Determinants and Outcomes for Long-Term Opioid Use in Hospitalized Patients

Siyana Kurteva
Department of Epidemiology, Biostatistics and Occupational Health
McGill University, Montreal, Canada
July 2021

A thesis submitted to McGill University in partial fulfillment of the requirements of the degree of Doctor of Philosophy in Epidemiology

Abstract

Background

Over the past 20 years, North America has witnessed an opioid epidemic with a major increase in the use of prescription opioids. In Ontario, this epidemic has been characterized by an alarming 250% increase in overdose deaths over the past two decades. In addition to prescription opioids being an important driver of the opioid epidemic, illicit and diverted use have also been shown to be an important contributor to the observed trends of opioid-related deaths. This dramatic rise has also been mirrored by increased rates of opioid-related dependence and addiction. Although opioids are commonly used in management of chronic pain, studies have not demonstrated opioids' therapeutic advantage in comparison to other pharmacological pain treatments. Moreover, chronic opioid use has been associated with numerous adverse health events including serious infections, respiratory arrest, opioid use disorder, and overdose deaths. Patients who are hospitalized represent a population at high risk of chronic opioid use as hospitalization itself may inadvertently be a risk factor for initiating opioid use. Inadequate communication of changes in medications at the time of discharge is a well-established problem. Although medication reconciliation and communication at discharge is a hospital accreditation requirement, adoption rates are notoriously low. As a result, community physicians may continue opioids started in the hospital as they do not readily have access to information about the treatment indication nor the expected duration of therapy.

In randomized trials, opioids have been shown to be associated with increased risk of adverse events but no trial followed patients for longer than 6 months and thus, the body of evidence for assessing the risk profile of different treatment durations with opioids is insufficient. In addition, in observational studies, opioid use has been shown to be associated with an increased risk of opioid-related mortality and morbidity, but the majority of the studies focused on outcomes such as opioid overdose and death. The prevention of other opioid-related adverse events is of equal importance. Furthermore, studies that examined associations between opioid use and other adverse effects have several methodological limitations, including: poor confounding control and failure to adequately model opioid exposure by taking into account the dynamic treatment regimen or complexity of cases with overlapping prescriptions. To date, no study has used flexible modeling techniques to explore the empirical associations of time-varying opioid use

with potential risk of harm to assess how the risk depends on the pattern and duration of previous use and, thus, try to inform a clinically relevant definition of chronic, potentially harmful opioid use.

Objectives

The goal of my doctoral dissertation was to identify potential modifiable determinants of long-term opioid use among hospitalized patients in the period following hospital discharge and assess the risk of post-discharge adverse events associated with various opioid consumption profiles. To achieve this goal, my program of research addressed four specific objectives:

Objective 1: To estimate the incidence and predictors of a) the receipt of an opioid prescription and b) having opioid-related medication errors such as omissions, duplications or dose-changes at transitions from the hospital to the community, and its associated risk of emergency department (ED) visits, re-admissions or death in the 30- and 90-days post-discharge.

Objective 2: To estimate a) the proportion of hospitalized patients on long-term opioid therapy, and b) identify modifiable patient-, prescriber- and system-level risk factors for long-term prescription opioid use compared to episodic use in the one year after hospital discharge.

Objective 3: To assess the impact of treatment duration and dose of opioid use on the risk of ED visits and hospital re-admissions in the one year following hospital admission, and to determine if the risk was modified by treatment indication, age or concurrent benzodiazepines use.

Objective 4: To determine if the risk of adverse events varied as a function of current and past opioid use, and if the results and conclusions varied depending on the methodological approach used to model time-varying opioid exposures.

Data sources

Multiple sources of data were assembled and linked to address the four objectives of my research program. A cohort of medical and surgical hospitalized patients who were enrolled as part of a cluster randomized controlled trial on medication reconciliation was used to address the study objectives. For three of the studies, patients needed to fill at least one opioid prescription during

the 90 days following their hospital discharge. For each patient, demographic, clinical, health care service use and prescription claims have been retrieved from the admission note as well as provincial health care administrative databases (RAMQ medical services and RAMQ prescription claims data) in the year prior to and after the hospitalization, for which the patient was enrolled. Data on hospital discharge experiences were obtained via telephone interview 30-days post-discharge with trained interviewers. This is one of the only data sources in the world that links information on medication use prior to admission, during the hospital stay, medications prescribed at discharge, and medications dispensed in the community post-discharge.

Methods and results

Manuscript 1: In this paper, I estimated the incidence of and characteristics associated with the receipt of an opioid prescription and opioid-related medication errors (ME) at hospital discharge. In addition, I also determined the rates of adverse drug events and risk of ED visits, readmissions or death in the immediate post-discharge period. Overall, I found that rates of MEs were higher in handwritten prescriptions compared to the computer-based reconciliation discharge prescriptions (20.6% vs 1.2%). Computer-based prescriptions were associated with a 69% lower risk of opioid-related MEs (adjusted odds ratio [aOR]: 0.31, 95% CI: 0.14 – 0.65)) and 63% lower risk of receiving an opioid prescription. In addition, opioid-related MEs were associated with a two-fold increase in the risk of healthcare utilization in the 30-days post-discharge period (aOR: 2.32, 95% CI:1.24 – 4.32)).

Manuscript 2: In this paper, I examined patient-, medication- and system-level characteristics associated with the development of long-term opioid therapy (LTOT). LTOT was defined as time-varying cumulative opioid duration of ≥ 60 days. A multivariable Cox Proportional Hazards (PH) model was used to determine which factors were associated with the occurrence of LTOT. I found that overall, 22.4% of the 1511 study patients who filled an opioid prescription in the 90 days' post-discharge were classified as LTOT. Having no drug copay status (adjusted hazard ratio (aHR) 1.91, 95% CI: 1.40 – 2.60), being a previous LTOT user (aHR 6.05, 95% CI: 4.22 – 8.68) or having history of benzodiazepine use (aHR 1.43, 95% CI: 1.12 – 1.83) in the year prior to admission were all associated with an increased likelihood of LTOT. Cardiothoracic surgical patients had a 40% lower risk of LTOT (aHR 0.55, 95% CI: 0.31 – 0.96) as compared to medical patients. In addition, initial opioid dispensation of > 90 MME (morphine milligram equivalent) was also associated with

higher likelihood of LTOT (hare 2.08, 95% CI: 1.17 – 3.69).

Manuscript 3: In this paper, I conducted an observational cohort study to assess the risk of opioid-related re-admissions or ED visits associated with various patterns of opioid type, duration and dose. I also determined whether the risk was modified by treatment indication, age or benzodiazepines use. I constructed several time-varying measures of opioid use including current use, daily dose, cumulative and continuous duration of use, and type of opioid. I found that among those with at least one opioid dispensation within 90-day post' discharge, 16% (n = 241) experienced an opioid-related ED visit, re-admission or death. Results from marginal structural Cox PH models showed more than a two-fold increase in the risk of opioid-related adverse events associated with a cumulative opioid duration of > 90 days (adjusted hazard ratio (hare) of 2.56 (95% CI:1.25 – 5.27), compared to 1-30 days. There was a three-fold increase in risk with a mean daily dose of ≥ 90 morphine milligram equivalent (MME), aHR of 3.24 (95% CI: 1.43-7.35) compared to users of ≤50 MME.

Manuscript 4: In this paper, I investigated how novel modelling techniques and the use of different methodological approaches to measure time-varying opioid exposures could improve our understanding of the how opioid-related adverse events may vary depending on the current and past opioid use. I used marginal structural Cox PH models and their flexible extensions, and a weighted cumulative exposure model to address the objectives for this study. I found that for each exposure metric, the flexible modelling improved the models' fit to data. Overall, the results indicate that both non-linear effects of continuous exposure metrics and weighted cumulative effects of past use or doses should be considered when assessing how the risks vary depending on the opioid exposure pattern. The estimated non-linear effect of cumulative opioid duration shows that the risk of opioid-related adverse events increases gradually with total past exposure duration increasing to about 50-60 days of cumulative use. The results from the weighted cumulative exposure models suggested that the risk is mostly affected by use in the past 30 to 40 day.

Conclusions

This thesis found that hospitalized medical patients, previous LTOT, having previously used benzodiazepines and having an initial post-discharge opioid dispensation of >90 MME were associated with an increased risk of receiving an opioid prescription at discharge and becoming a long-term opioid user in the one year post-discharge. These results could be used to help stratify patients who are at high-risk of continuing opioids beyond clinical practice guideline recommendations and inform policies and intervention programs to curb excessive opioid prescribing. The thesis also provided evidence of increased risk of opioid-related adverse events with prolonged opioid duration and high doses. The results of the final study also provided an insight into the mechanism underlying potential adverse events of opioid exposure by assessing the impact of recency of exposure on the risk of acute healthcare events. The results from my doctoral work generated important scientific knowledge for the development of effective prevention strategies to minimize long-term opioid dependency and reduce the risk of opioid-related morbidity among the vulnerable population of hospitalized medical and surgical patients.

Résumé

Contexte

Au cours des 20 dernières années, l'Amérique du Nord a été témoin d'une épidémie d'opioïdes avec une augmentation importante de l'utilisation d'opioïdes sur ordonnance. En Ontario, cette épidémie a entraîné une augmentation alarmante de 250% des décès par surdose au cours des deux dernières décennies. En plus du fait que les opioïdes sur ordonnance sont un moteur important de l'épidémie d'opioïdes, il a également été démontré que l'usage illicite et le détournement des opioïde prescrits contribue grandement aux tendances observées des décès liés aux opioïdes. Cette augmentation dramatique s'est également reflétée par une augmentation des taux de dépendance et de toxicomanie liées aux opioïdes. Bien que les opioïdes soient couramment utilisés dans la prise en charge de la douleur chronique, les études n'ont pas démontré l'avantage thérapeutique des opioïdes par rapport à d'autres traitements pharmacologiques de la douleur. De plus, la consommation chronique d'opioïdes a été associée à de nombreux événements indésirables pour la santé, notamment des infections graves, un arrêt respiratoire, une dépendance et des décès par surdose. Les patients hospitalisés représentent une population à haut risque d'utilisation chronique d'opioïdes, car l'hospitalisation elle-même peut, par inadvertance, être un facteur de risque d'initier l'utilisation d'opioïdes. La communication inadéquate des changements de médicaments au moment de la sortie de l'hôpital est un problème bien établi. Bien que le bilan comparatif des médicaments et la communication à la sortie soient une exigence d'accréditation des hôpitaux, les taux d'adoption sont bas. Par conséquent, les médecins communautaires peuvent continuer à utiliser les opioïdes commencés à l'hôpital car ils n'ont pas facilement accès aux informations sur l'indication du traitement ni sur la durée prévue du traitement.

Dans les essais randomisés, il a été démontré que les opioïdes étaient associés à un risque accru d'événements indésirables, mais aucun essai n'a suivi les patients pendant plus de 6 mois et, par conséquent, l'ensemble des preuves permettant d'évaluer le profil de risque des différentes durées de traitement par opioïdes est insuffisant. De plus, dans les études observationnelles, il a été démontré que l'utilisation d'opioïdes était associée à un risque accru de mortalité et de morbidité liées aux opioïdes, mais la majorité des études se sont concentrées sur des résultats tels que la surdose d'opioïdes et la mort. La prévention d'autres événements indésirables liés aux opioïdes

est d'une importance égale. De plus, les études qui ont examiné les associations entre l'utilisation d'opioïdes et d'autres effets indésirables présentent plusieurs limites méthodologiques, notamment: un mauvais contrôle des facteurs de confusion, l'incapacité à modéliser adéquatement l'exposition aux opioïdes en tenant compte du schéma thérapeutique dynamique ou de la complexité des cas avec des prise en compte des risques concurrents. À ce jour, aucune étude n'a utilisé des techniques de modélisation flexibles pour explorer les associations empiriques de l'utilisation d'opioïdes variant dans le temps avec le risque potentiel des effets indésirables, afin d'évaluer en quoi le risque dépend du modèle et de la durée de l'utilisation précédente et, par conséquent, essayer d'informer un contexte cliniquement pertinent à la définition de l'usage chronique d'opioïdes.

Objectifs

L'objectif général de mon travail de doctorat était de renforcer la recherche sur l'innocuité des opioïdes. Plus précisément, cela a été fait en identifiant les déterminants modifiables potentiels de l'utilisation d'opioïdes à long terme chez les patients hospitalisés au cours de la période suivant la sortie de l'hôpital et en évaluant l'impact de divers profils de consommation d'opioïdes sur le risque des patients d'événements de soins de santé aigus après la sortie à l'aide de plusieurs sources de données. Pour atteindre cet objectif, mon programme de recherche visait quatre objectifs spécifiques:

Objectif 1: Estimer l'incidence et les prédicteurs de a) la réception d'une ordonnance d'opioïdes et b) des erreurs de médication liées aux opioïdes telles que des omissions, des duplications ou des changements de dose lors des transitions de l'hôpital à la communauté, et les taux associés de événements indésirables liés aux médicaments et risque de visites d'urgence, de réadmissions ou de décès dans les 30 et 90 jours suivant le congé.

Objectif 2: Estimer a) la proportion de patients hospitalisés sous traitement opioïde à long terme, et b) incorporer les informations cliniques et administratives sur les palourdes sur ordonnance pour identifier les facteurs de risque modifiables au niveau du patient, du prescripteur et du système pour l'utilisation d'opioïdes sur ordonnance à long terme par rapport à utilisation épisodique dans l'année suivant la sortie de l'hôpital.

Objectif 3: Évaluer l'impact de la durée du traitement et de la dose d'utilisation d'opioïdes sur le risque de visites aux urgences et de réadmissions à l'hôpital dans l'année suivant l'hospitalisation, et de déterminer si le risque a été modifié par l'indication du traitement, l'âge ou utilisation de benzodiazépines.

Objectif 4: Appliquer une modélisation statistique flexible pour déterminer si le risque d'événements indésirables variait en fonction de l'utilisation actuelle et passée d'opioïdes. Un objectif secondaire était de déterminer si les résultats et les conclusions variaient selon l'approche méthodologique utilisée pour modéliser les expositions aux opioïdes variant dans le temps.

Source de données

De multiples banque de données ont été rassemblées et liées pour répondre aux quatre objectifs de mon programme de recherche. Une cohorte de patients hospitalisés en médecine et en chirurgie qui ont été recrutés dans le cadre d'un essai contrôlé randomisé en grappes sur le rapprochement des médicaments a été utilisée pour atteindre les objectifs de l'étude. Pour trois des études, les patients devaient remplir au moins une prescription d'opioïdes au cours des 90 jours suivant leur sortie de l'hôpital. Pour chaque patient, les demandes de règlement démographique, clinique, d'utilisation des services de santé et d'ordonnance ont été extraites de la note d'admission ainsi que des bases de données administratives provinciales des soins de santé (RAMQ services médicaux et demandes de règlement RAMQ) au cours de l'année précédant et suivant l'hospitalisation, pour lequel le patient a été inscrit. Les données sur les expériences de sortie de l'hôpital ont été obtenues par entrevue téléphonique 30 jours après la sortie de l'hôpital avec des intervieweurs spécialement formés. Il s'agit de l'une des seules sources de données au monde qui relie les informations sur l'utilisation des médicaments avant l'admission, pendant le séjour à l'hôpital, les médicaments prescrits à la sortie et les médicaments dispensés dans la communauté après la sortie.

Méthodes et résultats

Manuscrit 1: Dans cet article, j'ai estimé l'incidence et les variables associées à la réception d'une ordonnance d'opioïdes et aux erreurs de médication (EM) liées aux opioïdes à la sortie de

l'hôpital. De plus, j'ai également déterminé les taux d'événements indésirables liés aux médicaments et le risque de visites à l'urgence, de réadmissions ou de décès dans la période suivant immédiatement le congé. Dans l'ensemble, j'ai constaté que les taux d'EM étaient plus élevés dans les ordonnances manuscrites sur papier que dans les ordonnances informatisées (20,6% contre 1,2%). Les ordonnances informatisées étaient associées à un risque 69% plus faible d'EM liées aux opioïdes (rapport de cotes ajusté [aOR]: 0,31, IC à 95%: 0,14 - 0,65)) et à 63% moins de risque de recevoir une prescription d'opioïdes. De plus, les EM liées aux opioïdes étaient associées à une multiplication par deux du risque d'utilisation des soins de santé dans les 30 jours suivant la sortie de l'hôpital (aOR: 2,32, IC à 95%: 1,24 - 4,32)).

Manuscrit 2: Dans cet article, j'ai examiné les caractéristiques au niveau des patients, des médicaments et du système associées au développement de l'utilisation à long terme d'opioïdes (LTU). Le LTU était défini comme la durée cumulative des opioïdes variant dans le temps ≥ 60 jours. Un modèle de risques proportionnels (PH) de Cox à plusieurs variables a été utilisé pour déterminer les facteurs associés à la survenue du CLD. J'ai constaté que dans l'ensemble, 22,4% des 1511 patients de l'étude qui ont rempli une ordonnance d'opioïdes dans les 90 jours suivant leur congé ont été classés comme LTU. Une prescription active d'opioïdes à l'admission (aHR 2,29, IC 95%: 1,64 - 3,21), l'utilisation d'opioïdes (aHR 1,78, IC 95%: 1,23 - 2,58) ou l'utilisation d'antidépresseurs (aHR 1,62, IC 95%: 1,10 - 2,38) dans le l'année précédant l'admission étaient associés à une probabilité accrue de CLD. Les patients chirurgicaux avaient un risque de LTU 50% inférieur (aHR 0,50, IC à 95%: 0,29 - 0,88) par rapport aux patients médicaux. De plus, les CLD étaient plus susceptibles d'avoir une prescription d'opioïdes après le congé de> 90 MME et un approvisionnement> 7 jours (aHR 2,19, IC à 95%: 1,20 - 4,00, aHR 1,34, IC à 95%: 1,05 - 1,71)).

Manuscrit 3: Dans cet article, j'ai mené une étude de cohorte observationnelle pour évaluer le risque d'événements de santé aigus tels qu'une hospitalisation liée aux opioïdes ou une visite à l'urgence associée à divers schémas de type, de durée et de dose d'opioïdes. J'ai également déterminé si le risque était modifié par l'indication du traitement. J'ai construit plusieurs mesures de la consommation d'opioïdes variant dans le temps, notamment l'utilisation actuelle, la dose quotidienne, la durée cumulative et continue et le type d'opioïde. J'ai constaté que parmi les

personnes bénéficiant d'au moins une dispensation d'opioïdes dans les 90 jours suivant leur congé, 16% (n = 241) ont subi une visite aux urgences, une réadmission ou un décès lié aux opiacés. Les résultats des modèles de Cox PH structurels marginaux ont montré une augmentation de plus du double du risque d'événements indésirables liés aux opioïdes associés à une durée cumulative d'opioïdes> 90 jours (rapport de risque ajusté (aHR) de 2,56 (IC à 95%: 1,25 - 5,27), comparativement à 1 à 30 jours. Le risque a été multiplié par trois avec une dose quotidienne moyenne ≥ 90 équivalents de morphine en milligramme (MME), aHR de 3,24 (IC à 95%: 1,43-7,35) par rapport aux utilisateurs de ≤50 MME.

Manuscrit 4: Dans cet article, j'ai étudié comment de nouvelles techniques de modélisation et l'utilisation de différentes approches méthodologiques pour mesurer les expositions aux opioïdes variant dans le temps pourraient améliorer notre compréhension de la façon dont les événements indésirables liés aux opioïdes peuvent varier en fonction de l'utilisation actuelle et passée d'opioïdes. J'ai également tenté de définir un seuil cliniquement pertinent pour l'utilisation d'opioïdes à haut risque en utilisant une modélisation non linéaire flexible des fonctions de réponse à la dose et à la durée des opioïdes. J'ai utilisé des modèles de PH structurels marginaux de Cox et leurs extensions flexibles, ainsi qu'un modèle d'exposition cumulative pondérée pour répondre aux objectifs de cette étude. J'ai constaté que pour chaque métrique d'exposition, la modélisation flexible améliorait l'ajustement des modèles aux données. Dans l'ensemble, les résultats indiquent que les effets non linéaires des paramètres d'exposition continue et les effets cumulatifs pondérés de l'utilisation ou des doses passées doivent être pris en compte lors de l'évaluation de la variation des risques en fonction du profil d'exposition aux opioïdes. L'effet non linéaire estimé de la durée cumulative des opioïdes montre que le risque d'événements indésirables liés aux opioïdes augmente progressivement, la durée totale de l'exposition passée passant à environ 50 à 60 jours d'utilisation cumulative. Les résultats des modèles d'exposition cumulée pondérée suggèrent que le risque est principalement affecté par l'utilisation au cours des 30 à 40 derniers jours, avec un doublement du risque d'exposition continue au cours du mois dernier.

Conclusions

Cette thèse a révélé que les patients médicaux hospitalisés, ayant déjà utilisé des benzodiazépines et ayant une dispensation initiale d'opioïdes après la sortie de > 90 MME étaient associés à un risque accru de recevoir une prescription d'opioïdes à la sortie de l'hôpital et de devenir un utilisateur d'opioïdes à long terme dans l'année suivant la sortie. Ces résultats pourraient être utilisés pour aider à identifier les patients à haut risque de continuer à prendre des opioïdes au-delà des recommandations des lignes directrices et éclairer les politiques et les programmes d'intervention pour freiner la prescription excessive d'opioïdes. La thèse a également fourni des preuves d'un risque accru d'événements indésirables liés aux opioïdes avec une durée d'utilisation prolongée des opioïdes et des doses élevées. Les résultats de l'étude finale ont également fourni un aperçu méthodologique du mécanisme sous-jacent des événements indésirables potentiels de l'exposition aux opioïdes en évaluant l'impact de la récence de l'exposition sur le risque d'événements de santé aigus. Les résultats de mon travail de doctorat ont généré des connaissances scientifiques importantes pour le développement de stratégies de prévention efficaces afin de minimiser la dépendance aux opioïdes à long terme et de réduire le risque de morbidité liée aux opioïdes parmi la population vulnérable de patients hospitalisés en médecine et en chirurgie.

Acknowledgements

This has been a long, challenging and yet, a spectacularly fulfilling experience. I can confidently say that I have never learned so much in such a short period of time. Before embarking on the journey of becoming an epidemiologist, I hardly knew of its existence as a field of research. A path I never imagined possible became the most comfortable direction I could have hoped to follow. I feel beyond fortunate and blessed to have met and worked with so many fantastic people. I would like to take a moment to express my appreciation to those who helped me succeed along the way.

First, I want to acknowledge my supervisor, Dr. Robyn Tamblyn, who has been so instrumental at every level in my development as a professional. Dr. Tamblyn - a lot of my inspiration, drive, and insight for the work and research I did over the past five years has come from you. Thank you for your down-to-earth approach to supervising. You truly gave me a perfect balance between academic support and freedom to pursue my research interests. I also appreciate your generous financial support throughout my PhD, allowing me to attend multiple national and international conferences, which helped advance my professional and leadership skills and gave me an opportunity for career information and inspiration. I can confidently say that because of the training I received from you, I feel equipped and empowered to step into this next stage of my career and work towards building the future of my dreams.

I would like to thank my thesis committee members, Drs. Michal Abrahamowicz and Tara Gomes for their tireless reviewing and bottomless patience throughout the process. Dr. Abrahamowicz - thank you for your enormously insightful and rigorous feedback. Your dedication to the methodological side of this project has truly changed my way of understanding and appreciating high-quality research. Dr. Gomes, thank you for all your clear, concise and practical suggestions that you provided to improve the thesis as well as for always being the first to get back to me with your feedback.

I would also like to thank Dr. Meguerditchian for his clinical input, support and encouragement throughout my PhD. As a collaborator, you have exceeded all my expectations and provided me with opportunities for growth, for which I am deeply appreciative.

I want to thank Ms. Marie-Eve Beauchamp and Ms.Teresa Moraga. Ms. Beauchamp, thank you for all your methodological input, countless hours of trouble shooting and endless patience with my programming skills. Ms. Moraga, thank you for your technical, analytical and continued support throughout my thesis.

I want to express my special gratitude for Andre Yves Gagnon and Katherine Haydes for all their administrative support throughout my Master's and PhD. I also want to acknowledge the whole team at the Clinical and Health Informatics Research group, who has been of an incredible support to me. Ms. Rosalba Pupo, thank you for being my coffee supplier throughout my last few years of PhD and for being a constant support for all my administrative, funding and all other unrelated questions. Thank you to Ms. Patricia Pluffe and Ms. Lidia Rizzo for outstandingly handling all my meeting requests, dealing with all my letters of support and travel expense reports. Your sweet demeanour and professionalism have no rival. I want to also acknowledge Lina Petrella, who was the first person I worked with at the lab. Her guidance, patience and above all, kindness, helped me believe in my abilities and confidence as a researcher prior to my application for graduate school.

I want to thank my parents for their enormous sacrifice, both personally and professionally, when they made the hard decision to immigrate to Canada. Their love and dedication to me has carried me through all this time.

Lastly, I would want to acknowledge two very special people in my life, Kristina Cummings and Miranda Gallo. The final year of my PhD has been one of the most mentally challenging years in my life. Through panic disorder, depression and suicidal thoughts, you truly were the hands and feet of Jesus for me. You were willing to step away from your personal comfort to help and support me when I most needed it, and for this I will be forever grateful.

Above all, I thank God for all His favour and for giving me the opportunity to study at McGill. His endless love is my anchor.

Contributions of authors

The findings of this thesis were reported in four manuscripts:

Manuscript 1: Kurteva S, Habib B, Moraga T, Tamblyn R. Incidence and Variables Associated With Inconsistencies in Opioid Prescribing at Hospital Discharge and Its Associated Adverse Drug Outcomes. *Value Health*. 2021 Feb;24(2):147-157. doi: 10.1016/j.jval.2020.07.015. Epub 2020 Nov 10. PMID: 33518021.

Manuscript 2: Kurteva S, Abrahamowicz M, Weir D, Gomes T, Tamblyn R. Determinants of Long-Term Opioid Use in Hospitalized Patients.

Manuscript 3: Kurteva S, Abrahamowicz M, Gomes T, Tamblyn R. Association of Opioid Consumption Profiles After Hospitalization With Risk of Adverse Health Care Events. *JAMA Netw Open*. 2021 May 3;4(5):e218782. doi: 10.1001/jamanetworkopen.2021.8782. PMID: 34003273.

Manuscript 4: Kurteva S, Abrahamowicz M, Beauchamp ME, Tamblyn R. Flexible modeling of opioid exposure provides new insights in its association with adverse outcomes.

The objectives of these manuscripts were completed and developed under the supervision of Dr. Robyn Tamblyn. Through constant collaboration with my co-authors, I conceptualized and designed this program of research. For all studies, I was responsible for the database management and linkage to construct the final Régie de l'assurance maladie du Québec datasets, conducted the statistical analyses, interpreted the results, and drafted the final manuscripts.

Dr. Robyn Tamblyn is a Distinguished James McGill Chair, a Professor in the Department of Medicine and the Department of Epidemiology, Biostatistics and Occupational Heath at McGill University, a Scientist at the Research Institute of the McGill University Health Centre, the

Director of Clinical Epidemiology at McGill University, and the Scientific Director of the Clinical and Health Informatics Research Group. Dr. Tamblyn provided substantive, methodological guidance and feedback, assisted with the interpretation of the results, and provided feedback on all manuscripts. Dr. Tamblyn also provided data from the RightRx clinical trial and the RAMQ databases.

Dr. Michal Abrahamowicz is a James McGill Professor in the Department of Epidemiology, Biostatistics, and Occupational Health at McGill University. Dr. Abrahamowicz provided support regarding the statistical methodology, substantive and editorial feedback, and interpretation of results in manuscript two, three and four.

Dr. Tara Gomes is an Assistant Professor at the Institute of Health Policy Management and Evaluation at the University of Toronto, a Scientist at the Li Ka Shing Knowledge Institute of St. Michael's Hospital and ICES in Toronto. She provided substantive, methodological feedback, input on the interpretation of the results as well as editorial feedback on objectives two and three.

Ms. Marie-Eve Beauchamp is an Analyst at the Centre for Outcomes Research and Evaluation. She provided methodological guidance, analytical support and editorial feedback on the fourth manuscript.

Ms. Teresa Moraga is an Analyst at the Clinical and Health Informatics Research Group. She provided analytical help and editorial feedback on the first manuscript.

Ms. Bettina Habib is a Research Coordinator at the Clinical and Health Informatics Research Group. She provided feedback on the first manuscript.

Dr. Daniala Weir is an Assistant Professor in the Division of Pharmacoepidemiology and Clinical Pharmacology at Utrecht University, Netherlands. She provided editorial clinical and methodological guidance as well as feedback on the second manuscript.

Statement of originality

The work in this thesis represents original and distinct contributions that advance knowledge about optimal opioid treatment durations and doses and illustrates novel analytic methods to properly measure time-varying opioid exposures and its associated risk with adverse outcomes. Manuscript 1 provides unique knowledge on prevalence of medication errors, measured by administrative and clinical data, associated with opioid prescriptions written at hospital discharge. It further provides insight into predictors of these prescriptions in addition to exploring risk factor associated with each type of medication error. Manuscript 2 is the first study to use an empirically-derived definition of long-term opioid use and study its association with various patient-, prescriber- and system-related characteristics. Manuscript 3 is one of the only studies to use advanced analytic techniques to measure opioid use, and account and adjust for the presence of time-varying medical conditions and medication history, which are expected to change over the course of patient therapy. In addition, it explores how the variation in patient opioid consumption changes based on treatment indication and various patters of use, including cumulative and continuous opioid exposures, as well as opioid dose. Finally, Manuscript 4 is the first study to use flexible spline-based extensions of the Cox Proportional Hazards models to provide additional insight into the mechanism linking opioid use to the risk of adverse events. The results from the thesis further our understanding of how risks vary depending on the duration of opioid therapy and/or opioid consumption patterns. This knowledge is instrumental in developing evidence-based prescribing guidelines and public health strategies for addressing the growing problem of the opioid epidemic.

Statement of financial support

I am beyond grateful for all the financial support I received over the course of my doctoral studies at McGill University. I was grateful to receive funding from the Rossy Cancer Network Kuok Scholarship for the first two years of my doctoral studies. The third year was jointly funded by the CIHR-Drug Safety and Effectiveness Cross-Disciplinary Training Program (DSECT) and the Burke Scholarship (Faculty of Medicine, McGill University). In the final year of my graduate studies, I was fortunate to receive a doctoral award from the Fonds de Recherché du Québec-Santé (FRQS). Throughout all my years as a doctoral student, Dr. Tamblyn has graciously supplemented my stipends.

I am also grateful for all the travel funding I received, which enabled me to present my thesis work at international and national conferences. In 2018 and 2019, I presented preliminary results from objective three at two international conferences: the International Population Data Linkage Network, which granted me a travel award and the International Conference on Pharmacoepidemiology and Therapeutic Risk Management, from which I received funding from the conference organizers and the Canadian Institutes of Health Research. In 2020, I received an Scholar-in-Training Award from the American Association for Cancer Research to present findings from third manuscript at their annual meeting. The same year I also received funding from the Canadian Agency for Drugs and Technologies in Health to present results from the first objective of the thesis. In 2021, I presented findings from the fourth manuscript at the International Society for Health Economics and Outcomes Research virtual conference as well as the 2020 International Society for Clinical Biostatistics meeting.

Table of contents

List of figures

List of tables

List of appendices

1. Introduction

1.1. Opioids in pain management

Prescription opioids are an important contributor to the public health crisis of opioid addiction and mortality in North America. [1] Over the past 20 years, increases in opioid prescribing rates and average prescription volumes have been documented in both the United States and Canada. [1-3] Canada is one of the world's second-largest consumer of opioids when measured using defined daily doses and the highest when considering morphine equivalents dispensed, with more than 800 morphine equivalents per capita worldwide in 2015. [4,5] Although opioid analgesics remain the treatment of choice for the management of moderate-to-severe cancer pain [6], substantial increases in the prescription of opioids for chronic non-cancer pain have been documented in North America, with some studies suggesting a nearly 100% increase over the past decade. These temporal trends in prescription opioid use have been accompanied by marked increases in opioid-related mortality and morbidity. [7,8] Opioid use is now the leading cause of accidental death in Canada with drug overdose deaths surpassing motor vehicle collisions. [9] In addition to prescription opioids being an important driver of the opioid epidemic in North America, illicit and diverted opioid use have also been shown to be an important contributor to the observed trends of opioid-related deaths. [10,11] In Canada, the rate of opioid-related deaths involving non-prescribed fentanyl has increased substantially between 2013 and 2016, not only among people being prescribed opioids but also among those with no evidence of prescription opioid use. Chronic pain, the main indication for opioid use, is common, with survey estimates of 20 and 30% in the general population. [12-14] Chronic postsurgical pain is also common, with an incidence ranging from 15% to 58%, depending on the type of surgical procedure. [15,16] However, despite opioids being increasingly used to treat pain, there is uncertainty about their long-term benefits. A recent meta-analysis of randomized controlled trials of opioids for chronic non-cancer pain found that there were similar improvements in pain and physical functioning for opioids with nonopioid alternatives. [17] Moreover with longer trials, there was less pain relief with opioids which was attributed to opioid tolerance or opioid-induced hyperalgesia. [17] The reduction in the efficacy of opioids in pain management with long term use may contribute to an escalation

in the dose and potency of opioids which, in turn, may augment the risk of harm with long term use. Yet, no trial of opioid efficacy followed patients for longer than 6 months [18], whereas most observational studies only examine associations with dose and duration of initial opioid prescriptions. [19-21] *Thus, the body of evidence assessing the risk profile of different treatment durations and dose with opioids is insufficient.*

1.2. Prevalence of high-dose opioid prescribing

Despite the publication of multiple clinical guidelines to optimize the use of opioids and minimize risk of harm and dependency, studies have shown that only 40 to 60 % of chronic non-cancer pain management in primary care settings is compliant with guideline recommendations. [12] A time-series analysis in Ontario, Canada, from 2003 to 2014, examined the impact of opioid prescribing guidelines on prevalence of high-dose opioid prescribing (exceeding 200 mg morphine equivalent (MME) doses daily) and rates of hospitalizations, but found no change in prescribing or rates of fatal opioid overdose after implementation of these guidelines. [22] Moreover, between 2006 and 2011, more than 30 million tablets or patches of high-dose opioids were dispensed in Canada annually, despite recommendation to avoid high-dose opioid therapy in patients. A population-based study using data from Ontario found that 40% of opioids prescribed to new opioid users for the treatment of postsurgical pain were generally more than 50 MME, and at least 25% were prescribed 90 MME or more. [23] One third of patients treated for non-cancer pain received initial opioid prescription durations of >7 days. Findings from the literature confirm that the majority of opioid initiations are for acute indications (dental, postsurgical, trauma-indicated). [23,24] Thus, prescription opioids do continue to play a role in the opioid epidemic, despite the fact that more recent climbs in overdose deaths are also attributable to non-prescription opioids. [10] There is significant provincial variation, with the highest rates of high dose prescribing observed in Ontario and Alberta. [25] What is not known is whether high-dose opioids are being prescribed for new patients, or higher prescribed doses and longer term use is occurring for existing patients, or a combination of these factors. [22,26] In addition, there has been a debate and uncertainty surrounding the definition of a "high" opioid dose as well as how the risk of opioid-related adverse events varies with lower doses and the degree to which the risk changes based on the clinical indication for opioids. [27] *Understanding the risk associated with*

extended treatment duration, which, in turn, may lead to opioid dose escalations is important and needs to be elucidated to inform clinical and public health policies.

