allow measurement of interobserver agreement and be designed for consistent use across different types of studies. Finally, since this methodology is specifically designed to be used in a deprescribing setting it needs to be capable of identifying and labeling ADWEs. As I go through our new method for ADE adjudication, I will highlight how these important elements come into play.

*New Method for ADE Adjudication*

***Step 1: Review Case Report (Pre-Adjudication Step)***

The first step before beginning the adjudication process needs to be a review of the patient's medications and medical history. In the deprescribing stage the adjudicator should be presented with the following information: 1) the patients complete past medical history (PMH); 2) The timing of certain events (e.g. stent placements, gastrointestinal bleeding, and stroke), as the timing of some events affects the timing of deprescribing- mainly when it comes to anticoagulation and antiplatelets; 3) if the patient was hospitalized, the timing of the admission and discharge, as well as the reason for admission and any new medical condition introduced or discovered during the hospitalization should be noted. All of this information should be included in the case report presented to the adjudicator and ideally is presented in an

electronic format, and not on paper, for ease of data compiling and analysis. This report will be useful in the adjudication process as it will provide the adjudicator with a complete overview of all conditions.

Next, the medication history should be provided including the following information if possible: generic/trade name; dose; and route. Medications should be separated as chronic usual medications, new medications and medications that were stopped or deprescribed should be properly identified. For medications that were tapered, some measure of timing and the expected final dose should be presented. Depending on the study, the time frame for follow-up should be incorporated into the case report. For example, a study that follows patients for six months may need to display conditions and medication changes that arise during the six months with respect to any events that occur in that timeframe. A decision as to whether to monitor the patient for repeated events should also be taken.

Finally, the case reports should capture events of interest and associate them with a timeline. It may be important to blind the adjudicator to the intervention status and so data should be presented accordingly. Examples of outcomes of interest may include the following (we suggest that outcomes be harmonized and that all of the following should be collect if possible): falls and the context of the fall, including whether it was injurious or not; planned and unplanned visits with the healthcare system and the outcome in brief (including new diagnoses or medication changes); visits to the emergency room and any hospitalizations, in as much detail as possible, with a focus on events that may be related to medications (e.g., episodes of hypoglycemia, falls, fractures, gastrointestinal bleeding, delirium, constipation, and etc.) and finally death and the circumstances.

Step one is completed prior to beginning the adjudication process and thus can vary based on information available and the deprescribing intervention. This is an important first step, as having a complete understanding and consideration of the full picture will simplify the rest of the steps and ensure accuracy. While there is no specific template which can be used due to the variation of a patient's course of treatment, step 1 will prompt the adjudicator to review the patient's file while providing examples as to what information needs to be considered (past medical history, all conditions, contact with the healthcare system, etc.). Once

the adjudicator has familiarized themselves with the conditions, medications and timing of any changes and any events of interest, they can move on to step 2.

***Step 2: Adverse Event (AE) determination***

In step two the adjudication process begins. The adjudicator needs to take all the knowledge they have on the patient into consideration when determining if an adverse event (AE) has occurred. From this point onwards, *the examples given for each step will be geared towards a patient population that was deprescribed in a clinical trial with a 30-day follow up since discharge for illustrative purposes*. This was the follow-up time for the recently completed MedSafer trial and so our team has thousands of case examples that relate to this time period that have been used to inform this process. This method can be modified for clinical use in an outpatient population, and I will make note of which steps require modifications along the way. Starting off by determining if an AE occurred before identifying the cause will result in an increased rate of capture, especially when the cause is hard to pinpoint (e.g. geriatric syndrome).

This does however raise the question of <u>what should be considered an adverse event</u>? This should be *standardized* and decided *a priori* prior to study adjudication. We propose the following: most falls, ED visits and hospitalizations should be considered an adverse event. Other symptoms may be considered "events" as well if they lead to interactions with the healthcare system, are injurious, or require medication changes, in order to capture complications related to drugs. The term “event” can be misleading and may result in some medication related complications going unrecognized or incompletely captured and identified. These include: worsening of symptoms requiring a medical intervention (e.g. worsening of symptoms of congestive heart failure/edema/shortness of breath); severe constipation leading to a visit to the emergency department or decreased oral intake/nausea; recurrent episodes of dizziness or feelings of instability (possibly related to blood pressure mediation or medications that act on cognition and balance); rash; cough (e.g. from and ACE inhibitor); new profound weakness or fatigue. We propose that the definition of adverse event should be kept broad, and the adjudicator needs to keep an open mind. Many symptoms that older adults experience

can be mistaken for signs of aging and it may go missed that these could be related to medications or combinations of medication.

"Did this patient have an adverse event (AE) starting within 30 days of discharge"

- ☐ Yes
- ☐ No

If no: The adjudication ends here, and the file is closed.

If Yes: The adjudicator will be prompted to move onto the next step.

***Step 3: Did this patient suffer an Adverse Drug Event (ADE)?***

The next step will be to consider if the AE was caused by an adverse drug event. In this step, we have opted to adapt the Leape & Bates 6-point Likert scale, as it provides a clinical judgment component while also guiding the evaluator towards a medication related cause vs a disease related cause when considering the event of interest. The advantage of using a Likert scale is that it is simple to use, easy to quantify, and it does not force the evaluator to provide a concrete yes or no answer. However, we feel the language needs to be updated to reflect the current day context. The current version of the Leape and Bates method is as follows:

"Was there an adverse drug event (ADE)?"

1. Outcome definitely caused by the patient's disease
2. Outcome probably caused by the patient's disease
3. Outcome more than likely caused by the patient's disease
4. Outcome more than likely caused by the patient's medications
5. Outcome probably caused by the patient's medications
6. Outcome definitely caused by the patient's medications

ADES are considered only if response 5 or 6 is selected. Based on reviewing several thousands of case files, there are limitations to the language in the above schema. Because of patient complexity and an average of 10 or more medications, it is very difficult to definitely adjudicate an event as an ADE based on the above. This is evidenced by the fact that in the original trials

that used the Leape and Bates methods, the rate of ADEs was much higher (20 years ago) in their studies than in current studies (10-15% vs 4-6%). This language needs to be adapted to capture events where medications contributed. There are many scenarios where the adjudicator is faced with an event that was clearly an interplay between disease and medications. However, in the current schema, this is not an option. We therefore propose the following:

1. Event definitely caused by a medical condition alone
2. Event probably caused by a medical condition alone
3. Event probably caused by a medical condition, but medication(s) were a factor
4. Event equally caused by a combination of medical condition(s) and medication(s)
5. Event probably caused by the patient's medication(s), but medical conditions were a factor
6. Outcome probably caused by the patient's medications alone
7. Outcome definitely caused by the patient's medications alone

This language and structure allow for the traditional method of ADE adjudication to be maintained (choice 6 and 7) and allows for sensitivity analyses to be performed and captures the reality of modern day medical and medication regimen complexity with choices 3-5. It also maintains the option of selecting pure condition related events with options 1 and 2 as the older method did, prior.

We propose that for choices 1 and 2, the case file be closed after highlighting the adverse event that took place and the file be adjudicated as "no ADE".
For selections 3-7, the adjudicator would move on to the next step, where additional information about the medications of interest would be elucidated.

***Step 4: Implied Causal Relationship of ADE***

This step will only be available when adjudicating a patient who has been identified as having had an event whereby medications contributed in some way to the outcome. In order to

further confirm that the patient had an ADE the implied causal relationship between the event and the drug requires identification. The traditional stringent definition could be preserved with choice 6 or 7 being a "pure" ADE. The adjudicator would have the added option of selecting choices 3-5 to highlight events where medications played an important role in the outcome. For selections 3-5 the adjudicator would be prompted to "indicate which medications you suspect contributed to the adverse event". Whereas, "indicate which medication you suspect to have caused the ADE" would apply to selections 6 and 7.

Depending on the software/case file used in step 1 (e.g. MedSafer) the adjudicator can either go back through the MedSafer report and check off the available boxes beside the medications or manually input the causal relationship in the designated area below this step. Through my research I understand the complexity of ADEs and disease interactions in older adults, and that it may not always be possible to pinpoint the culprit, as there may be multiple factors involved. ADEs in this population may present as geriatric syndromes such as falls, cognitive impairment, and functional decline rather than a clearly attributable single medication interaction. Therefore, we allow the adjudicator the flexibility to take all medications and conditions combined with their expertise into consideration in this step and explicitly express what they believe to have caused the ADE and additionally allow them to highlight when a medication may have contributed to the adverse event.

***Step 5: Preventable/Ameliorable***

The next step is to gather more information on the ADE. This data can contribute to the safer prescribing and use of medications. The adjudicator is first asked to consider if the flagged ADE was preventable, and thus an injury resulting from a medication error. Also, they are asked if an event was ameliorable meaning that the severity or duration of the injury could have been minimized if different actions were taken.

"Was at least one event preventable?"

- ☐ Yes
- ☐ No
- ☐ Unable to determine

"Was at least one event ameliorable"

☐ Yes

☐ No

☐ Unable to determine

Without depending on the response to both these questions the adjudicator will then move on to the next step.

***Step 6: Tying the adverse event to the trial (optional)***

This next step is relevant if it is important to the researcher to capture whether the event was related to the intervention. This becomes more relevant the longer the period of follow-up after the intervention. For example, if a patient is in a trial and is discharged in January and then followed for six months, they patient may develop an ADE in March that was completely unrelated to the trial (e.g. they receive Septra in March for a UTI and develop Stevens Johnson Syndrom, and this is captured in the case report form).

"Was the ADE related to the index hospitalization?" could be a helpful question to sort this out.

☐ Yes, the ADE was related to the hospitalization

☐ No, the ADE was <u>NOT</u> related to the hospitalization

This question also allows for the gathering of more information surrounding the ADE helping with the collection of data and understanding. Without depending on the response to this question the adjudicator will then move on to the final step.

***Step 7: Adverse Drug Withdrawal Event (ADWEs)***

This step looks at an important outcome of deprescribing, adverse drug withdrawal events (ADWEs). This component in our newly proposed adjudication methodology was not seen in any of the currently available methodologies in our literature review (it is briefly addressed with Naranjo but is not straight-forward). This step is prompted if options 6 or 7 are selected. The adjudicator must review the patient's medications and conditions while paying

close attention to any changes of medications made either through reducing, tapering, or stopping a medication.

"Was this ADE related to a withdrawal event (e.g. secondary to reducing, tapering, or stopping a medication)?"

- ☐ Yes
- ☐ No

If no: The adjudication ends here.

If yes: These patients are quantified as having had an ADWE, and the adjudicator will be prompted to move on to the next step. This captures an important counter-balancing outcome and picks up events related to deprescribing.

***Step 8: Implied Causal Relationship of ADWE***

This step will only be available when adjudicating a patient which has been identified as having had an ADWE. In order to further confirm that the patient had an ADWE the implied causal relationship between the event and the drug changes require identification.

"Indicate which medication you suspect to have caused the ADWE"

Similar to step 4, depending on the software used in step 1 (e.g. MedSafer) the adjudicator can either go back through the MedSafer report and check off the available boxes beside the medications or manually input the causal relationship in the designated area below this step. With the complexity of deprescribing in this population, we allow the adjudicator the flexibility to take everything into consideration and use their expertise when identifying the cause of the ADWE.

This is the last step of my newly proposed adjudication methodology.

*Strengths and Limitations*

I went into a lot of details regarding my new method of adjudication yet based on our expertise we believe this is a relatively easy and simple to use method if the adjudicator has full knowledge of the patient/context, and information on ADE/ADWEs. I essentially took the Leape & Bates method and updated it for the current medical context, which is one of medical complexity and much larger medication regimens than 20 years ago, and provided it with more

structure and guidance. I also added in important elements which were lacking to conduct a complete review for deprescribing and added in some components that address older adults specifically. A strength of this newly proposed methodology is that it is easy to use across a variety of settings and patients, and therefore will hopefully more accurately capture the outcome of interest. It is important to have a method that is widely applicable across studies as this will allow for comparison, inter-rater agreement, meta-analysis of trials and improved accuracy of deprescribing data. Additionally, having an added component of implied causality when identifying both an ADE and ADWE is also very important as it encourages the adjudicator to take the time needed to consider how different medications and disease may play a role in the observed event. I also do not limit the adjudicator to selecting one medication and proving a direct relationship through test results or re-exposure to the offending drug, instead, I allow for multiple medications and diseases to be considered and selected based on expert knowledge. This is a very important component which I was made aware of through my research on risky medications and special populations. Finally, another strength of my method is that it has a component that no other method included, ADWEs. Logically, when adjudicating deprescribing trials you are looking at patients who have had multiple medications added, removed, or doses changed, and therefore you must be able to consider how all of these factors play a part in the adverse event which has occurred. By specifically promoting the adjudicator to consider ADWEs this will increase the identification of the outcomes of interest, bringing the statistic closer to the true value. **In fact, the adjudicator should be able to adjudicate for the presence of ADEs and ADWEs as both may occur for a given patient and the implications differ.**

There are some limitations to my method which also need to be taken into consideration. First, my method was designed with the an electronic deprescribing software in mind (MedSafer) and may be ideally suited using a generated report from this software when it comes to adjudicating. That said, this method can of course be used without MedSafer, but it works best when you have access to all of the patient's information (e.g. medications, conditions, changes since deprescribing intervention). Also, in order to properly record this information and have the right steps prompted for the adjudicator, it works best to have this

method as part of an automated system, similar to what I added to the adjudication component of the MedSafer software. Another limitation is that while this method is quite intuitive it still requires expert knowledge and expertise when adjudicating. While I provide important information, which needs to be considered when adjudicating, the person must still have the knowledge and an understanding of medicine, deprescribing, and polypharmacy in order adults. I have attempted to provide guidelines for standardizing several outcomes so that it is easier to train an adjudicator and so that inter-observer agreement is maximized. Most importantly, this method has yet to be validated and compared head to head with Leape and Bates to see if it improves the capture rate for adverse events/ADEs. This can be done with the results of the MedSafer trial as a future study.

*Implications*

The main implication of my findings is through the application of this new methodology that I designed through a critical evaluation of the current literature, we will hopefully be able to increase the accuracy and capture rate of the outcome measurements used in deprescribing clinical trials. This will result in safer interventions, and reduced costs in both the expenditure on PIMs and hospital costs due to the use of PIMs, ADEs, and ADWEs. Another important implication of my findings is that by utilizing a (hopefully) more sensitive measurement of adjudication we will be able to assure patients and healthcare providers that deprescribing is possible in a safe manner. It may be that stopping PIMS, improving quality of life and sleep and preventing geriatric syndrome over time may be as important an outcome as a reduction in pure ADEs. Even if deprescribing is not successful in 20% of patients and they need to go back on their medications, it is likely still worth it for the 80% in which we were able to decrease PIMs and their pill burden. This can be especially important in high-risk populations, and by having a proven adjudication method which shows the proof of benefit it, may serve to comfort patients in knowing that it was due to their inappropriate medications that a given event occurred and not due to the removal.

*Future Studies*

The first step in testing my new method will be to have an expert review the proposed method, and then evaluate its ease of use in individual scenarios by both experts and non-experts comparing the interrater agreeability. The next steps would be to test this new methodology in a variety of settings including in both research and possibly even in a clinical context. Based on my design it theoretically is applicable in both settings, but future research and use will be necessary in order to confirm this. Inter-observer measurements also need to be evaluated. Under this method, each patient would be required to be adjudicated two separate times by independent adjudicators in order to measure inter-rater agreement using the Kappa score. Finally, by using this method in future studies and promoting its use in deprescribing literature, this will lead to more consistent measurement outcomes.

There are opportunities for many other future studies as identified by my research and detailed in this thesis. The Gabapentinoid brochure can be further studied by its deployment in a randomized trial to demonstrate its effectiveness at deprescribing in older adults admitted to the hospital. Also, both the HIV and HD project protocols are already designed and ready to be tested once non-essential non-COVID research is able to resume in the hospital.

*Conclusion*

My thesis contributes to the field of deprescribing and polypharmacy in older adults, while providing the groundwork for future studies. This work further progresses research within the field by identifying gaps in the literature with regards to adjudicating ADEs in deprescribing trials and by providing a new and improved methodology for future studies. I better define outcomes and provide a standardized method to be used, allowing for consistency and rigorous measurements across trials. I have also contributed to an overall safer environment for older adults by identifying new risky medications and special populations that are at an increased risk for PIMs and ADEs. Through Covid-19 I have also highlighted an unforeseen consequence of polypharmacy and PIMs which is extremely relevant and important to take into consideration in today's uncertain climate. Finally, my preliminary work looking at special populations will lay the foundation for future studies and researchers to continue

investigating and improving the quality of care provided to all older adults in our society. One thing in life is for sure, and that is that we will all age, and with age may come chronic illnesses, but through research in this important and essential field, we can achieve a society where we are all, “Med-Safer”.

**Master Reference List (Introduction and Discussion):**


1. Masnoon N, Shakib S, Kalisch-Ellett L, Caughey GE. What is polypharmacy? A systematic review of definitions. *BMC geriatrics.* 2017;17(1):230-230.
2. Salive ME. Multimorbidity in older adults. *Epidemiol Rev.* 2013;35:75-83.
3. Benjamin RM. Multiple chronic conditions: a public health challenge. *Public Health Rep.* 2010;125(5):626-627.
4. Nguyen TN, Ngangue P, Haggerty J, Bouhali T, Fortin M. Multimorbidity, polypharmacy and primary prevention in community-dwelling adults in Quebec: a cross-sectional study. *Family practice.* 2019;36(6):706-712.
5. Spinewine A, Schmader KE, Barber N, et al. Appropriate prescribing in elderly people: how well can it be measured and optimised? *Lancet (London, England).* 2007;370(9582):173-184.
6. Woodhouse KW, O'Mahony MS. Frailty and ageing. In: Oxford University Press; 1997.
7. Mangoni AA, Jackson SHD. Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. *Br J Clin Pharmacol.* 2004;57(1):6-14.
8. Beers MH, Ouslander JG, Rollingher I, Reuben DB, Brooks J, Beck JC. Explicit criteria for determining inappropriate medication use in nursing home residents. UCLA Division of Geriatric Medicine. *Arch Intern Med.* 1991;151(9):1825-1832.
9. American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. *J Am Geriatr Soc.* 2015;63(11):2227-2246.
10. Gallagher P, Lang PO, Cherubini A, et al. Prevalence of potentially inappropriate prescribing in an acutely ill population of older patients admitted to six European hospitals. *Eur J Clin Pharmacol.* 2011;67(11):1175.
11. Simonson W, Feinberg JL. Medication-Related Problems in the Elderly. *Drugs & Aging.* 2005;22(7):559-569.
12. Hamilton H, Gallagher P, Ryan C, Byrne S, O'Mahony D. Potentially Inappropriate Medications Defined by STOPP Criteria and the Risk of Adverse Drug Events in Older Hospitalized PatientsPIMs Defined by STOPP Criteria and Risk of ADEs. *Archives of Internal Medicine.* 2011;171(11):1013-1019.
13. *Medication Overload: America's Other Drug Problem; How the drive to prescribe is harming older Americans.* Lown Institute; April 2019.
14. Ellenbogen MI, Wang P, Overton HN, et al. Frequency and Predictors of Polypharmacy in US Medicare Patients: A Cross-Sectional Analysis at the Patient and Physician Levels. *Drugs & Aging.* 2020;37(1):57-65.
15. Poudel DR, Acharya P, Ghimire S, Dhital R, Bharati R. Burden of hospitalizations related to adverse drug events in the USA: a retrospective analysis from large inpatient database. *Pharmacoepidemiology and Drug Safety.* 2017;26(6):635-641.
16. Forster AJ, Kyeremanteng K, Hooper J, Shojania KG, van Walraven C. The impact of adverse events in the intensive care unit on hospital mortality and length of stay. *BMC Health Serv Res.* 2008;8:259.
17. Zhan C, Miller MR. Excess length of stay, charges, and mortality attributable to medical injuries during hospitalization. *Jama.* 2003;290(14):1868-1874.

18. Kaushal R, Bates DW, Franz C, Soukup JR, Rothschild JM. Costs of adverse events in intensive care units. *Crit Care Med.* 2007;35(11):2479-2483.
19. Wardle G, Wodchis WP, Laporte A, Anderson GM, Ross Baker G. The sensitivity of adverse event cost estimates to diagnostic coding error. *Health Serv Res.* 2012;47(3 Pt 1):984-1007.
20. Kjellberg J, Wolf RT, Kruse M, et al. Costs associated with adverse events among acute patients. *BMC Health Serv Res.* 2017;17(1):651.
21. Encinosa WE, Hellinger FJ. The impact of medical errors on ninety-day costs and outcomes: an examination of surgical patients. *Health Serv Res.* 2008;43(6):2067-2085.
22. American Geriatrics Society Beers Criteria Update Expert P. American Geriatrics Society 2019 Updated AGS Beers Criteria(R) for Potentially Inappropriate Medication Use in Older Adults. *J Am Geriatr Soc.* 2019;67(4):674-694.
23. Morgan SG, Hunt J, Rioux J, Proulx J, Weymann D, Tannenbaum C. Frequency and cost of potentially inappropriate prescribing for older adults: a cross-sectional study. *CMAJ Open.* 2016;4(2):E346-351.
24. Hohl CM, Nosyk B, Kuramoto L, et al. Outcomes of emergency department patients presenting with adverse drug events. *Ann Emerg Med.* 2011;58(3):270-279.e274.
25. Bates DW, Spell N, Cullen DJ, et al. The costs of adverse drug events in hospitalized patients. Adverse Drug Events Prevention Study Group. *Jama.* 1997;277(4):307-311.
26. Shehab N, Lovegrove MC, Geller AI, Rose KO, Weidle NJ, Budnitz DS. US Emergency Department Visits for Outpatient Adverse Drug Events, 2013-2014. *JAMA.* 2016;316(20):2115-2125.
27. Bourgeois FT, Shannon MW, Valim C, Mandl KD. Adverse drug events in the outpatient setting: an 11-year national analysis. *Pharmacoepidemiology and drug safety.* 2010;19(9):901-910.
28. Fernández EV, Warriner CL, David T, Gordon E, Twigg G, Carroll NV. Potential cost savings by prevention of adverse drug events with a novel medication review program. *J Am Pharm Assoc (2003).* 2020;60(3):462-469.e464.
29. Friend DG. Polypharmacy; multiple-ingredient and shotgun prescriptions. *The New England journal of medicine.* 1959;260(20):1015-1018.
30. Riker GI, Setter SM. Polypharmacy in Older Adults at Home: What It Is and What to Do About It— Implications for Home Healthcare and Hospice. *Home Healthcare Now.* 2012;30(8).
31. Milton JC, Hill-Smith, I., & Jackson, S. H. D. . Prescribing for older people. *BMJ : British Medical Journal.* 2008;336(7644):606–609.
32. Maher RL, Hanlon J, Hajjar ER. Clinical consequences of polypharmacy in elderly. *Expert Opin Drug Saf.* 2014;13(1):57-65.
33. Doan J, Zakrzewski-Jakubiak H, Roy J, Turgeon J, Tannenbaum C. Prevalence and risk of potential cytochrome P450-mediated drug-drug interactions in older hospitalized patients with polypharmacy. *Ann Pharmacother.* 2013;47(3):324-332.
34. Bushardt RL, Massey EB, Simpson TW, Ariail JC, Simpson KN. Polypharmacy: misleading, but manageable. *Clin Interv Aging.* 2008;3(2):383-389.
35. Cadogan CA, Ryan C, Hughes CM. Appropriate Polypharmacy and Medicine Safety: When Many is not Too Many. *Drug safety.* 2016;39(2):109-116.