1.3. Prescription opioids and rates of emergency department visits/hospitalizations

Minimizing unnecessary healthcare has become a focal point of value-based health care systems to optimize health and reduce healthcare-related costs. [28-30] Emergency department (ED) visits and hospital admissions for health problems that may have either been avoided entirely or effectively managed in other outpatient or community settings are increasingly targeted. [29,31,32] As prescription opioid use and overdose has steadily increased over the past two decades, a dramatic increase in hospitalizations attributed to opioid poisonings has been witnessed. [33] In Ontario, there were significant increases in both high-dose opioid prescribing and opioid-related hospital visits between 2003 and 2014. [25] Among the recipients of long- acting opioid, 40% received doses exceeding 200 mg of MME doses, whereas 20% received > 400 mg MME. Recent studies have also demonstrated that opioid-related overdose risk is dose-dependent, with higher opioid dosages associated with increased overdose risk. [2,22,25]A recent report from the Canadian Institute of Health Information reported that opioid-related toxicity accounts for 13 hospitalizations every day in Canada. [34] Also, the annual rates of hospitalizations vary across provinces and territories, from a high of 21% in Saskatchewan to a low of about 10% in Quebec. However, between 2006 and 2016, Quebec has witnessed increases in the prevalence of opioid use in people aged 55 and older as well as in the use of high potency opioids, such as hydromorphone, and mean duration of treatment across all age groups. [35] *Thus, opioid use places a significant burden on the healthcare system and the association between opioid use patterns and the risk of opioid-related ED visits and re-admissions needs to be elucidated.*

1.4. High-dose opioid prescribing and its related morbidity and mortality

A growing body of evidence documents multiple specific adverse effects associated with opioid therapy. [36,37] These include dependence and addiction [2,27,38], fractures [36,39,40], and other events requiring hospitalization [36], overdose [26,41-43] and death [27,42,43], especially among older adults treated for pain. [37,40,44,45] Moreover, mortality risk has also been associated with chronic use of high doses of opioids. [8] Daily doses exceeding 100 MME have been associated with a 9-fold increased risk of overdose and a doubling risk of opioid-related death compared to lower doses.

[26] Moreover, observational studies demonstrated important dose-response effects of opioids on adverse events such as increased risks of fractures, road trauma, and opioid-related mortality. [39,42,46,47] A main concern related to LTOT is that patients become physically dependent on opioids, experiencing opioid withdrawal symptoms upon treatment cessation, which can lead to continued opioid therapy as an attempt to resolve withdrawal symptoms. [48] Review of high-quality evidence from 36 studies including 14,440 patients demonstrated that, when compared to continued non-opioid pharmacologic therapy, opioid add-on therapy increased the rate of opioid-related gastrointestinal adverse events in adult patients with chronic non-cancer pain. [17,49] *Therefore, it is important to understand the risk of opioid-related adverse events associated with different opioid consumption patterns in order to reduce opiod-related morbidity and mortality.*

1.5. Defining long-term opioid use

The Centers for Disease Control and Prevention (CDC) guideline defines long-term opioid therapy (LTOT) as use of opioids on most days for more than 3 months. [50] However, studies on opioids safety have used different definitions and follow-up periods to measure LTOT. [51,52] A recent 2019 systematic review on chronic opioid therapy found that 50% of studies define LTOT as more than three months of cumulative opioid duration of opioid use, as per the CDC guideline and less than 5% used an alternative cut-off of 60 days or less. [53] In addition, the authors pointed out that the widely-used most common LTOT definition has been considered conservative and the most recent literature (after 2016) is trending toward shorter duration criteria. [53] The results from their systematic review identified 41 unique variations of definitions across the 34 studies they included in the review, which differed by cumulative duration of opioid use for LTOT, the time points used to define LTOT, and consistency of opioid use. [53] Identifying continual use is important because it more closely reflects actual opioid therapy characteristics, compared with fills at various time points during follow-up. While the adoption of consistent definition criteria across studies has been recommended, the variability in defining LTOT highlights the lack of empirical evidence on the opioid treatment duration that may represent an increase in harm over episodic use. *Observational studies, quantifying the risk of harm associated with various opioid treatment durations are needed.*

1.6. Risk factors for long-term opioid use and opioid misuse

Hospitalization: Implementing a treatment strategy for pain control poses many challenges for hospitalized patients. Inadequate pain control at discharge may lead to an increased reliance on opioids post-discharge as well as an escalation in dose and potency of opioids prescribed. [54-58] Moreover, inadequate communication of changes in medication at the time of discharge is also a well-established problem. [59] As a result, community physicians may continue opioids started in the hospital, for acute pain relief, as they have no information about the treatment indication nor the expected duration of therapy. [60,61] For many patients, their first exposure to opioids is following surgery, and without intention, hospital-based prescribers of opioids may initiate long-term opioid use after discharge. Estimates for patients with long-term opioid use after surgery diverge greatly and range from 3% to 36% depending on the type of surgery and different methodologies of defining long-term opioid use and follow-up periods. [53] A 2017 study found that, between 2013 and 2014, the incidence of long-term opioid use for more than 90 days was not significantly different between minor and major surgical procedures. [62,63] Another recent population-based cohort study aimed to characterize potential risk factors for long-term opioid use following major elective surgery in acute care hospitals in Ontario and found a 3.1% risk of incident long-term opioid use that was significantly different across surgery types, with thoracic surgical procedures being associated with the highest risk. [64] However, different definitions of long-term opioid use make comparisons across estimates difficult. [53] *In addition, the majority of studies used administrative claims for prescriptions dispensed by community pharmacies and information about in-hospital medications has not been considered when calculating risks of long-term opioid use.* [64-68]

Patient and Prescription Characteristics: Previous studies have identified that the most common factors associated with an increased risk of LTOT included age, sex [66,67,69-71], opioid dose and duration at initiation [62,67,69], arthritis [62,69,70], race [67,69], the presence of chronic pain [67,69,70] and mental illnesses such as anxiety and depression. [62,67,71,72] Additionally, nearly 30% of fatal opioid overdoses in the US also involve benzodiazepines, raising the possibility that some of the increases in opioid related deaths might be caused by increases in concurrent benzodiazepine/opioid use over time. [73] Studies examining opioid prescriptions in the US and Canada similarly found that patients who were prescribed opioids and had a concurrent prescription for benzodiazepines were at a significant two to three-fold increase in the risk of

death compared to patients on opioids only. [26,50,74-76] Moreover, a recent report on opioid-related deaths in Ontario found that in 2020, there was a 10-fold increase in the detection of non-prescription benzodiazepines, thus acknowledging the impact of unregulated drug supply to the observed deaths across the province. [77]

Opioid Prescribing at Hospital Discharge: In addition to patient-related factors which may increase one's risk of opioid misuse [78], high-risk medications also heighten the risk of harm. [79] It has been argued that inadequate pain regimen and overprescribing of opioids after surgery could lead to increased risk of adverse outcomes and adverse opioid-related behaviors such as prescription opioid misuse, opioid diversion, and new or unintended prolonged opioid use. [80-82] Previous studies, which have looked at overall predictors of opioid prescription at discharge in hospitalized patients have found that specific medical interventions such undergoing thoracic surgery, patients with diagnoses for pain syndromes were all at a higher risk of receiving an opioid prescription at discharge. [83-85] Opioid medications represent a high-risk class of drugs [79], which have also been shown to be associated with the highest rate of reported medication errors (MEs). [78,86] Opioid-related MEs could have a significant impact on patient health and may result in potentially preventable adverse patient outcomes and contribute to the prescription opioid misuse crisis. [87,88] The literature on predictors of overall MEs and discrepancies shows that higher age, polypharmacy, patient gender and specific medical interventions are associated with increased likelihood of MEs. [89-91] Computer-based prescribing platforms have also shown to be effective in successful prevention of overall MEs. [92,93] *However, the occurrence of and specific predictors of opioid-related errors during these care transitions is an under-explored area, which warrants further investigation.*

1.7. Research objectives

The goal of my doctoral dissertation was to identify potential modifiable determinants of long-term opioid use among hospitalized patients in the period following hospital discharge and assess the risk of post-discharge adverse events associated with various opioid consumption profiles. To achieve this goal, my program of research addressed four specific objectives:

Objective 1: To estimate the incidence and predictors of a) the receipt of an opioid prescription and b) having opioid-related medication errors such as omissions, duplications or dose-changes

at transitions from the hospital to the community, and its associated risk of emergency department visits (ED), re-admissions or death in the 30- and 90-days post-discharge.

Objective 2: To estimate a) the proportion of hospitalized patients on long-term opioid therapy, and b) identify modifiable patient-, prescriber- and system-level risk factors for long-term prescription opioid use compared to episodic use in the one year after hospital discharge.

Objective 3: To assess the impact of treatment duration and dose of opioid use on the risk of ED visits and hospital re-admissions in the one year following hospital discharge, and to determine if the risk was modified by treatment indication, age or concurrent benzodiazepines use.

Objective 4: To determine if the risk of adverse events varied as a function of current and past opioid use, and if the results and conclusions varied depending on the methodological approach used to model time-varying opioid exposures.

1.8. Organization of the thesis

This thesis is organized around four research manuscripts. Chapter 2 reviews the available evidence and methodology from previous opioid safety studies that have looked at risk factors of long-term opioid use and its impact on opioid-related morbidity and mortality. Chapter 3 details the data sources used and the eligibility criteria for the study cohort used in the four manuscripts. The following four chapters (Chapters 4 to 7) contain the manuscripts that address the thesis objectives. Chapter 4 estimated the incidence and factors associated with the receipt of an opioid prescription and opioid-related medication errors at hospital discharge. In addition, it also determined the rates of adverse drug events and risk of ED visits, readmissions or death in the immediate post-discharge period. This manuscript was published in the *Value in Health* journal under the title, “Incidence and Variables Associated with Inconsistencies in Opioid Prescribing at Hospital Discharge and Its Associated Adverse Drug Outcomes”. Chapter 5 examined patient-, medication- and system-level characteristics associated with the development of long-term opioid use. This manuscript was submitted to the *Journal of the American Medical Association* under the title, “Determinants for Long-Term Opioid Use in Hospitalized Patients”. Chapter 6 reports the findings of an observation cohort study assessing the risk of acute healthcare events such as hospital admission and emergency department visits associated with various opioid use

patterns, and the changes in risk by various treatment indications. This manuscript was published in the *Journal of the American Medical Association Network Open* under the title, "Association of Opioid Consumption Profiles After Hospitalization with Risk of Adverse Health Care Events". Chapter 7 investigated how novel modelling techniques and the use of different methodological approaches to measure time-varying opioid exposures could improve our understanding of the how opioid-related adverse events may vary depending on the current and past opioid use. Furthermore, I also attempted to define a clinically relevant threshold for high-risk opioid use by using flexible non-linear modeling of the opioid dose- and duration-response functions. This manuscript was submitted to the *American Journal of Epidemiology* under the title, "Flexible modelling of opioid exposures provides new insights into its association with adverse outcomes". Finally, Chapter 9 summarizes the main findings and contributions of the thesis, highlights some important considerations, and discusses new directions for future research on opioid use.

2. Background

In this chapter, I summarize the most recently published studies that have examined 1) the association between opioid prescribing patterns and subsequent harm (Section 2.1) as well as 2) different patient-, medication- and system-related risk factors associated with the risk of developing long-term opioid use (Section 2.2). The characteristics of these studies, the modelling approaches and measurement methods used, and their main findings are presented in the following text and tables. Finally, I discuss the limitations of these studies and highlight the current gaps in evidence in opioid safety research.

2.1. Previous studies that have examined the impact of opioid use and the risk of harm and opioid-related adverse events

I retrieved the most recent (since 2010) and relevant (similar exposure definitions and study endpoints) observational opioid safety studies, which have looked at various opioid consumption patterns and its associated harmful effects, such as fatal and non-fatal opioid overdose, fractures and other side effects such as nausea, dizziness and bowel dysfunction and all-cause mortality and healthcare utilization as defined by emergency department visits and hospitalizations. A summary of the information, which included study design, population, data sources, exposure

(opioid use), opioid safety outcomes studies, measurement and methodological approaches and potential risk of bias can be found in Table 2-1. A previous review of the opioid safety literature, which detailed some limitations of the opioid safety studies and provided extensive recommendations for strengthening the evidence base, has also been used in identifying the limitations of previous research and guiding my work. [94] Based on these recommendations, I reviewed all the studies included in the CDC guidelines to further assess gaps in knowledge.

2.1.1. Study characteristics

The majority of studies on opioid safety considered opioid-related outcomes such as opioid abuse [95,96], overdose [26,42,43,96] and death. [25,42,74] Some studied other opioid-related effects such road trauma [47], fractures [39,97,98] as well as healthcare utilization such as emergency department visits and re-admissions. [97,99,100] Among studies included in the CDC guidelines [50], a similar trend was observed: most studies assess fatal safety outcomes such as overdoses (n=10) while only three examined other opioid-related side effects, of which all were randomized clinical trials.

2.1.2. Study design, population characteristics and data sources used

The majority of studies on opioid safety used observational study designs [39,41,42,74,95,97-99], two case-control studies [25,47], one cross-sectional [2], and one descriptive study. [96] Most studies were conducted in patients with chronic non-cancer pain [39,74,95]; others were conducted among all opioid users including cancer, acute and chronic pain patients [42,96,101]; a few conducted them in specific medical populations such as hemodialysis patients [97] and surgical patients. [99,100,102] Most studies included both new and prevalent opioid users [25,42,43,47,96,97,99,100,102] with a few including only opioid-naive patients. [41,74,95] Data sources included predominantly health insurance claims data, with only one study including electronic health records (EHRs). [100] Similar findings were observed by the authors of a review looking at the methodological limitations of prescription opioids safety research. [94] Among the 27 opioid safety studies used in the development of the CDC guidelines [50], the majority (n=12) were observational, followed by randomized trials (n=6), case-control (n=5), cross-sectional (n=3) and case-cohort studies (n=2). The predominant population studied were chronic non-cancer pain patients (n=15); however, there were some

studies which also looked at opioid users with all pain diagnoses (n=10). Again, most of the data sources used included health insurance claims, with only the RCTs using EMR data.

2.1.3. Main methods and findings

Overall, all studies found that opioid consumption, whether represented as daily use, duration of therapy, daily dose or duration of action were associated with an increased risk of fatal and non-fatal opioid-related harms and healthcare utilization. Even low opioid doses were associated with an increased risk of opioid abuse/dependence. [95] As compared to low dose, higher doses were associated with an increased risk of fatal opioid overdose [25,42,74] and non-fatal overdose. [74,96] Higher opioid doses were also associated with increased risk of road trauma [47], fractures [39,97,98] and hospital re-admissions. [99,100,102] Patients on long-acting opioids were more likely to experience an opioid prescription overdose. [41] Most studies have examined average daily dose [39,42,47,74,95,98] and duration of opioid therapy [39,95,98] as their main opioid exposure. Studies that included patients who had undergone surgeries examined the association of opioid prescription at discharge with the risk of healthcare utilization and opioid-related events. They all found that adverse health outcomes were higher in patients who were given an opioid at discharge and had higher opioid doses prescribed to them [96,100,102], except for one study. [99]

In the few longitudinal observational studies, the main opioid exposure was mainly time-fixed in nature, represented by a single binomial/multinomial variable constructed based on opioid supply and average daily dose. [41,95,96,98] Other studies looked at characteristics of the initial opioid dispensation or opioid prescription at discharge. [99,100,102] The studies, which modeled their exposure as time-varying, used daily dose as their main opioid metric [42,74,97]; one study modelled both daily use and dose time-varying. [39] Additionally, most of the studies included in the CDC review also used time-fixed definitions. [50] The most common analytic approaches were logistic regression [47,95,102,103] and Cox PH models [39,41,42,74,97-99] with some studies being purely descriptive in nature, examining rates of healthcare utilization across categories of opioid users. [2,43,96,100] All studies adjusted for time-fixed confounders derived from administrative databases such as health insurance claims. Only one study modelled pain and other medical diagnoses as time-varying. [26] A few studies used an appropriate active comparator. [42,74,98] One study that examined the effect of duration of opioid action on the risk of unintentional prescription opioid overdose compared

SA to LA. [41] Most studies, that examined the effect of opioid use or duration of use used no opioid use as their reference category. [39,95,97,99] When daily dose was used as the main opioid exposure metric, some authors have chosen the non-use (0 dose) category [39,95,97,99], while others have selected as a comparator the low dose category. [42,74]

2.1.4. Conclusions from the literature and gaps in evidence

Overall, few of the opioid safety studies have taken a longitudinal approach. As such, we know that opioid use carries a risk of fatal outcomes such as overdose and all-cause mortality, but how the risk changes over time is yet to be elucidated. Some studies have looked at the duration of the initial opioid prescription, but this fails to account for changes in patients' pain management over time. As a result, we do not know how much of the risk of opioid-related morbidity and mortality is attributed to daily use, cumulative or continuous use. Most studies also fail to account for time-varying opioid exposure and confounding by indication. In randomized trials, opioids have been shown to be associated with increased risk of adverse events but no trial followed patients for longer than 6 months and thus, the body of evidence for assessing the risk profile of different treatment durations with opioids is insufficient. [94] In addition, in observational studies, opioid use has been shown to be associated with an increased risk of opioid-related mortality and morbidity, but the majority of the studies focused on outcomes such as opioid overdose and death, and examining other opioid-related adverse effects is of equal importance. Studies that examined other adverse effects of opioid use have several methodological limitations, including: poor confounding control, failure to adequately model opioid exposure by taking into account the dynamic treatment regimen or complexity of cases with overlapping prescriptions as well as lack of accounting for competing risks. The majority of the evidence uses administrative prescription claims data and lack detailed comorbidity and patient adherence information. Most studies suffered from improper confounding control by either lacking information on clinical confounders or lack of proper adjustment by only measuring certain medical diagnoses and medication use only at baseline. The potential benefits of using multiple data sources that could improve measurement of important confounders in opioid safety studies has not been evaluated yet. In my thesis, I used data from a variety of sources, including: dispensing pharmacy records, in-hospital medical records, detailed information on opioid prescriptions written at hospital discharge and interviews with patients in the post-discharge period, in order to enhance internal

validity of the proposed studies by adjusting for a wealth of confounders. Moreover, none of the studies assessed the impact of a potentially important unmeasured confounder on their findings. As part of the analyses of the third objective, I conducted sensitivity analyses and quantitative bias analyses to quantity the risk of bias in the presence of an unmeasured confounder. Most studies quantifying chronic opioid use used arbitrary cut-offs to operationalize this definition and might have introduced immortal time bias by relying on patterns of future refills to estimate medication supply; other studies introduced immortal time bias by relying on two diagnoses to define their study cohort (including patients newly diagnosed with chronic non-cancer pain), whose authors chose to begin the study follow-up at the first diagnosis, making the time between the first and the last diagnosis immortal. [95] To date, no study has used flexible modeling techniques to explore the empirical associations of time-varying opioid use with potential risk of harm to assess how the risk depends on the pattern and duration of previous use and, thus, try to inform a clinically relevant definition of chronic opioid use. In my third and fourth objective, I addressed this gap in evidence and investigated how modern time-varying approaches improve our understanding of the risk of opioid use on opioid-relate harms. Finally, to deepen the understanding as to the mechanism behind various opioid consumption patterns, my thesis included a large population of opioid users to see how their use and risk of adverse events changes over time while comparing risk of opioid-related harm across different subgroups of populations.

2.2. Previous studies that have examined the risk factors of long-term opioid use

I have summarized the most recent (since 2010) and relevant studies (similar study endpoint) which have examined predictors of long-term opioid use. A summary of the information extracted from the studies, which included population, data sources, potential risk factors studied, outcome definition of long-term opioid use, measurement and methodological approaches and relevant findings is found in Table 2-2. The findings from a recent 2019 systematic review on long-term opioid therapy definitions and predictors have also been presented, in brief, in the text below, and have been used as criteria to identify potential risk factors and construct an appropriate definition for long-term opioid use. [53]

2.2.1. Study characteristics

All studies, which examined predictors associated with long-term opioid treatment (LTOT) were observational in nature and compared differences in characteristics between short-term and long-term opioid users. Components of the definitions of LTOT included multiple distinct observation periods, number of prescriptions, days' supply, gaps and overlaps between prescriptions. There was a great variation in the approach to define LTOT. Follow-up time differed from three months to three years, with most common follow-up being 1 year. Duration of opioid use used to define LTOT ranged from 6 weeks to one year, with most studies using three months. Most studies used one or two distinct observational periods during the follow-up to measure LTOT. Similarly, the authors of the recent systematic review found that only 7 out of the 41 studies included (17%) on LTOT definitions used an approach taking into account multiple consecutive observational periods to calculate LTOT. [104] However, most definitions, used the number of prescriptions to define LTOT and only 11 studies (27%) used days' supply, with the most common threshold being 90 days. [53]

2.2.2. Study populations and data sources used

All studies examined were conducted in the Unites States or Canada, which made comparison across studies easier as these countries have similar population characteristics. Most used administrative claims data with only two studies using medical records. [63,70] However, even among the studies who had access to clinical information, there were none which used this information to examine potential clinical predictors such as provider and practice environment characteristics. All studies used a new user design. [19,62,63,66-68,70,72,105] Some studies used the surgery date as an index date in their definitions of LTOT [62,63,66-68], while other started their follow-up as of patients' first opioid prescription and followed their transition from short-term to long-term opioid use. [19,21,70,72,95,105,106] The 2019 systematic review by Karmali et al. [53] also found that most studies, 71%, included the surgery date as their start of follow-up, with 10% of studies starting follow-up as of the first opioid prescription. As a result, most of the evidence on LTOT predictors is based on surgical patient populations. The definitions of LTOT also varied by duration of follow-up with half of the studies following patients for less than a year.

2.2.3. Main findings

Estimates of LTOT prevalence varied across studies depending on the target study population; for opioid-naïve patients after surgery, the prevalence ranged from 5.3 % to 13%. [66,67] Among chronic non-cancer pain (CNCP) opioid-naïve patients, the prevalence of LTOT ranged from 1.3 % to 25%. [69,70] The main predictors examined were patient-related characteristics. There were no studies that measured predictors related to the practice environment or prescriber characteristics. With respect to patient characteristics, determinants were characterized as medical and mental health diagnoses, sociodemographic, pain etiology, and patients' prior healthcare utilization and medication use. Almost all studies used logistic regression, with one study using a Cox PH model as their choice of analyses. [20]

The most common predictors identified were age, sex, race, opioid dose at baseline, presence of chronic pain, arthritis, tobacco use, substance use disorders and mental health diagnoses. The factors associated with increased risk for LTOT were younger age [62,67,69,70,72], being female [62,67,69,70,72], race (as compared to white, black are at an increased risk) [62,67,70], tobacco use [62,69,72], alcohol and/or substance abuse disorders [62,66,67,69,72], mental illness such as depression and anxiety disorder [66,67,69,72], anxiety and pain diagnosis such as arthritis [62,69,70], osteoporosis [70,105] and chronic pain [67,69,70], use of a non-opioid analgesic [67,69], benzodiazepines use [67,69] and having received surgery. [62,66] Increased risk of LTOT was also observed with early opioid prescribing/consumption patterns; characteristics of the first opioid prescription such as opioid doses of >90MME and longer duration (days' supply). [20] Lower opioid doses and lower cumulative durations of use within the initial 30-day opioid exposure window were also strong determinants of LTOT. [20,21,107]

2.2.4. Conclusions from the literature and gaps in evidence

Across all studies, most of the evidence about risk factors associated with long-term opioid use was derived from health administrative data and the investigators were unable to include predictors related to the practice environment or prescriber characteristics. Only one study incorporated clinical information and thus, we have limited knowledge of the extent to which detailed covariate information from clinical and patient-related data sources could improve our knowledge about potential determinants of prolonged opioid use. In addition, there was a great

variation in the definitions of LTOT across all the retrieved studies. The 2019 Karmali et al. systematic review on LTOT predictors [53] also noted that among the studies they considered, there were 41 unique definitions of what LTOT. This is not surprising as there is no consensus as to what interval of prescribing should be considered when defining long-term opioid use. Moreover, most studies also did not account for consistent use; the majority used a cumulative duration definition but only three of the studies included in their review accounted for the possibility of overlapping prescriptions. In order to reflect the changes in opioid therapy over time, it is important to measure and model opioid use by continually updating patients' exposure to opioids as opposed to comparing fills at different time points during the follow-up. In objective 2 of my thesis work, I used an evidence-derived approach to identity an appropriate threshold for LTOT and to model opioid use using a time-varying approach, which reflects the natural progression of and changes in opioid therapy, by considering gaps and overlaps in opioid supply. The impact on the progression of long-term opioid use associated with the attending physician characteristics such as years of practice as well as the training status of the person who prescribed opioids at discharge has yet to be evaluated. The analyses of my second objective used clinical information on patient and organizational characteristics to help stratify patients who are at high-risk of continuing opioid therapy beyond guideline recommendations and inform policies and intervention programs needed to curb excessive opioid prescribing.

Table 2-1. Previous studies that have looked at the effect of opioid consumption profiles and the risk of opioid-related adverse events.

Authors	**Population/Data Source/Study Design**	**Opioid use metric**	**Outcome**	**Methodology used: measurement/modelling of opioid use/comparator/statistical approach**	**Findings**	**Risk of Bias**
Edlund *et al.*, 2014	US Health insurance claims. Newly diagnoses CNCP defined as two or more claims containing primary or secondary diagnoses of the same type of CNCP. Opioid-naïve patients. Observational study.	Average daily dose and duration of opioid therapy defined	Opioid abuse/ dependence	A single multinomial variable was constructed describing opioid days' supply and average daily dose. Time-fixed opioid use definition. Comparator: no use. Logistic regression model	Patients with opioid abuse disorder – 0.1%. Opioid prescribing patterns are associated with opioid use disorders, with opioid duration more important than daily dose.	Immortal time bias: start of follow-up time begun at the first diagnosis: the time between the first and the last diagnosis of CNCP is immortal.
Miller *et al.*, 2015	US Health insurance claims. All opioid-naive patients. Observational study.	Duration of opioid action (SA vs LA)	Unintentional prescription opioid overdose	Time-fixed definition. Comparator; SA opioids; PS-adjusted Cox PH models: analyses stratified by opioid duration.	The risk of unintentional opioid overdose injury is related to the prescribed drug's duration of action, with LA opioids being	Improper confounding control: time fixed adjustment of covariates at baseline; no effect measure modification tested.

					associated with an increased risk.	
Bonhert *et al*., 2011	US Health insurance claims. Opioid-naïve and prevalent users. Observational study	Dose and Schedule	Unintentional prescription opioid overdose and death	Time-varying opioid dose. Comparison group: low dose Cox PH models; analyses stratified by treatment indication.	Patients with opioid overdose - 0.04%. The risk of opioid overdose increased with higher opioid dose>50MME.	No effect measure modification tested.
Dunn *et al.*, 2010	US Health insurance claims. CNCP, opioid-naïve patients. Observational study	Average daily opioid dose over the 90 days prior to event period	Fatal (resulted in deaths) and non-fatal opioid overdose	Time-varying opioid dose. Some confounders (sedative meds) were time-varying. Comparator: low dose Cox PH models.	Overall, patients with opioid overdose - 0.5%, out of which 12% were fatal. Increased risk of drug-related adverse events with opioid doses >50MME.	Improper confounding control: most the medical diagnoses were time-fixed
Gomes *et al.*, 2018	Canada Health insurance claims. All opioid users. Cross-sectional study;	Active and recent opioid prescriptions	Opioid overdose hospitalizations	Rates of opioid-related hospitalizations stratified by province.	Overall, high prevalence of active opioid prescription prior to an	Cross-sectional study.

					opioid-related hospitalization.	
Gomes *et al.*, 2011	Canada Health insurance claims. All CNCP patients. Case-control study.	Daily opioid doses	Opioid-related death	Controls matched on disease risk index. Conditional logistic regression: models adjusted for the opioid treatment duration.	Patients who died - 0.2%. Higher doses associated with an increased risk of death.	
Gomes *et al.*, 2013	Canada, health insurance claims; nested case-control; all opioid users	Opioid dose	Road trauma	Matched on disease risk score; Conditional logistic regression	Risk of trauma increased with higher doses.	Lack of information on indication for opioid therapy.
Saunders *et al.*, 2010	US Health insurance claims; CNCP patients with >3 opioid prescriptions measured within the first 90-day time periods; observational study	Opioid use and dose	Fractures	Time-varying opioid use and average daily dose. Comparator: no use Cox PH models.	Higher dose opioid use (≥50 mg/day) was associated with an increased risk of fractures.	Competing Risk: Significant proportion (25% died before end of follow-up period).
Ishida *et al.*, 2018	US Health insurance claims data. Patients on hemodialysis. Observational study.	Opioid dose	Altered mental status, fall, fracture that requires an ER visit, hospitalization.	Time-varying opioid dose. Comparator: no use. Cox PH models.	17% event rate; opioids were associated with adverse outcomes and this risk was present even at	Time-fixed confounders. Lack of generalizability.

					lower dose (>60MME)	
Miller *et al.*, 2011	US Health insurance claims. Opioid-naïve patients with arthritis. Observational study	Opioid dose and duration of the first initial prescription	Fractures	Single measurement of opioid use: characteristics of initial prescription. Comparator: NSAIDs Cox PH models.	12% event rate; older people with arthritis who initiate therapy with opioids are more likely to experience a fracture than those who initiate NSAIDs.	Limited generalizability. No longitudinal patters assessed.
Liberman *et al.*, 2019	US study questionnaire. Opioid-naïve and prevalent users. Observational study.	Opioid prescription at hospital discharge	Healthcare utilization within 90 days' post-discharge (any ED visit or re-admission)	Single measurement of opioid use: prescription of an opioid at discharge. Comparator: no use Cox PH models.	No statistical association was found with unplanned healthcare use.	No longitudinal patterns. Improper confounding control due to lack of clinical information.
Schlosser *et al.*, 2020	US EMR data. Patients with knee joint arthroplasty. Opioid-naïve and prevalent users. Descriptive study.	Opioid dose at hospital discharge	30-day readmission rate	Comparative rates	Lower doses (<40 MME) led to a reduction in rate of re-admissions as compared to higher doses.	Limited generalizability: looked at a subpopulation of patients who used opioids; selection bias: excluded patients with missing data.

						Improper confounding control: no other medication use, time-fixed covariates
Paulozzi *et al.*, 2014	US Health insurance claims. CNCP, opioid-naïve and prevalent users. Descriptive study.	Opioid use: daily users, other users and nonusers	Drug abuse, overdose	Opioid use and dose were measured every 6 mo. Descriptive study: rates, CI and proportion of patients with adverse events.	Adverse health outcomes (drug abuse and overdose) can increase with accumulating opioid use and increasing dosage.	Descriptive study
Desai *et al*., 2018	US EMR and health insurance claims. Surgical patients. Opioid naïve and prevalent users. Observational study.	Opioid prescription at discharge	30-day readmission rate	Single measurement of opioid use: prescription of an opioid at discharge. Logistic regression.	Patients receiving opioids only were at an increased risk of hospital readmission within 30 days compared to opioids and another analgesic.	No longitudinal patterns assessed, improper confounding control (time-fixed and no adjustment for other non-pain medication use)

Table 2-2. Previous studies that have looked at risk factors of long-term opioid use.

Authors	**Population/Data Source**	**Potential Risk Factors**	**Outcome Definition**	**Analytic Approach**	**Findings (rate, % LTOT)**
Brumett *et al.*, 2017	US Health insurance claims. Opioid-naïve surgical and medical patients.	Age, gender, race, education, region of residence, medical comorbidities, pain diagnoses and mental health classifications.	Opioid prescription fill 90 to 180 days after surgery.	Multivariable logistic regression.	Minor surgery - 5.9% and major surgery - 6.5%, medical patients – 0.4%
Ray *et al.*, 2017	US EMR. Opioid-naïve patients.	Sex, age, medical diagnoses; sedative use, healthcare utilization	At least 3 months of opioid use with either more than 120 days of opioid supply or 10 or more opioid prescription fills during the 3-year follow-up period.	Multivariable logistic regression.	25% prevalence of long-term opioid users
Sun *et al.*, 2016	US Health insurance claims. Opioid-naïve surgical and medical patients.	Sex, age, preoperative history of depression, psychosis, drug or alcohol abuse, and preoperative use of benzodiazepines, antipsychotics, and antidepressants	LTOT for surgical patients: defined as having filled 10 or more prescriptions or more than 120 days' supply of an opioid in the first year after surgery, excluding the first 90 postoperative days. LTOT for medical patients, defined as	Multivariable logistic regression.	LTOT: 0.119% for Caesarean delivery (95% CI, 0.104%-0.134%) to 1.41% for TKA (95% CI, 1.29%-1.53%; For non-surgical patients: 0.14%. Male sex, age older than 50 years, and preoperative history of drug abuse, alcohol abuse, depression, benzodiazepine use, or

			having filled 10 or more prescriptions or more than 120 days' supply following a randomly assigned "surgery" date.		antidepressant use were associated with chronic opioid use among surgical patients.
Calcaterra et al., 2016	US EMR. Opioid-naïve medical and surgical patients.	Sociodemographic (age, gender, race, insurance status), medical diagnoses, receipt of surgery during hospitalization, baseline healthcare use	LTOT: an opioid use episode lasting > 90 days with a total of 120+ day supply of opioids or > 10 opioid prescriptions dispensed over 1 year.	Multivariable logistic regression.	4.1% proportion of LTOT; Patients with opioids at discharge were more likely to be cancer patients, have acute pain at admission, having had surgery; less likely to have mental health disorder, more likely to become chronic users (aOR: 4.9, 95% CI: 3.22 – 7.45), more subsequent opioid refills (aOR: 2.67, 95% CI 2.29 – 3.13)
Johnson *et al.*, 2016	US Health insurance claims. Opioid-naïve surgical patients.	Sociodemographic (age, gender, median income, insurance status), medical diagnoses: Elixhauser comorbidity index, mental health disorder and substance disorder, history of pain, type of surgery	LTOT: fill of a perioperative opioid prescription followed by a prescription between 90 and 180 days after surgery.	Multivariable logistic regression.	Patients on LTOT – 13.1%. Younger age, female gender, lower income, comprehensive insurance, higher Elixhauser comorbidity index, mental health disorders, and tobacco dependence or abuse were associated with increased risk of LTOT.