36. Brennan TA, Leape LL, Laird NM, et al. Incidence of adverse events and negligence in hospitalized patients: results of the Harvard Medical Practice Study I. 1991. *Qual Saf Health Care.* 2004;13(2):145-152.
37. Leape LL, Brennan TA, Laird N, et al. The nature of adverse events in hospitalized patients. Results of the Harvard Medical Practice Study II. *New England Journal of Medicine.* 1991;324(6):377-384.
38. Bates DWDMDM, Boyle DLBA, Vliet MBVRN, Schneider JR, Leape LMD. Relationship between medication errors and adverse drug events. *Journal of General Internal Medicine.* 1995;10(4):199-205.
39. Institute of Medicine Committee on Quality of Health Care in A. In: Kohn LT, Corrigan JM, Donaldson MS, eds. *To Err is Human: Building a Safer Health System.* Washington (DC): National Academies Press (US)

40. Morimoto T, Gandhi TK, Seger AC, Hsieh TC, Bates DW. Adverse drug events and medication errors: detection and classification methods. *Qual Saf Health Care.* 2004;13(4):306-314.
41. WHO. International drug monitoring: the role of national centres. Report of a WHO meeting. *World Health Organ Tech Rep Ser.* 1972;498:1-25.
42. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. *Lancet.* 2000;356(9237):1255-1259.
43. Graves T, Hanlon JT, Schmader KE, et al. Adverse events after discontinuing medications in elderly outpatients. *Arch Intern Med.* 1997;157(19):2205-2210.
44. Veilleux O, Lee TC, McDonald EG. Rebound adrenal insufficiency after withdrawal of ritonavir in a 65-year-old man using inhaled budesonide. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne.* 2017;189(37):E1188-e1191.
45. Scott IA, Hilmer SN, Reeve E, et al. Reducing inappropriate polypharmacy: the process of deprescribing. *JAMA Intern Med.* 2015;175(5):827-834.
46. Reeve E, Gnjidic D, Long J, Hilmer S. A systematic review of the emerging de fi nition of 'deprescribing' with network analysis: implications for future research and clinical practice. *Br J Clin Pharmacol.* 2015;80(6):1254-1268.
47. Garfinkel D, Ilhan B, Bahat G. Routine deprescribing of chronic medications to combat polypharmacy. *Therapeutic Advances in Drug Safety.* 2015;6(6):212-233.
*48.* Page AT, Potter K, Clifford R, Etherton-Beer C. Deprescribing in older people. *Maturitas.* 2016;91:115-134.
49. Reeve E, To J, Hendrix I, Shakib S, Roberts MS, Wiese MD. Patient barriers to and enablers of deprescribing: a systematic review. *Drugs Aging.* 2013;30(10):793-807.
50. Anderson K, Stowasser D, Freeman C, Scott I. Prescriber barriers and enablers to minimising potentially inappropriate medications in adults: a systematic review and thematic synthesis. *BMJ Open.* 2014;4(12):e006544.
51. Vitry AI, Zhang Y. Quality of Australian clinical guidelines and relevance to the care of older people with multiple comorbid conditions. *Med J Aust.* 2008;189(7):360-365.

52. Boyd CM, Darer J, Boult C, Fried LP, Boult L, Wu AW. Clinical practice guidelines and quality of care for older patients with multiple comorbid diseases: implications for pay for performance. *Jama.* 2005;294(6):716-724.
53. McDonald EG, Wu PE, Rashidi B, et al. The MedSafer Study: A Controlled Trial of an Electronic Decision Support Tool for Deprescribing in Acute Care. *Journal of the American Geriatrics Society.* 2019;67(9):1843-1850.
54. Ross SB, Wilson MG, Papillon-Ferland L, et al. COVID-SAFER: Deprescribing Guidance for Hydroxychloroquine Drug Interactions in Older Adults. *Journal of the American Geriatrics Society.* 2020;n/a(n/a).
55. Hanlon JT, Semla TP, Schmader KE. Alternative Medications for Medications in the Use of High-Risk Medications in the Elderly and Potentially Harmful Drug-Disease Interactions in the Elderly Quality Measures. *Journal of the American Geriatrics Society.* 2015;63(12):e8-e18.
56. Ross SB, Wu PE, Atique A, et al. Adverse Drug Events in Older Adults: Review of Adjudication Methods in Deprescribing Studies. *J Am Geriatr Soc.* 2020.

# Appendices

## Appendix A. Additional Material for Manuscript 1 (Chapter 2)

**Supplementary Table S2.1.** Cochrane Search Strategy

| ID | Search | Hits |
|---|---|---|
| #1 | MeSH descriptor: [Drug-Related Side Effects and Adverse Reactions] explode all trees | 3274 |
| #2 | ((drug NEXT/5 (safe or safety or side effect* or undesirable effect* or treatment emergent or tolerabilit* or toxic* or adrs or (adverse NEXT/2 (effect or effects or reaction or reactions or event or events or outcome or outcomes))))):ti,ab,kw | 213800 |
| #3 | MeSH descriptor: [Adverse Drug Reaction Reporting Systems] explode all trees | 86 |
| #4 | #1 OR #2 OR #3 | 215120 |
| #5 | ((deprescrib* or deprescription* or ((inappropr* or over) NEXT/3 (prescrib* or prescription*)))):ti,ab,kw | 556 |
| #6 | MeSH descriptor: [Inappropriate Prescribing] explode all trees | 113 |
| #7 | MeSH descriptor: [Iatrogenic Disease] explode all trees | 1180 |
| #8 | ((iatrogen* NEXT/3 (diseas* or disorder*))):ti,ab,kw | 321 |
| #9 | #5 OR #6 OR #7 OR #8 | 1974 |
| #10 | #4 AND #9 | 361 |
| #11 | (newborn* or new-born* or neonat* or neo-nat* or infan* or child* or adolesc* or paediatr* or pediatr* or baby* or babies* or toddler* or kid or kids or boy* or girl* or juvenile* or teen* or youth* or pubescen* or preadolesc* or prepubesc* or preteen or tween):ti | 117178 |
| #12 | (pediatr* or paediatr*):so | 31821 |
| #13 | #11 OR #12 | 126673 |
| #14 | #10 NOT #13 | 332 |

**Note:** A similar strategy was used in the Medline search.

**Supplementary Table S2.2.** Subgroup of Studies Not Limited to Older Adults (includes all ages)

| Author/Year | Location | Study | Age (Years) | F/U (Mos) | Setting | Adjudication Method | ADE Definition |
|---|---|---|---|---|---|---|---|
| Al-Tajir, G. K.; Kelly, W. N., 2005[1] | UAE | P | All | 12 | H | Naranjo | WHO |
| Aparasu, R. R., 1998[2] | USA | R | All | 12 | ED | Trigger Tool | AD |
| Bates, D W. et al., 1995[3] | USA | P | Adults | 6 | H | Leape & Bates | AD |
| Beaudoin, F. L., et al., 2015[4] | USA | R | All | 39 | ED | Trigger Tool | AD |
| Borenstein, J. et al., 2013[5] | USA | P | ≥ 35 | 1 | H | Trigger tool | NR |
| Briant, R. et al., 2004[6] | NZ | R | Adults | 12 | H | Leape & Bates | AD |
| Buajordet, I., et al., 2001[7] | Norway | P | All | 24 | H | Clinical Judgment | WHO |
| Campbell, N. L. et al., 2019[8] | USA | P | Adults | N/A | H | Naranjo | NR |
| Dalleur, O., et al., 2017[9] | USA | R | Adults | 12 | H | Naranjo | NR |
| de Vries, S. T. et al., 2014[10] | Netherlands | P | Adults | 12 | C | Naranjo | AD |
| Dehours, E., et al., 2014[11] | France | P | Adults | 24 | ED | French Method | AD |
| Farcas, A., et al., 2014[12] | Romania | P | Adults | 18 | H | Karch & Lasagna | WHO |
| Forster, A. J., et al., 2004[13] | Canada | R | Adults | 12 | H | 6-point scale [Leape & Bates] | AD |
| Forster, A. J., et al., 2004[14] | Canada | P | Adults | 4 | H | 6-point scale [Leape & Bates] | AD |
| Forster, A. J., et al., 2003[15] | Canada | P | Adults | 3 | H | 6-point scale [Leape & Bates] | AD |
| Gandhi, T. K., et al., 2003[16] | USA | P | Adults | 1 | H | 6-point scale [Leape & Bates] | Bates et al. |
| Hafner, J. W., Jr., et al., 2002[17] | USA | R | All | 3 | ED | Naranjo | Bates et al. |
| Hohl, C. M., et al., 2012[18] | Canada | P | Adults | 7 | ED | Naranjo + Leape & Bates + WHO-UMC | WHO+Edwards & Aronon |
| Isacson, D., et al., 2008[19] | Sweden | P | Adults | 2 w | C | Self-Reported | NR |
| Jonville-Bera, A. P., et al., 2009[20] | France | P | All | 12 | H | French Method | AD |
| Leape, L. L., et al., 1991[21] | USA | R | All | 12 | H | Leape & Bates | AD |
| Lehmann, L. S. et al., 2005[22] | USA | P | All | 5 | H | Karch & Lasagna | AD |
| Lin, S. H.; Lin, M. S., 1993[23] | Taiwan | R | All | 10 | H | Karch & Lasagna | WHO |
| Macedo, A. F., et al., 2011[24] | Portugal | R | All | 9 y | H | WHO-UMC | WHO |
| Motola, D., et al., 2007[25] | Italy | R | All | 15 y | C | WHO-UMC | WHO |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Murff, H. J., et al., 2003[26] | USA | P | All | 6 | H | Leape & Bates | Bates et al. |
| Phillips, A. L., et al., 2014[27] | Australia | P | Adults | 2 | H | Clinical Judgment | AD |
| Queneau, P. et al., 2007[28] | France | P | All | 2 w | H | French Method | WHO |
| Rothschild, J. M. et al., 2005[29] | USA | P | Adults | 12 | H | Leape & Bates et al. | AD |
| Schmiedl, S., et al., 2018[30] | Germany | P | All | 8.5 y | H | French Method | WHO |
| Schnipper JL et al., 2009[31] | USA | P | ≥ 50 | 2 | H | Leape & Bates | WHO |
| Stausberg, J.; Hasford, J., 2011[32] | Germany | R | All | 5 y | H | Trigger Tool | Bates et al. |
| Steven, I. D. et al., 1999[33] | Australia | P | All | 24 | C | Clinical Judgment | AD |
| Tafreshi, M. J., et al., 1999[34] | USA | P | All | 2 | ED | Naranjo | AD |
| Zaidenstein, R. et al., 2002[35] | Israel | P | Adults | 3 | H | Naranjo | WHO |

P: prospective; R: retrospective; F/U: follow-up duration (months); Y: years; W: weeks; ED: emergency department; C: community, H: in-hospital; AD: author defined; NR: not reported

**Supplementary Text S2.3.** Examples of ADEs and ADWEs

1. **Leape and Bates method Likert Scale:**[16,36]

1. Outcome definitely caused by the patient's disease
2. Outcome probably caused by the patient's disease
3. Outcome more than likely caused by the patient's disease
4. Outcome more than likely cause by the patient's medication
5. Outcome probably caused by the patient's medication
6. Outcome definitely caused by the patient's medication

2. **Naranjo Algorithm:**[37]

| | | Yes | No | Do Not Know | Score |
|---|---|---|---|---|---|
| 1. | Are there previous conclusive reports on this reaction? | +1 | 0 | 0 | |
| 2. | Did the adverse event appear after the suspected drug was administered? | +2 | -1 | 0 | |
| 3. | Did the adverse reaction improve when the drug was discontinued, or a specific antagonist was administered? | +1 | 0 | 0 | |
| 4. | Did the adverse reaction reappear when the drug was readministered? | +2 | -1 | 0 | |
| 5. | Are there alternative causes (other than the drug) that could on their own have caused the reaction? | -1 | +2 | 0 | |
| 6. | Did the reaction reappear when a placebo was given? | -1 | +1 | 0 | |
| 7. | Was the drug detected in the blood (or other fluids) in concentrations known to be toxic? | +1 | 0 | 0 | |
| 8. | Was the reaction more severe when the dose was increased, or less severe when the dose was decreased? | +1 | 0 | 0 | |
| 9. | Did the patient have a similar reaction to the same or similar drugs in any previous exposure? | +1 | 0 | 0 | |
| 10. | Was the adverse event confirmed by any objective evidence? | +1 | 0 | 0 | |
| | | | | | Total Score |

Scenarios:

The following scenarios are **adapted from a clinical trial[38] on deprescribing in acute care** using an electronic tool, MedSafer, and relate to an 86 year old woman with a variety of medical conditions and who takes multiple daily medications. Each scenario represents a potential post-discharge outcome for the patient with a discussion of whether an ADE or ADR has occurred as scored by both the Leape and Bates and Naranjo methods respectively. These examples are meant to **illustrate the strengths and weakness of the two most common adjudication methods** through comparing and contrasting them using various scenarios that we encountered in our clinical trial of deprescribing. The scenarios change slightly from one example to the next.

Each scenario will address the case of an 86-year-old female who has the following medical conditions:

Hypertension, diabetes type 2, atrial fibrillation, a remote myocardial infarction 9 years ago, congestive heart failure with preserved ejection fraction and diastolic dysfunction, mild neurocognitive disorder (mild cognitive impairment) with a history of a fall at home that lead to hospitalization. On admission she is found to have mild acute kidney injury with a rise in creatinine from 85 to 130 umol/L.

She takes the following medications identified on admission (this is her best possible medication history taken by the pharmacist upon admission to hospital); this list is considered her "chronic" medications.

Warfarin 3 mg po daily
Aspirin 80 mg po daily
Losartan 50 mg po daily
Ramipril 5 mg po daily
Bisoprolol 5 mg po daily
Furosemide 40 mg po daily
Atorvastatin 40 mg po QHS
Pantoprazole 40 mg po daily
Sitagliptin 50 mg po daily,
Glyburide 10 mg po BID
Lorazepam 1 mg po QHS

She has an uncomplicated course in hospital and potential triggers for fall that are identified are lorazepam, frailty, orthostatic hypotension from volume contraction, and osteoarthritis of the knees. Her acute kidney injury resolves with holding furosemide, losartan and ramipril.