Thornton *et al*., 2018	US Health insurance claims. Non-cancer opioid-naïve patients.	Opioid regimen characteristics, pain conditions, physical and mental health conditions, concomitant medications use (i.e., benzodiazepine, stimulants, nonopioid analgesics, and polypharmacy), patient characteristics, and health insurance type	LTOT: at least a 90-day supply of opioids within 120 days after the index date (initiation of opioid therapy).	Multivariable logistic regression.	Patients on LTOT - 1.3%. Opioid duration of action, drug abuse and presence of pain conditions were associated with an increased risk of LTOT.
Mosher *et al*., 2018	US Health insurance claims. Opioid-naïve medical and surgical patients.	Number of days' supply of the initial prescription durations (compared to <7 days)	LTOT: continuous opioid supply lasting a minimum of 90 days and beginning within 30 days of the initial prescription.	Multivariable logistic regression.	Surgical patients on LTOT – 5.3% medical patients on LTOT – 15.2%. Initial dose and days prescribed within 3 days of hospital discharge were associated with increased risk of LTOT.
Fritz *et al.*, 2018	US Health insurance claims. Opioid-naïve non-cancer patients with low back pain.	Socioeconomic and demographic variables, healthcare utilization, medication use, diagnostic procedures, medical and health diagnoses	LTOT: ≥120 days or >90 days with ≥10 fills during the 1-year follow-up period.	Multivariable logistic regression.	Patients on LTOT: 4.3%. Having an anxiety comorbidity, smoking, and older age, benzodiazepine use were all associated with increased risk of LTOT.
Shah *et al.*, 2017	US Health insurance claims. Opioid-naïve non-cancer patients.	Characteristics of the first opioid prescription; a variable for treatment indication was also included in the model–	Opioid discontinuation (at least 180 days without opioid use)	Cox PH models.	Patients on LTOT - 5.3% Longer durations and doses of initial opioid prescription were

		trauma, surgery, chronic pain.			associated with increased risk of LTOT.
Hadlandsmyth *et al.*, 2019	US Health insurance claims. Opioid-naïve non-cancer patients.	Initial opioid exposure: days' supply, daily dose, number of fills within the first 30 days.	Long-term opioid use (6 or more opioid filled following the initial 30-day assessment period).	Logistic regression models.	Patients on LTOT: from 1.6% to 39.2% depending on method used, number of fills and dose in the initial month. Initial opioid duration was associated with increased risk of LTOT.
Deyo *et al.*, 2017	US Health insurance claims. Opioid-naïve non-cancer patients.	Initial (within 30 days of study entry) prescribing patterns: Numbers of prescription fills and cumulative MMEs dispensed during 30 days following opioid initiation.	Long-term opioid use - proportion of patients with six or more opioid fills in the 12 months following the initiation month; hospitalizations for opioid-related adverse events.	Logistic regression models.	Long-term opioid users: 5.0% Having more than 2 fills during the initiation month and higher opioid doses were associated with increased risk of LTOT.

3. Data Sources

3.1. The primary cohort

A subset of the cohort of medical and surgical hospitalized patients who were enrolled in a cluster randomized controlled trial on medication reconciliation were used to address the study objectives. [108] The MUHC is an over 1000-bed quaternary care teaching hospital in Montreal (Canada) that operates within the universal health care plan of the province of Quebec (RAMQ). This plan covers all hospitalizations, essential medical care and drug insurance for registrants 65 years of age and older, income security recipients, and those not insured through their employer (approximately 50% of the Quebec population). Ethics approval was obtained from the MUHC ethics board, and privacy commissioner approval to link clinical and administrative data from the Commission d'access a l'information de Quebec.

3.2. Eligibility

The study population included all surgical and medical patients discharged from McGill University Health Center between October 2014 and November 2016. To be eligible for the original trial, patients had to be 18 years of age or older at admission, be admitted from the community or transferred from another hospital, with at least one-year of continuous provincial healthcare coverage prior to hospital admission. For the studies outlined for this thesis, patients needed to fill at least one opioid prescription during the 90 days following their hospital discharge.

3.4. Data sources

Multiple sources of data were assembled and linked to address the objectives of the proposed project. For each patient, demographic, clinical, health care service use and prescription claims were retrieved from the admission note as well as provincial health care administrative databases (RAMQ medical services and RAMQ prescription claims data) in the year prior to and after the hospitalization, for which the patient was enrolled. RAMQ prescription claims database covers approximately 50% of all Quebec residents including Medicare registrants who are 65 years of age and older, income security recipients, and registered not insured through their employer. Dates of admission and discharge, admitting and discharge unit, patient demographics, health problems at admission and discharge, major procedures (surgeries, treatment interventions), were

retrieved from the MED-ECHO hospitalization database. Physical findings, laboratory results, diagnoses, medications taken at admission, in-hospital as well as those prescribed at discharge were abstracted from the McGill University Health Center Data Warehouse. Data on hospital discharge experiences were obtained via telephone interview 30-day post-discharge with trained interviewers, and adverse drug event occurrence was adjudicated by two reviewers using the Leape-Bates method. [87,109,110] This is one of the only data sources in the world that links information on medication use prior to admission and during the hospital stay as well as which medications are prescribed at discharge and dispensed medications in the community post-discharge.

4. Objective 1

Kurteva S, Habib B, Moraga T, Tamblyn R. Incidence and Variables Associated With Inconsistencies in Opioid Prescribing at Hospital Discharge and Its Associated Adverse Drug Outcomes. Value Health. 2021 Feb;24(2):147-157. doi: 10.1016/j.jval.2020.07.015. Epub 2020 Nov 10. PMID: 33518021.

4.1. Preamble

The first manuscript presents the results of a cohort study describing opioid-related medication errors (MEs) at transitions in care such as a hospitalization. The intent of this study was to better understand what patient-, medication- and system- level characteristics contribute to the receipt of an opioid prescription at discharge and opioid-related medication errors. The status of the opioid prescriptions at hospital discharge was ascertained using patients' charts and an electronic reconciliation software. I considered three different types of medication-related errors: omissions duplications, and unintended dose changes. I also explored the impact of opioid-related MEs on its associated rates of adverse drug events and risk of emergency department visits, readmissions, or death in the 30 and 90 days' post-discharge.

The study has already been published in the *Value in Health* journal. The published article is provided in Appendix 8 at the end of the thesis.

4.2 Title page and footnotes

Title: Incidence and Variables Associated with Inconsistencies in Opioid Prescribing at Hospital Discharge and Its Associated Adverse Drug Outcomes

Contributing authors: Siyana Kurteva, BSc [1,2], Bettina Habib, MSc MScPH [2], Teresa Moraga, MSc [2], Robyn Tamblyn, BScN MSc PhD [1,2,3]

Affiliations of all contributing authors:

[1] Department of Epidemiology and Biostatistics, McGill University, Montreal, Canada

[2] Clinical and Health Informatics Research Group, Department of Medicine, McGill University, Montreal, Canada

[3] Department of Medicine, McGill University Health Center, Montreal, Canada

Corresponding author:

Siyana Kurteva

Clinical & Health Informatics Research Group, Department of Medicine, McGill University

1140 Pine Ave W., Montreal, Quebec, Canada, H3A 1A3

Email: siyana.kurteva@mail.mcgill.ca

Tel: +1 (514) - 632 – 5838

ABSTRACT

Objectives: Opioid-related medication errors (MEs) can have a significant impact on patient health and contribute to opioid misuse. The objective of this study was to estimate the incidence of and variables associated with the receipt of an opioid prescription and opioid-related MEs (omissions, duplications or dose-changes) at hospital discharge. We also determined rates of adverse drug events and risks of emergency department (ED) visits, re-admissions or death 30-days and 90-days post-discharge associated with MEs.

Methods: A cohort of hospitalized patients discharged from the McGill University Health Centre between 2014 and 2016 was assembled. The impact of opioid-related MEs was assessed in a propensity-score adjusted logistic regression models. Multivariable logistic regression was used to determine characteristics associated with MEs and discharge opioid prescription.

Results: 1530 (43.9%) of 3486 patients were prescribed opioids, of which 13.4% (n = 205) patients had at least one opioid-related MEs. Rates of MEs were higher in handwritten prescriptions compared to the electronic reconciliation discharge prescription group (20.6% vs 1.2%). Computer-based prescriptions were associated with a 69% lower risk of opioid-related MEs (adjusted odds ratio [aOR]: 0.31, 95% CI: 0.14 – 0.65)) and 63% lower risk of receiving an opioid prescription. Opioid-related MEs were associated with a 2.3 times increased risk of healthcare utilization in the 30-days post-discharge period (aOR: 2.32, 95% CI:1.24 – 4.32)).

Conclusions: Opioid-related MEs are common in handwritten discharge prescriptions. Our findings highlight the need for computer-based prescribing platforms and careful review of medications during critical periods of care such as hospital transitions.

4.4 Introduction

Opioid use is associated with both fatal and nonfatal adverse effects. In the US, rates of opioid-related hospitalizations increased by 64% between 2005 and 2014. [111] In addition to patient-related factors which may increase one's risk of opioid misuse [78], errors associated with high-risk medications also heighten the risk of harm. [79] Opioid medications represent a high-risk class of drugs [79] which have been shown to be associated with the highest rate of reported medication errors (MEs). [78,86] Opioid-related MEs could have a significant impact on patient health and may result in potentially preventable adverse patient outcomes and contribute to the prescription opioid misuse crisis. [87,88]

Transitions in care represent a particularly high-risk period in the patient pathway.[112-114] Previous studies have found between 1.2 and 5.3 MEs per patient in transitions from hospital discharge to the community.[112,115,116] The literature on predictors of MEs and discrepancies shows that higher age, polypharmacy, patient gender and specific medical interventions are associated with increased likelihood of MEs. [89-91] However, the occurrence of and specific predictors of opioid-related errors during these care transitions is an under-explored area, which warrants further investigation. Inadequate communication of changes in medication at the time of discharge is a well-established problem and hospital physicians may discontinue or initiate opioids without fully knowing a patient's medication history, including their history of opioid use prior to hospitalization.[54-58]Moreover, the hospitalization itself may inadvertently be a risk factor whereby opioids are prescribed for acute pain during hospitalization and inadvertently continued at discharge, increasing the risk for chronic use. [60,61]

Medication reconciliation, introduced as a potential solution to identifying and reducing MEs, could be used as an intervention to reduce opioid medications errors and associated preventable harm. [117-119] A recent systematic review quantifying the burden of opioid MEs in adult oncology settings highlighted the lack of research on opioid errors incidence, type and patient impact. [120,121] The objective of this study was to estimate the incidence of opioid-related MEs (omissions, duplications or dose-changes) at transitions in care, and its associated rates of adverse drug events and risk of emergency visits (ED), re-admissions or death in the 30- and 90-

days post-discharge. In addition, we also explored potential predictors associated with 1) the receipt of an opioid prescription and 2) having an opioid-related ME at hospital discharge.

4.5 Methods

Setting: The study took place within the context of a cluster-randomized trial on discharge medication reconciliation conducted at the McGill University Health Centre (MUHC).[108] The MUHC is an over 1000-bed quaternary care teaching hospital in Montreal (Canada) that operates within the universal health care plan of the province of Quebec (RAMQ). This plan covers all necessary medical care and includes prescription drug insurance for registrants 65 years of age and older, income security recipients, and those not insured through their employer. Ethics approval was provided by the MUHC Research Ethics Board. Privacy Commissioner approval was obtained to link clinical and administrative data from the Commission d'accès à l'information du Quebec.

Participants: A prospective cohort hospitalized patients discharged from medical and surgical units of the MUHC between October 2014 and November 2016 was followed for up to 90-days post-discharge. To be eligible for the original trial and for this study, patients had to be 18 years of age or older at admission, admitted from the community or transferred from another hospital, with at least one year of continuous provincial healthcare and prescription drug coverage prior to hospital admission.

Data Sources: Multiple sources of data were assembled and linked to address the objectives of the proposed study. For each patient, demographic, clinical, health care service use and prescription claims data were retrieved from the admission note and provincial health care administrative databases (RAMQ medical services and prescription claims data) in the year prior to and following the hospitalization for which the patient was enrolled. The RAMQ prescription claims database covers approximately 50% of all Quebec residents, including medicare registrants who are 65 years of age and older, income security recipients, and those not insured through their employer. The RAMQ medical services database covers 100% of residents. Dates of admission and discharge, admitting and discharge unit, patient demographics, health problems at admission and discharge, and major procedures (surgeries, treatment interventions) were

retrieved from the MED-ECHO hospitalization database. Physical findings, laboratory results, diagnoses, medications taken at admission, in-hospital as well as those prescribed at discharge were abstracted from the MUHC Data Warehouse. Data on hospital discharge experiences and adverse drug events were obtained via telephone interview 30-day post-discharge with trained interviewers and adverse drug event occurrence was adjudicated by two reviewers using the Leape-Bates method. [87,109,110] This is one of the only data sources in the world that links information on medication use prior to admission, during the hospital stay, and medications prescribed at discharge and dispensed in the community post-discharge.

Outcomes

Opioid Medications Administered In-Hospital: We used the Anatomical Therapeutic Chemical Classification System (ATC) code used to search the in-hospital pharmacy databases and identify opioids (ATC included: N02A, R05DA) and other concurrent medications such as benzodiazepines, antidepressants and analgesics that the patient was administered while in the hospital.

Opioid Prescriptions at Discharge: The status of opioid prescriptions at hospital discharge was ascertained using patients' charts (handwritten prescriptions) and the electronic reconciliation software (electronic prescriptions). For patients, whose prescription was finalized using the RightRx software, opioid discharge prescriptions were grouped by reconciliation action: stop, modify, continue from the community, and new prescription. For patients who left the hospital with a paper discharge prescription, we determined the opioid status based on what was indicated in the patient's chart. Patients were considered to have left the hospital with an opioid prescription when the status of the opioid medication was continued, modified or newly prescribed. Patients with multi-modal analgesia were defined as those who were prescribed an opioid medication at discharge with at least one other analgesic agent. [122]

MEs at Discharge: Three different types of medication-related errors were considered as part of our main outcome: omissions, duplications and unintended dose changes. An unintended error of omission was defined as a drug that was in the community drug list that was not prescribed at discharge and for which there was no documented evidence of having been stopped in the medical chart. On the other hand, an unintended therapy duplication was defined as one drug with an active

prescription in the community drug list and a second drug in the same four-digit ATC [123] in the discharge prescription, where there was no evidence in the medical chart that the community drug had been stopped, or that it was to be intentionally continued. Omissions and therapy duplication errors were further classified into two categories depending on whether they were due to a reconciliation error or a history error. For example, an omission that was considered as due to reconciliation error was defined as a drug that was in the community drug list that was prescribed at discharge but for which there was no documented evidence of the status in the medical chart (continued, prescribed, stopped or modified). An unintended dose change was defined as a 25% or more increase or decrease in the prescribed dose of a community medication that was not documented in the medical chart as a change. To calculate the difference in dose between community drugs and those prescribed at discharge, the strength, quantity and duration of community-based medications were used to calculate daily dose for all opioid medications. Refer to the Appendix for full conceptualization of definitions for MEs.

Medication-related error definitions were based on information on medications dispensed in 3 months prior to hospitalization, from RAMQ, medications listed at hospital admission indicating whether or not the patient is taking the drug, drugs at discharge as well as status of drugs at discharge. The community drug list generated using the RAMQ prescription claims data for each patient was considered the "gold standard", as these records identify over 40% more medications than are noted in the emergency department chart. [124]

Adverse Drug Events (ADEs)*:* We used information from patient interviews conducted post-discharge to assess the presence of ADEs, defined as the presence of a new health problem or worsening of a pre-existing condition that could be medication-related. Information from patients' self-reported symptoms and medications dispensed following hospital discharge was collected and independently rated using the Leape-Bates adverse drug event classification. ADEs were further classified as definitely/probably preventable to definitely/probably not preventable using the same categories to classify probability. These categorizations were previously described elsewhere. [108]

Emergency Department Visits, Hospital Readmissions, Death Post-Discharge: The outcome was a combined measure of an emergency department visit, hospital re-admission or death in the 30-

days post-discharge and was ascertained using RAMQ provincial medical services claims databases and the Ministry of Health and Social Services discharge abstract database. This approach ensured that all ED visits and re-admissions are included, not just those occurring to the MUHC. In addition, we also explored the potential long-term impact of opioid-related MEs by determining rates of healthcare utilization in the 90-day post-discharge period.

Variables Potentially Associated with the Receipt of an Opioid Prescription at Discharge, MEs and Adverse Outcomes: Potential risk factors for receiving an opioid prescription at discharge and factors associated with MEs were identified from the literature. In addition, variables associated with increased risk of healthcare utilization were also considered. This included patient demographics, co-existing comorbidities that may increases one's risk of receiving an opioid prescription at discharge, healthcare utilization in the one year prior to the hospitalization and patients' medications dispensed in the one year before the admission as well as in-hospital use of medications.

4.6 Analysis

Descriptive statistics were used to summarize and characterize the study cohort including patient demographics, co-existing comorbidities (using the ICD-9 classification), drug and healthcare utilization in the one year prior to hospitalization, diagnoses recorded at hospital admission as indicated in patients' admission notes (using ICD-10 classification), medications administered in-hospital, as well as characteristics of medications prescribed for pain at hospital discharge. Generalized estimating equation (GEE) extension of multivariable logistic regression with an exchangeable correlation structure was used to estimate the independent association among medical history, patient and medication-related characteristics and the receipt of an opioid prescription at discharge, while accounting for clustering of opioid prescriptions within in-hospital physicians. [125] A separate model was also fitted to explore potential variables associated with having at least one of the above-mentioned medication-related errors. The two models included all variables, selected a priori based on the literature and not on statistical significance. The incidence of opioid-related MEs was estimated, overall, by type of error, and by type of prescription (electronic versus handwritten). The rates of ADEs and healthcare encounters were estimated and stratified by the presence or absence of an opioid medication-related error at

discharge. A propensity-score adjusted logistic regression model was used to assess the risk of ED visits, readmission or death associated with opioid-related MEs in the 30- and 90-days post-discharge. The same exploratory variables as in the GEE model were used in building the propensity score model.

4.7 Results

Overall, 3486 patients were discharged alive from study units, 57.7% were male and the mean age was 69.6 (SD=14.9) (Table 4-1). Among the 1530 patients (43.9%) prescribed an opioid at discharge, 82.3% were prescribed to surgical patients and the rate of opioid prescriptions for surgical patients was 73%. Patients with or without an opioid prescription at discharge shared similar characteristics, except that patients prescribed an opioid were more likely to have received opioids, benzodiazepines and analgesics during their hospital stay. Overall, most patients were opioid-naïve with 65% (n=2280) having had no history of opioid use in the one year prior to their admission and 72% had been administered an opioid during their stay. More than half of the patients prescribed an opioid at discharge received a handwritten prescription. Overall, patients who received an opioid at discharge (n=1530) had, on average, 10.5 medications (SD=5.0) with a mean number of changes in the community medications of 7.5 (SD=4.9) (Table 4-2).

Figure 1 shows the flowchart of patients with an opioid prescription at discharge, according to use prior to admission and after discharge. Interestingly, there was an equal split of discharge opioid prescriptions comparing previous users of opioids and opioid-naïve patients. Among patients who did not receive an opioid prescription at discharge, almost one third (22%) of patients with history of opioid use and 12% of opioid-naïve patients had an opioid dispensed in the community 30 days following the hospitalization. More than two thirds of patients filled their opioid prescription within 7-days post-discharge (n = 1070, 69.9%) (Table 4-2) with an overall rate of opioid dispensations of 74.6% during the follow-up period of 30-days post-discharge.

The proportion of patients with at least one opioid-related ME was 13.4% (n = 205), with the incidence of omission errors (40.0%) and unintended dose change errors (44.4%) being the highest, followed by therapy duplication errors (15.6%) (Table 4-2). Of the dose change errors made, 68.1% were a decrease in the dose of the opioid. The overall rate of MEs in hand written

prescriptions was higher than electronic prescriptions (20.6% vs 1.2%). There were no duplication or omission errors among patients where the medication reconciliation software was used for their discharge prescription.

Overall, 27.9% (n=427) of all patients with an opioid prescription at discharge, regardless of the presence of an opioid-related ME, had an acute health service encounter (emergency department visits, hospitalization) or died in the 30-day follow-up period (Table 4-3). Of the 62 ADEs, 82.2% were adjudicated by reviewers as definitely preventable, 4.8% as definitely or probably not preventable. Patients with an opioid-related ME had slightly higher rates of adverse drug events (5.4% vs 3.9%) and more than three times the number of hospital re-admissions (23.4% vs 8.5%) in the 30-days post-discharge. Similarly, they had higher rates of the composite outcomes of visiting the ED, being re-admitted or died within 30-days or 90-days of hospital discharge. Results from propensity-score adjusted logistic regression models showed that patients with opioid-related MEs were 2.32 times more likely to have a re-admissions 30-days post-discharge as compared to patients without MEs (aOR: 2.32, 95% CI: 2.32 (1.24 – 4.32)) (Table 4-4). Other healthcare encounters during the 30- or 90-day post-discharge follow-up period showed increased risk associated with MEs in crude analyses but the associations were no longer significant in propensity-score adjusted analyses.

A number of characteristics were associated with an increased risk of receiving an opioid prescription at discharge (Table 4-5). First, patients of age 35-64 had a 38% increase in the likelihood of being given an opioid upon leaving the hospital (adjusted odds ratio [aOR] 1.38, 95% CI: 1.07 – 1.76), while the age group of 64-79 had more than a two-time higher risk of receiving an opioid (aOR 2.19, 95% CI:1.47 – 3.24). Having been admitted for thoracic surgery (aOR 4.53, 95% CI: 3.17 – 6.48), having received chemotherapy in the one year prior to admission (aOR 2.17, 95% CI: 1.15 – 4.08), and having a diagnosis for a pain syndrome (aOR 1.27, 95% CI:1.03 – 1.57), were all associated with increased likelihood of receiving a prescription for opioids. The presence of an active opioid prescription at discharge (aOR 1.72, 95% CI: 1.22 – 2.44) and having been administered an opioid in the hospital also showed a positive association with having an opioid prescription at discharge (aOR 17.9, 95% CI: 11.0 – 29.3). Similarly, receiving an analgesic medication in the hospital as well as at discharge were both associated with an increased risk of giving an opioid medication upon hospital discharge,

aOR 1.43, 95% CI: 1.14 – 1.82 and aOR 6.51, 95% CI: 4.57 – 9.25, respectively. Finally, patients with more than 10 medications prescribed at discharge and more than 10 changes made to their discharge medication list were also more likely to be given an opioid as part of their discharge drug regimen, aOR 1.92, 95% CI:1.37 – 2.69 and 1.48, 95% CI: 1.09 – 2.03, respectively. Variables associated with a decreased risk of receiving an opioid at discharge were having a computerized-discharge prescription (aOR 0.37, 95% CI: 0.28 – 0.49), having more than one ED visits in the 1-year pre-admission (aOR 0.72, 95% CI: 0.62 – 0.85), previous history of analgesics (aOR 0.74, 95% CI: 0.58 - 0.96) and being administered an antidepressant in the hospital (aOR 0.60, 95% CI: 0.46 – 0.79).

With respect to the potential predictors of opioid-related MEs, the only variable associated with a higher risk was having an active opioid prescription at admission (aOR 5.15, 95% CI: 3.03 – 8.78). On the contrary, having the discharge prescription finalized with the electronic reconciliation software was associated with a 69% lower risk of having a ME for an opioid medication (aOR 0.31, 95% CI: 0.14 – 0.65). Albeit associations being non-significant, older ages were also positively associated with increased risk of MEs related to their opioid prescriptions.

4.8 Discussion

Our study showed that almost one in every two hospitalized patients left the hospital with an opioid prescription, with more than 80% of these prescriptions given to patients discharged from surgical units. Moreover, most patients with an opioid discharge prescription were opioid-naive prior to admission. Most patients filled their opioid prescription in the 30-days post-discharge period with 11% of patients with no discharge opioid prescription filling prescriptions from community physicians in the 30-days post-discharge. As such, findings from our study should be viewed as a reflection of either a communication gap between in-patient and community-based care teams or potentially gaps in access to care, as patients who experience acute pain after discharge but cannot reach their hospital-based team will reach out to a primary care provider for relief. Moreover, similarly to other studies looking at overall predictors of opioid prescription at discharge, in this cohort of hospitalized patients, we found that older patients, specific medical interventions such undergoing thoracic surgery, patients with diagnoses for pain syndromes were

all at a higher risk of receiving an opioid prescription at discharge. [83-85] In addition, higher number of medications and medication changes prescribed at hospital discharge were also associated with a higher likelihood of receiving an opioid medication at discharge, findings not previously investigated elsewhere.

In addition, we found that using an electronic medication software was associated with a substantially lower risk of having a ME associated with an opioid-related ME as well as with receiving an opioid prescription at discharge, which is in accordance with previous literature on the effectiveness of successful medication reconciliation to prevent MEs. [92,93]

Most studies, which looked at the amount of opioid prescriptions given at hospital discharge, focused largely on the surgical group of patients [126,127], and they estimated that the proportion of patients with an opioid prescription at discharge ranged from 6%, in Dutch patients, to 82% in US patients, for the same type of surgeries. [128] Multiple comparison studies demonstrated persistent and striking differences between North America, and particularly USA, and other countries in their opioid prescribing practices. [103,129] Our estimates are close to the ones found in the US, with 73% of surgical patients in our cohort having received an opioid prescription at discharge. Research within the USA has also shown that the quantity and the number of dispensed opioids has increased over time [80,130,131], suggesting that many are receiving opioids which are most likely not needed at all for adequate relief. It has been argued that overprescribing of opioids after surgery could lead to increased risk of adverse outcomes and adverse opioid-related behaviors such as prescription opioid misuse, opioid diversion and new or unintended prolonged opioid use. [80-82] While we cannot comment on the causal link between opioid exposure and these outcomes, we did observe high rates of ED visits, re-admissions or deaths in the one month post-discharge for patients with an opioid prescription at discharge. We also noticed that these rates were almost twice as high in patients with an opioid-related MEs such as therapy omissions, duplications or dose changes, and while for the majority statistically insignificant, the associations of opioid-related MEs pointed to an increased risk of healthcare utilization as compared to no MEs. Multiple interventions have been proposed to minimize opioid prescribing at the provider, system and patient level [132-135]. Future research should further explore whether accumulation of opioid use post-discharge is a

reflection of over-prescription by some in-hospital or community prescribers or of patient drug-seeking behavior.

Our results for opioid-related medication-errors found that most errors occurred in handwritten prescriptions, which reflects results from previously published studies. [117,121,136-139] However, most of these studies which looked at differences in rates of MEs between electronic and handwritten prescriptions focused largely on any medication-related errors [136,138,139], or have separated them in high- and low-risk groups. [138] Our findings reflect those of other studies, [87,117,139,140] which showed that MEs could be prevented using computer-generated prescriptions as we observed very low rate of opioid-related MEs in the groups of patients who received an electronic opioid prescription at discharge. Errors in prescriptions written by hand are largely introduced because of inaccurate medication reconciliation at time of discharge or incomplete retrieval of community medications list at the time of hospital admission. Given the importance of prescription opioids on the public health crisis of opioid-related mortality, our findings highlight the need for an accurate medication list and careful review of medications at transitions of care such as hospitalization. Policy efforts should be targeted at the implementation of feasible methods to audit errors in pharmacies and feed the data back to hospitals. [140]

The strength of this study is its ability to link data on medication use prior to admission, during the hospitalization as well as to integrate information on patient discharge prescriptions and dispensations post-discharge to comprehensively describe opioid-related MEs and quantify adverse drug events in the community. Most of what is known about the incidence and types of medication-related errors uses different, single-focus and narrow definitions of medication-related errors were used, which made comparison across these studies difficult.[121] Another recent study which looked at errors in opioid prescription for adult outpatients analyzed prescriptions as error-related if they deviated from best practice guidelines, had incorrect dates, medication frequencies, and lacked information on pill quantity. [139] None of these studies had the advantage of integrating multiple data sources and most used either only discharge prescriptions or pharmacy claims to determine the status of discharge prescriptions. In addition, none of these studies reported the extent of patient harms from the resulting opioid errors. In this study, we compared profiles of patients who received a discharge opioid prescriptions and further provided information on the

type of errors that may occur at transitions in care as well as the occurrence of adverse drug-related events and healthcare encounters.

Some limitations of our work merit emphasis. This is a descriptive study and as such, results should be interpreted with caution. First, we reported rates of adverse drug events across patients with and without opioid-associated ME and therefore, no causality should be inferred for these associations. Moreover, there is a potential for recall bias as measurement of information on adverse events was collected through self-reported interviews with patients. Third, we reported the risk of healthcare utilization such as ED visits, re-admission and death up to 3 months' post-discharge associated with an opioid-related ME and, while we used a propensity score to adjust for a number of patient and medical characteristics, confounding could still be a problem. Lastly, we did not build a predictive model but rather explored potential variables associated with the presence of a discharge opioid prescription and medication-related errors based on substantive knowledge and not statistical significance. Thus, our results should be considered as hypothesis-generating rather than definitive and reported associations should be further investigated in future studies.

4.9 Conclusion

In conclusion, we found a 13.4% rate of errors in opioid prescriptions written for hospitalized adults and, in this sample, almost exclusively present in handwritten prescriptions. A significant number of these errors were due to reconciliation errors or history errors. The utilization of computer-based prescribing and medication reconciliation software has the potential to improve the safety of opioid and medication prescribing, especially during critical periods of care such as hospital discharge after surgery.

Table 4-1. Baseline characteristics of the 3486 patients and of 1511 patients who filled of an opioid prescription within 90 days of hospital discharge.

	Overall (n = 3486)	**Opioid Prescription at Discharge**	
		No n = 1956 (56.1%)	**Yes** n = 1530 (43.9%)
Mean age (SD)	69.6 (14.9)	71.8 (15.5)	66.6 (13.7)
	N (%)	**N (%)**	**N (%)**
Male	2010 (57.7)	1083 (55.4	927 (60.6)
Surgical discharge units	1677 (48.1)	417 (21.3)	1260 (82.3)
Electronic reconciliation used	1464 (42.0)	893 (45.6)	571 (37)
Length of hospital stay (≥ 6 days)	2930 (84.0)	1689 (86.3)	1241 (81.1)
Health Services Utilization: 1 Year Before Admission	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
Emergency department visits	8.4 (8.5)	9.9 (15.1)	6.2 (14.1)
Hospitalizations	0.8 (1.9)	0.78 (2.2)	0.7 (1.5)
Physicians visits	10.9 (14.5)	11.3 (17.2)	10.4 (11.4)
Number of prescribing physicians	4.2 (3.4)	4.5 (3.4)	3.9 (3.2)
Number of physicians prescribing opioids	0.6 (1.2)	0.6 (1.1)	0.7 (1.3)
Number of dispensing pharmacies	1.4 (0.9)	1.4 (0.9)	1.4 (0.8)
Number of pharmacies dispensing opioids	0.4 (0.6)	0.39 (0.6)	0.4 (0.6)
Active Prescriptions at Admission	9.8 (10.1)	10.6 (11.0)	7.1 (8.2)
	N (%)	**N (%)**	**N (%)**
Active Opioid Prescription at Admission	504 (14.5)	272 (13.9)	232 (15.2)
Radiotherapy	215 (6.2)	70 (3.6)	145 (9.5)
Chemotherapy	262 (7.5)	77 (3.9)	185 (12.1)
Medication Use: 1 Year Before Admission	**N (%)**	**N (%)**	**N (%)**
History of opioid use	1206 (34.6)	670 (34.2)	536 (35.0)
≥ 3 opioid dispensations	104 (2.9)	49 (2.5)	55 (3.6)
History of long-acting opioids	146 (4.2)	60 (3.1)	86 (5.6)
Opioid dispensation within previous 30 days	666 (19.1)	353 (18.1)	313 (20.5)
History of methadone/buprenorphine	13 (0.4)	0 (0)	13 (0.9)
History of benzodiazepine use	1088 (31.2)	638 (32.6)	450 (29.4)
History of antidepressant use	706 (20.3)	431 (22.0)	275 (17.9)
SSRIs	336 (9.6)	220 (11.2)	116 (7.6)
SNRIs	167 (4.8)	96 (4.9)	71 (4.6)
TCAs	34 (1.0)	20 (1.0)	14 (0.9)
Other	189 (5.4)	108 (5.5)	81 (5.3)
History of analgesics use	1068 (30.6)	735 (37.6)	589 (38.5)
Acetaminophen	775 (22.2)	463 (23.7)	312 (20.4)
NSAIDS	563 (16.2)	257 (13.1)	306 (20.0)
COX-2	271 (7.8)	107 (5.5)	107 (6.9)
Targeted Comorbidities	**N (%)**	**N (%)**	**N (%)**
Mental illness	511 (14.7)	315 (16.1)	196 (12.8)
Depression	190 (5.5)	113 (5.8)	77 (5.0)

Anxiety	261 (7.5)	138 (7.1)	123 (8.0)
Bipolar disorders	165 (4.8)	131 (6.7)	34 (2.2)
Dementia	213 (6.1)	179 (9.2)	34 (2.2)
Substance & alcohol abuse	115 (3.3)	76 (3.9)	39 (2.6)
Pain Syndromes	1352 (38.8)	748 (38.2)	604 (39.5)
Neck and back pain	334 (9.6)	172 (8.8)	162 (10.6)
Arthritis and joint pain	1272 (36.5)	704 (35.9)	568 (37.1)
Cancer	1253 (35.9)	658 (43.0)	595 (30.4)
Digestive	309 (8.9)	144 (7.7)	165 (10.8)
Lung	488 (14.0)	156 (7.9)	332 (21.7)
Breast cancer	274 (7.9)	154 (7.9)	120 (7.8)
Urologic	248 (7.1)	126 (6.4)	122 (7.9)
Unspecified Cancer	88 (2.5)	51 (2.6)	37 (2.4)
Other Comorbidities That May Increase the Risk of Hospitalizations/ED visits	**N (%)**	**N (%)**	**N (%)**
Cardiovascular Diseases	1817 (52.1)	849 (55.5)	968 (49.5)
Cerebrovascular Diseases	334 (9.6)	222 (11.3)	112 (7.3)
Pneumonia	338 (9.7)	231 (11.8)	107 (6.9)
Chronic obstructive pulmonary disease	751 (21.5)	448 (22.9)	303 (19.8)
Renal Disease	364 (10.4)	266 (13.6)	98 (6.4)
Diabetes	791 (22.7)	488 (24.9)	303 (19.8)
Primary Reasons for the Hospitalization	**N (%)**	**N (%)**	**N (%)**
Cancer	388 (11.2)	93 (4.7)	295 (19.3)
Cardiovascular	1047 (30.1)	439 (22.4	608 (39.7)
Respiratory	532 (15.3)	391 (20.0)	141 (9.2)
Urinary Infections	173 (4.5)	139 (7.1)	34 (2.2)
Other Infections	110 (3.2)	91 (4.7)	19 (1.2)
Injection Poisonings	59 (1.7)	40 (20.4)	19 (1.2)
Digestive	256 (7.4)	188 (9.6)	68 (4.4)
Blood and Immune System	73 (2.1)	49 (2.5)	24 (1.6)
Musculoskeletal	121 (3.5)	51 (2.6)	70 (4.6)
Alcohol-related	47 (1.3)	46 (2.4)	1 (<0.1)
Fractures and Injuries	98 (2.8)	41 (2.1)	57 (3.7)
Endocrine and Metabolic	84 (2.4)	70 (3.6)	14 (0.9)
Skin	82 (2.4)	72 (3.7)	10 (0.6)
Other [1]	372 (10.7)	258 (13.2)	113 (73.8)
In-Hospital Medication Use	**N (%)**	**N (%)**	**N (%)**
Antidepressants	628 (18.0)	401 (20.5)	227 (14.8)
Opioids	2509 (72.0)	997 (50.9)	1512 (98.8)
Benzodiazepines	2278 (65.4)	1036 (52.9)	1242 (81.2)
Analgesics	1813 (52.0)	634 (32.4)	1179 (77.1)

[1] Other: nausea, dizziness, vomiting, swelling

Table 4-2. Characteristics of discharge prescription for patients who received an opioid at discharge according to previous history of opioid use

	Overall n = 1530	**Electronic Reconciliation Software**	
		Not Used (n=959, 63%)	**Used** (n=571, 37%)
Surgical Units	1260 (82.3)	775 (61.5)	485 (38.5)
Overall Medications	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
Number of medications prescribed	10.6 (5.0)	9.5 (5.2)	12.4 (4.1)
Number of changes in community medications	7.5 (4.9)	5.8 (4.7)	10.3 (3.7)
Number of new medication	5.5 (3.2)	4.4 (2.9)	7.3 (2.8)
Number of stopped medications	1.4 (2.6)	0.9 (2.6)	2.3 (2.1)
Number of unintended dose changes	0.5 (1.0)	0.5 (0.9)	0.7 (1.0)
Opioid Medications	**N (%)**	**N (%)**	**N (%)**
Medication-related errors	205 (13.4)	198 (20.6)	7 (1.2)
Type of medication-related errors			
Omission [1]	82 (40.0)	82 (41.4)	0
Status of medication discrepancy			
Omission - Reconciliation error	38 (46.3)	38 (46.3)	0
Omission - History error	44 (54.7)	44 (54.7)	0
Duplication [2]	32 (15.6)	32 (16.1)	0
Status of medication discrepancy			
Duplication - Reconciliation error	15 (46.9)	15 (46.9.)	0
Duplication - History error	17 (53.1)	17 (53.5)	0
Unintended dose changes [3]	91 (44.4)	84 (42.4)	7 (100)
Dose increases	29 (31.9)	22 (26.2)	7 (100)
Dose decreases	62 (68.1)	62 (73.8)	0
Type of Pain Regimen at Discharge	**N (%)**	**N (%)**	**N (%)**
Unimodal pain regimen	144 (9.4)	128 (13.3)	16 (2.3)
Opioid multi-modal regimen	1390 (90.8)	834 (86.9)	556 (97.4)
Opioid Dispensations Post-Discharge	**N (%)**	**N (%)**	**N (%)**
Filled an opioid prescription within 7 days	1070 (69.9)	669 (69.8)	401 (70.2)
Filled an opioid prescription within 30 days	1141 (74.6)	721 (75.2)	420 (73.6)

[1] Error of Omission was defined as a drug that was in the community drug list that was not prescribed at discharge and for which there was no documented evidence of having been stopped in the medical chart.
[2] Therapy duplication was defined as one drug with an active prescription in the community drug list and a second drug in the same four-digit Anatomic Therapeutic Class (ATC)[123] in the discharge prescription, where there was no evidence in the medical chart that the community drug had been stopped, or that it was to be intentionally continued.
[3] Unintended dose change was defined as a 25% or more increase or decrease in the prescribed dose of a community medication that was not documented in the medical chart as a change.

Table 4-3. Number of adverse-drug events in the 30 days' post-discharge period according to opioid-related medication error patients with an opioid prescription at discharge.

	Overall n = 1530	**Opioid-related Medication Error**	
		Yes (n= 205, 13.3%)	**No** (n = 1325, 86.6%)
Adverse drug event	62 (4.1)	11 (5.4)	51 (3.8)
Definitely preventable	51 (82.2)	8 (72.7)	43 (84.3)
Probably preventable	8 (12.9)	3 (1.4)	5 (9.8)
Definitely/probably not preventable	3 (4.8)	0 (0)	3 (5.9)

Table 4-4. Results from propensity-score adjusted model of the association of having an opioid-related medication error at hospital discharge as compared to no medication error and patients' healthcare utilization in the 30- and 90-days post-discharge.

	Overall (n = 1530)	**Patients with MEs** (n= 205, 13.3%)	**Patients without MEs** (n = 1325, 86.6%)	**Crude OR[1], 95% CI[2]**	**PS- Adjusted OR[3], 95% CI**
Healthcare encounters 30 days' post-discharge	**N (%)**	**N (%)**	**N (%)**		
ED visits	397 (25.1)	79 (38.5)	318 (24.0)	1.54 (1.20 – 1.98)	1.18 (0.69 – 1.82)
Readmission to hospital	161 (10.2)	48 (23.4)	113 (8.5)	1.96 (1.46 – 2.65)	2.32 (1.24 – 4.32)
ED visit, readmission, death	427 (27.9)	87 (42.4)	340 (25.7)	1.55 (1.21 – 1.98)	1.23 (0.76 – 1.98)
Healthcare encounters 90 days' post-discharge	**N (%)**	**N (%)**	**N (%)**		
ED visits	643 (42.0)	119 (58.0)	524 (39.5)	1.59 (1.25 – 2.01)	1.10 (0.70 – 1.72)
Readmission to hospital	254 (16.0)	71 (34.6)	183 (13.8)	1.86 (1.44 – 2.41)	1.10 (0.66 – 1.84)
ED visit, readmission, death	674 (44.1)	127 (61.9)	547 (41.3)	1.64 (1.29 – 2.10)	1.05 (0.67 – 1.65)

[1] OR = odds ratio

[2] CI = Confidence interval

[3] Variables considered in the construction/calculation of the propensity score of having an opioid-related medication error (omission, duplication, dose changes): 1) demographic characteristics: indicator for a patient randomized to the RightRx intervention group, age at admission, sex, 2) medical, prescription and healthcare use one-year before admission: number of dispensing pharmacies and prescribers, hospitalizations and emergency department visits, the receipt of

radiotherapy and/or chemotherapy services, history of cancer diagnoses, mental health diagnoses, substance and/or alcohol abuse/dependence, respiratory diseases, cardiovascular and cerebrovascular diseases, diabetes, previous use of psychotropic medications, 3) in-hospital characteristics: hospital unit discharged from (medical vs surgical) from, length of hospital stay, opioid administration during the index hospitalization, non-opioid pain medication administration, use of antidepressant and benzodiazepines, having a non-opioid medication prescribed at discharge, total number of medications prescribed at discharge and the total number of changes (news, stopped, dose changes) made to medications at discharge.

Table 4-5. Exploratory analyses of potential predictors of receiving an opioid prescription and having an opioid-related medication error at discharge.

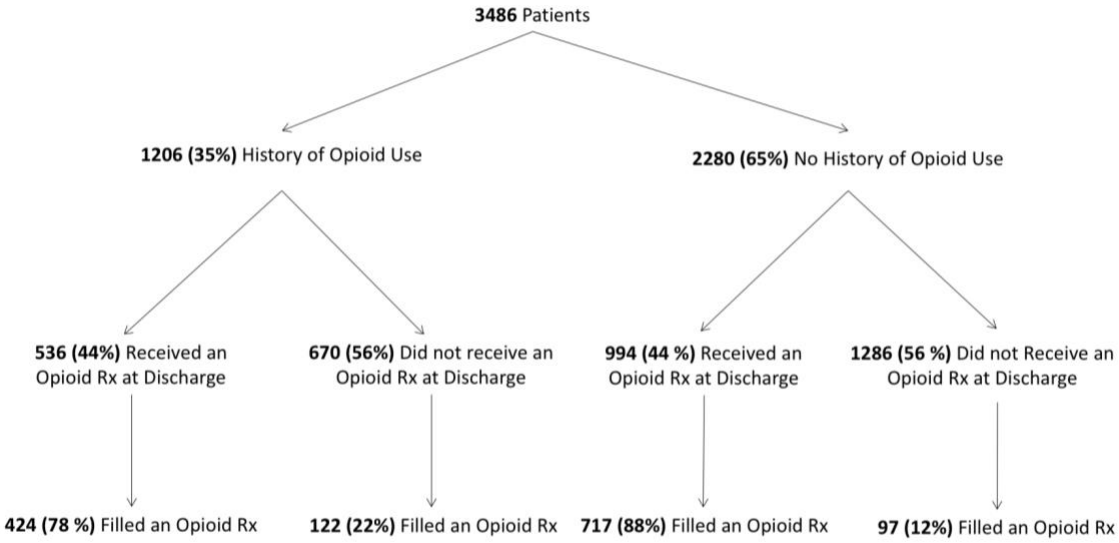
Variable	Adjusted OR[1] (95% CI)[2] Opioid Prescription	Adjusted OR (95% CI) Opioid-related Medication Error [3]
Patient Level		
Demographics		
Age, years		
18-35	Reference	Reference
35-64	1.38 (1.07 – 1.76)	1.38 (0.87 – 2.18)
65-79	2.19 (1.47 – 3.24)	1.59 (0.81 – 2.98)
80+	0.32 (0.16 – 0.59)	2.37 (0.48 – 11.5)
Sex		
Male	Reference	Reference
Female	0.92 (0.76 – 1.10)	0.94 (0.62 – 1.42)
Hospital unit discharge from		
Internal medicine	Reference	Reference
Cardiac surgery	0.67 (0.42 – 1.09)	0.41 (0.15 – 1.01)
Thoracic surgery	4.53 (3.17 – 6.48)	0.30 (0.12 – 0.72)
Electronic reconciliation used		
No	Reference	Reference
Yes	0.37 (0.28 – 0.49)	0.31 (0.14 – 0.65)
Length of hospital stay		
<6 days	Reference	Reference
≥ 6 days	1.03 (0.77 – 1.36)	0.61 (0.34 – 1.10)
Health Services Utilization: 1 Year Before Admission		
Emergency department visits		
0	Reference	Reference
1+	0.72 (0.62 – 0.85)	1.41 (0.81 – 2.46)
Hospitalizations		
0	Reference	Reference
1+	1.01 (0.88 – 1.16)	1.12 (0.74 – 1.69)
Radiotherapy		
No	Reference	Reference
Yes	1.37 (0.85 – 2.21)	1.57 (0.89 – 2.77)
Chemotherapy		
No	Reference	Reference
Yes	2.17 (1.15 – 4.08)	0.84 (0.54 – 1.29)
Medication Use: 1 Year Before Admission		
Active opioid prescription at admission		
No	Reference	Reference
Yes	1.72 (1.22 – 2.44)	5.15 (3.03 – 8.78)
History of opioid use		
No	Reference	Reference
Yes	1.22 (0.88 – 1.66)	NA[4]

History of benzodiazepine use		
No	Reference	Reference
Yes	1.02 (0.78 – 1.32)	0.88 (0.48 – 1.63)
History of antidepressant use		
No	Reference	Reference
Yes	0.81 (0.61 - 1.07)	0.98 (0.51 – 1.88)
History of analgesics use		
No	Reference	Reference
Yes	0.74 (0.58 – 0.96)	0.98 (0.51 – 1.89)
Targeted Comorbidities		
Mental illness		
No	Reference	Reference
Yes	1.17 (0.81 – 1.66)	1.12 (0.65 – 1.91)
Pain Syndromes		
No	Reference	Reference
Yes	1.27 (1.03 – 1.57)	0.91 (0.55 – 1.49)
Cancer Diagnoses		
No	Reference	Reference
Yes	1.12 (0.90 – 1.39)	1.02 (0.63 – 1.66)
In-Hospital Medication Use		
Antidepressants		
No	Reference	Reference
Yes	0.60 (0.46 – 0.79)	1.06 (0.58 – 1.96)
Opioids		
No	Reference	Reference
Yes	17.9 (11.0 – 29.3)	0.71 (0.23 – 2.17)
Benzodiazepines		
No	Reference	Reference
Yes	0.88 (0.12 – 1.15)	0.79 (0.43 – 1.45)
Analgesics		
No	Reference	Reference
Yes	1.43 (1.14 – 1.82)	1.38 (0.85 – 2.26)
Pain medicine injection		
No	Reference	Reference
Yes	1.18 (0.86 – 1.62)	1.42 (0.88 – 2.29)
Medications Prescribed at Discharge		
Analgesics		
No	Reference	Reference
Yes	6.51 (4.57 – 9.25)	1.51 (0.83 – 2.74)
Total number of medications prescribed at discharge		
0-4	Reference	Reference
5-6	0.98 (0.76 – 1.26)	0.72 (0.32 – 1.62)
7-9	0.92 (0.69 – 1.22)	0.74 (0.39 – 1.42)
10+	1.92 (1.37 – 2.69)	1.10 (0.48 – 2.53)
Total number of medication changes at discharge		
0-4	Reference	Reference

5-6	0.78 (0.56 – 1.08)	0.69 (0.42 – 1.17)
7-9	0.70 (0.49 – 0.98)	0.71 (0.43 – 1.21)
10+	1.48 (1.09 – 2.03)	1.07 (0.57 – 1.99)

[1] OR = odds ratio
[2] CI = Confidence interval
[3] The model was fitted only among patients who had received an opioid prescription at discharge (n=1530).
[4] This variable was not included in the model exploring variables potentially predicating medication discrepancies due to sparseness of data. Since the conceptualization of the main variable of opioid-related medication errors relied on information of the previous history of patient's opioid use, all patients with/without a medication error were previous users of opioids and by definition, there is no patient who was opioid-naïve and had a discrepancy in their opioid medication written at discharge.

Figure 4-1. Flowchart of patients with an opioid prescription at discharge, according to use prior to admission and after discharge



Appendix 4- 1. Omissions for control patients (**excluding all those with status = "OTHER"**) and in intervention patients where RightRx was not used

	CDL tab		DRx tab			
Omission	**Drug in CDL**	**Listed in Hospital**	**Taking**	**Drug at Discharge**	**Status of drug at discharge**	**New status given to drug**
NO	A	YES	= YES/ YES, but not as prescribed/ "-"	A	Continue/modify /stop	Prescribed/ prescribed/ stopped
NO	A	NO	-	A	New	Prescribed
YES – Reconciliation Error	A	YES	= YES/ YES, but not as prescribed/ "-"	A	Not indicated in chart	DELETE
YES – History Error	A	NO	-	-	-	DELETE
YES – Seemingly Intended	A	YES	= NO/ Tx Completed	-	-	DELETE

Drug in CDL indicates whether or not the medication was in the CDL list (i.e. medications dispensed in 3 months prior to hospitalization, from RAMQ);

Listed in Hospital represents the variable in the CDL tab of the chart abstraction tool that indicates whether or not the medication was found in the patient's chart (given values of YES and NO, respectively);

Taking represents the variable in the CDL tab of the chart abstraction tool that indicates whether or not the patient was taking the drug at the time of admission; this variable can have values of "YES", "YES, but not as prescribed", "Treatment (Tx) completed", "NO", "Not indicated in chart", or can be missing/blank (which is indicated in this table as "-");

Drug at Discharge indicates whether or not the medication was listed in the DRx tab of the chart abstraction tool ("-" in the table indicates that it was not listed in the DRx tab);

Status of drug at discharge indicates the status the drug was given in the DRx tab of the chart abstraction tool; this variable can have values of "continue", "modify", "stop", "new", "not indicated in chart", or can be missing/blank entirely (represented as "-" in the table).

New status given to drug indicates the status we will give to drugs in the discharge prescription as it is presented to PADE pharmacist reviewers; it can take on one of two values, "Prescribed" or "Stopped". "DELETE" indicates that the medication needs to be removed from the discharge prescription list presented to pharmacists. N/A = not applicable.

<u>Interpretation of line 1:</u>

IF

1. The patient was control patient who did not have the status of OTHER, *and*
2. Drug A is listed in the CDL, *and*
3. Drug A had a value of "YES" for the **Listed in Hospital** variable in the CDL tab of the chart abstraction tool, *and*
4. Drug A had a value of "YES" or "YES, but not as prescribed" for the **Taking** field in the CDL tab of the chart abstraction tool *or* had a missing value for this field, *and*
5. Drug A was also listed in the DRx tab of the tool, *and*
6. Drug A was given a status of "continue", "modify", or "stop" in the DRx tab of the tool,

THEN **this is not an omission**, and the drug should be given a status of "prescribed", "prescribed", or "stopped" in list presented to pharmacist reviewers, accordingly.

Interpretation of line 3:

IF

1. The patient was control patient who did not have the status of OTHER, *and*
2. A drug A is listed in the CDL, *and*
3. Drug A had a value of "YES" for the **Listed in Hospital** variable in the CDL tab of the chart abstraction tool, *and*
4. Drug A had a value of "YES" or "YES, but not as prescribed" for the **Taking** field in the CDL tab of the chart abstraction tool *or* had a missing value for this field, *and*
5. Drug A was also listed in the DRx tab of the tool, *and*
6. Drug A was given a status of "not indicated in chart" in the DRx tab of the tool,

THEN **this is an omission, due to a reconciliation error**, and the medication should be deleted from the list of discharge prescription medications presented to pharmacist reviewers.

Interpretation of line 4:

IF

7. The patient was control patient who did not have the status of OTHER, *and*
8. A drug A is listed in the CDL, *and*
9. Drug A had a missing value for the **Listed in Hospital** variable in the CDL tab of the chart abstraction tool, *and*
10. Drug A had a missing value for the **Taking** field in the CDL tab of the chart abstraction tool, *and*
11. Drug A was also NOT listed in the DRx tab of the tool, *or* had a missing value in the DRx tab of the tool,

THEN **this is an omission, due to a history error**, and the medication should be deleted from the list of discharge prescription medications presented to pharmacist reviewers.

Appendix 4 -1a. Omissions in control patients with **taking = not indicated in chart** and in intervention patients where RightRx was not used

Omission	Drug in CDL	Listed in Hospital	Taking	Drug at Discharge	Status of drug at discharge	Frequency (at discharge)	Units per intake (at discharge)	Dose (at discharge)	New status given to drug
NO	A	YES	Not indicated in chart	A	Not indicated in chart	value	value	-	Prescribed
NO	A	YES	Not indicated in chart	A	Not indicated in chart	value	-	value	Prescribed
YES – Seemingly intended	A	YES	Not indicated in chart	A	Not indicated in chart	- / Not indicated in chart	- / Not indicated in chart	- / Not indicated in chart	DELETE
YES – Seemingly intended	A	YES	Not indicated in chart	A	Not indicated in chart	value	- / Not indicated in chart	- / Not indicated in chart	DELETE
YES – Seemingly intended	A	YES	Not indicated in chart	A	Not indicated in chart	- / Not indicated in chart	value	- / Not indicated in chart	DELETE
YES – Seemingly intended	A	YES	Not indicated in chart	A	Not indicated in chart	- / Not indicated in chart	- / Not indicated in chart	value	DELETE

Interpretation of line 3:

IF

12. The patient was control patient who had a status of "not indicated in chart" in the **Taking** field , *and*
13. A drug A is listed in the CDL, *and*
14. Drug A had had a value of "YES" for the **Listed in Hospital** variable in the CDL tab of the chart abstraction tool, *and*
15. Drug A was listed in the DRx tab of the tool, *and*
16. Drug A had a status of "not indicated in chart" in the DRx tab as well as in the **Frequency**, **Units Per Intake** and **Dose** fields

THEN **this is an omission, that is seemingly intended**, and the medication should be deleted from the list of discharge prescription medications presented to pharmacist reviewers.

Appendix 4- 1b. Omissions in control patients with **status=OTHER** and in intervention patients where RightRx was not used

Omission	**Drug in CDL**	**Listed in Hospital**	**Drug at Discharge**	**Status of drug at discharge**	**Frequency (at discharge)**	**Units per intake (at discharge)**	**Dose (at discharge)**	**New status given to drug**
NO	A	NO	A	New	value	value	-	Prescribed
NO	A	NO	A	New	value	-	value	Prescribed
NO	A	YES	A	Not indicated in chart	value	value	-	Prescribed
NO	A	YES	A	Not indicated in chart	value	-	value	Prescribed
YES – Reconciliation error	A	YES	A	Not indicated in chart	- / Not indicated in chart	- / Not indicated in chart	- / Not indicated in chart	DELETE
YES – Reconciliation error	A	YES	A	Not indicated in chart	value	- / Not indicated in chart	- / Not indicated in chart	DELETE
YES – Reconciliation error	A	YES	A	Not indicated in chart	- / Not indicated in chart	value	- / Not indicated in chart	DELETE
YES – Reconciliation error	A	YES	A	Not indicated in chart	- / Not indicated in chart	- / Not indicated in chart	value	DELETE

YES – History Error	A	NO	-	-	-	-	-	DELETE

Appendix 4-1c. Omissions in intervention patients where RightRx was used or partially used

Omission	Drug in CDL	Taking	Drug at Discharge	Status of drug at discharge	New status given to drug
NO	A	= YES/ YES, but not as prescribed/ NO/ "-"	A	Continue/modify/stop	Prescribed/Prescribed/ Stopped
YES – Seemingly Intended	A	= Tx Completed	-	-	N/A

Appendix 4-2. Therapy Duplications in control patients and in intervention patients where RightRx was not used

Therapy duplication?	**Patient Status**	**Drug in CDL**	**Listed in Hospital**	**Taking**	**Drug at Discharge**	**Status of drug at discharge**	**New status given to drug**
NO	≠ OTHER	A	YES	= YES/YES, but not as prescribed/ Missing	A	Stop	Stopped
					A’	NEW	Prescribed
YES – Reconciliation Error	≠ OTHER	A	YES	= YES/YES, but not as prescribed/ Missing	A	Not indicated in chart	DELETE
					A’	NEW	Prescribed
YES - Seemingly intended if new status=prescribed	Any	A	YES	= Not indicated in chart	A	Not indicated in chart	Follow rules on page 3
					A’	NEW	Prescribed
YES –-Seemingly intended if new status=prescribed	OTHER	A	YES	= YES/YES, but not as prescribed/ Missing/ Not indicated in chart	A	Not indicated in chart	Follow rules on page 4

					A’	NEW	Prescribed
YES – Seemingly intended	≠ OTHER	A	YES	= YES/YES, but not as prescribed/ Missing	A	Continue/modify	Prescribed
					A’	NEW	Prescribed
YES - Seemingly intended	≠ OTHER	A	NO	Missing	A	NEW	Prescribed
					A’	NEW	Prescribed
YES – Seemingly intended	≠ OTHER	A	YES	= NO/Tx Completed	A	NEW	Prescribed
					A’	NEW	Prescribed

Appendix 4-2a. Therapy duplications in intervention patients where RightRx was used

Therapy duplication?	**Drug in CDL**	**Listed in Hospital**	**Taking**	**Drug at Discharge**	**Status of drug at discharge**	**New status given to drug**
NO	A	YES	= YES/YES, but not as prescribed/ Missing	A	Stop	Stopped
				A’	NEW	Prescribed
YES – Seemingly intended	A	YES	= YES/YES, but not as prescribed/ NO/ Missing	A	Continue/modify	Prescribed

				A’	NEW	Prescribed
YES – Seemingly intended	A	YES	= Tx Completed	A	NEW	Prescribed
				A’	NEW	Prescribed

Overall information guiding rationale for definition of omissions (and duplications)

- Every drug in the CDL list in the chart abstraction tool, which is pulled from the RAMQ and modified by chart abstractors based on patient charts, is transferred over to the DRx tab unless Listed in Hospital = “NO” or Taking = “NO” or “Treatment Completed”.
- Chart abstractors then compare a patient’s discharge prescription with medications listed in the DRx tab.
    - If a medication is in the DRx tab (having been carried over from the CDL tab), but is missing from the discharge prescription, it is given the status of “Not indicated in chart”
    - If a physician has not accounted for home meds at discharge (variable “resume home meds” = “NO” in chart abstraction tool), all home meds are given the status “Not indicated in chart” unless otherwise specified in the LG form.
    - If chart abstractors did not have access to sufficient sources to identify/properly document CDL meds (i.e. CDL missing or partially missing, aside from what has been pulled from the RAMQ), patients are given the status “Other” and all CDL meds pushed over to the DRx tab will be given the status “Not indicated in chart”, **even if they have been listed in the patient’s discharge prescription.**

- If a pharmacy fax lists a med as “unfilled” or “not dispensed”, then in the CDL tab this med is labelled taking = “not indicated in chart” and, when this drug is transferred over to the DRx tab, its status becomes “not indicated in chart”, whether or not it has been prescribed at discharge

5. Objective 2

Kurteva S, Abrahamowicz M, Weir D, Gomes T, Tamblyn R. Determinants of Long-Term Opioid Use in Hospitalized Patients. [Prepared for journal submission]

5.1 Preamble

The second manuscript aimed to provide knowledge as to which patient-, system- and prescriber-characteristics are associated with the development of long-term opioid use one year post-discharge. Based on analyses reported in Objective 4, long-term opioid therapy (LTOT) was defined as 60 days of opioid cumulative use during the follow-up period. Demographic, clinical, healthcare and prescription claims data were used to retrieve information on various potentially modifiable factors. Their independent associations with time to LTOT were studied using Cox proportional hazards model.

This manuscript has been written as a standalone paper for journal submission.

5.2. Title page and footnotes

Title: Determinants of Long-Term Opioid Use in Hospitalized Patients

Contributing authors: Siyana Kurteva [1,2], Michal Abrahamowicz [1], Daniala Weir [3], Tara Gomes [4,5,6], Robyn Tamblyn [1,2,7,8]

Affiliations of all contributing authors:

[1] Department of Epidemiology and Biostatistics, McGill University, Montreal, Canada

[2] Clinical and Health Informatics Research Group, McGill University, Montreal, Canada

[3] Division of Pharmacoepidemiology and Clinical Pharmacology, Department of Pharmaceutical Sciences, Utrecht, Utrecht, Netherlands

[4] Institute of Health Policy Management and Evaluation, Toronto, Canada

[5] Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, Canada

[6] ICES, Toronto, ON, Canada

[7] Department of Medicine, McGill University Health Center, Montreal, Canada

[8] McGill University Health Centre, Montreal, Canada

Corresponding author:

Siyana Kurteva

Clinical & Health Informatics Research Group, Department of Medicine, McGill University

1140 Pine Ave W., Montreal, Quebec, Canada, H3A 1A3

Email: siyana.kurteva@mail.mcgill.ca

Tel: +1 (514) - 632 – 5838

ABSTRACT

Background: Long term opioid use is an increasingly important problem related to the ongoing opioid epidemic. Hospitalization has been identified as a risk factor for both initiation of opioids and long term use, yet particular hospitalization-related risk factors have not been well defined. The purpose of this study was to identify patient, hospitalization and system level determinants of long term opioid therapy (LTOT) among patients recently discharged from hospital.

Methods: A cohort of hospitalized patients in Quebec, Canada, who filled an opioid prescription within 3 months' post-discharge was assembled. We retrieved data from the provincial health insurance agency to measure medical service and prescription drug use in the year prior to and after hospitalization. LTOT was defined as time-varying cumulative opioid duration of ≥ 60 days. A multivariable Cox Proportional Hazards model was utilized to determine which factors were associated with time to the first LTOT occurrence.

Results: Overall, 22.4% of the 1,551 study patients were classified as LTOT, who had a mean age of 66.3 years (SD=14.3) and 52.9% were female. Having no drug copay status (adjusted hazard ratio (aHR) 1.91, 95% CI: 1.40 – 2.60), being a LTOT user before the index hospitalization (aHR 6.05, 95% CI: 4.22 – 8.68) or having history of benzodiazepine use (aHR 1.43, 95% CI: 1.12 – 1.83) in the year prior to admission were all associated with an increased likelihood of LTOT. Cardiothoracic surgical patients had a 40% lower LTOT risk (aHR 0.55, 95% CI: 0.31 – 0.96) as compared to medical patients. In addition, initial opioid dispensation of > 90 milligram morphine equilants (MME) was also associated with higher likelihood of LTOT (aHR 2.08, 95% CI: 1.17 – 3.69).

Conclusion: Several patient-level characteristics associated with an increased risk of ≥ 60 days of cumulative opioid use. The results could be used to help identify patients who are at high-risk of continuing opioids beyond guideline recommendations and inform policies and intervention programs to curb excessive opioid prescribing.

5.3 Introduction

LTOT has been associated with an increased risk of opioid-related adverse events. [50,96,141] While opioids may be appropriate for short-term treatment for pain, long-term opioid use has not been shown to improve pain relief. [17,49,50] Patients on long-term opioid therapy may become physically dependent and experience opioid withdrawal symptoms upon treatment cessation. [17] Therefore, they may continue opioid therapy as an attempt to resolve their withdrawal symptoms and continue treatment for reasons other than analgesic benefits.[48]

The Centers for Disease Control and Prevention (CDC) guideline defines long-term opioid therapy (LTOT) as use of opioids on most days for more than 3 months [50], but in a recent empirical study we have found that the risk of opioid-related adverse events does not increase considerably beyond 60 days (Appendix 5-D.1.a). [142] We observed only moderate increases in risk above 60 days of cumulative use with no evidence of further impact of durations longer than 100 days of use.
There is a gap in evidence related to determinants of risk of LTOT using this empirically- derived definition of 60 days.

Previous studies have reported that the most common predictors associated with an increased risk for LTOT included age [66,67,69-71], sex [66,67,69-71], arthritis [62,69,70], race [67,69], the presence of chronic pain [67,69,70] and mental illnesses such as anxiety and depression. [62,67,71,72] Increased LTOT risk was also observed with certain opioid prescribing/consumption patterns; characteristics of the first opioid prescription such as opioid doses of >90MME and longer duration (days' supply). [20,62,67,69] However, the evidence regarding the predictors associated with LTOT is limited to the data elements available in administrative data, such as patient characteristics and prescription charactertistics in the community, and these databased do not typically have data on medications used in hospital or discharge information. [53]

Hospitalization itself may inadvertently be a risk factor to initiating opioids. [67] It could also be a window of opportunity for in-hospital practitioners to curb prescribing and reduce the risk of opioid-related morbidity and mortality. However, inadequate communication of changes in medication at the time of hospital discharge is also a well-established problem. [59] As a result, community physicians may continue opioids started in the hospital, for acute pain relief, as they

have no information about the treatment indication nor the expected duration of therapy, which could be an opportunity for reducing unnecessary opioid prescribing. [60,61]

There is a large variation in prescribing of opioids between providers [143], which is unrelated to patient characteristics. The association between organizational factors/in-hospital prescriber characteristics and their contribution to the initiation, maintenance or prevention of LTOT is poorly understood. In addition, the type of opioid prescribed at hospital discharge varies across different attending physicians and residents. [144,145] This may be due to differences in physician knowledge regarding pain management strategies as well as variation in attending opioid prescribing patterns when working alone vs supervising a resident. In addition, certain provider characteristics such as greater number of years in practice, white race, male sex, as well as provider's specialty, have been associated with increased likelihood of prescribing an opioid and at a higher dose. [145-149] Thus, physician-prescribing behavior for post-discharge analgesia may be associated with an increased risk of LTOT, with some physicians prescribing opioids beyond what is required for appropriate pain management and guideline recommendations. In this study, in addition to patient demographics and medical characteristics, we were able to incorporate information on provider characteristics to better understand their contribution to the development of post-discharge LTOT.

Objectives: The purpose of this study was a) to estimate the proportion of hospitalized patients with LTOT in the one year after hospital discharge, and b) to identify modifiable patient, prescriber and system-level risk factors for long-term prescription opioid use compared to episodic use.