Examples of Adverse Drug Events:

**Scenario 1:**

The patient returns to the hospital 3 weeks post discharge with a **gastrointestinal hemorrhage** and undergoes endoscopy; a gastric ulcer appearing to be NSAID induced is identified and requires endoscopic intervention. She is transfused one unit of packed red blood cells.

She was discharged on the following medication regimen (**identical to her admission medication list**):

**Warfarin 3 mg po daily, aspirin 80 mg po daily**, pantoprazole 40 mg po daily, losartan 50 mg po daily, ramipril 5 mg po daily, bisoprolol 5 mg po daily, atorvastatin 40 mg po QHS, lorazepam 1 mg po QHS, glyburide 10 mg po BID, sitagliptin 50 mg po daily, furosemide 40 mg po daily

Using the Leape and Bates method, two independent adjudicators decide that the outcome (gastrointestinal bleed) was **probably caused by the patient's medication** (5 on 6 on the Likert scale). **This is considered an ADE**.

Using the Naranjo algorithm:

1. Are there previous conclusive reports in this reaction? YES→ aspirin and warfarin are known to increase the risk of gastrointestinal bleeding (+1)
2. Did the adverse event appear after the suspected drug was administrated? YES (2)
3. Did the adverse reaction improve when the drug was discontinued, or a specific antagonist was administered? Yes (+1)
4. Did the adverse reaction reappear when the drug was re-administered? Not applicable (0)
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction? Yes (-1)
6. Did the reaction reappear when a placebo was given? Not applicable (0)
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic? no
8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased? Possible? Stopped bleeding when warfarin reversed (0)
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure? Don't think so- can't tell for sure (0)
10. Was the adverse event confirmed by any objective evidence? No- patient self-reported (0)

**Total score: 3 (ADR possible);** ADR is considered definite if ≥ 9, probable 5 to 8, possible 1 to 4, and doubtful ≤ 0.

Discussion: this was a case of gastrointestinal hemorrhage in an older woman who had been taking dual anticoagulation for several years without an evidence-based indication for combination anticoagulation. In the context of a recent hospitalization she developed a GI bleed. **It is intuitive to identify this as an ADE using Leape and Bates**. It is harder to identify this event as an ADR using the Naranjo algorithm (adjudicated as "ADR possible").

**Scenario 2:**

The same patient returns to the hospital **1 week post initial discharge** with **epistaxis** and **her INR is found to be 10**. She is transfused one unit of packed red blood cells and receives prothrombin complex concentrate with reversal of the INR and the bleeding stops.

She was discharged on the following medication regimen:

**Warfarin 4 mg po daily (increased at discharge)**, pantoprazole 40 mg po daily, ramipril 5 mg po daily, bisoprolol 5 mg po daily, atorvastatin 40 mg po QHS, lorazepam 1 mg po QHS, glyburide 10 mg po BID, sitagliptin 50 mg po daily, furosemide 40 mg po daily

Stopped at discharge: aspirin 80 mg po daily, losartan 50mg po daily

New medications prior to presenting with a supratherapeutic INR: **ciprofloxacin for an uncomplicated UTI**

Using the Leape and Bates method, two independent adjudicators decide that the outcome (epistaxis) was definitely caused by the patient's medication (6 on the Likert scale). **This is considered an ADE**.

Using the Naranjo algorithm:

1. Are there previous conclusive reports in this reaction? YES→ ciprofloxacin is known to interact with warfarin and increase the INR (+1)
2. Did the adverse event appear after the suspected drug was administrated? Yes- the INR increased one-week post discharge after the ciprofloxacin was initiated (+2)
3. Did the adverse reaction improve when the drug was discontinued, or a specific antagonist was administered? Yes (+1)
4. Did the adverse reaction reappear when the drug was re-administered? Not applicable (0)
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction? Possibly yes (-1)
6. Did the reaction reappear when a placebo was given? Not applicable (0)
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic? yes (+1)
8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased? Possible? Stopped bleeding when medications were held, warfarin reversed, and ulcer clipped endoscopically (+1)
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure? Don't think so- can't tell for sure (0)
10. Was the adverse event confirmed by any objective evidence? yes- INR was 10 (+1)

Total score: **9 (ADR definite);** ADR is considered definite if ≥ 9, probable 5 to 8, possible 1 to 4, and doubtful ≤ 0.

Discussion: this is a **classic example of an ADR** with a **supratherapeutic INR** developing after combining coumadin with a fluoroquinolone antibiotic, and the problem improved with the **administration of an antidote**. This is readily identifiable with Naranjo as a probable ADR- this is the type of scenario that Naranjo works best to identify.

**Scenario 3:**

The patient returns to the hospital **2 weeks post initial discharge** with **acute kidney injury** with a rise in creatinine to 280 umol/L. She is found to be **hypovolemic** on exam with decreased urine output.

She was discharged on the following medication regimen:

Warfarin 3 mg po daily, **ramipril 5 mg po daily, losartan 50 mg po daily**, bisoprolol 5 mg po daily, atorvastatin 40 mg po QHS, lorazepam 1 mg po QHS, glyburide 10 mg po BID, sitagliptin 50 mg po daily, **furosemide increased to 60 mg po daily**

Stopped: aspirin 80 mg po daily, pantoprazole 40 mg po daily

New medications at discharge: none

Using the Leape and Bates method, two independent adjudicators decide that the outcome (acute kidney injury) was **probably caused by the patient's medication(s)** (5 on 6 on the Likert scale). **This is considered an ADE**.

Using the Naranjo algorithm:

1. Are there previous conclusive reports in this reaction? Yes→ combination of ACE-inhibitor and ARB can cause renal failure; as can increasing her dose of furosemide (+1)
2. Did the adverse event appear after the suspected drug was administrated? Yes- the kidney injury occurred after increasing her furosemide at discharge (+2)
3. Did the adverse reaction improve when the drug was discontinued, or a specific antagonist was administered? Unable to tell as do not have details relate to the hospitalization (0)
4. Did the adverse reaction reappear when the drug was re-administered? Not performed (0)
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction? Possibly yes (-1)
6. Did the reaction reappear when a placebo was given? Not applicable (0)
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic? Not relevant (0)
8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased? Not sure (0)
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure? Don't think so- can't tell for sure (0)
10. Was the adverse event confirmed by any objective evidence? Yes- creatinine value (+1)

Total score: **3 (ADR possible);** ADR is considered definite if ≥ 9, probable 5 to 8, possible 1 to 4, and doubtful ≤ 0.

Discussion: using the Leape and Bates we decide that the **combination of ACE-inhibitor, ARB and increased furosemide** led to acute kidney injury and readily classify this as an ADE. Using Naranjo, it is not so clear that this was an ADR (possible).

**Scenario 4:**

The patient returns to the hospital **2 weeks post initial discharge** with **acute kidney injury** with a rise in creatinine to 280 umol/L. She is found to be **euvolemic** on exam with decreased urine output. She has **recent symptoms of cough, myalgias and runny nose** and is diagnosed with an upper respiratory tract infection.

She was discharged on the following medication regimen:

Warfarin 3 mg po daily, **ramipril 5 mg po daily, losartan 50mg po daily**, bisoprolol 5 mg po daily, atorvastatin 40 mg po QHS, lorazepam 1 mg po QHS, glyburide 10 mg po BID, sitagliptin 50 mg po daily, furosemide 40 mg po daily

Stopped: aspirin 80 mg po daily, pantoprazole 40 mg po daily

New medications at discharge: none

Using the Leape and Bates method, two independent adjudicators decide that the outcome (acute kidney injury) was **possibly caused by the patient's medication** (4 on the Likert scale). This would **NOT be considered an ADE.**

Using the Naranjo algorithm:

1. Are there previous conclusive reports in this reaction? Yes→ combination of ACE-inhibitor and ARB can cause renal failure (+1)
2. Did the adverse event appear after the suspected drug was administrated? YES (+2)
3. Did the adverse reaction improve when the drug was discontinued, or a specific antagonist was administered? Unable to tell (0)
4. Did the adverse reaction reappear when the drug was re-administered? Not performed (0)
5. **Are there alternative causes** (other than the drug) that could on their own have caused the reaction? Yes- URTI (-1)
6. Did the reaction reappear when a placebo was given? Not applicable (0)
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic? No (0)
8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased? Not sure (0)
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure? Don't think so- can't tell for sure (0)
10. Was the adverse event confirmed by any objective evidence? Yes- creatinine value (+1)

Total score: 3 (possible); ADR is considered definite if ≥ 9, probable 5 to 8, possible 1 to 4, and doubtful ≤ 0.

Discussion: this patient was discharged on an ACE-inhibitor and an ARB and developed acute kidney injury in the context of a recent URTI. Using Leape and Bates, this was "possibly due to the patient's medications" (4/6) but would not have been considered an ADE because it was not adjudicated as a 5 or 6- *even though the medications were likely contributory to the patient's presentation and there are clear guidelines to avoid co-prescription of these classes of medications*. The trouble is, it is hard to know how much of the kidney injury was due to her

age, co-morbidities, medications, and an intercurrent illness. This is a **limitation of the Leape and Bates** method. The method may be more sensitive to capturing ADEs in the setting of deprescribing studies if we include 4/6, in addition to 5 and 6/6. This has not been studied.

**Scenario 5 - Example of an ADE prevented:**

The patient returns home and at 30-days post discharge she is well. She has not returned to the healthcare system for any unplanned visits and feels at her baseline.

She was discharged on the following medication regimen:

Warfarin 3 mg po daily, ramipril 5 mg po daily, bisoprolol 5 mg po daily, atorvastatin 40 mg po QHS, glyburide 10 mg po BID, sitagliptin 50 mg po daily, furosemide 40 mg po daily

**Stopped**: aspirin 80 mg po daily, pantoprazole 40 mg po daily, losartan 50mg po daily. A 6-week taper of lorazepam was prescribed.

New medications at discharge: none

This patient did not have an ADE. It is the counterfactual/opposite of the examples presented above. Her losartan is stopped at discharge and she does not return to the hospital with acute kidney injury. Her aspirin is also stopped, and she does not return to the hospital with a gastrointestinal bleed. Her lorazepam is tapered, and she does not have any symptoms related to decreasing the medication gradually.

**Scenario 6 - Example of an Adverse Drug Withdrawal Event (ADWE):**

The patient returns home and at 3-weeks post discharge **she returns to the hospital with hyperglycemia**, weakness and acute kidney injury. There has been no intercurrent illness. She reports 2 weeks of polydipsia and polyurea.

She was discharged on the following medication regimen:

Warfarin 3 mg po daily, ramipril 5 mg po daily, bisoprolol 5 mg po daily, atorvastatin 40 mg po QHS, gliclazide MR 30 mg po daily, furosemide 40 mg po daily

Stopped: aspirin 80 mg po daily, pantoprazole 40 mg po daily, losartan 50mg po daily, glyburide 10 mg po BID, sitagliptin 50 mg po daily, lorazepam 1 mg po QHS

Using the Leape and Bates method, two independent adjudicators decide that the outcome (hyperglycemia) was probably caused by (stopping) the patient's medication (5 on the Likert scale). This would be considered an ADWE. The acute kidney injury is considered secondary to the hyperglycemia, although this is not specifically mentioned in the adjudication (there is no mechanism to capture this).

Using the modified Naranjo algorithm:

1. Are there previous conclusive reports in this reaction? Yes→ stopping 2 medications to treat diabetes could lead to hyperglycemia (+1)
2. Did the adverse event appear after the suspected drug was **withdrawn**? Yes (+2)
3. Did the adverse reaction improve when the drug was **readministered**? Yes (+1)
4. Did the adverse reaction reappear when the drug was **withdrawn again**? Not performed (0)
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction? Possibly (-1)
6. Did the reaction reappear after a placebo withdrawal? Not applicable (0)
7. Did the patient previously use the drug chronically? YES (+1)
8. Was the reaction less severe when the dose was increased, or more severe when the dose was decreased? Not applicable (0)
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure? Don't think so- can't tell for sure (0)
10. Was the adverse event confirmed by any objective evidence? Yes- glucose was measured as high (+1)

Total score: 5 (ADR probable); ADR is considered definite if ≥ 9, probable 5 to 8, possible 1 to 4, and doubtful ≤ 0.