5.4 Methods

Setting: We carried out a secondary analysis of a cluster-randomized trial on discharge medication reconciliation conducted at the McGill University Health Centre (MUHC).[108] The MUHC is an over 1000-bed quaternary care teaching hospital in Montreal (Canada) that operates within the universal health care plan of the province of Quebec (RAMQ). This plan covers all hospitalizations, and essential medical care for provincial residents. It also provides drug insurance for registrants 65 years of age and older, income security recipients, and those not insured through their employer (approximately 50% of the Quebec population). Ethics approval was provided by

the MUHC Research Ethics Board. Privacy Commissioner approval was obtained to link clinical and administrative data from the Commission d'accès à l'information du Quebec.

Participants: A prospective cohort of medical and surgical hospitalized patients discharged from the MUHC between October 2014 and November 2016 were followed 12 months' post-discharge. To be eligible for the original trial, patients had to be 18 years of age or older at admission, admitted from the community or transferred from another hospital, with at least one-year continuous provincial healthcare coverage prior to hospital admission. To be included in this study, patients needed to fill at least one opioid prescription during the 90 days following their hospital discharge. Cohort entry corresponded to the date of the first opioid dispensation.

Data Sources: Multiple data sources were assembled and linked to address the study objectives. For each patient, demographic, clinical, healthcare use and prescription data were retrieved from admission notes as well as provincial healthcare administrative databases (RAMQ medical services and prescription claims) in the year prior to and after the hospitalization, for which the patient was enrolled. Dates of admission/discharge, admitting/discharge unit, patient demographics, diagnoses at admission and discharge, major procedures (surgeries, treatment interventions), were retrieved from the MED-ECHO hospitalization database. Medications at admission, in-hospital as well as those prescribed at discharge were abstracted from the MUHC Data Warehouse. This is one of the only databases in the world that links information on medication use prior to admission, during the hospitalization as well as medications prescribed at discharge and dispensed in the community post-discharge.

Study Measurements and Predictors of Long-Term Opioid Use:

Long Term Opioid Use (LTOT): Opioid use in the one-year post-discharge period was ascertained using RAMQ pharmacy administrative claims. For each prescription filled, these claims document the specific medication using the drug identification number (DIN), strength, dispensing date and quantity, duration of the prescription, and prescribing physician. DINs that mapped to Anatomical Therapeutic Chemical Classification System (ATC) codes N02A, R05DA were used to identify opioids (see Appendix 5-A for opioid inclusion criteria and dose calculation). Duration of opioid use was based on the number of days of medication supplied in each dispensed prescription. A

drug-by-day matrix was created for each patient, for the 12 months following discharge, using the date and duration of each opioid prescription. On each day, an individual was classified as having a dispensed supply of an opioid available or not. As definitions of LTOT vary in different studies, standardized and evidence-driven definitions are needed. [53] In our recent study, the estimated non-linear effect of cumulative opioid duration showed no further increases in risk of opioid-related adverse events beyond 2 months of use (Appendix 5-D.1.a). [142] Thus, in this study we used this empirically-defined 60 days' threshold to define LTOT.

Patient-Related Characteristics: Patient demographic characteristics and comorbidities are important modifiers of a patient's health condition and have been associated with increased risk of opioid-related morbidity and mortality. [66,67,70] Socioeconomic status, which has also been hypothesized to be related to important risk factors for long-term opiate use, was measured by using income-indexed information on the patient's copay status in the RAMQ drug program. Information on age at admission, and sex was extracted from hospital charts. Pain disorders, cancer diagnosis, mental health diagnoses, and conditions associated with abuse were measured at the time of hospital admission and during the hospital stay as fixed-in-time covariates identified by using ICD-9 from medical service claims and ICD-10 codes from hospitalization data. Other co-existing illnesses were measured and adjusted for using the Charlson comorbidity index (CCI), using unformation collected during the one-year baseline period (see Appendix 5-B for a full list of covariates included in the model).

Drug and Healthcare Utilization: Drug and healthcare utilization are important measures involved in key pathways linking opioid prescribing patterns and risk of prescription opioid harm. Psychoactive drugs such as antidepressants, benzodiazepines, Z-drugs or antipsychotics, when used together with opioids, have been associated with an increased risk of opioid-dependency and rates of adverse events. [62,72,76] Using RAMQ medical services databases in the one year prior to admission, we measured previous number of emergency department (ED) visits, hospitalizations as well as the distinct number of prescribing physicians.

Medication Use and Hospitalization Characteristics: Opioid and non-opioid (NSAIDs, COX2 inhibitors, gabapentin, acetaminophen) medications administered as part of the in-hospital pain regimen as well as other medications such as antidepressants and benzodiazepines, which may

increase patients' risk of becoming long-term opioid users were extracted from the hospital pharmacy system using corresponding ATC codes. Use of these medications prior to admission was identified using RAMQ pharmacy administrative claims. For surgical patients, information on the type of surgery received (thoracic vs upper-gastrointestinal) was retrieved from the MED-ECHO hospitalization database.

Prescribing Physician and System-level Characteristics: Information on the attending physician's gender, language, training status (resident, attending physician) and number of years since licensure were abstracted from the patient medical chart, the medication reconciliation software databases and the hospital data warehouse.

Opioid Discharge Prescription and Initial Dispensation: Treatment changes made to opioid medications from the community were evaluated by using data retrieved from patients' discharge prescriptions in comparison to their community drug list. A categorical variable for whether a given opioid was stopped, continued or newly prescribed was derived. A binary variable for the presence of an opioid as part of the discharge pain regimen was constructed: patients with newly added or continued opioids were flagged as having an opioid prescription. In addition, dose, duration and type of initial opioid dispensed (e.g. oxycodone, hydromorphone) were extracted from the RAMQ pharmacy claims.

Statistical Analyses: Descriptive statistics were used to compare LTOT patients versus episodic users with respect to patient, provider and hospital unit characteristics. Main analyses relied on time-to-event methodology. [150]A multivariable Cox Proportional Hazards (PH) model was utilized to determine which factors were associated with the development of LTOT within the one year post-discharge period. Start of follow-up corresponded to the date of the first opioid dispensation. End of follow-up corresponded to the day when the patient first met the criteria for LTOT, or to right censoring at the end of follow-up or death, whichever came first. Moreover, since a patient is considered exposed based on periods of medication possession, patients were temporarily censored during subsequent hospital admissions as opioid use during hospitalization was not available if admitted to non-MUHC hospitals. Since the goal of the analyses was to explore the independent associations of various factors potentially related to LTOT, all *a priori* selected covariates were retained in the model. In addition, since patients could have subsequent

hospitalizations and emergency department visits that could influence their risk of LTOT, a time-varying variable for the cumulative number of past post-discharge hospitalizations and ED visits, updated during the follow-up period, was included to adjust for any changes made to patient's medications influenced by subsequent hospital re-admissions and emergency department visits. We tested the PH assumption and, for continuous covariates their possibly non-linear relationships with the logarithm of the hazard using the flexible spline-based extension of Cox model. [151] For each covariate, the results were presented as adjusted hazard ratios (HR), with 95% confidence intervals (CI).

Sensitivity Analyses: To account for the fact that patient medications and medical history (comorbidities) would most likely change over the course of one year, in sensitivity analyses, updated information on selected co-morbidities was represented by additional time-varying covariates. In addition, we adjusted for a time-varying count of number of distinct prescribers, from discharge until a given day, updated during the follow-up. This was done to assess if and how the hazard of LTOT may vary with increasing number of prescribers - an indicator of fragmentation in care which which may be due to increased opioid seeking behavior and increasing dependence. [44,46] These analyses were additionally adjusted for a time-varying indicator of being currently exposed to ≥2 opioid products. Moreover, to account for the fact that the association of interest may vary depending on previous opioid use, we stratified the analyses by (i) previous LTOT and (ii) new opioid users. For these stratified analyses, due to small sample sizes within each stratum, variable selection was necessary and was based on a combination of substantive knowledge and backward selection. All MSM Cox PH models were implemented with SAS version 9.4 (SAS Institute, Cary, NC). All non-lineaar relationships were tested using customized programs in R, including the CoxFl*ex* function for NL/TD effects and the WCE package. [152]

5.5 Results

Overall, 1511 patients were discharged alive from study units and filled an opioid prescription within 3 months' post-discharge. The proportion of patients who went on to become LTOT by accumulating more than 60 days' supply of opioids was 22.4% (n=338) (Table 5-1), for the incidence rate of 26.8 (95 % CI: 24.0 – 29.9) per 100 person-years. Among those 338 patients, the mean time to LTOT was 115.5 (SD = 76.8) days. As compared to episodic opioid users, LTOT patients had higher mean starting daily opioid doses (42.0 vs 33.8 MME). LTOT patients also had

higher mean-over-time daily doses during the follow-up (57.4 vs 35.7 MME) (Table 5-1).

Figure 5-1 shows the breakdown of patients with respect to their previous history of opioid use, opioid administration during the hospitalization and the receipt of an opioid prescription at hospital discharge. Among patients who filled at least one opioid dispensation three months' post-discharge, more than half were opioid-naïve with no history of documented opioid use one year prior to their admission (n=884, 58.5%). Almost one third of all patients (n=627, 41.5%) who simultaneously met the following 3 criteria: 1) filled a opioid prescription within three month's post-discharge, 2) were previous users, and 3) were administered an opioid during the index admission, did not receive an opioid at discharge (n=158, 27.2%)

The average age for LTOT patients was 66.3 (SD = 14.3) and more than half were female (179, 52.9%) (Table 5-2). As compared to episodic users, LTOT patients were more likely to have no drug copay status as they were income security recipients (32.8% vs 15.0%). Among all patients who later became LTOT users in a post-discharge year, 41.7% met the definition of a LTOT user in the year prior to admission (in contrast to only 4.3% among the episodic users). In the year prior to admission, LTOT patients were more likely to have used benzodiazepines, antidepressants or other non-opioid analgesics, have had a history of mental illness, pain syndromes and higher CCI, and were more likely to be non-surgical patients (61.2% vs 25.3%), less likely to receive an opioid prescription at discharge (65.7% vs 82.4%), and more likely to have more than a 7-day supply on their first dispensation post-discharge (Table 5-2b).

In multivariable analysis, patients who had no copayment status had almost twice higher hazard of becoming LTOT users as compared to patients who had a 'full' copay drug insurance status (aHR 1.91, 95% CI: 1.40 – 2.60). As expected, patients who were previous LTOT users were several times more likely to also meet the criteria for LTOT in one-year post-discharge (aHR: 6.05, 95% CI: 4.22 – 8.68). History of benzodiazepine use (aHR: 1.43, 95% CI: 1.12 – 1.83), having a higher CCI (aHR: 1.77, 95% CI: 1.06 – 2.98)) and a starting daily opioid dose of >90 MME (aHR: 2.08, 95% CI: 1.17 – 3.69) were all independently associated with increased likelihood of becoming a LTOT user. Having undergone cardiothoracic surgery, as compared to internal medicine patients, was associated a 45% lower risk of LTOT in the post-discharge period (aHR 0.55, 95% CI: 0.31 – 0.96).

Results from sensitivity analyses that adjusted for selected time-varying characteristics were generally similar, with a few exceptions. First, we found an association between recent cancer diagnoses and the risk of LTOT, showing an increased risk (aHR: 1.39, 95% CI: 1.07 – 1.81) (Appendix 5-C.1). Second, after having adjusted for a time-varying count of distinct prescribing physicians and an indicator for using ≥2 opioid products, there was a 34% increased risk of LTOT use associated with having an initial days' supply of >7 days (aHR: 1.34, 95% CI: 1.05 – 1.72). Finally, having between 2 and 3 prescribing physicians led to more than doubling in the risk of becoming a LTOT user, relative to patients with only 1 prescriber (aHR: 2.43, 95% CI: 1.85 – 3.19) (Appendix 5-C.2). In stratified analyses, out of all opioid-naïve patients (n=1050), 117 (11.1%) went on to become LTOT users. On the other hand, among patients who were LTOT users in the year pror to admission (n=192), only 68 (35.4%) were LTOT during the follow-up period. The risk of LTOT was 54% higher among patients with a history of pain syndromes compared to patients with no history (aHR: 1.54, 95% CI: 1.01 – 2.23) *(*Appendix 5-C.4*).* The risk of LTOT was more than doubling when initial days' supply post-hospitalization exceeded >7 (aHR: 2.62, 95% CI: 1.52 – 4.53).

5.6 Discussion

Our study showed that 22.4% of hospitalized patients were characterized as LTOT users, accumulating more than 60 days of opioid use in the one-year after discharge. There was an increased risk of LTOT among patients with no drug copay status, history of opioid use, history of benzodiazepine use, higher comorbidity index and higher starting daily dose in the first opioid prescription dispensed post-discharge, whereas, surgical compared to medical patients had a decreased risk of LTOT.

Other studies have also confirmed that previous opioid use leads to greater risks of developing LTOT. [66,69-72] Previous research, which used the more conservative, 90-day definition of LTOT, also found that mental health diagnoses, history of pain diagnoses and benzodiazepine use to be associated with an increased the risk of LTOT. [66,67,69] In our study, these patients' characteristics were also associated with an increased risk, albeit some of these associations were non-significant. Having the first opioid prescription written by an in-hospital prescriber was not associated with an increased risk of LTOT. In addition, it has been frequently argued that prescribing behavior and characteristics of physicians may contribute to the opioid epidemic.

[153,154] In our study, however, none of the physicians' characteristics such as years of practice, sex or having a resident approve the discharge prescription were associated with greater risks of LTOT post-discharge. One study found that LTOT patients of residents were more likely to receive early refills following their primary care clinic visits when compared to attending physicians' patients. [144] Another report has found no significant association between having a resident physicians and opioid misuse. [155] In our study, the lack of difference in risk of LTOT associated with the status of the in-hospital prescriber might be attributed to the fact that residents provided similar care with respect to opioid prescribing when compared to attending physicians because they are being trained and monitored by the same physicians. These findings, which reflect opioid prescribing by the in-hospital physician, show that in-hospital prescribers may have the opportunity to reduce the occurrence of prolonged opioid use by providing patients with adequate pain treatment strategies, without contributing to the development of LTOT.

We found that initial post-discharge dose and days' supply of the opioid dispensation both lead to an increased likelihood of transitioning into LTOT, with initial doses having a greater impact on the risk of LTOT than opioid days' supply in the main analyses. As previously reported [67], among patients who became LTOT users, we also observed escalation in doses during the follow-up, leading up to their development of LTOT, which was not the case for episodic users. Previous research has also found that both initial dose and duration of opioid use were associated with an increased risk of LTOT. [19,21,106]A few of the studies, which examined the initial opioid prescription characteristics and the likelihood of long-term opioid use, found initial duration of use to be associated with a higher likelihood of LTOT than initial doses. [20,21,156] We observed a similar trend in stratified analyses, when looking at the risk among previous LTOT users only. However, similar to other studies, opioid dose was associated with greater increases in risk of LTOT for opioid-naïve patients. [62,67] These findings suggest that limiting and selecting an optimal initial opioid duration may be more important than initial dose to reduce the risk of subsequent opioid use, especially for previous opioid users. Moreover, initial opioid exposure characteristics should be used to profile patients who might be at risk of transitioning into LTOT.

This study's strength is its ability to link data on medication use prior to admission, during the hospitalization and dispensations post-discharge. Using multiple data sources, such as

administrative prescription and medical services claims as well as clinical information, enhances the internal validity of the study by providing detailed covariate information. This allowed us to consider not only patient-, but also provider- and system-level predictors of LTOT. Accounting for any healthcare services use during the follow-up period and including measures such as number of unique prescribing physicians allowed us to examine the effect of poor coordination of care, flare-ups and complications requiring walk-in and ED visits, on the risk of LTOT. We also assessed the impact of any new conditions or diagnoses recorded post-discharge that may impact the risk of LTOT by time-updating these indicators. The risk for continued opioid use has been considered as a central component of quality care assessment. [157,158] Measuring and defining LTOT is key to understanding potential risk factors, monitoring prevalence and incidence of LTOT, and potentially improving clinical practices. [159] Yet, in previous studies, arbitrarily-defined measures of LTOT were used without addressing the appropriateness of their cut-offs. In this study, we apply a novel and evidence-driven approach to defining LTOT, which selected cumulative duration of 60 days as the primary definition. This was based on our previous findings examining the impact of various opioid-consumption patterns and the risk of opioid-related adverse events. [142]In addition, definitions in previous studies did not incorporate prescription characteristics such as fill date and days' supply and only relied on having prescriptions filled during a specified window. [69,160-163] In this study, we used a time-varying definition of cumulative opioid duration constructed based on days' supply and fill dates of the opioid prescriptions. This allowed us to account for gaps between prescriptions and overlapping dispensations, and capture more accurately consistent opioid use.

Some limitations of our work merit emphasis. First, in our analyses, we used prescription duration as recorded by the pharmacist, but since opioids are usually prescribed on a *prn* basis, exposure mismeasurement is possible. We did not capture actual opioid consumption. Nevertheless, subsequent opioid prescription fills are suggestive of patient's continual opioid consumption. Moreover, a consistent limitation across all opioid research using administrative datasets, including this one, is the inability to account for non- prescription opioid use. However, a study conducted in a similar cohort of universally covered patients in the province of Quebec found older adults to be less likely to experience an opioid overdose and seek illicit opioids as compared to younger people. [164] Most patients in this study cohort were 64 years of age or older and thus, we expect illicit use to have little impact on the main findings. Future research should use consistent

and evidence-driven definitions of LTOT was well as data from multiple healthcare systems to incorporates measures on patients' healthcare providers and practice environments and replicate our findings in larger populations cohorts. In addition, definitions of LTOT should be validated with patient self-reports. There is also a possibility of residual confounding due to unmeasured confounders, such as pain severity. Our decision to include only patients with at least one opioid dispensation post-discharge, as well as to include time-varying measures of selected comorbities and patient's healthcare utilization, which reflect changes in patient's physical condition, disease progression and comorbidity profile, reduces concerns about potential bias due to confounding by indication.

5.7 Conclusion

We found increases in the risk of chronic opioid use with multiple patient-level characteristics such as patients with no drug copay status, surgical patients, patients with history of opioid use, history of benzodiazepine use, higher comorbidity index and higher starting daily dose in the first opioid prescription dispensed post-discharge. Quantifying factors associated with the development of LTOT post-discharge is an important step in identifying and targeting patients who need more frequent clinical vigilance and better pain treatment strategy.

Table 5-1. Comparison of average daily and starting opioid dose between episodic and long-term opioid users by number of cumulative and number of continuous days of use to define long term use.

	Number of People	Time to Long-Term Use (Mean, SD)	Average Daily Dose (MME) Mean, SD	Average Starting Dose (MME) Mean, SD
Cumulative ≥60 days' supply of opioids				
Episodic Opioid Users	1173	343.0 (69.6)	35.7 (27.4)	33.8 (22.7)
Long-Term Opioid Users	338	115.5 (76.8)	57.4 (76.5)	42.0 (44.9)

Figure 5-1. Flowchart of patients' history of opioid use prior to admission, during the hospitalization, at hospital discharge and 3 month's post-discharge

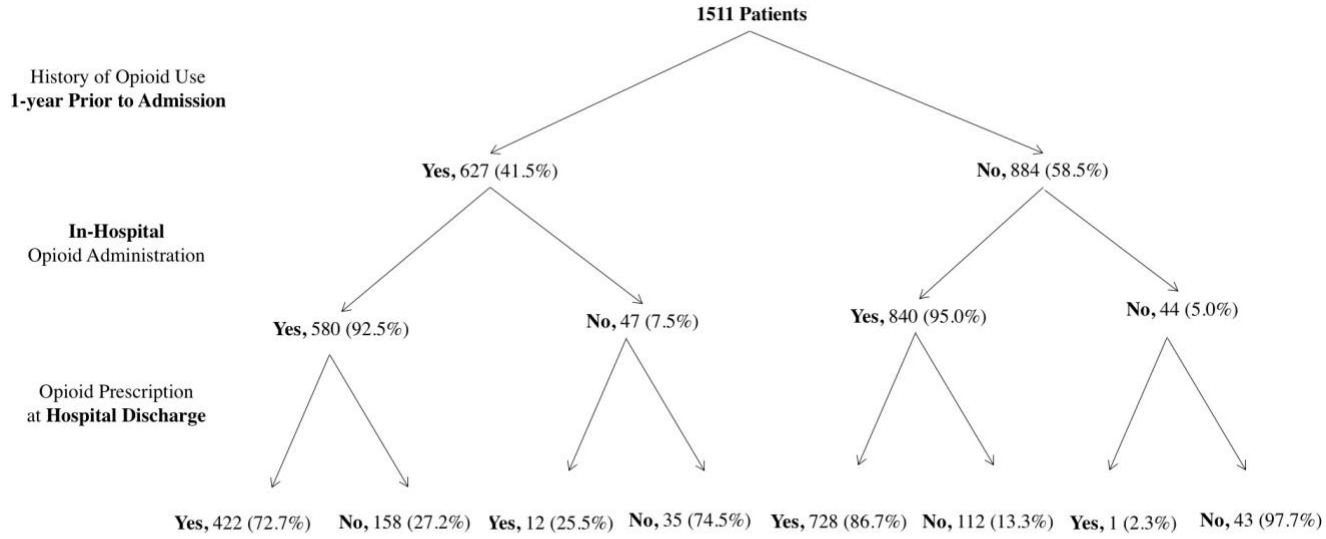


Table 5-2a. Characteristics of long term opioid users' vs episodic opioid users based on cumulative opioid ≥60 days' supply of opioids to define long-term use

	Long-term Opioid Users n = 338 (22.4%)	**Episodic Opioid Users** n = 1173 (77.6%)
Patient Demographics		
	N (%)	***N (%)***
Age		
Mean (SD)	66.3 (14.3)	67.0 (13.0)
≤64	128 (37.9)	360 (30.7)
>64	210 (62.1)	813 (69.3)
Sex		
Female	179 (52.9)	449 (38.3)
Male	159 (47.0)	724 (61.7)
Drug copay status		
None	111 (32.8)	176 (15.0)
Partial	76 (22.5)	249 (21.2)
Full	151 (44.7)	748 (63.8)
Healthcare and Medication Use: One Year Before Admission		
	N (%)	***N (%)***
Emergency department visits/Hospitalizations	98 (29.0)	406 (34.6)
Opioid use		
No use	125 (36.9)	935 (79.1)
Episodic use (1-60 days)	72 (21.3)	187 (15.9)
Long-term opioid use (≥ 60 days)	141 (41.7)	51 (4.3)
Benzodiazepine use	178 (52.7)	333 (28.4)
Antidepressant use	140 (41.4)	201 (17.1)
Non-opioid pain medications use	198 (58.6)	355 (30.3)
Comorbidities		
Mental illness/Substance & alcohol abuse	80 (23.7)	153 (13.0)
Charlson Comorbidity Index		
0	24 (7.1)	195 (16.6)
1-2	97 (28.7)	438 (37.3)
≥3	217 (64.2)	540 (46.0)
Characteristics Measured During the Hospitalization		
Medications Administered		
Opioids	300 (88.8)	1120 (95.5)
Non-opioid pain medications	226 (66.9)	885 (75.4)
Type of Surgery Received		
No surgery	207 (61.2)	297 (25.3)
Cardiothoracic	45 (13.3)	469 (39.9)

Gastrointestinal	7 (2.1)	45 (3.8)
Thoracic	69 (20.4)	308 (26.3)
Unrelated	10 (3.0)	54 (4.6)
Admission to the ICU	29 (8.6)	169 (14.4)
Hospital Discharge Prescription		
Pain Regimen		
Opioid prescription coming from the in-hospital prescriber	222 (65.7)	967 (82.4)
Treatment Indication		
Surgery	131 (39.8)	876 (74.7)
Cancer	268 (79.3)	966 (82.4)
Pain Syndromes	222 (65.7)	735 (62.7)
System Level Characteristics		
Years of Practice		
0-20	104 (30.5)	229 (19.5)
20-40	164 (48.5)	808 (68.9)
>40	70 (20.7)	136 (11.6)
Sex		
Male	247 (73.3)	1046 (89.8)
Female	90 (26.7)	117 (10.1)
Pharmacist on the Discharging Unit	227 (67.2)	674 (57.5)
Discharge Prescription Signed By		
Attending physician	93 (27.5)	217 (18.5)
Resident	245 (72.5)	956 (81.5)
Hospital Discharge Destination		
Home	325 (96.2)	1153 (98.3)
Long-term care facility	13 (3.8)	20 (1.7)

Note: 174 people died during the follow-up, which is one year since their first opioid dispensation within 3 months' post-discharge. These patients were censored at the time of death.

Table 5-2b. Characteristics of the first opioid dispensation within 90 days' post-discharge

	Long-term Opioid Users n = 338 (22.4%)	**Episodic Opioid Users** n = 1173 (77.6%)
Type of Opioid Dispensed		
Codeine	21 (6.2)	26 (2.2)
Hydromorphone	138 (40.8)	281 (23.9)
Morphine	24 (7.1)	44 (3.8)
Oxycodone	136 (40.2)	816 (69.6)
Fentanyl	18 (5.3)	4 (0.3)
MME Dose		

≤20	101 (29.9)	316 (26.9)
20-50	169 (50.0)	707 (60.3)
50-90	44 (13.0)	142 (12.2)
>90	24 (7.1)	8 (0.7)
Days' Supply		
≤7	123 (36.4)	660 (56.3)
>7	215 (63.6)	513 (43.7)

Table 5-3. The association between patient, medication and system-level characteristics and time to long term use within the one-year post-discharge.

	Hazard Ratio	**95% CI**
Patient Characteristics		
Age		
≤64	Reference	Reference
>64	1.19	0.88 – 1.60
Sex		
Male	Reference	Reference
Female	1.22	0.97 – 1.55
Drug copay status		
Full	Reference	Reference
Partial	1.12	0.82 – 1.52
None	1.91	1.40 – 2.60
Healthcare and Medication Use: One Year Before Admission		
Emergency department visits/hospitalizations		
0	Reference	Reference
≥1	0.93	0.72 – 1.21
Opioid use		
No use	Reference	Reference
Episodic use (1-60 days)	1.94	1.43 – 2.69
Long-term opioid use (≥ 60 days)	6.05	4.22 – 8.68
Benzodiazepine use		
No use	Reference	Reference
Use	1.43	1.12 – 1.83
Antidepressant use		
No use	Reference	Reference
Use	1.20	0.92 – 1.58
Non-opioid medications use		
No use	Reference	Reference
Use	1.21	0.92 – 1.57
Comorbidities		
Mental illness/Substance & alcohol use disorder		

No	Reference	Reference
Yes	1.04	0.78 – 1.39
Charlson Comorbidity Index		
0	Reference	Reference
1-2	1.54	0.94 – 2.51
≥3	1.77	1.06 – 2.98
Characteristics Measured During the Hospitalization		
Medications Administered		
Opioids		
No	Reference	Reference
Yes	1.15	0.73 – 1.83
Non-opioid pain medications		
No use	Reference	Reference
Use	0.60	0.37 – 1.02
Type of Surgery Received		
No surgery	Reference	Reference
Cardiothoracic	0.55	0.31 – 0.96
Gastrointestinal	0.81	0.34 – 1.93
Thoracic	0.88	0.53 – 1.47
Unrelated	0.64	0.30 – 1.39
Hospital Discharge Prescription		
Pain Regimen		
Opioid prescription coming from the in-hospital prescriber		
No	Reference	Reference
Yes	0.87	0.67 – 1.14
Treatment Indication		
Cancer		
No	Reference	Reference
Yes	1.01	0.74 – 1.38
Pain Syndromes		
No	Reference	Reference
Yes	1.23	0.96 – 1.59
System Level Characteristics		
Attending Physician Characteristics		
Years of Practice		
0-20	Reference	Reference
20-40	1.13	0.83 – 1.54
>40	1.21	0.83 – 1.77

Sex		
Male	Reference	Reference
Female	0.99	0.71 – 1.39
Language		
English	Reference	Reference
French	1.05	0.77 – 1.43
Discharge Prescription Signed By		
Attending physician	Reference	Reference
Resident	0.95	0.73 – 1.25
Hospital Discharge Destination		
Home	Reference	Reference
Long-term care facility	1.06	0.58 – 1.96
System Level Characteristics		
Type of Opioid Dispensed		
Codeine	Reference	Reference
Hydromorphone	0.78	0.47 – 1.31
Morphine	0.78	0.40 – 1.44
Oxycodone	0.68	0.39 – 1.17
Fentanyl	0.85	0.39 – 1.86
MME Dose		
≤20	Reference	Reference
20-50	1.00	0.75 – 1.35
50-90	0.99	0.65 – 1.52
>90	2.08	1.17 – 3.69
Days' Supply		
≤7	Reference	Reference
>7	1.21	0.95– 1.56

Note: All results obtained using a Cox Proportional Hazards Model. All variables were included in the model.

Appendix 5-A. Codes Used for Drug Classification

ATC codes used to identify opioids: N02A (opioids), R05DA (opium alkaloids and derivatives)
Exclusions: Not all drug forms were included in the analyses. Only patches and tablets of these medications were kept. Injectable, liquid and rectal forms were excluded. Methadone and buprenorphine/naloxone combinations were kept to define subclinical patient populations but were excluded from all dosing/duration calculations as these medications are used to treat addiction and we want to focus on the association of duration/dose of opioids used for pain relief.

Appendix 5-A.1. Opioid Morphine Equivalent Conversion Factor [1]

Drug Name	Conversion Factor
Buprenorphine patch[2]	12.6
Buprenorphine tab or film	10
Butorphanol	7
Codeine	0.15
Dihydrocodeine	0.25
Fentanyl buccal or SL tablets, or lozenge/troche[3]	0.13
Fentanyl film or oral spray[4]	0.18
Fentanyl nasal spray[5]	0.16
Fentanyl patch[6]	7.2
Hydrocodone	1
Hydromorphone	4
Levorphanol tartrate	11
Meperidine hydrochloride	0.1
Methadone	3
Morphine	1
Nalbuphine	1
Opium	1
Oxycodone	1.5
Oxymorphone	3
Pentazocine	0.37
Tapentadol	0.4
Tramadol	0.1

[1] Centers for Disease Control and Prevention, Atlanta, GA, May 2014.
[2] The MME conversion factor for buprenorphine patches is based on the assumption that one milligram of parenteral buprenorphine is equivalent to 75 milligrams of oral morphine and that one patch delivers the dispensed micrograms per hour over a 24-hour day. Example: 5 ug/hr buprenorphine patch * 24 hrs = 120 ug/day buprenorphine = 0.12 mg/day buprenorphine = 9 mg/day oral morphine milligram equivalent. In other words, the conversion factor not accounting for days of use would be 9/5 or 1.8. However, since the buprenorphine patch remains in place for 7 days, we have multiplied the conversion factor by 7 (1.8 X 7 = 12.6). In this example, MME/day for four 5 μg/hr buprenorphine patches dispensed for use over 28 days would work out as follows: Example: 5 ug/hr buprenorphine patch * (4 patches/28 days) * 12.6 = 9 MME/day.
[3] The MME conversion factor for fentanyl buccal tablets, sublingual tablets, and lozenges/troche is 0.13. This conversion factor should be multiplied by the number of micrograms in a given lozenge/troche.
[4] The MME conversion factor for fentanyl film and oral spray is 0.18. This reflects a 40% greater bioavailability for films compared to lozenges/tablets and 38% greater bioavailability for oral sprays compared to lozenges/tablets.
[5] The MME conversion factor for fentanyl nasal spray is 0.16, which reflects a 20% greater bioavailability for sprays compared to lozenges/tablets.
[6] The MME conversion factor for fentanyl patches is based on the assumption that one milligram of parenteral fentanyl is equivalent to 100 milligrams of oral morphine and that one patch delivers the dispensed micrograms per hour over a

24 hour day. Example: 25 ug/hr fentanyl patch * 24 hrs = 600 ug/day fentanyl = 60 mg/day oral morphine milligram equivalent. In other words, the conversion factor not accounting for days of use would be 60/25 or 2.4. However, since the fentanyl patch remains in place for 3 days, we have multiplied the conversion factor by 3 (2.4 X 3 = 7.2).
In this example, MME/day for ten 25 µg/hr fentanyl patches dispensed for use over 30 days would work out as follows: Example: 25 ug/hr fentanyl patch * (10 patches/30 days)* 7.2 = 60 MME/day.