Discussion: In this case, the patient had their sitagliptin and glyburide deprescribed, and returned with hyperglycemia. Using the Leape and Bates method, the adjudicator must themselves recognize that a manipulation of the medication resulted in the adverse event. They must revise the language on their own to reflect that the event was caused by medication discontinuation. Naranjo has a series of questions that can be applied when the event is thought to be due to the withdrawal of a medication. That said, it still has the same limitations in that it relies heavily on determining causality, rather than an association between the event

and the withdrawal of the medication. Finally, we see the limitations of both methods in deprescribing trials in this example. In this case, this patient successfully had four medications deprescribed without a complication (she did not have a gastrointestinal bleed, she did not return to the hospital with acute kidney injury, she did not have a benzodiazepine induced fall). **Would she have had the adverse event if a more equipotent dose of gliclazide was chosen or if her sitagliptin was continued? Would this case of deprescribing be considered a success? Or a failure? It is not possible to ascertain using either method.**

**References Appendix A:**


1. Al-Tajir GK, Kelly WN. Epidemiology, comparative methods of detection, and preventability of adverse drug events. *Ann Pharmacother.* 2005;39(7-8):1169-1174.
2. Aparasu RR. Drug-related-injury visits to hospital emergency departments. *Am J Health Syst Pharm.* 1998;55(11):1158-1161.
3. Bates DW, Cullen DJ, Laird N, et al. Incidence of adverse drug events and potential adverse drug events. Implications for prevention. ADE Prevention Study Group. *JAMA.* 1995;274(1):29-34.
4. Beaudoin FL, Merchant RC, Janicki A, McKaig DM, Babu KM. Preventing iatrogenic overdose: a review of in-emergency department opioid-related adverse drug events and medication errors. *Ann Emerg Med.* 2015;65(4):423-431.
5. Borenstein J, Aronow HU, Bolton LB, Choi J, Bresee C, Braunstein GD. Early recognition of risk factors for adverse outcomes during hospitalization among Medicare patients: a prospective cohort study. *BMC Geriatrics.* 2013;13:72.
6. Briant R, Ali W, Lay-Yee R, Davis P. Representative case series from public hospital admissions 1998 I: drug and related therapeutic adverse events. *New Zealand Medical Journal.* 2004;117(1188):U747.
7. Buajordet I, Ebbesen J, Erikssen J, Brors O, Hilberg T. Fatal adverse drug events: the paradox of drug treatment. *J Intern Med.* 2001;250(4):327-341.
8. Campbell NL, Perkins AJ, Khan BA, et al. Deprescribing in the Pharmacologic Management of Delirium: A Randomized Trial in the Intensive Care Unit. *Journal of the American Geriatrics Society.* 2019;21:21.
9. Dalleur O, Beeler PE, Schnipper JL, Donze J. 30-Day Potentially Avoidable Readmissions Due to Adverse Drug Events. *J Patient Saf.* 2017;17:17.
10. de Vries ST, Haaijer-Ruskamp FM, de Zeeuw D, Denig P. Construct and concurrent validity of a patient-reported adverse drug event questionnaire: a cross-sectional study. *Health and quality of life outcomes.* 2014;12:103-103.
11. Dehours E, Bounes V, Bagheri H, Valle B, Ducasse JL, Montastruc JL. Adverse drug reactions in an emergency medical dispatching centre. *Eur J Clin Pharmacol.* 2014;70(7):881-887.
12. Farcas A, Bucsa C, Sinpetrean A, et al. Preventability analysis of adverse drug reactions detected in two internal medicine departments in Romania. *Intern.* 2014;9(2):187-193.
13. Forster AJ, Asmis TR, Clark HD, et al. Ottawa Hospital Patient Safety Study: incidence and timing of adverse events in patients admitted to a Canadian teaching hospital. *CMAJ.* 2004;170(8):1235-1240.
14. Forster AJ, Clark HD, Menard A, et al. Adverse events among medical patients after discharge from hospital. *CMAJ.* 2004;170(3):345-349.
15. Forster AJ, Murff HJ, Peterson JF, Gandhi TK, Bates DW. The incidence and severity of adverse events affecting patients after discharge from the hospital. *Annals of Internal Medicine.* 2003;138(3):161-167.
16. Gandhi TK, Weingart SN, Borus J, et al. Adverse drug events in ambulatory care. *The New England journal of medicine.* 2003;348(16):1556-1564.

17. Hafner JW, Jr., Belknap SM, Squillante MD, Bucheit KA. Adverse drug events in emergency department patients. *Annals of Emergency Medicine.* 2002;39(3):258-267.
18. Hohl CM, Nosyk B, Kuramoto L, et al. Outcomes of emergency department patients presenting with adverse drug events. *Ann Emerg Med.* 2011;58(3):270-279.e274.
19. Isacson D, Johansson L, Bingefors K. Nationwide survey of subjectively reported adverse drug reactions in Sweden. *Ann Pharmacother.* 2008;42(3):347-353.
20. Jonville-Bera AP, Saissi H, Bensouda-Grimaldi L, et al. Avoidability of adverse drug reactions spontaneously reported to a French regional drug monitoring centre. *Drug Safety.* 2009;32(5):429-440.
21. Leape LL, Brennan TA, Laird N, et al. The nature of adverse events in hospitalized patients. Results of the Harvard Medical Practice Study II. *New England Journal of Medicine.* 1991;324(6):377-384.
22. Lehmann LS, Puopolo AL, Shaykevich S, Brennan TA. Iatrogenic events resulting in intensive care admission: frequency, cause, and disclosure to patients and institutions. *American Journal of Medicine.* 2005;118(4):409-413.
23. Lin SH, Lin MS. A survey on drug-related hospitalization in a community teaching hospital. *Int J Clin Pharmacol Ther Toxicol.* 1993;31(2):66-69.
24. Macedo AF, Alves C, Craveiro N, Marques FB. Multiple drug exposure as a risk factor for the seriousness of adverse drug reactions. *J Nurs Manag.* 2011;19(3):395-399.
25. Motola D, Vargiu A, Leone R, et al. Hepatic adverse drug reactions: a case/non-case study in Italy. *Eur J Clin Pharmacol.* 2007;63(1):73-79.
26. Murff HJ, Forster AJ, Peterson JF, Fiskio JM, Heiman HL, Bates DW. Electronically screening discharge summaries for adverse medical events. *J Am Med Inform Assoc.* 2003;10(4):339-350.
27. Phillips AL, Nigro O, Macolino KA, et al. Hospital admissions caused by adverse drug events: an Australian prospective study. *Aust Health Rev.* 2014;38(1):51-57.
28. Queneau P, Bannwarth B, Carpentier F, et al. Emergency department visits caused by adverse drug events: results of a French survey. *Drug Safety.* 2007;30(1):81-88.
29. Rothschild JM, Landrigan CP, Cronin JW, et al. The Critical Care Safety Study: The incidence and nature of adverse events and serious medical errors in intensive care. *Critical Care Medicine.* 2005;33(8):1694-1700.
30. Schmiedl S, Rottenkolber M, Szymanski J, et al. Preventable ADRs leading to hospitalization - results of a long-term prospective safety study with 6,427 ADR cases focusing on elderly patients. *Expert Opin Drug Saf.* 2018;17(2):125-137.
31. Schnipper JL, Hamann C, Ndumele CD, et al. Effect of an electronic medication reconciliation application and process redesign on potential adverse drug events: a cluster-randomized trial. *Arch Intern Med.* 2009;169(8):771-780.
32. Stausberg J, Hasford J. Drug-related admissions and hospital-acquired adverse drug events in Germany: a longitudinal analysis from 2003 to 2007 of ICD-10-coded routine data. *BMC Health Serv Res.* 2011;11:134.
33. Steven ID, Malpass A, Moller J, Runciman WB, Helps SC. Towards safer drug use in general practice. *Journal of Quality in Clinical Practice.* 1999;19(1):47-50.
34. Tafreshi MJ, Melby MJ, Kaback KR, Nord TC. Medication-related visits to the emergency department: a prospective study. *Ann Pharmacother.* 1999;33(12):1252-1257.

35. Zaidenstein R, Eyal S, Efrati S, et al. Adverse drug events in hospitalized patients treated with cardiovascular drugs and anticoagulants. *Pharmacoepidemiol Drug Saf.* 2002;11(3):235-238.
*36.* Leape LL, Bates DW, Cullen DJ, et al. Systems Analysis of Adverse Drug Events. *JAMA.* 1995;274(1):35-43.
37. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther.* 1981;30(2):239-245.
38. McDonald EG, Wu PE, Rashidi B, et al. The MedSafer Study: A Controlled Trial of an Electronic Decision Support Tool for Deprescribing in Acute Care. *J Am Geriatr Soc.* 2019.

**Appendix B. Gabapentinoids Brochure**

**Newly Identified Risky Medications**

*Gabapentinoids EMPOWER Brochure for Older adults: Tool Development*

Through conducting a literature review regarding ADE adjudication methodologies, I was able to describe the complexity of the process and highlight how different components of medications and diseases may come into play. When deprescribing and adjudicating an ADE, it is important to have a thorough understanding of the drug's mechanism of action and an awareness of any off-target effects of a medication. Through my work in deprescribing, I recognized that the Gabapentinoids are a class of medications originally marketed for epilepsy which are commonly prescribed off-label for pain or without an evidence-based indication. In Montreal, almost 13% of admitted medical patients receive a gabapentinoid[1]. These drugs have many off-target effects such as fluid retention and they may impair cognition and lead to falls and fractures in older adults. As this is a newer class of medications that is being targeted for deprescribing, it became apparent that clinicians and patients/caregivers may be unaware of the potential harms and furthermore, that patients could benefit from a brochure that outlines the dangers of the medication in layperson language. Therefore, I identified an opportunity to increase awareness surrounding harms of Gabapentinoids and through tapering and deprescribing hopefully reduce the risk of associated ADEs. I will present the rationale behind why I chose this class of medications and the information included in the brochure which I developed in collaboration with the Canadian Deprescribing Network.

*Information on Gabapentinoids*

Gabapentinoids are a class of drugs that include gabapentin and pregabalin. Gabapentin was licensed in the 1990s in the United States and Canada as an anticonvulsant for the treatment of epilepsy whereas pregabalin was licensed in the mid-2000s for a number of indications including the treatment neuropathic pain.[2,3] Gabapentinoids are a common class of

medication, however, their success is widely due to the off-label prescription and marketing for the treatment of unapproved indications.[4-6] They are commonly prescribed at a high dose to older adults to treat migraines and lower back pain, with many not receiving any benefit, and being unaware of the potential harms.[4,7,8] There is low-quality to no evidence for Gabapentinoid benefit in both approved and unapproved indications, and a high risk of adverse drug events in older adults.[9,10] Despite this evidence, recent studies have shown that 1 in every 8 hospitalized patients is on a Gabapentinoid, and 95% of gabapentin is prescribed for off-label Indications.[1,11-13] Furthermore, from 2012 to 2016 the total spending on pregabalin in the United States has increased from $1.9 to $4.4 billion USD, ranking eighth in overall for specific drug spending.[14,15]

With the rate of Gabapentinoid prescribing increasing and the risk associated with this drug, I identified a need for an intervention, especially in the older adult population. Older adults with unspecific pain are most commonly prescribed this drug, where due to aging, physiological changes, and polypharmacy they are at the highest risk for adverse drug events.[16-18] Educational deprescribing brochures have been shown to be effective in altering risk perception surrounding inappropriate prescriptions and are effective for deprescribing sedatives in the hospital and in the community.[19-21] I partnered with the Canadian Deprescribing Network to design an EMPOWER brochure. We aimed to create a tool that increases patient knowledge and changes their beliefs and perceptions about Gabapentinoids. In order to achieve this, I applied constructive learning theory (activating learners to create new knowledge) to the development of this educational tool. Other learning strategies such as cognitive dissonance and self-assessment theory were also applied in the development process. Through knowledge acquisition, belief alteration, and by providing certain facts about the medication, this type of approach aims to stimulate a discussion about deprescribing Gabapentinoids between older adults and their healthcare providers, allowing them to engage in personal health improvement.

*Information included in the brochure*

The brochure is designed to be interactive allowing patients on these medications to read through the information, but also actively participate by answering questions, checking off symptoms they have had and write down any questions they have for their healthcare provider. The brochure also includes many warnings that patients should not deprescribe or change their medication regimen without first consulting with a doctor or their healthcare provider. Our team additionally developed a French version of this brochure, and both versions were tested in focus groups. The brochure is complete, has undergone focus group evaluation, and will soon be available online for patient use.