Sources:

1) Centers for Medicare & Medicaid Services. Opioid Oral Morphine Milligram Equivalent (MME) Conversion Factors. https:\\www.cms.govMedicarePrescription-Drug-CoveragePrescriptionDrugCovContraDownloadsOpioid-Morphine-EQConversion-Factors-vFeb-.pdf. Accessed: September 5, 2019
2) Svendsen, K., Borchgrevink, P., Fredheim, O., Hamunen, K., Mellbye, A., & Dale, O. (2011). Choosing the unit of measurement counts: the use of oral morphine equivalents in studies of opioid consumption is a useful addition to defined daily doses. Palliative Medicine, 25(7), 725–732. http://doi.org/10.1177/0269216311398300

Appendix 5-B. Inclusion of Covariates and Their Assessment in the Cox Proportional Hazards Models

Appendix 5-B.1. Description of available data on drug, patient, provider and system level characteristics

	Description	**Measurement**	**Timing of Measurement**	**Functional Form**
Opioid-related Characteristics				
Opioid Dispensations				
ATC code	Anatomical Therapeutic Chemical Classification System code used to identify opioids and other concurrent medications that the patient is taking **Opioids ATC Included: N02A, R05DA**	RAMQ prescription claims.	In the community one year prior to admission and one year post-discharge	N/A
Dose	The daily amount of drug taken by patient will be calculated based on information about the number of tablets prescribed, strength and number of days' supply; daily dose will be converted to milligram morphine equivalents to facilitate comparisons across opioids.	From RAMQ prescription claims	In the community one year prior to admission and one year post-discharge	Continuous, categorical, time-varying
Duration	The days' supply on the drug claim as entered by the pharmacist	From RAMQ prescription claims	In the community one year prior to admission and one year post-discharge	Continuous, categorical, time-varying
Type of opioid	Type of opioid ingredient. E.g; Hydromorphone, oxycodone, morphine, fentanyl, etc.	From RAMQ prescription claims	One year post-discharge	Categorical, time-varying

Opioid Administration in Hospital				
ATC code	Anatomical Therapeutic Chemical Classification System code used to identify administered opioids	Hospital pharmacy	In hospital	Categorical
Opioid Prescription at Hospital Discharge				
Status of opioid medication	Continued or stopped from community, newly prescribed at discharge	From patient chart	At hospital discharge	Categorical, time-fixed
Reason for opioid prescribing	Pain-related including having had surgery as well as other diagnoses such as having a cancer or a pain syndrome diagnose	From patient chart	In-hospital	Categorical, time-fixed
Presence of a multi-modal pain management regimen	The opioid prescription at hospital discharge was part of multi-modal pain treatment regimen	From patient chart	At hospital discharge	Categorical, time-fixed
Patient-level Characteristics				
Demographics				
Age		From patient chart	Admission to hospital	Continuous, time-varying
Sex	Male, Female	From patient chart	Admission to hospital	Binary, time-fixed
Drug insurance status	E.g.; Full copay, partial copay, no copay Serves as proxy for socio-economic status.	From RAMQ drug programs	Admission to hospital	Categorical, time-fixed
Co-Existing Illnesses				
History of mental health conditions	E.g.; Anxiety, depression, psychiatric diagnosis, mood disorder, and post-traumatic stress disorder	ICD-9 from RAMQ medical services and ICD-10 codes from hospitalization data	In community one year prior to admission, in hospital, post-discharge	Binary per condition, time-varying
Pain syndromes	E.g.; Chronic back pain, back and neck pain, back disorder, arthritis, migraine, headache, fibromyalgia, fracture	ICD-9 from RAMQ medical services and ICD-10 codes from hospitalization data	In community one year prior to admission, in hospital, post-discharge	Binary per condition, time-varying

Health conditions Associated with abuse	E.g.; Alcohol abuse, drug abuse	From patient chart. Also from RAMQ medical series and prescription claims	In community one year prior to admission, in hospital, post-discharge	Binary per condition, time-varying
Cancer diagnosis	E.g.; Metastatic, Non-metastatic, Lymphoma	ICD-9 from RAMQ medical services and ICD-10 codes from hospitalization data	In community one year prior to admission, in hospital, post-discharge	Binary per condition, time-varying
Other comorbidities	E.g.; Acute MI, cerebrovascular diseases, chronic kidney, COPD, diabetes, heart failure, hypertension, ischemic heart disease, liver, obesity	ICD-9 from RAMQ medical services and ICD-10 codes from hospitalization data	In community one year prior to admission, in hospital, post-discharge	Binary per condition, time-varying
Drug and Healthcare Utilization				
Use of potential interacting drugs increasing the risk of opioid misuse	E.g.; Selective serotonin reuptake inhibitors, other antidepressants, benzodiazepines, other antipsychotic drugs, central nervous system depressants, psychotropic medication	ATC codes, DIN, Generic Drug name used to extract information from RAMQ prescription claims, hospital data, patient chart.	In community one year prior to admission, in-hospital, post-discharge	Binary per drug, time-varying
Use of non-opioid pain medications	E.g.; NSAIDS, COX-2, Acetaminophen, Gabapentin, anti-migraine medications, muscle-relaxants, other anti-inflammatories and anti-rheumatoid medications	ATC codes, DIN, Generic Drug name used to extract information from RAMQ prescription claims, hospital data, patient chart.	In community one year prior to admission, in-hospital, post-discharge	Binary per drug, time-varying

Number of ED visits and hospitalizations	Total number of ED visits and hospitalizations	From RAMQ prescription claims and hospital data	One year prior to hospital admission & one year post-discharge	Categorical, continuous, time-varying
Number of physicians	Number of unique prescribing physicians	From RAMQ medical services	One year prior to hospital admission & one year post-discharge	Categorical, continuous, cumulative time-varying
Other Patient Drug Behavior Characteristics				
Time since hospital discharge	The time elapsed between patent's hospital discharge and their first opioid dispensation	From RAMQ prescription claims and hospital data	One year post-discharge	Continuous, time-fixed
Add-on opioid	Recent add-on of another opioid type in the past 2 weeks	From RAMQ medical services	One year post-discharge	Categorical, time-varying
In-hospital Characteristics				
Hospital patient is admitted to	Montreal General or Royal Victoria hospital	From hospital chart	Upon admission to the hospital	Binary, time-fixed
Hospital unit the patient is admitted to	Medical or surgical unit	From hospital chart	Upon admission to the hospital	Binary, time-fixed
Discharge destination	Home community, long term care	From hospital chart	Upon discharge	Binary, time-fixed
Attending Physician Characteristics				
Years of practice	Number of years practiced since graduation from medical school	From hospital chart, Collège des médecines du Quebec	Upon discharge	Categorical, time-fixed
Sex	Male, Female	From hospital chart	Upon discharge	Binary, time-fixed
Language	Home community, long term care	From hospital chart	Upon discharge	Binary, time-fixed
Discharge prescription signed by	Attending physician vs resident	From hospital chart	Upon discharge	Binary, time-fixed

Appendix 5-C. Sensitivity analyses

Appendix 5-C. 1. Sensitivity analyses including selected time-varying characteristics in the model.

	HR	**95% CI**
Non-opioid pain medications use		
No	Reference	Reference
Yes	1.39	0.97 – 1.82
Benzodiazepine use		
No	Reference	Reference
Yes	0.81	0.44 – 1.48
Antidepressant use		
No	Reference	Reference
Yes	1.67	1.16 – 2.41
Mental illness/substance & alcohol abuse		
No	Reference	Reference
Yes	0.87	0.66 – 1.15
Pain syndromes		
No	Reference	Reference
Yes	1.21	0.95 – 1.53
Cancer		
No	Reference	Reference
Yes	1.39	1.07 – 1.81

Appendix 5-C. 2. Sensitivity analyses including time-varying count of distinct prescribing physicians and an indicator for using ≥2 opioid products in the model.

	HR	**95% CI**
MME Dose		
≤20	Reference	Reference
20-50	1.10	0.82 – 1.49
50-90	0.97	0.64 – 1.48
>90	2.91	1.62 – 5.23
Initial days' supply		
≤7	Reference	Reference
>7	1.34	1.05 – 1.72
Prescribing physicians		
0-1	Reference	Reference
2-3	2.43	1.85 – 3.19
≥4	5.95	4.33 – 8.18

Appendix 5-C. 3. Sensitivity analyses including selected time-varying characteristics, distinct prescribing physicians and an indicator for using ≥2 opioid products in the model.

	HR	95% CI
Non-opioid pain medications use		
No	Reference	Reference
Yes	1.38	1.01 – 1.87
Benzodiazepine use		
No	Reference	Reference
Yes	0.81	0.44 – 1.48
Antidepressant use		
No	Reference	Reference
Yes	1.67	1.15 – 2.39
Mental illness/substance & alcohol abuse		
No	Reference	Reference
Yes	0.89	0.68 – 1.18
Pain syndromes		
No	Reference	Reference
Yes	1.07	0.84 – 1.36
Cancer		
No	Reference	Reference
Yes	1.06	0.81 – 1.39
Prescribing physicians		
0-1	Reference	Reference
2-3	2.41	1.83 – 3.17
≥4	5.99	4.34 – 8.26

Appendix 5 -C.4. The association between patient, medication and system-level characteristics and time to long term use within the one-year post-discharge among opioid-naïve users (n=1050)

	Hazard Ratio	95% CI
Drug copay status		
Full	Reference	Reference
Partial	1.27	0.80 – 2.01
None	2.25	1.46 – 3.47
Benzodiazepine use		
No use	Reference	Reference
Use	1.70	1.15 – 2.51
Cancer diagnoses		
No use	Reference	Reference
Use	1.42	0.96 – 2.10
Pain syndromes		

No use	Reference	Reference
Use	1.54	1.01 – 2.23
Pain Regimen		
Opioid prescription coming from the in-hospital prescriber		
No	Reference	Reference
Yes	0.59	0.39 – 0.91
MME Dose		
≤20	Reference	Reference
20-50	0.90	0.75 – 1.40
50-90	1.06	0.56 – 2.01
>90	6.99	2.05 – 23.8

Note: All results obtained using a Cox Proportional Hazards Model. All variables were included in the model.

Appendix 5-C.5. The association between patient, medication and system-level characteristics and time to long term use within the one-year post-discharge among previous opioid users (n=192)

	Hazard Ratio	**95% CI**
Drug copay status		
Full	Reference	Reference
Partial	2.03	1.13 – 3.64
None	2.05	1.14 – 3.70
Benzodiazepine use		
No use	Reference	Reference
Use	1.96	1.19 – 3.23
Non-opioid medications use		
No use	Reference	Reference
Use	1.76	1.08 – 2.88
Surgery during the index admission		
No	Reference	Reference
Yes	0.35	0.21 – 0.61
Pain Regimen		
Opioid prescription coming from the in-hospital prescriber		
No	Reference	Reference
Yes	0.61	0.36 – 1.01
MME Dose		
≤20	Reference	Reference
20-50	1.14	0.66 – 1.97
>50	1.89	0.87 – 4.13
Days' Supply		
≤7	Reference	Reference

>7	2.62	1.52– 4.53

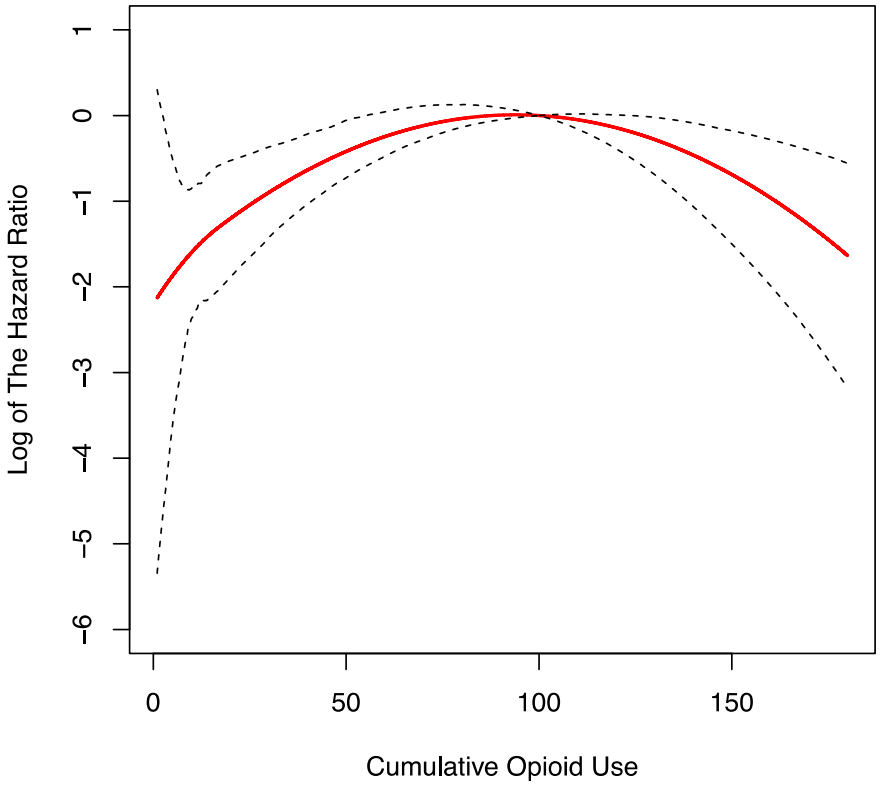
Note: All results obtained using a Cox Proportional Hazards Model. All variables were includein the model.

Appendix 5-D. Empirically-defined threshold for long-term opioid therapy.

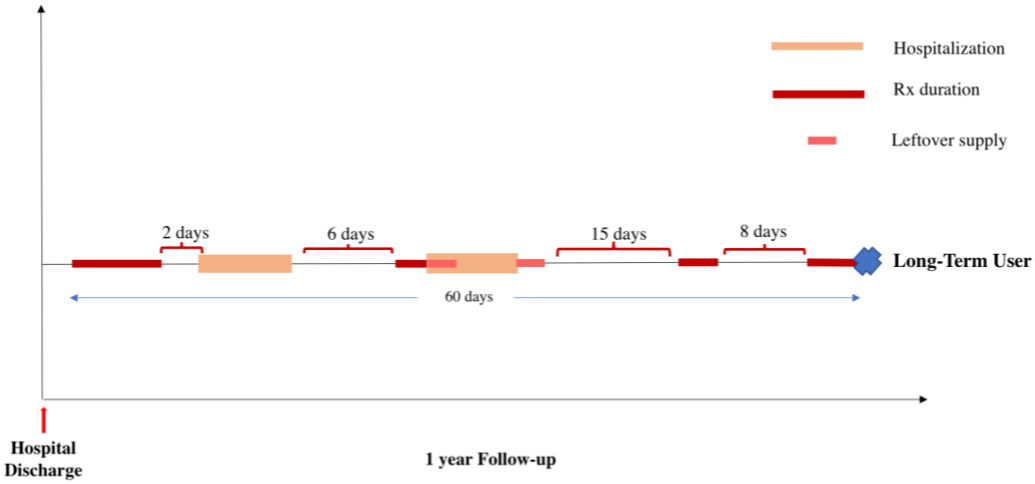
Appendix 5-D.1. Comparison of goodness of fit of flexible marginal structural models, with alternative time-varying opioid exposure metrics**.**

Opioid Exposure Metric	**Statistical Model**	**AIC**
Cumulative Use		
	Conventional Cox MSM	2606.3
	Flexible non-linear (NL) MSM	2584.0
Continuous Use		
	Conventional Cox MSM	2611.4
	Flexible non-linear (NL) MSM	2596.0

Appendix 5-D.1a Non-linear effect of ***duration of cumulative opioid use*** truncated at 180 days and the risk of opioid-related emergency department visits, re-admissions or deaths.



Appendix 5-D.1b. Operational definition of long-term opioid use therapy in the presence/absence of post-baseline hospitalizations.



6. Objective 3

Kurteva S, Abrahamowicz M, Gomes T, Tamblyn R. Association of Opioid Consumption Profiles After Hospitalization With Risk of Adverse Health Care Events. JAMA Netw Open. 2021 May 3;4(5):e218782. doi: 10.1001/jamanetworkopen.2021.8782. PMID: 34003273.

6.1 Preamble

The third objective had as a goal to provide more evidence as to how patterns of use are associated with the risk of potentially avoidable opioid-related adverse events. In addition to estimating the risk of harm associated with the prescribed opioid dose and duration, I also sought to ascertain whether the risk is modified by treatment indication and age. In this analysis, I included patients who had filled at least one opioid prescription three months after discharge. Time-varying measures of opioid use included current use, daily morphine milligram equivalent dose, cumulative and continuous use duration, as well as type of ingredient in prescription opioids used. Marginal structural Cox proportional hazards models were used as the analytic approach in this study to properly model the dynamic nature of opioid exposure and account for the presence of time-varying confounders.

This study has already been published in *JAMA Network Open*. The published article is provided in Appendix 8 at the end of the thesis.

6.2 Title page and footnotes

Title: Association of Opioid Consumption Profiles Following Hospitalization with the Risk of Acute Health Care Events.

Contributing authors: Siyana Kurteva, BSc [1,2], Michal Abrahamowicz, PhD [1], Tara Gomes, PhD [3,4,5], Robyn Tamblyn, PhD [1,2,5,7]

Affiliations of all contributing authors:

[1] Department of Epidemiology and Biostatistics, McGill University, Montreal, Canada

[2] Clinical and Health Informatics Research Group, McGill University, Montreal, Canada

[3] Institute of Health Policy Management and Evaluation, Toronto, Canada

[4] Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, Canada

[5] ICES, Toronto, ON, Canada

[6] Department of Medicine, McGill University Health Center, Montreal, Canada

[7] McGill University Health Centre, Montreal, Canada

Corresponding author:

Siyana Kurteva

Clinical & Health Informatics Research Group, Department of Medicine, McGill University

1140 Pine Ave W., Montreal, Quebec, Canada, H3A 1A3

Email: siyana.kurteva@mail.mcgill.ca

Tel: +1 (514) - 632 - 5838

ABSTRACT

Importance: While better pain management has guided policies for opioid use over the past few decades, there is limited evidence regarding how prescribed patterns of use are associated with the risk of potentially avoidable opioid-related adverse events.

Objective: To estimate the risk of opioid-related harms associated with opioid duration and dose, and determine if the risk is modified by treatment indication and age.

Design: A prospective cohort of hospitalized patients enrolled in a cluster randomized trial of medication reconciliation between October 2014 and November 2016 were followed 12 months' post-discharge.

Setting: Patients discharged from the McGill University Health Centre, Quebec, Canada. Data analyses took place between February 2019 and February 2020.

Participants: To be eligible for this study, patient needed to have filled at least one opioid prescription three-months post-discharge.

Exposures: Time-varying measures of opioid use included current use, daily dose, cumulative and continuous duration, and opioid type. Hospital charts, dispensed prescriptions records, and post-discharge interviews were used to measure adherence to the discharge opioid prescriptions.

Main Outcomes: Opioid-related emergency department (ED) visits, readmissions or all-cause death. Outcomes were ascertained using provincial medical services claims and hospitalization databases.

Results: The 1,511 patients had a mean age of 69 years (SD=10.3), 43% were female. Among those with at least one opioid dispensation, 16% (n = 241) experienced an opioid-related ED visit, re-admission or death. Results from marginal structural cox proportional hazards models showed more than a two-fold increase in the risk of opioid-related adverse events associated with a cumulative opioid duration of > 90 days (adjusted hazard ratio (aHR) of 2.56 (95% CI:1.25 – 5.27), compared to 1-30 days. There was a three-fold risk increase with a mean daily dose of ≥ 90 morphine milligram equivalent (MME), aHR of 3.24 (95% CI: 1.43-7.35) compared to users of ≤50 MME.

Conclusions and Relevance: The risk of acute healthcare events increased with higher doses and longer treatment duration. Policies limiting opioid duration and dose may attenuate the risk of avoidable morbidity.

6.3 Introduction

Over the past 20 years, opioid prescribing and average prescription volumes continued to increase in the United States and Canada. [25,31] Opioids remain the main treatment for the management of cancer pain, as recommended by the World Health Organization.[165] However, substantial increases in prescriptions for chronic non-cancer pain have also been documented. In North America, in 2010's opioid use increased by nearly 100% increase [8], with acute pain being the most common indication. [15,16] These trends in prescription opioids have been accompanied by marked increases in opioid-related morbidity and mortality. [7,8] Non-fatal opioid-related outcomes affect the elderly, even when taking the drug as directed. [166,167] Furthermore, long-term benefits are uncertain as even short-term use may lead to increased predisposition to adverse events. [63] Longer trials have shown less pain relief with opioids, possibly due to tolerance or opioid-induced hyperalgesia. This may, in turn, contribute to an escalation in the dose and potency of opioids, which subsequently may augment the risk of adverse reactions. Yet, no trial of opioid efficacy had followed patients for longer than 6 months [18], whereas most observational studies only examine associations with dose and duration of initial opioid prescriptions. [19-21]

For many patients, their first opioid exposure follows a hospitalization, making this a high-priority population for investigation. Inadequate communication of hospital-initiated changes in medication to community-based providers post-discharge is a well-established problem. [59] Consequently, community physicians may continue opioids started in the hospital, for acute pain relief, as they have no information about the treatment indication nor the expected therapy duration. Thus, prescribing practices during hospitalizations may contribute to opioid consumption growth and its related adverse outcomes.

This study aimed to estimate the risk of opioid-related harms associated with the dose and duration of opioid use.

6.4 Methods

Design & Setting: A prospective cohort of medical and surgical patients, enrolled in a cluster randomized trial of medication reconciliation at the McGill University Health Centre (MUHC) between October 2014 and November 2016 were followed 12 months' post-discharge. [108] The

MUHC is an over 1000-bed quaternary care teaching hospital in Montreal (Canada) that operates within the universal health care plan of the province of Quebec (RAMQ). The RAMQ plan covers all hospitalizations, essential medical care, and drug insurance for registrants: 65 years of age and older, income security recipients, and those not insured through their employer (approximately 50% of the Quebec population). Ethics approval was provided by the MUHC Research Ethics Board. Privacy Commissioner to link clinical and administrative data from the Commission d'accès à l'information du Quebec. This study follows the STROBE reporting guideline for observational studies. [168]

Participants: To be eligible for the original trial, patients had to be 18 years or older at admission, admitted from the community or transferred from another hospital, with at least one-year prior continuous provincial healthcare coverage. To be included in this study, patients needed to fill at least one opioid prescription in the 90 days' post-discharge. We excluded patients with history of using methadone or buprenorphine, which are given to treat opioid addiction. [169]

Data Sources: We linked multiple data sources. Demographic, clinical, healthcare use and prescription claims were retrieved from admission notes and RAMQ medical services and prescription claims in the year prior to and after the index hospitalization. Admission/discharge dates, units, and diagnoses, and major procedures were retrieved from the hospitalization database. Medications at admission, in-hospital and those prescribed at discharge were abstracted from the MUHC Data Warehouse. Hospital discharge experiences data were obtained via telephone interviews 30-day post-discharge.

Opioid Use Post-Discharge: Opioid use one-year post-discharge was measured using RAMQ pharmacy claims. For each prescription filled, these claims document the drug identification number (DIN), strength, dispensing date and quantity, prescription duration, and prescribing physician. DINs mapped to ATC codes N02A, R05DA were used to identify opioids (Appendix B). On each day, an individual was classified as having a dispensed opioid available or not. A 5-day grace period was added to the end of each dispensation as opioids are often prescribed on a take-as-needed basis, and patients are likely to take some unused pills for a few days after prescription ended. Appendix B describes opioid daily dose calculations.[170] We also constructed

time-varying binary indicators of recent opioid discontinuation, dose increases and opioid add-on therapy.

Uniquely to this study, administratively derived measures of opioid exposure were supplemented with information on individual patients' medication-taking behavior, extracted from interviews 30 days' post-discharge to construct a series of time-invariant indicators that identified patients who filled a prescription and (i) continued taking it, or (ii) started taking it but stopped, or (iii) never used it.

Outcomes: Outcome was defined as the time from the first opioid dispensation to the earliest of the first opioid-related ED visit, re-admission, or death due to any cause, in the one year post-discharge. Outcomes were ascertained using RAMQ medical services claims and hospitalization databases which identify all ED visits and re-admissions to any hospital. An adverse event was considered opioid-related if diagnosis indicated opioid abuse, opioid dependence, and/or opioid poisoning, and/or any of the more common side effects of opioids [171]: constipation, nausea, vomiting, dizziness [172-176] or fractures. [177-180] We combined all possible opioid-related side effects, because only 3 (0.2%) of patients were diagnosed with opioid abuse, dependence, and/or poisoning, and medication-related adverse events are vastly under-ascertained in the ED. [181]

Potential Modifiers of Opioid-related Harms:

We assessed potential effect modifications with age (dichotomized: <64 vs ≥64) and treatment indication, categorized: i) cancer-related pain, ii) post-surgical pain management, iii) or other chronic pain problems. Medical records were used to identify treatment indication.

Covariates (Appendix C***):*** Potential risk factors for long-term opioid use included patient demographics (age, sex, drug insurance status), co-existing illnesses (history of mental health conditions, pain syndromes, health conditions associated with abuse, tobacco use, cancer diagnoses, other comorbidities), drug and healthcare utilization (use of drugs increasing the risk of opioid misuse, non-opioid pain medications, number of ED visits and hospitalization, physicians seen and dispensing pharmacies) in the one year prior to hospitalization. We also measured reason of hospital admission, in-hospital administration of opioids, reason for opioid prescribing at discharge, having a multi-modal pain management regimen, and discharge

destination. [17,50] To measure healthcare fragmentation (associated with low quality of care and increased adverse outcomes), or opioid seeking behavior because of increasing dependence [44,46], we created time-varying covariates, updated daily during follow-up, for the cumulative numbers of distinct prescribers and dispensing pharmacies post-discharge.

Statistical Analyses: Descriptive statistics summarized patient, provider and healthcare system characteristics. For all main analyses, we relied on time-to-event methods. Specifically, we used multivariable marginal structural Cox proportional hazards (PH) models (MSM Cox) [182,183] to determine the association between time-varying opioid use and the risk of the outcome. Cohort entry was the date of the first opioid dispensation within 3 months after hospital discharge. Patients were followed until their first opioid-related ED visit/re-admissions, death or end of follow-up. We temporarily censored patients during hospitalizations for reasons unrelated to opioid use. Because of the uncertainty regarding how past opioid consumption patterns may be associated with adverse events, alternative time-varying metrics of opioid use, updated daily during the one year follow-up, were constructed: i) current use, (ii) cumulative, (iii) continuous duration of use, (iv) daily dose and (v) type of opioid ingredient (Appendix C). [184] All models included the same potential confounders, including time-invariant baseline variables and time-varying covariates, selected based on statistical and clinical significance. To account for time-varying potential confounders that could also be affected by prior opioid exposure, psychotropic medication use, targeted comorbidities, and cumulative numbers of prescribers and dispensing pharmacies were used to estimate stabilized time-varying inverse probability treatment (IPT) weights [185,186] for opioid exposure. The IPT weights were estimated, separately for each 10-day time interval during the one-year follow-up, using a series of multivariable logistic models [186] , and to avoid unstable estimates, truncated at the 95th percentile of their distribution. [187] We used the robust sandwich covariance estimator to calculate standard errors, while accounting for the IPT weighting. [188] To determine if the risk of opioid-related harms was modified by treatment indication or age, we used Wald tests of the respective two-way interactions at 2-sided α=0.05. All MSM Cox PH models were implemented with SAS version 9.4 (SAS Institute, Cary, NC).

Sensitivity Analyses: To account for potential chronic opioid use prior to study entry, in two sensitivity analyses we re-created our cohort excluding patients with, respectively, ≥1 or ≥3 opioid dispensations during the baseline period. Second, in separate analyses, we restricted the

outcome to either opioid-related ED visits/re-admissions or deaths. We also conducted sensitivity bias analyses where an interaction term between the main exposure and the adherence measure constructed from patient's interviews was tested to assess to what extent the potential nonadherence to opioid prescriptions could have affected the estimated association(s). Finally, to account for the differences in severity of opioid-related side effects, in two additional sensitivity analyses, we categorized the outcomes into fractures/dizziness and nausea/constipation.

Additional sensitivity analyses were performed to assess to what extent selected, statistically significant results could reflect potential bias due to unmeasured confounders. [189] This involved first simulating a potential confounder with pre-specified associations (odds ratios) with both (i) relevant opioid exposure and (ii) occurrence of the outcome, and then re-running the multivariable analyses with additional adjustment for the simulated confounder. [190]

6.5 Results

Among 3,486 participants of the original trial, 1,511 were included in the current cohort. Their mean age was 69.6 years (SD = 10.3) and 57.7% were males (Table 6-1). Most patients underwent surgery (n=1119, 74.1%). At discharge, 51.5% of medical and 88.2% of surgical patients received an opioid prescription. Among the remaining patients, 51.2% were dispensed an opioid in the 7 days' post-discharge (Table 6-3). Fewer surgical than medical patients used opioids prior to admission (30.7% vs 72.2%). Overall, 42.9% of all medical and 48.1% of all surgical patients had documented cancer diagnoses in a year before hospitalization and/or at hospital discharge.

In the year post-discharge, 15.9% (n=241) of patients had an opioid-related ED visit/hospitalization, or died. The most frequent potentially opioid-related adverse events included fractures (55.4%), nausea and vomiting (17.7%), and dizziness (14.4%) (Appendix 6-D).

Results from main models are presented in Table 6-4. Current daily opioid use, which identified patients with having active prescription at a given day during the follow-up, was associated with a 71% increased risk of opioid-related adverse events (aHR: 1.71, 95% CI (1.04 – 2.82)). Compared to shorter cumulative exposures (1-30 days), longer past use of 60-90 days (aHR of

2.45, 95% CI (1.18 – 5.09) and > 90 days (aHR: 2.56, 95% CI (1.25 – 5.27) were both associated with a two-fold increase in risk of adverse events). Uninterrupted continuous use for at least 60 consecutive days was associated with a three-fold increased risk in opioid-related acute healthcare events (aHR: 3.73, 95% CI (1.83 – 7.60)), relative to patients who were not current opioid users. In contrast, for a few patients who exceeded 90 days of continuous use, there was no evidence of an increased risk (aHR 0.86, 95% CI (0.37 - 1.96)).

The risk of opioid-related adverse events or death was three times higher for current daily doses of >90 MME (aHR: 3.51, 95% CI (1.58 – 7.82)), as compared to lower doses ≤90MMEs. Among different opioid types, only morphine showed statistically significant risk increase (aHR: 4.04, 95% CI (1.02 – 15.9) relative to codeine), albeit with wide confidence intervals.

Analyses by Treatment Indication: We found two statistically significant interactions between surgery and (i) current use (p-value = 0.003), and (ii) >90 days of use (p-value = 0.002). Among surgical patients both current daily use (aHR of 3.35 (95% CI: 1.82 – 6.85)) and cumulative duration of > 90 days of use (aHR: 7.82 (95% CI 3.20 – 19.1)) were associated with important, statistically significant increased risk of opioid-related adverse events or death. In contrast, both associations were not statistically significant for medical patients. The interaction between cumulative use of >90 days and having a cancer diagnosis was also significant, with the association stronger among cancer patients. Results for interaction analyses with age and treatment indication are in Appendix 6-D.

Excluding prior opioid users had a minimal impact on the results (Appendix 6-D). The absence of an interaction between adherence and current use (p=0.99) could be due to excellent adherence: 90% (n=1360), of patients reported that they took their dispensed opioids as prescribed, only 12% (n=169) discontinued their initial dispensation and 5% (n=70) had an opioid dispensed but never started taking it in the first month post-discharge. In bias sensitivity analyses, patients on higher daily opioid dose of >90 MME remained at a significantly increased risk of opioid-related acute healthcare events, even after adjusting for a moderately strong unobserved confounder, with odds ratios of 2 with both exposure (higher dose) and the outcome (Appendix 6-D, Table D.9). Analyses that restricted outcomes to either fracture-related or other opioid-related ED visits/re-admission showed consistent results (Appendix 6-D, Table D.10.)

6.6 Discussion

We assessed the association between longitudinal opioid use patterns, represented by time-varying measures of current daily use, daily dose, cumulative and continuous duration of use, generic molecule, and their associated risk of opioid-related adverse events/death. We found increased risks with daily dose, cumulative and continuous use. There were also variations in the magnitude of risk when considering different treatment indications. Our results highlight the importance of accounting for alternative opioid consumption patterns when quantifying the risk of acute healthcare events/death. Whereas most of the literature considers 90 days as a threshold for safe opioid use [20,61,126] , in this study we provided risk estimates for multiple duration categories of up to and beyond 90 days to better understand how the risk may vary with short and long-term use patterns.

There has been a paucity of observational research examining extended opioid treatment duration and related adverse events, with most of the evidence coming from clinical trials with a duration of less than a year and observational studies looking only at the initial opioid prescription duration. [20,49,191] In relationship to risks associated with opioid use duration, our results are similar to the findings from a recent 2017 Cochrane summary. [18] Our non-significant findings and wide confidence intervals for continuous use beyond 90 days could be a reflection of low statistical power as only a few patients had long un-interrupted use during the one-year follow-up. However, it has been previously documented as patients develop tolerance to the analgesic effect of opioids, the same is observed with their capacity to tolerate side effects. [192] In our study, average doses started to plateau for use of > 90 days and did not escalate with increasing durations beyond 90 days of use (data not shown), which could indicate that these patients potentially transitioned into chronic users.

We noted an increased risk of adverse events with daily MME doses. Previous studies have also demonstrated important effects of opioid dose on adverse events such as increased risks of fractures, road trauma, and opioid-related mortality. [2,25,39,42,47] Saunders et al showed that >50 MME was associated with two-fold increase in the risk of fractures. [39] Similarly to findings from our study, Ishida et al. found high doses to be associated with risks for all adverse outcomes. [36] Our findings showed most patients in this cohort did not exceed the recommended maximum

dose of 90 MME [50], and yet their risk of adverse events was still high relative to patients who were not currently exposed to opioids.

Existing data on the rates of morbidity and mortality as a function of drug potency among commonly prescribed opioids are somewhat conflicting. [193] [9,194,195] However, due to the relatively small sample size and overlapping confidence intervals, our comparisons of risks associated with different products were inconclusive, even if the results suggested morphine users may be at higher risk of composite endpoint and death.

This study's strength is its ability to use multiple data sources, which enhances the internal validity of the study by providing detailed covariate information to adjust for confounders and account for potential mediators. Most of what is known about extended opioid treatment and related adverse events is based on different and arbitrary definitions.[98,196-198] In this study, we compare various time-varying opioid use metrics to provide further insights into the mechanism involved in the development of opioid-related events. [184,199]

Limitations

Some limitations of our work merit emphasis. In our analyses, we used prescription duration as recorded by the pharmacist. Since opioids are given on a *prn* basis, exposure mismeasurement is possible. However, we expect the resulting exposure misclassification to be non-differential and thus, biasing the estimates toward the null. As in all observational studies, there is the potential for unmeasured confounding and confounding by indication. Our decision to only include patients with at least one opioid dispensation post-discharge (excluding never users) as well as selecting as a comparator patients on short-term or low-dose opioids reduces concerns about potential bias due to confounding by indication. Moreover, a consistent limitation across all claims-based studies, including this one, is the inability to account for opioid medications obtained through diversion or other illicit means. However, a study conducted in a similar cohort of universally covered patients in the province of Quebec found older adults to be less likely to experience an opioid prescription associated overdose death and seek outpatient prescriptions as compared to younger people. The majority of patients in this study cohort were 64 years of age or older and thus, we expect illicit use to have little impact on the main findings. [164] In this study, the choice of a broader outcome may be prone to confounding. However, we explored the

amount of hidden bias from an unmeasured confounder necessary to alter the conclusion that patients on higher daily doses have higher risk of opioid-related adverse events and the association was robust. Future research should use data from multiple healthcare systems to replicate our findings in larger populations cohorts and thus, providing greater generalizability.

6.7 Conclusion

We found an increased risk when using opioids for prolonged durations and at higher doses. Our results can inform prevention strategies aimed at minimizing the harm linked to opioid-related morbidity.

Table 6-1. Baseline characteristics of the overall eligible patients (n=3486) and of the study cohort patients (n=1511) who filled of an opioid prescription within 90 days of hospital discharge stratified by discharge unit.