*Future steps*

To test this tool, we plan on deploying the newly developed brochure in a randomized trial to demonstrate its effectiveness at deprescribing Gabapentinoids in older adults admitted to the hospital. I believe this to be a successful strategy as it has previously been tested using similar EMPOWER brochures for sedative-hypnotic medications and proton-pump inhibitors (PPIs), where this method and tool were demonstrated to be feasible, safe, and effective in deprescribing.[19,20]

The Gabapentinoid project serves as an example of the complexity surrounding deprescribing PIMs when it comes to adjudicating ADEs. Coming off of Gabapentinoids requires tapering, as abruptly stopping has been associated with seizures, and continuing the drug could contribute to falls and fractures. Adjudicating a case scenario in a trial where Gabapentinoids were deprescribed needs to factor in the risk of harm from continuation, balanced with the potential risk of harm from discontinuation. My research further solidifies the need for a method of adjudication which allows the adjudicator to take this type of knowledge into consideration when determining if an ADE has occurred. Understanding how a medication is used, why it is taken, and its harms and benefits will result in better identification and classification of ADEs. While this was a smaller complimentary project, I was able to take what I learned from designing this brochure into consideration in chapter 4 where I layout the design of my newly proposed method of adjudication.


# You May Be at Risk

You are taking one of the following medications for pain:

○ Gabapentin (Neurontin®)

○ Pregabalin (Lyrica®)

CIHR IRSC Canadian Institutes of Health Research / Instituts de recherche en santé du Canada

Centre de recherche iugm Institut universitaire de gériatrie de Montréal

Affiliated with Université de Montréal

Michel Saucier Chair in Pharmacy, Health & Aging
La Chaire pharmaceutique Michel-Saucier en santé et vieillissement

CaDeN Canadian Deprescribing Network


# Vous pourriez être à risque

## Vous prenez l'un des médicaments suivants contre la douleur :

○ Gabapentine (Neurontin®)

○ Prégabaline (Lyrica®)

CIHR IRSC

iugm

Université de Montréal

Michel Saucier Chair in Pharmacy, Health & Aging
La Chaire pharmaceutique Michel-Saucier en santé et vieillissement

ReCaD
Réseau canadien pour la déprescription

# QUIZ: TRUE OR FALSE

## Gabapentin and pregabalin

1. This medication will reduce pain for everyone who takes it. ◯ True ◯ False

2. This medication is safe and effective, even at higher doses. ◯ True ◯ False

3. New side effects can appear, even after taking this medication for several years at the same dose. ◯ True ◯ False

4. It can be dangerous to use this medication with opioid medications (narcotics). ◯ True ◯ False

# ANSWERS

## 1. FALSE

A lot of people who take gabapentin or pregabalin do not see a reduction of their pain with these medications. To make sure the medication is working, your pain levels should be re-evaluated on a regular basis.

## 2. FALSE

Increasing the dose of gabapentin or pregabalin doesn't always improve pain control, yet it will increase your risk of side effects. Side effects are frequent and can include feeling sleepy, dizzy, and losing your balance.

## 3. TRUE

New side effects may develop after years of taking the same dose of medication. This could be due to age-related changes in your body such as decreased kidney function, or to new diseases or new medications.

## 4. TRUE

Gabapentin and pregabalin should not be used with opioid medication (narcotics) due to the risk of serious breathing problems, which can lead to death.

# Important things to know about gabapentin (Neurontin®) and pregabalin (Lyrica ®)

As your body ages, you become more sensitive to the side effects of these medications for various reasons, including changes in your kidney function and more sensitivity of your brain to sedative medications.

Pregabalin and gabapentin can cause falls, fractures, memory problems and confusion. Even if you are not experiencing these symptoms, speak to your doctor, nurse or pharmacist to decide if there are better options to treat your pain.

Taking gabapentin or pregabalin with alcohol or other sedative medications such as sleeping pills or opioids (narcotics) increases the risk of severe sedation, breathing problems and can even cause death.


If gabapentin and pregabalin are not reducing your pain or are causing you side effects, the best way to stop the medication is to reduce the dose gradually with the help of your doctor, pharmacist or nurse (*see page 6 for more information on how to reduce the dose*).

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

# Are you experiencing side effects?

| | Yes | No |
|---|---|---|
| 1. Do you feel more tired than usual, dizzy, or off balance? | ◯ | ◯ |
| 2. Do you have problems with attention or memory? | ◯ | ◯ |
| 3. Are you experiencing leg swelling or weight gain? | ◯ | ◯ |

If you answered YES to any of these questions, speak to your doctor, nurse or pharmacist to see if the medication could be causing these symptoms.

| Ask yourself yes or no: | Yes | No | I don't know |
|---|---|---|---|
| 1. Have you recently talked with your doctor, nurse or pharmacist about the best treatment options for your nerve pain or chronic lower back pain? | ◯ | ◯ | ◯ |
| 2. Do you have a plan to review your gabapentin or pregabalin dose regularly? | ◯ | ◯ | ◯ |
| 3. Are you on the lowest possible dose of this medication? | ◯ | ◯ | ◯ |

If you answered NO or I DON'T KNOW to any of these questions, bring this brochure to your next appointment with your doctor, pharmacist or nurse to review if your pain is well managed and your medication dose is as effective as possible.

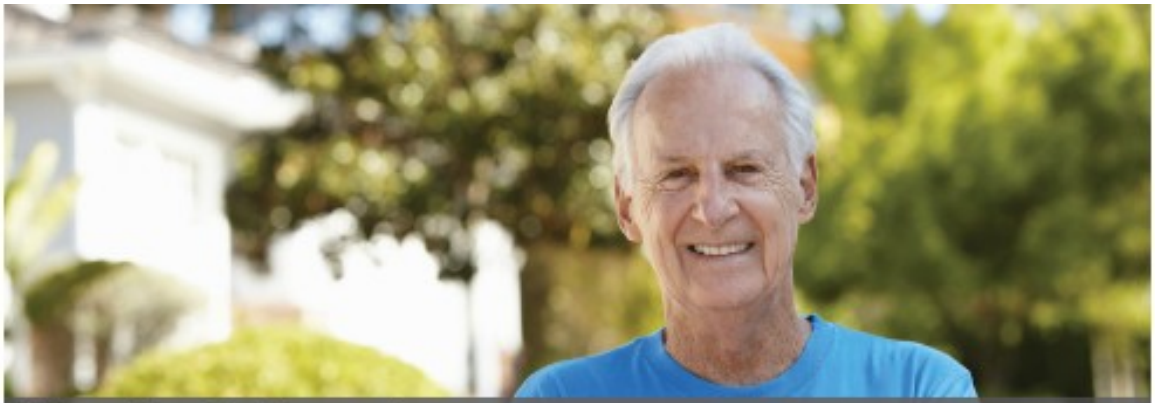
# Other ways to deal with pain

Depending on your reason for taking gabapentin or pregabalin, there are alternative ways to deal with pain with less treatment side effects. Here are some examples:

- Talk to a therapist about a **self-management program for pain**. A self-management program can help you take control of how you deal with pain.
- Speak to a therapist about **cognitive behavioral therapies or mindfulness based interventions for pain**. These therapies change the way you think about pain so that your body and mind react better when you experience pain.
- Depending on your diagnosis, **physiotherapy or massage therapy** might help the pain you are experiencing. Some physical activities such as **yoga, tai chi, pilates** and other structured exercise programs also have benefits for dealing with pain.
- Ask your doctor if a **specialist pain clinic** could better help you deal with pain. Specialist pain clinics provide a range of treatments and services for people with chronic pain, tailored to your individual needs.

Lifestyle changes can also help to improve your overall health, such as:

- Regular physical exercise.
- Quitting smoking.
- Healthy eating.
- Reducing excessive alcohol or other harmful drugs.



# Mr. Reid's story

## He had been taking gabapentin, a medication just like yours.

"I'm 73 years old and have suffered from chronic lower back pain for several years from an old sports injury. Three years ago, my doctor prescribed gabapentin (Neurontin©) to help relieve my chronic pain. I wasn't sure the gabapentin was working to relieve my lower back pain but I didn't notice side effects either. So I continued renewing it at the pharmacy and taking gabapentin three times a day.

During the past year, I started noticing my legs would swell up, particularly in the evening. I also had "dizzy spells" during the day. One morning, I got out of bed and started walking down the stairs to make coffee. I was a bit dizzy and I missed a step. Luckily, I caught myself on the bannister at the last minute. Even though I was not hurt, it scared me quite a bit.

At my next doctor's appointment, I mentioned this scary episode. I also complained about my leg swelling. My doctor asked me a few questions about how I had been feeling over the last few months and told me that the gabapentin could have been causing these side effects. I wasn't sure if it was still helping me control my back pain, so we agreed that we would try to gradually reduce the medication over a few weeks and see how I went. The doctor also prescribed physiotherapy to help with my lower back pain.

After reducing my medication over a few weeks and starting physiotherapy, my lower back pain has actually improved! I feel stronger and surer on my feet and my leg swelling is practically gone. I also feel like a fog has lifted from my thinking.

I wish I had asked my doctor before, rather than having taken this medication for so long. I realize now that asking my doctor the right questions and being aware of changes in my body has helped me improve my health."

# Gradually reducing your dose

**Is it time to reduce the dose or stop your medication?**
Take this brochure to your doctor, pharmacist or nurse to begin a discussion about gabapentin or pregabalin.

**How do I gradually reduce the dose of pregabalin or gabapentin?**
Everyone is different. To reduce your dose, you will need a tapering program designed just for you.

Some people who reduce their dose of gabapentin or pregabalin may experience withdrawal reactions (for example, insomnia, nausea, anxiety or headaches). Slowly reducing the dose over time can help reduce these symptoms. If you have been on very high doses or have been taking the medication for a long time, your doctor, pharmacist or nurse may consider a slower tapering program. The tapering program table on page 9 can help you have this discussion.

**If I reduce my dose of medication, will my pain get worse?**
Not necessarily. Higher doses of gabapentin or pregabalin do not always improve pain and are likely to cause side effects.

**DO NOT STOP OR CHANGE THE DOSE OF YOUR MEDICATION WITHOUT SPEAKING WITH YOUR DOCTOR, PHARMACIST OR NURSE**

# Tapering program

Here is an example of a tapering schedule for someone taking pregabalin. Speak to you doctor, nurse and pharmacist to develop a tapering plan that's right for you.

**TAPERING PROGRAM EXAMPLE* (PREGABALIN)**

| WEEK | TIME | MO | TUE | WE | TH | FR | SA | SU |
|---|---|---|---|---|---|---|---|---|
| 1 | Morning | ¾ | ¾ | ¾ | ¾ | ¾ | ¾ | ¾ |
| | Night | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 2 | Morning | ¾ | ¾ | ¾ | ¾ | ¾ | ¾ | ¾ |
| | Night | ¾ | ¾ | ¾ | ¾ | ¾ | ¾ | ¾ |
| 3 | Morning | ½ | ½ | ½ | ½ | ½ | ½ | ½ |
| | Night | ¾ | ¾ | ¾ | ¾ | ¾ | ¾ | ¾ |
| 4 | Morning | ½ | ½ | ½ | ½ | ½ | ½ | ½ |
| | Night | ½ | ½ | ½ | ½ | ½ | ½ | ½ |
| 5 | Morning | ¼ | ¼ | ¼ | ¼ | ¼ | ¼ | ¼ |
| | Night | ½ | ½ | ½ | ½ | ½ | ½ | ½ |
| 6 | Morning | ¼ | ¼ | ¼ | ✕ | ✕ | ✕ | ✕ |
| | Night | ¼ | ¼ | ¼ | ¼ | ¼ | ¼ | ✕ |

**What the symbols mean:**

- Full dose
- Three quarters of a dose
- Half a dose
- One quarter of a dose
- ✕ No dose

* Do not cut your capsules. Not all dosing fractions may be available for your medication or your starting dose.

# 5 questions to ask your health care provider

1. Do I need to continue my medication?
2. How do I reduce my dose?
3. Is there a safer alternative treatment?
4. What symptoms should I look for when I reduce or 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

**References Appendix B:**


1. Gingras MA, Lieu A, Papillon-Ferland L, Lee TC, McDonald EG. Retrospective Cohort Study of the Prevalence of Off-label Gabapentinoid Prescriptions in Hospitalized Medical Patients. *J Hosp Med.* 2019;14:E1-e4.
2. Product and Consumer Medicine Information. In: TGA eBusiness Service; 2020.
3. Product Monograph Lyrica. In: Upjohn Canada ULC; 2020.
4. Giladi H, Choinière M, Fitzcharles M-A, Ware MA, Tan X, Shir Y. Pregabalin for chronic pain: does one medication fit all? *Current Medical Research and Opinion.* 2015;31(7):1403-1411.
5. Granger AK. Gabapentinoids for Chronic Pain: Do the Harms Outweigh the Benefits? *j anesthesiol pain res.* 2018;2(113).
6. Goodman CW, Brett AS. A Clinical Overview of Off-label Use of Gabapentinoid Drugs. *JAMA Intern Med.* 2019.
7. Landefeld CS, Steinman MA. The Neurontin legacy--marketing through misinformation and manipulation. *The New England journal of medicine.* 2009;360(2):103-106.
8. Shanthanna H, Gilron I, Rajarathinam M, et al. Benefits and safety of gabapentinoids in chronic low back pain: A systematic review and meta-analysis of randomized controlled trials. *PLOS Medicine.* 2017;14(8):e1002369.
9. Goodman CW, Brett AS. Gabapentinoids for Pain: Potential Unintended Consequences. *Am Fam Physician.* 2019;100(11):672-675.
10. Vickers-Smith R, Sun J, Charnigo RJ, Lofwall MR, Walsh SL, Havens JR. Gabapentin drug misuse signals: A pharmacovigilance assessment using the FDA adverse event reporting system. *Drug Alcohol Depend.* 2020;206:107709.
11. Peckham AM, Evoy KE, Ochs L, Covvey JR. Gabapentin for Off-Label Use: Evidence-Based or Cause for Concern? *Subst Abuse.* 2018;12:1178221818801311-1178221818801311.
12. Fukada C, Kohler JC, Boon H, Austin Z, Krahn M. Prescribing gabapentin off label: Perspectives from psychiatry, pain and neurology specialists. *Can Pharm J (Ott).* 2012;145(6):280-284.e281.
13. Hamer AM, Haxby DG, McFarland BH, Ketchum K. Gabapentin use in a managed medicaid population. *J Manag Care Pharm.* 2002;8(4):266-271.
14. Aitken MK, M. Medicines use and spending in the US.
15. Viniol A, Ploner T, Hickstein L, et al. Prescribing practice of pregabalin/gabapentin in pain therapy: an evaluation of German claim data. *BMJ open.* 2019;9(3):e021535-e021535.
16. Spinewine A, Schmader KE, Barber N, et al. Appropriate prescribing in elderly people: how well can it be measured and optimised? *Lancet (London, England).* 2007;370(9582):173-184.
17. Woodhouse KW, O'Mahony MS. Frailty and ageing. In: Oxford University Press; 1997.
18. Mangoni AA, Jackson SHD. Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. *Br J Clin Pharmacol.* 2004;57(1):6-14.

19. Martin P, Tannenbaum C. Use of the EMPOWER brochure to deprescribe sedative-hypnotic drugs in older adults with mild cognitive impairment. *BMC geriatrics.* 2017;17(1):37-37.
20. Turner JP, Richard C, Lussier M-T, et al. Deprescribing conversations: a closer look at prescriber-patient communication. *Therapeutic advances in drug safety.* 2018;9(12):687-698.
21. Wilson MG, Lee TC, Hass A, Tannenbaum C, McDonald EG. EMPOWERing Hospitalized Older Adults to Deprescribe Sedative Hypnotics: A Pilot Study. *Journal of the American Geriatrics Society.* 2018;66(6):1186-1189.

## Appendix C. Special Populations

*Introduction*

I will also present two other smaller complimentary research projects that I designed and how they relate to my thesis as a whole.

My research allowed me to identify a gap in deprescribing research and monitoring of polypharmacy related to special populations. I consider special populations as groups of individuals that have chronic conditions that may affect their physiologic age (as opposed to their natural biologic age), that requires multiple medications for long-term treatment, and a course of disease progression which separates them from the general population, in terms of chronicity. Usually, with deprescribing research in older adults, all adults above the identified cut off age of usually 60 or 65 years old are evaluated for PIMs and adjudicated for ADEs in a similar fashion. In the critical analysis for an adjudication method that is able to capture all types of ADEs, I determined that there are certain chronic conditions and populations in which their specific chronic illness should ideally be taken into consideration. I identified two special populations of interest in my work; the human immunodeficiency virus (HIV) population and the hemodialysis (HD) population. I also describe how being aware of and understanding these illnesses play a crucial role in deprescribing and ADE adjudication. They may in fact benefit from deprescribing interventions at a younger age for a variety of factors.

I will present each special population, the rationale for why I chose them and how further research tailored to these groups will be beneficial. In collaboration with my supervisors and other key contributors, I designed a study protocol for the HIV and HD projects, submitted and received complete ethics approval for the HIV project and conditional approval for the HD project. Unfortunately, due to COVID-19 and the shutdown of non-essential research which occurred in early March 2020, we were unable to proceed with these two projects, and thus have no results at this point. Although these projects were not carried out, they still contribute to the thesis in a descriptive manner, as the identification of these possible special populations further enforces our recommendations for an ADE adjudication methodology which is able to

take these special circumstances into consideration. I will present both study protocols, laying the foundation for future research. The detailed methods for each study and the statistical analysis can be found in appendix C. Special Populations Methods and Statistical Analysis Protocols.

*Protocol 1: HIV Study*

*Title:* Deprescribing Potentially Inappropriate Medications in Polypharmacy Older Adults Living with HIV: A MedSafer Associated Study

1. *Background and Study Rational*

The risk of adverse drug events (ADEs) due to polypharmacy, defined as five or more daily medications, is a recognized problem for adults aged 65-years and older in the general population.[1] Several large trials are underway to address this growing problem through deprescribing common PIMs such as PPIs, sedative-hypnotics for sleep, and off-label use of antipsychotics for insomnia, among others.

In the HIV population, older adulthood has a different age cut-off and is defined as 50 years of age and older, as aging may begin prematurely, increasing the risk of developing age-related comorbidities.[2] With the success of antiretroviral therapy, the lifespan of people living with HIV is increasing, where it is projected that by 2020, 70% of the HIV infected population will be 50 years or older.[3] The aging of this population poses new challenges for physicians as people living with HIV are more likely to have complicated comorbidities at a younger age, which can result in polypharmacy (in this case defined as the concurrent use of 5 or more non-antiretroviral medications).[4] This population is also at increased risk of ADEs at a younger age due to the complexity of their disease and rates of comorbid illnesses, possibly compounded by a high prescription of PIMs. As we have already discussed, patients hospitalized with an ADE have an increased length of stay, higher costs and an increased risk of in-hospital death. Polypharmacy and PIMs can not only lead to hospitalization in this fragile population but may also decrease adherence to life-saving HIV medications.

*2. Objectives, Hypothesis and Study Questions*

With a need to consider the consequences of polypharmacy in the polymorbid complex aging HIV population, there is great potential for translating deprescribing interventions to this population. The objectives of this study were to apply MedSafer;[5] a Canadian-made electronic deprescribing software to describe the prevalence of polypharmacy and PIMs in the older adults HIV patients (aged 50 and above). I aimed to determine if polypharmacy is a common problem in this population, and how age-associated comorbidities and medications affect the patient's HIV-treatment adherence and quality of life. I also aimed to describe the type of PIMs encountered in HIV patients and compare them to the non-HIV population. I hypothesized there would be a high prevalence of inappropriate polypharmacy amongst HIV patients that could benefit from deprescribing at a younger age than the general population, due to an earlier onset of frailty and cognitive dysfunction. I hypothesized that between the ages of 50-65, this population would have a similar prevalence of PIMs as adults aged 65 and older who are non-HIV. I also suspected that similar drug classes of PIMs might be seen in both populations. This work will inform a deprescribing intervention in the outpatient HIV clinic at the McGill University Health Centre.

*3. Study Methods*

*a. Study Design*

I aimed to perform a retrospective descriptive study as a preliminary evaluation to quantify the needs of deprescribing in this high-risk population. One-years' worth of patient data will be extracted from an already established HIV database (outpatient clinic) from Dr. Marina Klein's chronic viral illness research group and will be linked with the electronic medical record, OACIS. For each patient, their co-morbidities and medications will be entered into MedSafer.[5] This tool uses a combination of rules from Beers, STOPP, and Choosing Wisely Canada criteria to generate a list of PIMs. I would have described the prevalence of polypharmacy and PIMs seen in my group of interest (HIV and >50 years old) and compare to community-dwelling older adults (>65 years old) from our MedSafer Database. I would have used anonymized data. Each patient would have been given a unique identifier in the database.

I would have looked at markers of frailty and medication of adherence to see if these are linked to polypharmacy. This study aims to evaluate the need for a deprescribing intervention in HIV patients in the community.

*b. Study Population*

*Inclusion/Exclusion Criteria:*

Study inclusion criteria HIV population: Patients aged 50 years and older, living with HIV, on 5 or more non-HIV treatment medications plus antiretroviral therapy.

Study inclusion criteria non-HIV population: Patients aged 65 years and older, on 5 or more medications, and in our MedSafer cohort. Patients in this cohort will have a wide variety of comorbidities, and we would not have selected them based on this parameter as we would want a representative population of older adults with a variety of conditions.

*Sample Size:*

Based on the number of patients who meet the inclusion criteria in this outpatient HIV database, within 1-year worth of data.

*c. Study Period*

I would have included all patients in the database who meet the inclusion criteria over a 1-year period from January 1st, 2018 to December 31st, 2018. If the sample size is too small, I would have included subsequent 1-year periods prior to 2018 until we meet sample size requirements, up to a maximum of 5 years.

*d.* Description of data being retrieved

Patient Characteristics: Age, sex, age of HIV diagnosis/Years of exposure, list of comorbidities, medications: name, dose, route, frequency; emergency department and hospital admissions, smoking status, and measure of frailty.

HIV measures: Last CD4 count, last viral load, complete blood count (CBC), hemoglobin a1c, creatinine, or measure of renal function.

*4. Data Analysis*

I would have compared categorical and continuous variables with chi-square, Wilcoxon rank, and t-tests as appropriate. I would have uses general descriptive measures to compare patients with and without polypharmacy and to compare to a population of patients without HIV from an existing MedSafer database of hospitalized patients. As part of the analysis, in my control population I would have described the proportions of the major comorbidities seen. I would have calculated odds ratios and use logistic regression to look for risk factors for emergency department visits and hospitalization related to polypharmacy. The analysis would have been performed using STATA 15 and 16.

*Protocol 2: HD Study*

*Title:* A MedSafer Study: Deprescribing Potentially Inappropriate Medications in a Hemodialysis Population

*1. Introduction*

Polypharmacy, or concurrent use of multiple medications, can alternatively be defined as the use of more medications than medically necessary.[6,7] This is increasingly being recognized as a problem, especially in chronically ill older patients.[7] Hemodialysis patients have a higher risk of polypharmacy, due to multiple common chronic conditions being associated with end-stage renal disease (ESRD), such as diabetes, hypertension and, cardiovascular disease.[8,9] Due to this complicated course of illness, dialysis patients have the highest pill burden of all chronically ill patients taking an average of 19 medications daily.[10,11] Polypharmacy may result in a decreased adherence to medication regimens and an increased risk of adverse drug events (ADEs) including falls, hospitalization, and mortality.[8,12-14]

Deprescribing, the process of intentionally tapering or stopping potentially inappropriate medications (PIMs) is a proposed solution to ensure all patients in the dialysis community are receiving appropriate, effective, and safe medications.[9,12,14] In the general population, deprescribing is geared towards older adults with polypharmacy and has been

shown to have benefits, decreasing mortality risk, and improving quality of life.[12] In the hemodialysis population medication reviews every 3 months are standard practice, yet due to the complexity of their treatment and the fragmentation of the health care system, many practitioners lack the time and knowledge to properly identify PIMs.[9]

The MedSafer, deprescribing software is a Canadian-made electronic tool that identifies polypharmacy and PIMs, providing practitioners with opportunities for safer prescribing.[5] This tool generates a list of deprescribing recommendations for each individual patient by using a combination of rules from the American Geriatric Society Beers Criteria, STOOP/START, and choosing wisely Canada.[15-17] MedSafer has been validated in an older adult general population, and has been shown to increase deprescribing of PIMs in the hospital.[5] ADEs due to PIMs are costly and can even be deadly especially in hemodialysis patients who have a complex course of disease and treatment, and have a high pill burden, compared to the general population.[9,13] With a need for increased rationalization during the medication review process in the hemodialysis population, there is great potential for translating deprescribing interventions to this setting. Therefore, the aim of this quality improvement study is to 1) assess the feasibility of deploying a facilitated medication review with MedSafer in the outpatient hemodialysis population 2) evaluate the effectiveness of the tool at identifying potentially inappropriate medications specific to this population and 3) deprescribe PIMs.

*Protocol 2: HD Study*

*2. Methods*

*2.1 Study Sites*

This study is a quality improvement intervention to be performed on the hemodialysis units of the McGill University Health Centre (MUHC), under the auspices of the Clinical Practice Assessment Unit of the Department of Medicine (Director: E.G.M). The MUHC hemodialysis outpatient unit consists of the 3 sites; the Lachine Hospital, the Royal Victoria Hospital (RVH), and Montreal General Hospital (MGH). There are similarities and differences between the 3 sites in terms of the number of patients, the treating physicians, and the severity of the ESRD

seen. Across these units a total of 268 patients receive dialysis. The Lachine site (88 patients) is a community-based hospital that typically treats the healthiest patients, while the RVH (20 patients) is a kidney transplant center and therefore usually has some of the sickest patients, and the MGH (180 patients) are usually somewhere in-between. Differences in patient health between the sites is also influenced by location, as each hospital is located in a different region within Montreal, and when visiting the hospital 3 times a week convenience may play a role. The same Nephrologists round at both the Lachine and RVH site while a separate set of physicians work at the MGH.