	Overall n = 3486	**Hospital Discharge Unit**	
		Internal Medicine n = 392 (21.7%)	**Surgery** n = 1119 (66.7%)
Mean age (SD)	69.6 (14.9)	67.7 (16.8)	66.9 (11.9)
	N (%)	***N (%)***	***N (%)***
Male	2010 (57.7)	200 (51.0)	683 (61.0)
Length of hospital stay (≥ 6 days)	2930 (84.0)	351 (89.5)	875 (78.2)
Health Services Utilization: One Year Before Admission			
	Mean (SD)	***Mean (SD)***	***Mean (SD)***
Emergency department visits	8.4 (8.5)	15.3 (20.3)	4.4 (8.1)
Hospitalizations	0.8 (1.9)	0.9 (1.9)	0.7 (1.8)
Physicians visits	10.9 (14.5)	14.0 (16.3)	9.9 (8.4)
Number of prescribing physicians	4.2 (3.4)	6.3 (4.4)	3.6 (2.4)
Number of physicians prescribing opioids	0.6 (1.2)	1.9 (2.2)	0.5 (0.9)
Number of dispensing pharmacies	1.4 (0.9)	1.6 (0.9)	1.4 (0.8)
Number of pharmacies dispensing opioids	0.4 (0.6)	0.9 (0.7)	0.4 (0.6)
Active Prescriptions at Admission	9.8 (10.1)	14.3 (14.1)	6.6 (6.5)
	N (%)	***N (%)***	***N (%)***
Radiotherapy	215 (6.2)	77 (19.6)	133 (11.9)
Chemotherapy	262 (7.5)	83 (21.2)	176 (15.7)
Medication Use: One Year Before Admission			
	N (%)	***N (%)***	***N (%)***
Active Opioid Prescription at Admission	504 (14.5)	186 (47.4)	105 (9.4)
History of opioid use	1206 (34.6)	283 (72.2)	344 (30.7)
≥ 3 opioid dispensations	104 (2.9)	61 (15.6)	18 (1.6)
History of long-acting opioids	146 (4.2)	89 (22.7)	35 (3.1)
History of methadone/buprenorphine	13 (0.4)	10 (2.6)	1 (0.1)
History of benzodiazepine use	1088 (31.2)	175 (44.6)	336 (30.0)
History of antidepressant use	706 (20.3)	133 (33.9)	208 (18.6)
History of non-opioid pain medications use	1068 (30.6)	243 (61.9)	406 (36.3)
In-Hospital Medication Use			
Antidepressants	628 (18.0)	112 (28.6)	153 (13.7)
Opioids	2509 (72.0)	307 (78.3)	1113 (99.5)
Benzodiazepines	2278 (65.4)	196 (50.0)	997 (89.1)
Analgesics	3161 (90.7)	168 (43.1)	942 (84.2)
Pain Regimen at Hospital Discharge			
Opioids	1530 (43.9)	202 (51.5)	987 (88.2)
Non-opioid analgesics	2209 (63.4)	227 (57.9)	990 (88.5)
Targeted Comorbidities that May Increase the Risk of Hospitalizations/ED visits			

Mental illness	511 (14.7)	74 (18.9)	132 (11.8)
Dementia	213 (6.1)	25 (6.4)	13 (1.2)
Substance & alcohol abuse	115 (3.3)	27 (6.9)	19 (1.7)
Pain Syndromes	1352 (38.8)	221 (56.4)	408 (36.5)
Cancer	1253 (35.9)	168 (42.9)	538 (48.1)
Other Comorbidities that May Increase the Risk of Hospitalizations/ED visits			
Cardiovascular Diseases	1398 (40.1)	154 (39.3)	657 (58.7)
Cerebrovascular Diseases	334 (9.6)	49 (12.5)	69 (6.2)
Pneumonia	338 (9.7)	46 (11.7)	63 (5.6)
Chronic obstructive pulmonary disease	751 (21.5)	102 (26.0)	236 (21.1)
Renal Disease	364 (10.4)	53 (13.5)	41 (3.7)
Diabetes	791 (22.7)	92 (23.5)	223 (19.9)

Table 6-2. Overall characteristics of the opioid prescriptions dispensed by patients according to opioid type and potency

Ingredient [1] (molecule)	**MME Conversion Factor [2]**	**Patients [3]** *N (%)*	**Days' Supply of Initial dispensation** *Mean (SD)*	**Mean Dose of Initial Dispensation** *Mean (SD) [4]*	**Filled ≥2 Opioid Prescriptions** *N (%)*	**Filled ≥1 Type of Opioid** *N (%)*
Codeine	0.15	215 (14.2)	13.2 (10.1)	19.9 (12.4)	201 (93.5)	11 (5.1)
Morphine	1	244 (16.1)	10.4 (8.3)	27.4 (27.2)	226 (92.6)	159 (65.2)
Oxycodone	1.5	1044 (69.1)	8.6 (6.3)	35.3 (17.7)	610 (58.4)	441 (42.2)
Hydromorphone	4	689 (45.6)	9.8 (7.4)	31.8 (26.0)	594 (86.2)	180 (6.1)
Fentanyl	7.2	109 (7.2)	22.5 (11.3)	137.2 (121.5)	108 (99.1)	16 (14.7)
Methadone		44 (2.9)	-	-	37 (84.1)	33 (75.0)
Total	-	1511	-	-	950 (62.8)	595 (39.4)

[1] Only tablets and patches form of these medications were considered
[2] Opioid Oral Morphine Milligram Equivalent Conversion Factors.
[3] Number of patients who filled at least one of the opioid ingredients throughout the follow-up period. A given patients can be in more than one category as they fill multiple type of opioids.
[4] Dose reported in morphine milligram equivalents
* *Total* refers to the total number of patients who filled at least one opioid dispensation. This total is not equivalent to the sum of the number of patients in each opioid ingredient categories.

Sources:

1) Centers for Medicare & Medicaid Services. Opioid Oral Morphine Milligram Equivalent (MME) Conversion Factors. https:\\www.cms.govMedicarePrescription-Drug-CoveragePrescriptionDrugCovContraDownloadsOpioid-Morphine-EQConversion-Factors-vFeb-.pdf. Accessed: September 5, 2019
2) Svendsen, K., Borchgrevink, P., Fredheim, O., Hamunen, K., Mellbye, A., & Dale, O. (2011). Choosing the unit of measurement counts: the use of oral morphine equivalents in studies of opioid consumption is a useful addition to defined daily doses. Palliative Medicine, 25(7), 725–732. http://doi.org/10.1177/0269216311398300

Table 6-3. Characteristics of first opioid prescription filled in the 90-day post-discharge period.

	Overall n=1511	**Opioid Prescription at Discharge**	
		Yes n = 1163, 76.9%	**No** n= 348, 23.0%
Opioid Prescription Filled within First 7 days	1228 (81.3)	1050 (90.3)	178 (51.2)
Opioid Prescription Filled within First 30 days	1360 (90.0)	1118 (96.1)	242 (69.5)
Morphine Equivalent Dispensed (Milligrams)			
Mean (SD)	34.9 (28.6)	34.9 (23.6)	34.8 (40.9)
Median	29.1	30.0	25.0
IQR	20.0 – 41.7	21.0 – 41.7	16.0 – 40.9
Morphine Equivalent Dispensed (Milligrams)			
≤90	1467 (97.1)	1137 (97.8)	330 (94.8)
>90	44 (2.9)	26 (2.2)	18 (5.2)
Type of Opioid Dispensed			
Codeine	47 (3.1)	21 (1.8)	26 (7.5)
Morphine	68 (4.5)	33 (2.8)	35 (10.1)
Oxycodone	952 (63.0)	814 (69.9)	138 (39.7)
Hydromorphone	419 (27.7)	286 (24.6)	133 (38.2)
Fentanyl	22 (1.5)	7 (0.6)	15 (4.3)
Combination Opioid Products Dispensed	308 (20.4)	209 (17.9)	99 (28.5)
Combination Non-Opioid Products Dispensed	1300 (86.0)	999 (85.9)	301 (86.5)

Table 6-4. The risk of emergency department visits, re-admissions or death for several opioid exposure definitions in marginal structural Cox PH models.

Opioid Exposure Metric	Events †	Person-years	Incidence Rate * (95% CI)	ED visits/re-admissions/death [1,2]	ED visits/re-admissions [3]	Death
Current Use						
No	128	1102.7	116.1 (96.8 – 138.0)	Ref	Ref	Ref
Yes	113	233.4	484.2 (399.0 – 582.1)	1.71 (1.04 – 2.82)	2.00 (0.98– 4.10)	1.56 (0.79 – 3.04)
Cumulative Opioid Use						
1-30	123	973.3	126.4 (105.0 – 150.8)	Ref	Ref	Ref
30-60	44	181.1	242.9 (176.6 – 326.2)	1.55 (0.95 – 2.52)	1.47 (0.69 – 3.14)	1.61 (0.86 – 3.03)
60-90	24	56.6	423.7 (271.5 – 630.4)	2.45 (1.18 – 5.09)	1.05 (0.22 – 3.92)	3.45 (1.41 – 8.47)
>90	50	125.1	399.8 (296.7 – 527.0)	2.56 (1.25 – 5.27)	2.07 (0.70 – 6.07)	2.89 (1.11 – 7.59)
Continuous Opioid Use						
0	128	1102.7	116.1 (96.8 – 138.0)	Ref	Ref	Ref
1-30	63	132.0	477.3 (366.7 – 610.6)	1.79 (1.00 – 3.22)	2.10 (0.72 – 5.86)	1.66 (0.84 – 3.29)
30-60	26	32.4	801.5 (523.5 – 1174.3)	3.73 (1.83 – 7.60)	5.19 (1.56 – 17.2)	3.10 (1.28 – 7.54)
>60	24	68.9	348.1 (223.1 – 517.9)	0.86 (0.37 – 1.96)	0.91 (0.32 – 2.49)	0.81 (0.26 – 2.47)
MME Daily Dose						
≤90	207	1302.2	158.9 (138.0 – 182.1)	Ref	Ref	Ref
>90	34	33.9	1003.1 (694.7 – 1401.7)	3.51 (1.58 – 7.82)	1.06 (0.30 – 2.78)	5.84 (2.12 – 16.09)
Type of Opioid Use						
Codeine	4	13.5	296.9 (80.9 – 760.2)	Ref	Ref	Ref
Morphine	19	18.1	1047.5 (630.7 – 1635.8)	4.04 (1.02 – 15.9)	1.81 (0.28 – 11.6)	9.36 (1.18 – 73.9)
Oxycodone	16	78.8	202.9 (115.9 – 329.5)	1.48 (0.35 – 6.25)	0.67 (0.10 – 4.27)	2.98 (0.33 – 27.0)
Hydromorphone	45	87.2	515.8 (376.3 – 690.2)	2.62 (0.64 – 10.7)	1.06 (0.18 – 6.41)	6.74 (0.83 – 54.6)
Fentanyl	11	15.3	718.7 (358.8 – 1286.0)	2.93 (0.57 – 15.0)	0.43 (0.03 – 6.01)	8.67 (0.87 – 86.1)
Multiple Opioid Products	18	20.4	883.3 (523.5 – 1396.0)	6.36 (1.42 – 28.4)	4.74 (0.69 – 32.4)	9.94 (1.01 – 98.3)

† The event counts are for the composite outcome of ED visits, re-admissions and/or death.

* Incidence rate reported as 1000 per year.

[1] Covariates considered in the construction/calculation of the treatment weights: 1) demographic characteristics: indicator for a patient randomized to the RightRx intervention group, age at admission, sex, copay status, 2) medical, prescription and healthcare use one-year before admission: unique number of dispensing pharmacies and prescribers, hospitalizations

and emergency department visits, the receipt of radiotherapy and/or chemotherapy services, type of cancer, history of mental health diagnoses, history of substance and/or alcohol abuse/dependence, targeted comorbidities which may increase someone's risk of opioid-related adverse events, history of chronic pain, previous opioid use, more than 3 opioid dispensations, previous use of psychotropic medications, 3) in-hospital characteristics: presence of an opioid-related reason for index admission, length of hospital stay, opioid administration during the index hospitalization, non-opioid pain medication administration, use of antidepressant and benzodiazepines, hospital unit discharged from (medical vs surgical) from, type of surgery (cardiac vs thoracic), 4) at discharge: receipt of an opioid prescription, prescribing reason (having had surgery, having anxiety or pain problems), 5) time-varying post-discharge characteristics: use of benzodiazepines, use of antidepressants, use of methadone/buprenorphine, cumulative number of physicians, cumulative number of dispensing pharmacies, recent discontinuation of opioid use, recent increases in opioid dose, recent add-on opioid therapy, updated targeted baseline medical comorbidities. The 95^{th} percentile for the stabilized weight was 2.88 (mean =0.81, SD = 0.71).

[2] AICs for the models with current use, cumulative use, continuous use, MME daily dose and type of opioid use were 2562.3, 2557.6, 2548.1, 2535.5 and 2548.1 respectively.

[3] Additional censoring weights were included to account for competing risk by death. Same covariates as the ones included in the treatment weights were used for the censoring weights.

Appendix 6-A. ICD-9-CM and ICD-10-CM Opioid-Related Diagnosis Codes Used in This Study

Appendix 6-A.1 ICD-9-CM and ICD-10-CM codes for opioid abuse

ICD-9-CM Code	Description
30550	Opioid abuse, unspecified
30551	Opioid abuse, continuous
30552	Opioid abuse, episodic

Appendix 6-A.2 ICD-9-CM codes for opioid dependence

ICD-9-CM Code	Description
30400	Opioid type dependence, unspecified
30401	Opioid type dependence, continuous
30402	Opioid type dependence, episodic
30470	Combinations of opioid type drug with any other drug dependence, unspecified
30471	Combinations of opioid type drug with any other drug dependence, continuous
30472	Combinations of opioid type drug with any other drug dependence, episodic

Appendix 6-A.3 ICD-9-CM codes for adverse effects of opioids

ICD-9-CM Code	Description
E9350	Heroin causing adverse effects in therapeutic use
E9351	Methadone causing adverse effects in therapeutic use
E9352	Other opiates and related narcotics causing adverse effects in therapeutic use
E9401	Adverse effects of opiate antagonists

Appendix 6-A.4 ICD-9-CM codes for opioid poisoning

ICD-9-CM Code	Description
96500	Poisoning by opium (alkaloids), unspecified
96501	Poisoning by heroin
96502	Poisoning by methadone
96509	Poisoning by other opiates and related narcotics
9701	Poisoning by opiate antagonists
E8500	Accidental poisoning by heroin
E8501	Accidental poisoning by methadone
E8502	Accidental poisoning by other opiates and related narcotics

Appendix 6-A.5 ICD-9-CM codes for other most commonly occurring adverse associated with opioid use

ICD-9-CM Code	Description
56400	Constipation, unspecified
54601	Slow transit constipation
54602	Outlet dysfunction constipations
56409	Other constipation
78040	Dizziness
78701	Nausea with vomiting
78702	Nausea alone
78703	Vomiting alone
80X, 81X, 82X	Fractures

Appendix 6-B. Codes Used for Drug Classification and Rationale for Opioid Dose Calculations.

Supplement Method 6-B.1. ATC codes used to identify opioids: N02A (opioids), R05DA (opium alkaloids and derivatives)

Exclusions: Not all drug forms were included in the analyses. Only patches and tablets of these medications were kept. Injectable, liquid and rectal forms were excluded. Methadone and buprenorphine/naloxone combinations were kept to define subclinical patient populations but were excluded from all dosing/duration calculations as these medications are used to treat addiction and we want to focus on the association of duration/dose of opioids used for pain relief.

Supplement Method 6-B.2. The daily dose of each opioid was calculated by first dividing the quantity of units dispensed by the prescription duration to determine the number of units per day, and then multiplying the number of units by the strength. To account for concurrent

prescriptions, a subsequent dispensation was considered as an early refill if days of overlap were ≤30% of the previous dispensation duration. Otherwise, the opioids were considered to be taken simultaneously. Daily dose of each dispensation was converted to MME doses using the Center for Disease Control Opioid Morphine Equivalent Conversion Factor and the opioid doses determined to be concurrently dispensed were added together.

Appendix 6-B.1. Opioid Morphine Equivalent Conversion Factor [1]

Drug Name	Conversion Factor
Buprenorphine patch[2]	12.6
Buprenorphine tab or film	10
Butorphanol	7
Codeine	0.15
Dihydrocodeine	0.25
Fentanyl buccal or SL tablets, or lozenge/troche[3]	0.13
Fentanyl film or oral spray[4]	0.18
Fentanyl nasal spray[5]	0.16
Fentanyl patch[6]	7.2
Hydrocodone	1
Hydromorphone	4
Levorphanol tartrate	11
Meperidine hydrochloride	0.1
Methadone	3
Morphine	1
Nalbuphine	1
Opium	1
Oxycodone	1.5
Oxymorphone	3
Pentazocine	0.37
Tapentadol	0.4
Tramadol	0.1

[1] Centers for Disease Control and Prevention, Atlanta, GA, May 2014.

[2] The MME conversion factor for buprenorphine patches is based on the assumption that one milligram of parenteral buprenorphine is equivalent to 75 milligrams of oral morphine and that one patch delivers the dispensed micrograms per hour over a 24-hour day. Example: 5 ug/hr buprenorphine patch * 24 hrs = 120 ug/day buprenorphine = 0.12 mg/day buprenorphine = 9 mg/day oral morphine milligram equivalent. In other words, the conversion factor not accounting for days of use would be 9/5 or 1.8. However, since the buprenorphine patch remains in place for 7 days, we have multiplied the conversion factor by 7 (1.8 X 7 = 12.6). In this example, MME/day for four 5 µg/hr buprenorphine patches dispensed for use over 28 days would work out as follows: Example: 5 ug/hr buprenorphine patch * (4 patches/28 days) * 12.6 = 9 MME/day.

[3] The MME conversion factor for fentanyl buccal tablets, sublingual tablets, and lozenges/troche is 0.13. This conversion factor should be multiplied by the number of micrograms in a given lozenge/troche.

[4] The MME conversion factor for fentanyl film and oral spray is 0.18. This reflects a 40% greater bioavailability for films compared to lozenges/tablets and 38% greater bioavailability for oral sprays compared to lozenges/tablets.

[5] The MME conversion factor for fentanyl nasal spray is 0.16, which reflects a 20% greater bioavailability for sprays compared to lozenges/tablets.

[6] The MME conversion factor for fentanyl patches is based on the assumption that one milligram of parenteral fentanyl is equivalent to 100 milligrams of oral morphine and that one patch delivers the dispensed micrograms per hour over a

24 hour day. Example: 25 ug/hr fentanyl patch * 24 hrs = 600 ug/day fentanyl = 60 mg/day oral morphine milligram equivalent. In other words, the conversion factor not accounting for days of use would be 60/25 or 2.4. However, since the fentanyl patch remains in place for 3 days, we have multiplied the conversion factor by 3 (2.4 X 3 = 7.2).
In this example, MME/day for ten 25 µg/hr fentanyl patches dispensed for use over 30 days would work out as follows: Example: 25 ug/hr fentanyl patch * (10 patches/30 days)* 7.2 = 60 MME/day.

Sources:

1) Centers for Medicare & Medicaid Services. Opioid Oral Morphine Milligram Equivalent (MME) Conversion Factors. https:\\www.cms.govMedicarePrescription-Drug-CoveragePrescriptionDrugCovContraDownloadsOpioid-Morphine-EQConversion-Factors-vFeb-.pdf. Accessed: September 5, 2019
2) Svendsen, K., Borchgrevink, P., Fredheim, O., Hamunen, K., Mellbye, A., & Dale, O. (2011). Choosing the unit of measurement counts: the use of oral morphine equivalents in studies of opioid consumption is a useful addition to defined daily doses. Palliative Medicine, 25(7), 725–732. http://doi.org/10.1177/0269216311398300

Appendix 6-C. Inclusion of Covariates and Their Assessment in Inverse Probability Treatment Weights Marginal Structural Models

Appendix 6-C.1. Description of available data on drug, patient, provider and system level characteristics

	Description	**Measurement**	**Timing of Measurement**	**Functional Form**
Opioid-related Characteristics				
Opioid Dispensations				
ATC code	Anatomical Therapeutic Chemical Classification System code used to identify opioids and other concurrent medications that the patient is taking **Opioids ATC Included: N02A, R05DA**	RAMQ prescription claims.	In the community one year prior to admission and one year post-discharge	N/A
Dose	The daily amount of drug taken by patient will be calculated based on information about the number of tablets prescribed, strength and number of days' supply; daily dose will be converted to milligram morphine equivalents to facilitate comparisons across opioids.	From RAMQ prescription claims	In the community one year prior to admission and one year post-discharge	Continuous, categorical, time-varying
Duration	The days' supply on the drug claim as entered by the pharmacist	From RAMQ prescription claims	In the community one year prior to admission and one year post-discharge	Continuous, categorical, time-varying
Type of opioid	Type of opioid ingredient. E.g; Hydromorphone,	From RAMQ prescription claims	One year post-discharge	Categorical, time-varying

	oxycodone, morphine, fentanyl, etc.			
Opioid Administration in Hospital				
ATC code	Anatomical Therapeutic Chemical Classification System code used to identify administered opioids	Hospital pharmacy	In hospital	Categorical
Opioid Prescription at Hospital Discharge				
Status of opioid medication	Continued or stopped from community, newly prescribed at discharge	From patient chart	At hospital discharge	Categorical, time-fixed
Reason for opioid prescribing	Pain-related including having had surgery as well as other diagnoses such as having insomnia or anxiety as recorder during the hospitalization	From patient chart	In-hospital	Categorical, time-fixed
Presence of a multi-modal pain management regimen	The opioid prescription at hospital discharge was part of multi-modal pain treatment regimen	From patient chart	At hospital discharge	Categorical, time-fixed
Patient-reported adherence to opioid prescription given at hospital discharge	Whether patient takes the medication as prescribed or deviated from the prescription posology (e.g.; medication taken less or more often than directed to patient due to pain complaints, complications, side-effects, etc.)	RAMQ prescription claims to determine whether opioid was filled post-discharge; Patient interview to assess if patients are taking the drugs as prescribed	30-days post-hospital discharge	Categorical, time-fixed
Patient-level Characteristics				
Demographics				
Age		From patient chart	Admission to hospital	Continuous, time-varying
Sex	Male, Female	From patient chart	Admission to hospital	Binary, time-fixed
Drug insurance status	E.g.; Full copay, partial copay, no copay Serves as proxy for socio-economic status.	From RAMQ drug programs	Admission to hospital	Categorical, time-fixed
Co-Existing Illnesses				

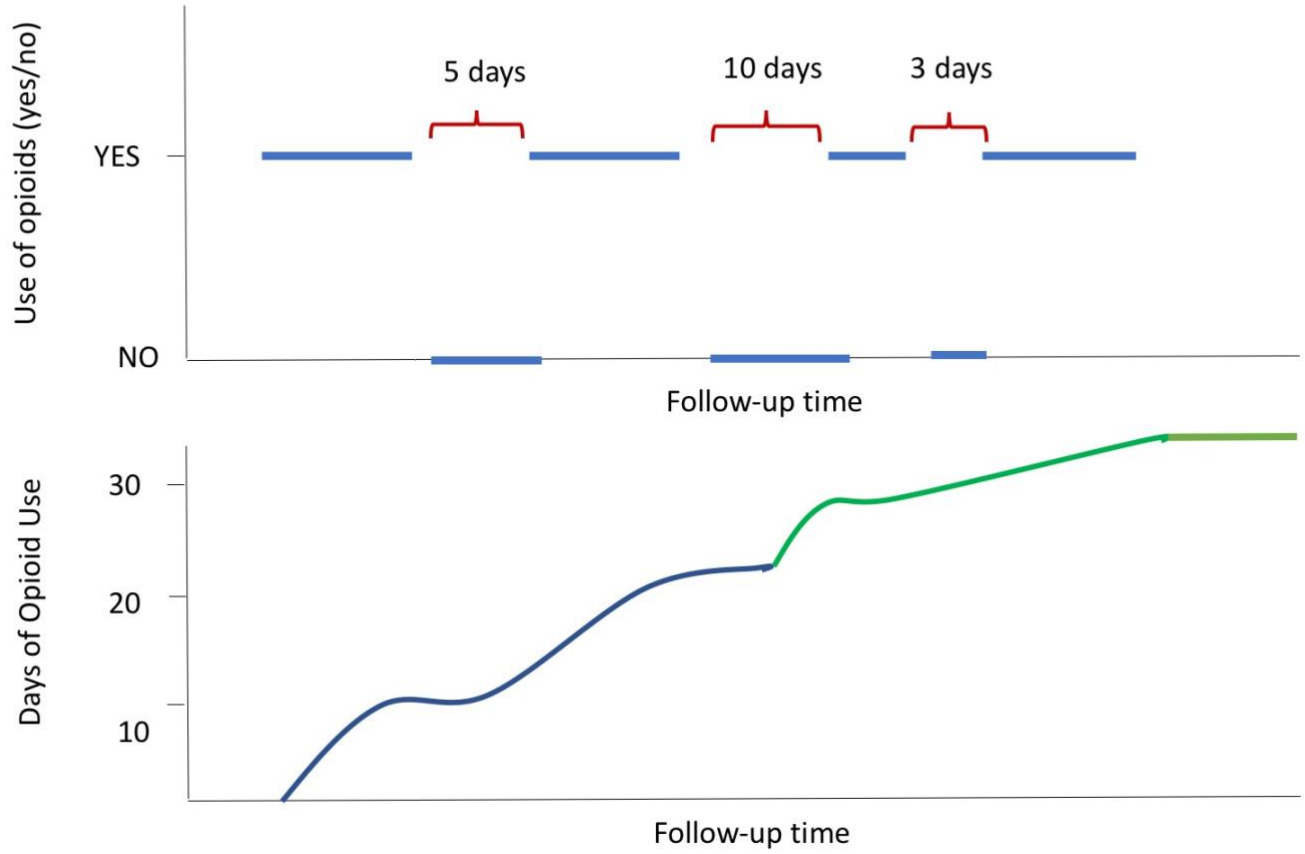
History of mental health conditions	E.g.; Anxiety, depression, psychiatric diagnosis, mood disorder, and post-traumatic stress disorder	ICD-9 from RAMQ medical services and ICD-10 codes from hospitalization data	In community one year prior to admission, in hospital, post-discharge	Binary per condition, time-varying
Pain syndromes	E.g.; Chronic back pain, back and neck pain, back disorder, arthritis, migraine, headache, fibromyalgia, fracture	ICD-9 from RAMQ medical services and ICD-10 codes from hospitalization data	In community one year prior to admission, in hospital, post-discharge	Binary per condition, time-varying
Health conditions Associated with abuse	E.g.; Alcohol abuse, drug abuse	From patient chart. Also from RAMQ medical series and prescription claims	In community one year prior to admission, in hospital, post-discharge	Binary per condition, time-varying
Tobacco use	Patient-reported history of tobacco use	From hospital charts	At admission	Binary, time-fixed
Cancer diagnosis	E.g.; Metastatic, Non-metastatic, Lymphoma	ICD-9 from RAMQ medical services and ICD-10 codes from hospitalization data	In community one year prior to admission, in hospital, post-discharge	Binary per condition, time-varying
Other comorbidities	E.g.; Acute MI, cerebrovascular diseases, chronic kidney, COPD, diabetes, heart failure, hypertension, ischemic heart disease, liver, obesity	ICD-9 from RAMQ medical services and ICD-10 codes from hospitalization data	In community one year prior to admission, in hospital, post-discharge	Binary per condition, time-varying
Drug and Healthcare Utilization				
Use of potential interacting drugs increasing the risk of opioid misuse	E.g.; Selective serotonin reuptake inhibitors, other antidepressants, benzodiazepines, other	ATC codes, DIN, Generic Drug name used to extract	In community one year prior to admission, in-	Binary per drug, time-varying

	antipsychotic drugs, central nervous system depressants, psychotropic medication	information from RAMQ prescription claims, hospital data, patient chart.	hospital, post-discharge	
Use of non-opioid pain medications	E.g.; NSAIDS, COX-2, Acetaminophen, Gabapentin, anti-migraine medications, muscle-relaxants, other anti-inflammatories and anti-rheumatoid medications	ATC codes, DIN, Generic Drug name used to extract information from RAMQ prescription claims, hospital data, patient chart.	In community one year prior to admission, in-hospital, post-discharge	Binary per drug, time-varying
Number of ED visits and hospitalizations	Total number of ED visits and hospitalizations	From RAMQ prescription claims and hospital data	One year prior to hospital admission & one year post-discharge	Categorical, continuous, time-varying
Measures of Care Continuity				
Number of physicians	Number of unique physicians that prescribed an opioid medication to a patient in the year post hospital admission	From RAMQ medical services	One year prior to hospital admission & one year post-discharge	Categorical, continuous, cumulative time-varying
Number of dispensing pharmacies	Number of unique pharmacies that a patient has opioid medications dispensed at in the one year post to hospital admission	From RAMQ medical services	One year prior to hospital admission & One year post-discharge	Categorical, continuous, cumulative time-varying
Other Patient Drug Behavior Characteristics				
Time since hospital discharge	The time elapsed between patent's hospital discharge and their first opioid dispensation	From RAMQ prescription claims and hospital data	One year post-discharge	Continuous, time-fixed
Discontinuation of opioid use	Recent discontinuation of opioid use in the past 2 weeks	From RAMQ medical services	One year post-discharge	Categorical, time-varying
Daily opioid dose increase	Recent increase in the daily opioid use in the past 2 weeks	From RAMQ medical services	One year post-discharge	Categorical, time-varying
Add-on opioid	Recent add-on of another opioid type in the past 2 weeks	From RAMQ medical services	One year post-discharge	Categorical, time-varying
In-hospital Characteristics				

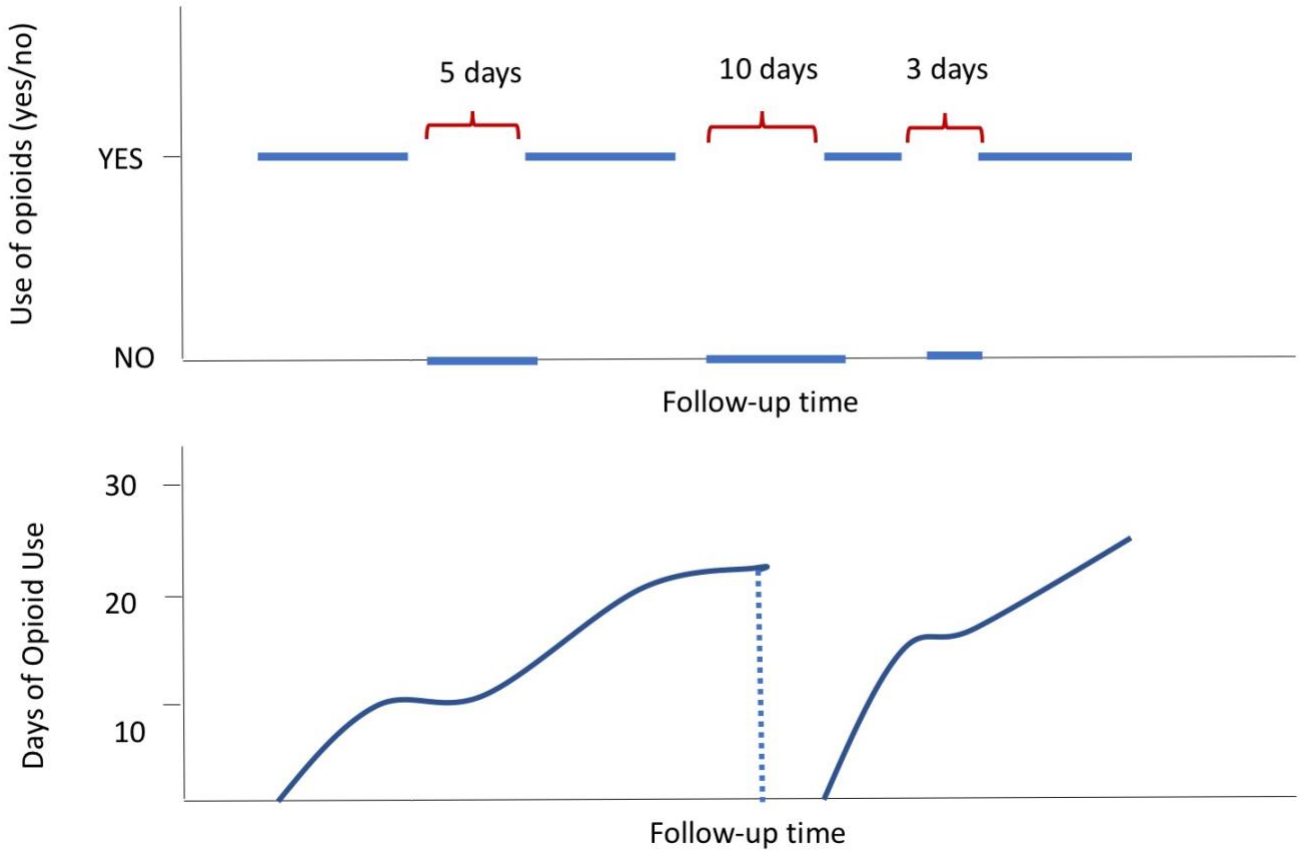
Hospital patient is admitted to	Montreal General or Royal Victoria hospital	From hospital chart	Upon admission to the hospital	Binary, time-fixed
Hospital unit the patient is admitted to	Medical or surgical unit	From hospital chart	Upon admission to the hospital	Binary, time-fixed
Reason for index hospital admission	Reasons were classified as opioid-related if patient presented to the hospital for an opioid-related disorder, poisoning by opioids, or fractures.	From hospitalization data	During the hospital stay	Binary, time-fixed
Discharge Destination	Home community, long term care	Patient chart	Upon discharge	Binary, time-fixed
RightRx patients	Patients, who were part of the initial randomized controlled trial	Patient chart	Upon discharge	Binary, time-fixed

Appendix 6-C.2. Operational definitions of opioid use duration.

a. Definition of opioid exposure based on cumulative duration of opioid use.



b. Definition of opioid exposure based on continuous duration of opioid use.