*2.2 Data Sources and Collection*

I would have collected the hemodialysis patient's information through Nephrocare, a comprehensive renal information system that electronically manages and reports patient data. The Nephrocare database contains an accurate and up-to-date list of chronic medications, medical conditions, and information on when the last medication review was completed and what changes were made. I would have then manually cross-referenced this information with OACIS, the electronic medical record system (at the RVH and MGH) and paper charts (at Lachine). Retrieved data would have been manually inputted into the MedSafer software by a research assistant including patient's sex, age, comorbid conditions required to analyze with MedSafer (Supplement), and medication history (name of drug, dose, route, frequency). I would have recorded information on what medications were deprescribed and the proportion of patients who receive a facilitated medication review with MedSafer, the time it takes to retrieve and enter in data, and the time spent by physicians to review reports and act on them.

*2.3 Intervention*

The Lachine hospital and the RVH sites will act as the intervention population, in a staggered manner. The intervention will first be deployed at the Lachine hospital to assess the effectiveness and feasibility of the MedSafer tool in a hemodialysis population. Once complete we could have deployed the tool at the RVH to ensure all patients had access to this quality improvement intervention across the sites. Patient information would have been collected and

entered into the software, generating a MedSafer report. MedSafer contains all the rules for deprescribing included in the American Geriatric Society Beers Criteria, STOOP/START, and choosing wisely Canada.[15-17] The electronic decision support tool identifies PIMs for each patient and generates a report, providing recommendations for deprescribing opportunities. At the intervention sites, these reports will be provided to the nephrologist for consideration, and they could then decide to deprescribe or not whether clinically appropriate. The report, when relevant also contains tapering instructions for medications (eg. Benzodiazepines). All recommendations whether carried out or not will be recorded, to evaluate the accuracy of the tool in this setting.

*2.4 Control*

The MGH site will act as the control population, where the same steps as the intervention will be carried out and a MedSafer report will be generated, but it will not be provided to the Nephrologist. The patients at the MGH will receive usual care, which is a manual medication review by the physician every 3 months. I would have recorded the changes in medications seen with the usual standard of care in the control population and compared them to both the MedSafer report we generated for the same patients (but did not provide) and the patients at the intervention sites. At the end of the study, I would have provided the reports to the Nephrologist for all dialysis patients in order to not withhold a quality improvement intervention that could lead to improved safety and patient care. The MGH site was chosen as the control population as it is isolated from the other 2 sites, with different attending physicians and therefore minimizing the risk of contamination of the intervention on the control group.

*2.5 Outcomes*

The primary outcome would have been to describe the nature of the problem in this population and determine the proportion of patients on one or more PIM. This proportion would have been identified by reviewing the MedSafer reports. Reports are also analyzed to determine if there were certain classes of medication that were commonly being prescribed

inappropriately in this population. The secondary outcome would have been the proportion of PIMs stopped or reduced in the intervention population after review with the MedSafer reports compared to the control population. I also would have record any ADEs due to changes in medications.

*3. Statistical Analysis*

I would have compared categorical and continuous variables with chi-square, Wilcoxon rank, and t-tests where appropriate. I would have used general descriptive measures to describe the scope of polypharmacy and the differences in common co-morbidities between the control and intervention groups. I also would have used qualitative descriptive measures to report voluntary feedback provided by the nephrologists on the feasibility of the intervention and its effectiveness. All analyses would have been performed using STATA 15 and 16.

*Conclusion*

Although I do not have any data from these two studies, the concepts add an element of complexity to the action of deprescribing and defining of outcomes. By identifying these special populations and pointing out how they require different consideration, I highlight the importance of a method of adjudication which can take these at-risk conditions into consideration when deterring if an ADE or an ADWE has occurred. This was work was taken into consideration later on in the thesis during the development of a new and inclusive method of ADE adjudication (chapter 4).

**References Appendix C:**


1. *Medication Overload: America's Other Drug Problem; How the drive to prescribe is harming older Americans.* Lown Institute; April 2019.
2. Ranzani A, Oreni L, Agro M, et al. Burden of Exposure to Potential Interactions Between Antiretroviral and Non-Antiretroviral Medications in a Population of HIV-Positive Patients Aged 50 Years or Older. *J Acquir Immune Defic Syndr.* 2018;78(2):193-201.
3. Marzolini C, Livio F. Prescribing issues in elderly individuals living with HIV. *Expert Review of Clinical Pharmacology.* 2019;12(7):643-659.
4. Ruzicka DJ, Imai K, Takahashi K, Naito T. Greater burden of chronic comorbidities and co-medications among people living with HIV versus people without HIV in Japan: A hospital claims database study. *Journal of Infection and Chemotherapy.* 2019;25(2):89-95.
5. McDonald EG, Wu PE, Rashidi B, et al. The MedSafer Study: A Controlled Trial of an Electronic Decision Support Tool for Deprescribing in Acute Care. *J Am Geriatr Soc.* 2019.
6. Masnoon N, Shakib S, Kalisch-Ellett L, Caughey GE. What is polypharmacy? A systematic review of definitions. *BMC geriatrics.* 2017;17(1):230-230.
7. Maher RL, Hanlon J, Hajjar ER. Clinical consequences of polypharmacy in elderly. *Expert Opin Drug Saf.* 2014;13(1):57-65.
8. McIntyre C, McQuillan R, Bell C, Battistella M. Targeted Deprescribing in an Outpatient Hemodialysis Unit: A Quality Improvement Study to Decrease Polypharmacy. *American Journal of Kidney Diseases.* 2017;70(5):611-618.
9. St Peter WL. Management of Polypharmacy in Dialysis Patients. *Semin Dial.* 2015;28(4):427-432.
10. Kaplan B, Mason NA, Shimp LA, Ascione FJ. Chronic hemodialysis patients. Part I: Characterization and drug-related problems. *The Annals of pharmacotherapy.* 1994;28(3):316-319.
11. Chiu Y-W, Teitelbaum I, Misra M, de Leon EM, Adzize T, Mehrotra R. Pill burden, adherence, hyperphosphatemia, and quality of life in maintenance dialysis patients. *Clin J Am Soc Nephrol.* 2009;4(6):1089-1096.
12. Scott IA, Hilmer SN, Reeve E, et al. Reducing Inappropriate Polypharmacy: The Process of DeprescribingReducing Inappropriate PolypharmacyReducing Inappropriate Polypharmacy. *JAMA Internal Medicine.* 2015;175(5):827-834.
13. Gallagher P, Lang PO, Cherubini A, et al. Prevalence of potentially inappropriate prescribing in an acutely ill population of older patients admitted to six European hospitals. *Eur J Clin Pharmacol.* 2011;67(11):1175.
14. Thompson W, Farrell B. Deprescribing: what is it and what does the evidence tell us? *Can J Hosp Pharm.* 2013;66(3):201-202.
15. O'Mahony D, O'Sullivan D, Byrne S, O'Connor MN, Ryan C, Gallagher P. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. *Age Ageing.* 2015;44(2):213-218.
16. Choosing Wisely Canada Recommendations. https://choosingwiselycanada.org/recommendations/. Accessed April, 15, 2020.

17. American Geriatrics Society Beers Criteria Update Expert P. American Geriatrics Society 2019 Updated AGS Beers Criteria(R) for Potentially Inappropriate Medication Use in Older Adults. *J Am Geriatr Soc.* 2019;67(4):674-694.

**Appendix D. Features of Published studies**

**Manuscript 1:** Adverse Drug Events in Older Adults: Review of Adjudication Methods in Deprescribing Studies

- Featured on the US Deprescribing Research Network Website

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A new review article says it's time to refine current adverse drug event adjudication methods to fit deprescribing studies.

Journal of the American Geriatrics Society

Review Article | Full Access

**Adverse Drug Events in Older Adults: Review of Adjudication Methods in Deprescribing Studies**

Sydney B. Ross, MSc candidate, Peter E. Wu MD, MSc, Anika Abique, MD candidate, Louise Papillon-Ferland BPharm, MSc, Robyn Tamblyn PhD, Todd C. Lee MD, MPH, Emily G. McDonald MD, MSc

First published 06 March 2020 | https://doi.org/10.1111/jgs.16382

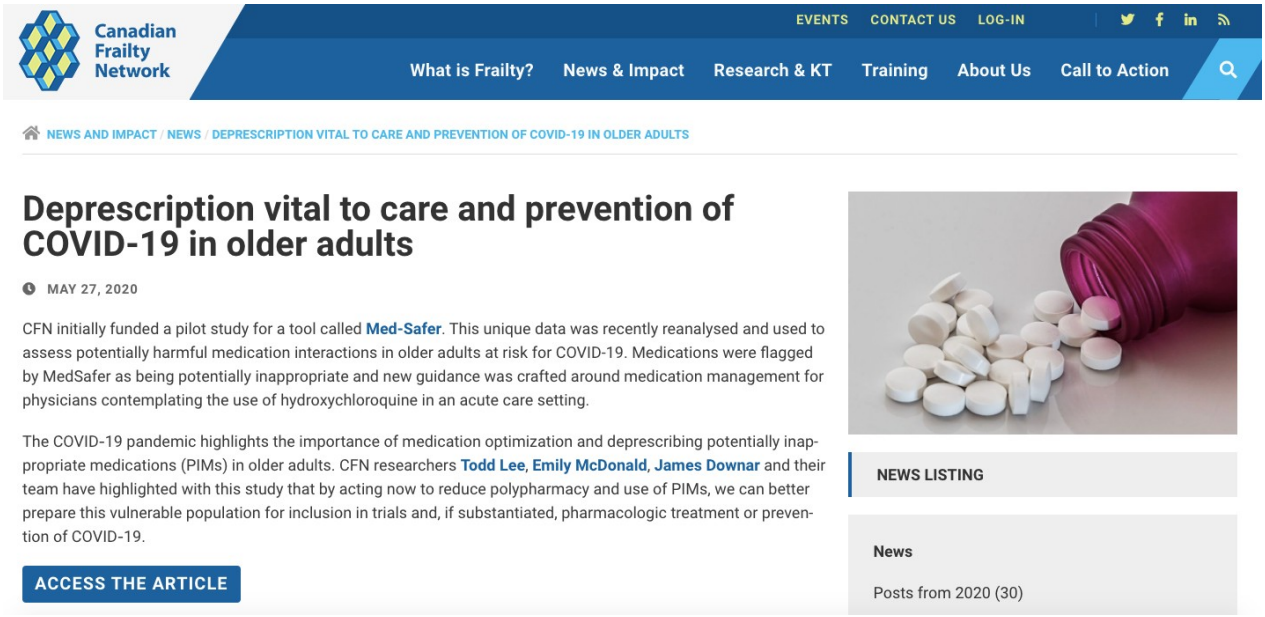
*Ross S, et al. Adverse Drug Events in Older Adults: Review of Adjudication Methods in Deprescribing Studies. J Am Geriatr Soc. 2020; doi: 10.1111/jgs.16382*

A recent review article published in the Journal of the American Geriatrics Society examined adverse drug event (ADE) adjudication methods in deprescribing studies. Ross and colleagues of McGill University in Montreal, Canada reviewed 175 articles and found 10 different types of adjudication methods for identifying ADEs. Among existing methods, the Leape and Bates method and the Naranjo algorithm adapted for drug withdrawal have features that make them better suited than others for evaluating ADEs in studies of deprescribing. However, all methods had several weaknesses including being tailored to detect ADEs for a single medication and generally detecting adverse drug reactions instead of ADEs more broadly. Additionally, no method was developed specifically for deprescribing contexts. The authors emphasize the need for a standardized method that is (1) intuitive for researchers; (2) geared towards clinical judgment; (3) sensitive to time constraints; (4) sensitive to ADEs broadly; (5) able to detect adverse drug withdrawal events (ADEs that arise as a result of discontinuation of a medication, or ADWEs) Standardizing this outcome will allow comparison across future deprescribing interventions.

*Emily McDonald, corresponding author of the manuscript and Assistant Professor of Medicine at McGill University said, "We hope*

**Manuscript 2:** COVID-SAFER: Deprescribing Guidance for Hydroxychloroquine Drug Interactions in Older Adults

- Featured on the Canadian Frailty Network Website

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