Supplement Method 6-C. Operational definitions of opioid use durations

Cumulative duration of past use assessed the long-term impact of opioids, where the effect on the outcome persisted upon discontinuation: defined as the total number of days exposed, calculated by summing the durations of all dispensations between cohort entry (first opioid dispensation) and a given day during the follow-up. Cumulative users represented patients who used opioids only

when needed, thus accumulating use over time. On the other hand, we assessed continuous duration where the effect of opioids accumulated by dispensation supply but the risk returned to baseline after discontinuation. Continuous duration was defined similarly but was allowed to increase only during the periods of un-interrupted use and was reset to zero if there was a gap of >5 days between subsequent dispensations.

Appendix 6-D. Additional results from descriptive analyses and main models.

Appendix 6-D.1. Overall characteristics of the opioid prescriptions dispensed by patients according to opioid type and potency.

Ingredient *(molecule)*	**Person-Months ***	**Quantity** *Mean (SD), Median, IQR*	**Days' Supply** *Mean (SD), Median, IQR*	**Daily Dose** *Mean (SD), Median, IQR*
Codeine	29.6	52.8 (44.9), 30.0, 16.0 – 70.0	14.9 (11.8), 8.0, 6.0 – 31.0	20.9 (11.0), 17.7, 14.5 – 26.3
Morphine	31.5	31.9 (31.7), 21.0, 7.0 – 50.0	11.4 (9.9), 8.0, 6.0 – 11.0	29.9 (31.4), 18.8, 15.0 – 35.0
Oxycodone	32.9	41.0 (41.6), 30.0, 14.0 – 60.0	12.1 (9.8), 8.0, 6.0 – 15.0	40.4 (35.7), 30.0, 21.8 – 52.5
Hydromorphone	28.9	37.5 (42.7), 21.0, 12.5 -60	10.3 (9.3), 8.0, 5.0 – 11.0	59.2 (65.2), 32.0, 20.6 – 69.7
Fentanyl	32.1	8.5 (4.5), 10.0, 5.0-10.0	22.0 (9.4), 27.0, 16.0 – 31.0	108.4 (110.9), 58.1, 27.9 – 168.7

*per 1000 per month; person-month represents person-time from discharge until last date when patients had a supply for that drug during the follow-up period.

Appendix 6-D.2. Sensitivity analyses excluding patients with more than three opioids dispensations in the one year before initial hospital admission (final cohort N=1468)

Opioid Exposure Metric	**HR Stabilized Weights**	**95% CI**
Current Opioid Use		
No use	Ref	Ref
Use	1.76	1.23 – 2.52
Cumulative Duration of Opioid Use		
1-30	Ref	Ref
30-60	1.53	0.98 – 2.40
60-90	2.15	1.15 – 4.02
>90	2.60	1.57 – 4.30

Appendix 6-D.3. Sensitivity analyses excluding patients with an opioid dispensation in the one-year prior to their initial admission (final cohort N=884)

Opioid Exposure Metric	HR Stabilized Weights	95% CI
Current Opioid Use		
Non-users	Ref	Ref
Users	2.40	1.31 – 4.41
Cumulative Duration of Opioid Use		
1-30	Ref	Ref
30-60	1.05	0.49 – 2.22
60-90	1.43	0.46 – 4.44
>90	9.46	4.69 – 19.08

Appendix 6-D.4. Breakdown of the reasons for the healthcare encounters in the one-year post-discharge among patients with at least one opioid dispensation.

	N (%) *
Drug dependence, morphine type	2 (3.9)
Fractures	219 (51.8)
General symptoms, dizziness and giddiness	78 (18.4)
Functional digestive disorders, constipation	58 (13.7)
Symptoms involving digestive system, nausea and vomiting	66 (15.6)

* Total number of reasons does not equal the total number of patients as multiple diagnoses may have been recorded per patient at admission.

Appendix 6-D.5. Analyses for current opioid use and cumulative duration of opioid use based on age.

Opioid Exposure Metric	Average Starting Dose (MME) Mean (SD)	Average Daily Dose (MME) Mean (SD)	HR Stabilized Weights	95% CI
Current Opioid Use				
Patients ≤64 years of age				
No use	34.9 (21.9)	-	Ref	-
Use	49.9 (51.9)	71.8 (91.1)	3.38	1.60 – 7.13

Patients >64 years of age				
No use	32.8 (17.9)	-	Ref	-
Use	35.9 (36.0)	48.1 (61.7)	2.01	1.20 – 2.34
Cumulative Duration of Opioid Use				
Patients ≤64 years of age				
1-30	41.2 (36.3)	49.2 (55.8)	Ref	-
30-60	47.4 (46.8)	67.3 (88.3)	2.79	1.24 – 6.28
60-90	49.9 (49.1)	76.6 (97.8)	0.65	0.13 – 3.24
>90	57.7 (62.4)	89.8 (107.3)	3.23	1.15 – 9.44
Patients >64 years of age				
1-30	33.5 (28.3)	37.4 (35.9)	Ref	-
30-60	35.1 (34.9)	42.1 (58.1)	1.54	0.84 – 2.82
60-90	27.2 (40.8)	54.1 (74.5)	4.31	2.08 – 8.93
>90	38.6 (42.1)	60.3 (77.1)	5.29	2.29 – 12.2

Note: Results in the Appendix were presented for all interactions, regardless of statistical significance, as, in previous research, these subgroups have been studied separately and having distinct estimates could serve to provide meaningful comparisons across these subclinical populations. The two-way interaction terms p-values with current opioid use and age (0.22); the two-way overall interaction terms p-values with cumulative duration of opioid use and age were 0.05. With respect to the various categories of cumulative duration of use, the respective p-values were the following: 0.24 (30-60 days), 0.03 (60-90 days), 0.41 (>90 days).

Appendix 6-D.6. Analyses for current opioid use and cumulative duration of opioid use based on treatment indication.

Opioid Exposure Metric	**Average Starting Dose (MME) Mean (SD)**	**Average Daily Dose (MME) Mean (SD)**	**HR Stabilized Weights**	**95% CI**
Current Opioid Use				
Medical Patients				
No use	25.9 (27.0)	-	Ref	-
Use	45.1 (58.4)	46.6 (53.9)	1.10	0.65 – 1.88
Surgical Patients				
No use	37.8 (17.3)	-	Ref	-
Use	37.6 (20.5)	68.0 (91.0)	3.55	1.82 – 6.85
Non-cancer patients				
No use	29.5 (18.3)	-	Ref	
Use	38.9 (48.9)	53.9 (77.2)	1.89	1.02 – 3.49

Cancer patients				
No use	38.8 (48.8)	-	Ref	
Use	43.6 (36.5)	59.9 (72.4)	1.58	0.87 – 2.87
Cumulative Duration of Opioid Use				
Medical Patients				
1-30	36.7 (49.7)	47.1 (63.9)	Ref	-
30-60	41.6 (53.8)	60.1 (83.2)	1.87	0.98 – 3.53
60-90	44.2 (56.9)	69.5 (92.6)	1.73	0.68 – 4.42
>90	50.2 (62.9)	79.7 (101.1)	2.26	0.94 – 5.43
Surgical Patients				
1-30	35.9 (18.8)	38.9 (31.5)	Ref	-
30-60	38.3 (20.9)	44.0 (59.3)	1.22	0.55 – 2.69
60-90	39.9 (20.9)	54.8 (74.1)	4.81	1.76 – 13.1
>90	39.9 (22.7)	59.7 (71.2)	7.80	3.20 – 19.1
Non-cancer Patients				
1-30	33.0 (35.8)	38.5 (47.6)	Ref	-
30-60	38.1 (47.4)	55.0 (84.7)	1.53	0.72 – 3.27
60-90	40.4 (51.8)	61.6 (90.6)	2.25	0.76 – 6.64
>90	44.4 (58.0)	66.9 (90.4)	2.25	0.78 – 6.50
Cancer Patients				
1-30	39.3 (25.8)	44.5 (39.7)	Ref	-
30-60	41.6 (32.5)	48.9 (58.4)	1.85	0.98 – 3.49
60-90	44.1 (36.2)	64.2 (79.4)	3.26	1.36 – 7.81
>90	48.6 (45.5)	78.3 (93.1)	4.43	1.85 – 10.6

Note: Results in the Appendix were presented for all interactions, regardless of statistical significance, as, in previous research, these subgroups have been studied separately and having distinct estimates could serve to provide meaningful comparisons across these subclinical populations. The two-way interaction terms p-values with current opioid use and discharged unit (0.003), cancer diagnoses (0.68); the two-way overall interaction terms p-values with cumulative duration of opioid use and discharged unit were 0.03 and with cancer diagnoses**,** 0.65. Despite the overall-value for the interaction between hospital discharge unit and cumulative duration of use, only the duration of more than 90 days showed to be significant (p-value = 0.02) as such, only results for this subclinical category were presented, along with the estimate for current opioid use, which also tested significant.

Appendix 6-D.7. Results from statistically significant additional interactions terms between current and cumulative duration of opioid use and concurrent use of buprenorphine/methadone and benzodiazepines.

Opioid Exposure Metric	Average Starting Dose (MME) Mean (SD)	Average Daily Dose (MME) Mean (SD)	HR Stabilized Weights	95% CI
Current Opioid Use				
No concurrent use with buprenorphine/methadone				
No use	33.4 (19.1)	-	Ref	-
Use	41.0 (43.3)	56.6 (74.9)	1.76	1.07 – 2.89
Concurrent use with buprenorphine/methadone				
No current daily opioid use	85.8 (51.7)	-	Ref	-
Current daily opioid use	52.1 (34.9)	81.1 (73.9)	0.08	0.01 – 1.21
Cumulative Duration of Opioid Use				
No concurrent use with benzodiazepines				
1-30	36.1 (31.2)	41.4 (43.9)	Ref	-
30-60	39.9 (40.1)	51.8 (72.0)	1.57	0.92 – 2.68
Concurrent use with benzodiazepines				
1-30	38.1 (41.6)	42.7 (48.6)	Ref	-
30-60	38.3 (46.9)	53.3 (79.8)	6.81	1.89 – 24.6

Note: The results in main text as well as in the Appendix table were presented only for interaction terms which were significant. For example, the likelihood ratio test for the interaction between current daily opioid use and opioid formulation had a p-value >0.05 and thus, results were not shown. The corresponding p-values for the two-way interaction terms between current opioid use and use of methadone/buprenorphine (0.03); the p-value for the two-way interaction terms between cumulative duration of opioid use of benzodiazepines (0.045). Despite the overall significant p-value for the interaction between concurrent users of benzodiazepines and cumulative duration of use, only the duration between 30-60 days of use showed to be significant for concurrent opioid and benzodiazepine use (p-value = 0.035) as such, only results for this subclinical category were presented.

Appendix 6-D.8. Characteristics of patients in the weighted study population according to the receipt of an opioid dispensation at 10 days since beginning of follow-up.

Characteristic	No Opioid Dispensation	Opioid Dispensation	Absolute Standardized Difference
Age, mean	67.1(13.6)	67.1 (13.2)	0.001
Male	60.40	58.92	0.03

Length of hospital stay (≥ 6 days)	77.15	82.27	0.13
Hospital unit			
Internal medicine	24.48	28.46	0.09
Cardiac Surgery	51.05	30.77	0.41
Thoracic surgery	24.47	40.77	0.35
Healthcare Utilization			
Number of dispensing pharmacies (>1)	0.3465	0.3257	0.04
Radiotherapy	0.1044	0.1500	0.13
Chemotherapy	0.1220	0.1836	0.17
Pain Regiment at Discharge			
Opioids	0.7980	0.7810	0.04
Analgesics	0.8433	0.7950	0.12
In-Hospital Medication Use			
Antidepressants	0.1138	0.1785	0.18
Opioids	0.9247	0.9333	0.03
Benzodiazepines	0.8131	0.7704	0.10
Analgesics	0.9624	0.9691	0.03
Medication Use			
History of opioid use	0.2912	0.4426	0.31
Benzodiazepines	0.0261	0.0201	0.04
Analgesics	0.0853	0.0801	0.02
Antidepressants	0.0242	0.0278	0.02
Targeted Comorbidities			
Cancer	0.6672	0.6191	0.10
Mental illness	0.1730	0.1553	0.05
Opioid and non-opioid substance abuse	0.0401	0.0292	0.06
Alcohol abuse	0.0179	0.0201	0.02
Pain Syndromes	0.4870	0.3975	0.18
Cardiovascular Diseases	0.5727	0.5441	0.06
Cerebrovascular Diseases	0.0905	0.1066	0.05
Chronic obstructive pulmonary disease	0.2160	0.2194	0.008

Appendix 6-D.9. Sensitivity analyses assessing the impact of unmeasured confounder on the risk of opioid-related adverse events associated with daily opioid use and daily opioid dose.

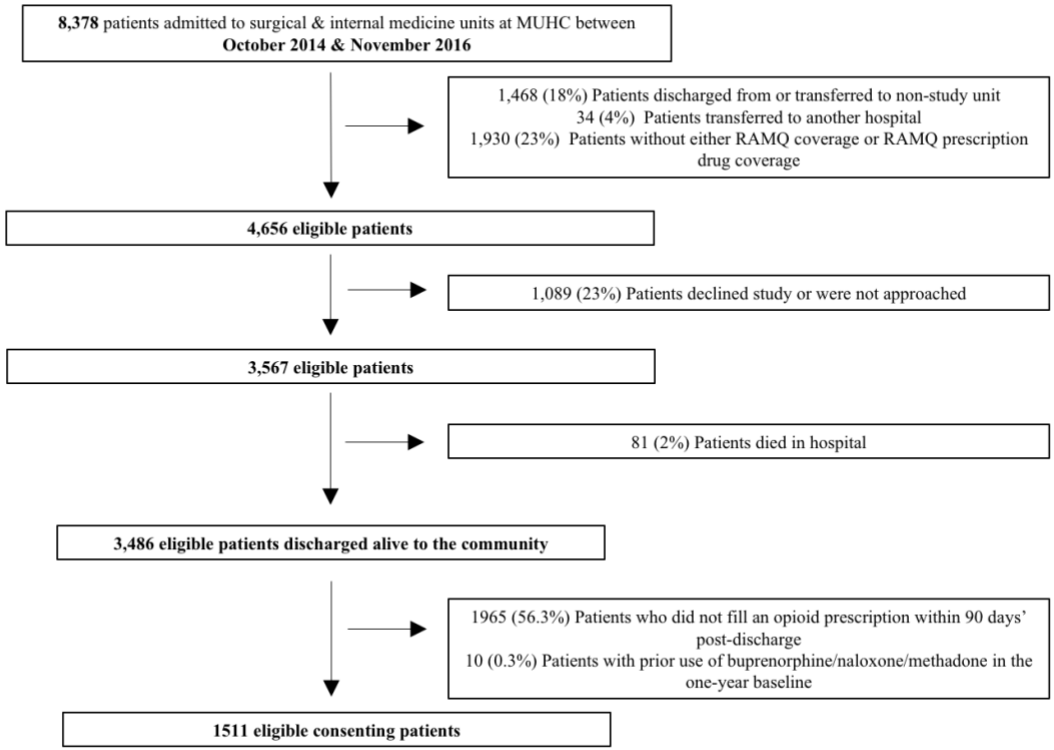
	ED visits/re-admission/death	**ED visits/re-admissions**	**Death**
Current Daily Use			
No	Ref	Ref	Ref
Yes	1.50 (0.91 – 2.49)	1.71 (0.86 – 3.42)	1.37 (0.69 – 2.71)
MME Daily Dose			
≤90	Ref	Ref	Ref
>90	3.49 (1.57 – 7. 73)	1.06 (0.30 – 3.76)	5.81 (2.11 – 16.03)

Appendix 6-D.10. Sensitivity analyses looking at the risk of opioid-related adverse events such as fractures and dizziness, which led to an ED visit or re-admission associated with daily opioid use and daily opioid dose.

Opioid Exposure Metric	**Fracture-related events**	**Fracture-related ED visits/re-admissions**	**Other opioid-related events**	**Other opioid-related resED visits/re-admissions**
Current Opioid Use				
No use	59	Ref	33	Ref
Use	29	1.46 (0.66 – 3.24)	26	1.69 (0.65 – 4.33)
Cumulative Duration of Opioid Use				
1-30	52	Ref	37	Ref
30-60	13	1.52 (0.69 – 3.33)	12	1.54 (0.60 – 3.94)
60-90	6	2.10 (0.62 – 7.10)	2	-
>90	17	2.21 (0.83 – 5.88)	8	1.60 (0.43 – 6.00)
Continuous Duration of Opioid Use				
0	59	Ref	33	Ref
1-30	15	1.18 (0.24 - 5.69)	20	2.58 (0.79 – 8.45)
30-60	5	3.86 (0.96 – 15.5)	2	1.76 (0.38 – 8.06)
>60	9	0.71 (0.23 – 2.16)	4	0.62 (0.13 – 3.06)

MME Daily Dose				
≤90	81	Ref	33	Ref
>90	7	1.88 (0.58 – 6.01)	26	0.82 (0.11 – 5.97)

Appendix 6-E. Flowchart of eligible patients.



7. Objective 4

Kurteva S, Abrahamowicz M, Beauchamp ME, Tamblyn R. Flexible modeling of opioid exposure provides new insights in its association with adverse outcomes. [Prepared for journal submission]

7.1 Preamble

This study used novel methods of modelling time-varying exposures to better understand the mechanism behind opioid-related morbidity/mortality and opioid use. Conventional models assume that the risk of adverse events is a linear function of the duration of use. In addition, they fail to consider that the impact of past exposure may depend not only on the total duration of past use but also on how recently past exposures occurred. In this paper, I investigated how flexible extensions of the marginal structural Cox proportional hazards models and the use of different methodological approaches to measure dynamic opioid exposures could improve our understanding of how opioid-related adverse events may vary depending on the current and past opioid use.

This manuscript has been written as a standalone paper for journal submission.

7.2 Title page and footnotes

Title: Flexible modeling of opioid exposure provides new insights in its association with adverse outcomes.

Contributing authors: Siyana Kurteva [1,2], Michal Abrahamowicz[1,3,], Marie-Eve Beauchamp[3], Robyn Tamblyn [1,2,3,4,5]

Affiliations of all contributing authors:

[1] Department of Epidemiology and Biostatistics, McGill University, Montreal, Canada

[2] Clinical and Health Informatics Research Group, McGill University, Montreal, Canada

[3] Centre for Outcomes Research and Evaluation, Research Institute of the McGill University Health Centre, Montreal, Canada

[4]Department of Medicine, McGill University Health Center, Montreal, Canada

[5] McGill University Health Centre, Montreal, Canada

Corresponding author:

Siyana Kurteva

Clinical & Health Informatics Research Group, Department of Medicine, McGill University

1140 Pine Ave W., Montreal, Quebec, Canada, H3A 1A3

Email: siyana.kurteva@mail.mcgill.ca

Tel: +1 (514) - 632 – 5838

ABSTRACT:

Background: Previous research linking opioid prescribing to adverse drug events failed to properly account for the time-varying nature of opioid exposure.

Objectives: To explore how the risk of opioid-related emergency department visits, re-admissions or deaths (composite outcome) varies with opioid dose and duration, using novel modeling techniques.

Methods: A prospective cohort of 1,511 hospitalized patients was followed from the first post-discharge opioid dispensation until one year post-discharge. Marginal structural Cox proportional hazards models (MSM Cox) and their flexible extensions were used to explore the association between time-varying opioid use and the composite outcome. Weighted cumulative exposure (WCE) models assessed cumulative effects of past use and explored how its impact depends on the recency of exposure.

Results: The patient mean age was 69.6 years (SD = 10.3), 57.7% were male. In MSM analyses current opioid use was associated with a 71% risk increase (aHR): 1.71, 95% CI (1.21 – 2.43). The WCE results suggested that the risk cumulates over the past 50 days of opioid consumption.

Conclusion: Flexible modeling techniques allowed us to better assess how the risk of opioid-related adverse events may be associated with the non-linear nature of continuous opioid exposures and the recency of past use.

7.3 Introduction

Opioids are the most commonly prescribed medications for the treatment of pain.[200] Trends of increasing use of prescribed opioids have been accompanied by marked increases in opioid-related morbidity and mortality. [7,8] Recent research suggests that even short-term use may lead to increased risk of adverse effects. [63]

Understanding how risks vary depending on the duration of opioid therapy and/or opioid consumption patterns is instrumental in developing evidence-based prescribing guidelines and public health strategies for addressing the growing problem of the opioid epidemic. [201] Yet, research linking opioid prescribing to adverse drug events has a number of methodological limitations. Most previous studies failed to account for dynamic changes in patients' comorbidities and concurrent medication use, which may induce bias, possibly due to confounding by indication. Currently, no consensus exists as to what duration of opioid use should be considered potentially harmful.[126] Furthermore, most published analyses relied on arbitrarily selected thresholds for "safe" duration of opioid use, such as 90 days. [20,50,62,68,202,203] Yet, it is plausible that the risks of adverse events increase gradually with increasing cumulative dose and/or duration of past opioid use. [204] Conventional models assume that the risk of adverse events is a linear function of the duration of use, and fail to consider that the impact of past exposure may depend not only on the total duration of past use but also on how recently past exposures occurred.

To avoid such limitations, the over-arching goal of the present study was to apply flexible statistical modeling to gain further insights regarding how risks of adverse events may vary depending on the current and past opioid use. First, we assessed the association between time-varying opioid exposures and the risk of opioid-related emergency department visits, hospital re-admissions or all-cause death in the one-year following hospital discharge, while accounting for duration, doses and recency of past opioid use. Second, we assessed whether the methodological approach used to model time-varying opioid exposures had an impact on the results and conclusions. To enhance the validity of the results, we adjusted for multiple potential

confounders measured using comprehensive data from multiple sources: dispensing pharmacy records, in-hospital medical records and opioid prescriptions written at hospital discharge.

7.4 Methods

Design and Study Population: A prospective cohort of opioid users who filled at least one opioid prescription 3 months' post-discharge was assembled from the participants of a cluster-randomized trial of medication reconciliation conducted at the McGill University Health Centre (MUHC) between October 2014 and November 2016. [205]

Data Sources: Demographic, clinical, health care service use and prescription claims were retrieved from the admission notes and provincial health care administrative databases (RAMQ medical services and RAMQ prescription claims data) in the year prior to and the year after the hospitalization. Dates of admission and discharge, admitting and discharge unit, patient demographics, health problems at admission and discharge, major procedures (surgeries, treatment interventions) were retrieved from the provincial hospitalization database. Diagnoses and medications taken (i) at admission, (ii) in-hospital, (iii) prescribed at discharge and (iv) dispensed in the community post-discharge were abstracted from the MUHC Data Warehouse and the RAMQ prescription files, one of the few databases in the world that links information on all four sources of medication use.

Outcomes: We used a composite endpoint of the earliest of the first opioid-related emergency department (ED) visit and/or re-admission, or death due to any cause, in the one year post-discharge. Outcomes were ascertained using RAMQ provincial medical services claims and hospitalization databases, to ensure that all ED visits and re-admissions were included. An adverse event was considered opioid-related if there was a diagnosis of opioid abuse, opioid dependence, and/or opioid poisoning at the time of the ED visit or hospitalization, or there was a diagnosis of one or more common opioids side effects [171]: constipation, nausea, vomiting, dizziness or fractures. [172-176] All recorded ICD-9 codes were retrieved to provide comprehensive information on the potential reasons for the opioid-related ED visits/re-admissions.

Opioid Use: Time-varying opioid use one-year post-discharge was measured using RAMQ pharmacy administrative claims, which document, for each prescription filled, the specific medication using the drug identification number (DIN), strength, dispensing date and quantity, and prescription duration. Appendix 7-B provides details of how daily exposure status and dose were re-constructed. DINs mapped to the Anatomical Therapeutic Chemical (ATC) codes N02A, R05DA were used to identify opioids. On each day, an individual was classified as having a dispensed opioid available or not. A 5-day grace period was added to the end of each dispensation because, for take-as-needed prescriptions, patients may take some of the unused pills for a few days after the prescription end. The daily dose of each opioid was reconstructed based on the number of pills dispensed, their strength and prescription duration. For concurrent prescriptions, a subsequent dispensation was considered as an early prescription if overlap was ≤30% of the previous dispensation duration. Otherwise, the opioids were considered to be taken simultaneously. Daily dose was converted to morphine milligram equivalent (MME) doses using the Center for Disease Control Opioid Morphine Equivalent Conversion Factor and the concurrently dispensed doses were added together. [170]

Opioid Exposure Metrics: As the potential mechanism that relates past and/or current opioid use to an increased risk is not known, ignoring the complex time-varying nature of the exposure may lead to etiologically incorrect conclusions. [184] Thus, based on the aforementioned daily exposure data, we used four alternative time-varying metrics of opioid use, updated at every day during follow-up: (i) cumulative or (ii) continuous duration of past opioid use, and (iii) current daily opioid dose, and (iv) a binary indicator of current opioid use. *Cumulative* duration of past use was defined as the total number of past days when the subject was exposed, calculated by summing the durations of all dispensations between cohort entry and the current day during follow-up. In contrast, *continuous* duration was limited to days of the current on-going *uninterrupted* exposure and, accordingly, was reset to zero each time there was a gap of more than 5 days between subsequent dispensations. [106].

Potential Confounders: Potential risk factors for long-term opioid use and opioid-related harms were identified from the literature. [62,74,161,206-211] The baseline time-invariant covariates included patient demographics and healthcare utilization in the one year prior to hospitalization. We also

accounted for time-varying comorbidities that may increase one's risk of having an opioid dispensation [17,50] (Appendix 7-A.1). To account for fragmentation in healthcare associated with lower quality of care and increased risk of adverse outcomes, or opioid seeking behavior because of increasing dependence [44,46] ,we measured the time-varying cumulative number of distinct prescribers and dispensing pharmacies since discharge. Time between hospital discharge and first opioid dispensation was included as a continuous covariate.

Statistical Analyses: Descriptive statistics were used to summarize patient, provider and healthcare system characteristics. For all analyses, we used multivariable marginal structural Cox proportional hazards (PH) models (MSM Cox) [182,212] and their flexible extensions. This allowed us to estimate the associations between time-varying opioid use and the time to the composite outcome, while controlling for any time-varying confounders that may also be affected by prior opioid exposure. Time zero corresponded to the start of the first post-discharge opioid dispensation, and patients who had no events until one year post-discharge were censored at that time. Time-varying and time-fixed covariates were used to estimate time-varying stabilized inverse probability treatment (IPT) weights [185,186] for opioid exposure, at each 10-day interval (see Appendix 7-A.1 for information on included covariates). To avoid variance inflation and/or unstable estimates due to extreme weights, stabilized IPT weights were truncated at the 95th percentile. [186]

For each exposure metric, we first fit the conventional MSM Cox PH model, which imposed two restrictive assumptions. Specifically, the linearity assumption implies that the logarithm of the hazard is a linear function of continuous exposure metrics, whereas the PH assumption implies that hazard ratios are constant across the follow-up. [213] Yet, either or both assumptions may often be violated (see Appendix 7-B, Supplement 7-B.3. for a detailed discussion). To avoid these restrictive assumptions and further explore if and how the hazards of the adverse events may vary depending on the duration, recency and/or dose of past opioid use, we employed two different flexible extensions of MSM Cox models. The first focused on the roles of (i) cumulative and (ii) continuous duration of past opioid use, and (iii) current daily MME opioid dose, log-transformed because of very skewed distribution. First, we tested for the association of each time-varying opioid exposure metric with the hazard of adverse events the (a) PH

assumption, and, for continuous exposure metrics, the (b) linearity assumption. [151] If at least one of these assumptions were rejected, at 2-tailed α=0.05 for the respective likelihood ratio tests, [151] we relied on the flexible extension of the Cox model to estimate, respectively, the (a) time-dependent (TD) and/or (b) non-linear (NL) effects of the corresponding exposure metric. [214] The estimated TD effect describes how the strength of the association between a given exposure metric and the hazard changed during follow-up, whereas the NL estimate indicates how the logarithm of the hazard changed with the increasing value of a metric [214] **,** and may possibly suggest an approximate threshold for the association of interest. [215] The 95% CI for NL and TD estimated effects were estimated using bootstrap resampling. [214] In sensitivity analyses, to provide a comprehensive assessment of the different aspects of exposure history, we estimated flexible models with non-linear effects of both current daily dose and either continuous or cumulative duration of opioid use.

The second type of flexible models helped explore if and how the potential adverse effects of past opioid exposure accumulate over time. [204] Specifically, we hypothesized that the impact of past exposure may depend not only on the total duration of past use or on the total past cumulative dose, but also on how recently the past exposures did occur. We used the flexible recency-weighted cumulative exposure (WCE) model, in which the cumulative effect of a time-varying exposure, at a given day during follow-up, is modeled as a *weighted* sum of (a) past doses or (b) binary indicators of use at different days in the past. [216] In contrast to the conventional (unweighted) metrics of (a) cumulative sum of all past doses or (b) total duration of past use, the time-varying WCE metrics assign *differential weights* to past exposures/doses. These weights depend on the time elapsed since exposure, and reflect the relative impact of doses taken, e.g., one week ago *vs*. three weeks ago on the current hazard. The weight function is estimated using flexible cubic regression splines. [217] We used the MSM WCE model with the same IPT weights as in the aforementioned conventional MSM Cox models. [218]

Preliminary WCE analyses indicated a lack of systematic association between opioids used more than four months ago and the current hazard of adverse events (data not shown). Thus, in the final WCE analyses we considered only opioid use within the most recent 120 days. We then fit alternative WCE models of increasing flexibility/complexity, with 1-3 interior knots uniformly

placed across the 120-day time window, and chose the best-fitting model based on the minimum Akaike Information Criterion (AIC). [217] The weight function was constrained to smoothly decay to zero at the end of the 120-day window. Based on the final best-fitting WCE model, we estimated hazard ratios for pre-specified, clinically relevant patterns of past opioid use, relative to no use of opioids in the past 120 days. [219] The 95% pointwise confidence bands for the weight functions were obtained using bootstrap re-sampling. [217]

AIC was also used to compare the goodness of fit of (i) flexible *versus* conventional models for the same exposure metric, and (ii) models that used alternative exposure metrics. Based on simulation results, an AIC difference of 4 or more points indicates that the model with lower AIC is more consistent with the true way time-varying exposure affects the risks. [184]

MSM Cox models were implemented with R and flexible spline-based were implemented with customized programs in R, including the CoxFl*ex* function for NL/TD effects and the WCE package. [152]

7.5 Results

The mean age was 69.6 years (SD=10.3) with slightly more males (57.7%) (Table 7-1). The most commonly dispensed opioids post discharge were oxycodone (69.1%) and hydromorphone (45.6%). Sixteen percent (n=241) of the cohort had a potentially opioid-related emergency department visit, hospitalization or died in the one year after hospital discharge, with a mean time from discharge to the event of 129.7 days. Fractures (55.4%), nausea and vomiting (17.7%) and dizziness (14.4%) accounted for most of the potentially opioid-related ED visits/re-admissions. In conventional MSM Cox models, current opioid use was associated with a 71% increased hazard of the composite outcome of adverse events or all-cause mortality (adjusted hazard ratio (aHR): 1.71, 95% CI (1.21 – 2.43)) (Table 7-2). Compared to short duration of use (1-30 days), there were two-fold hazard increases associated with past cumulative duration of opioid use between 60-90 days (aHR of 2.39, 95% CI (1.34 – 4.29)) and more than 90 days (aHR: 2.61, 95% CI (1.59 – 4.27). Uninterrupted continuous opioid use of 30 to 60 consecutive past days was also associated with a 2-fold increased risk (aHR: 2.57, 95% CI (1.45 – 4.55), compared to patients not currently using opioids. A dose-response relationship was observed for

increasing daily opioid dose. Compared to ≤50 MMEs, there was a four-fold hazard increase for current daily doses exceeding 90 MME (aHR of 4.84, 95% CI (2.94 – 7.99).

Among the four conventional exposure metrics, the log-transformed current MME dose fit the data best (lowest AIC, last column of Table 7-3). For each of the four opioid exposure metrics considered, flexible modeling improved the models' fit to data, with very substantial AIC reductions of 11 or more points (Table 7-3). On the other hand, there was no evidence of time-dependent effects of current opioids use or dose, or of duration of cumulative or continuous use (all p-values above 0.079 when the significant NL effect was accounted for; data not shown). This indicated that the proportional hazards assumption was approximately valid and, thus, the strengths of the corresponding associations did not vary during the one year follow-up. Overall, these results indicate that both non-linear effects of continuous exposure metrics and weighted cumulative effects of past use or past doses should be considered when assessing how the risks vary depending on opioid exposure patterns.

The non-linear estimate in Figure 7-1 shows that the risk of opioid-related adverse events increases gradually as total time-varying cumulative duration of past opioid use increases up to about 50-60 days. With further increases above 2 months of cumulative use, risk increases are only moderate and there is no evidence of further impact of durations longer than 100 days of use, when the curve reaches a plateau and the estimates become very imprecise with wide 95% CI (Figure 7-1), because only a relatively few subjects accumulated such long exposures during follow-up. This flexible NL MSM fits the data much better than the conventional linear Cox MSM (Table 7-3) and reveals much higher impact of increasing cumulative duration of past opioid use beyond a few weeks.

The NL estimate for the continuous uninterrupted duration of recent use suggests an even more pronounced non-linearity, with very steep risk increases within the first two weeks of recent uninterrupted use (Figure 7-2). However, the NL model for cumulative duration shows a much better fit (12 points improvement in AIC, Table 7-3), suggesting *continuous* duration of use is relatively less relevant. Finally, the NL estimate in Figure 7-3 indicates that the risk increases continuously with increasing current log-transformed daily opioid MME dose, with steeper increases for higher doses. This model showed the best fit among all possible models and opioid

exposures tested (Table 7-3).

In sensitivity analyses, where the duration of use was additionally adjusted for the non-linear effect of current daily dose, there were even greater improvements AIC reductions of 65 points for continuous and 35 points for cumulative use (Appendix 7-C, Table 7-C.1). The non-linear effect of cumulative duration of use shows similar patterns with or without adjusting for daily dose (Appendix 7- C, Figure 7- C.1a). However, for continuous duration of use, the NL estimate changes considerably when adjusted for daily dose and shows *decreasing* hazard for any increase in duration, even in the low range of first two weeks (solid curve in Figure 7-C.2b), where the NL estimate *not* adjusted for dose indicates increasing hazard (dashed curve in Figure 7- C.2b). This pattern of results suggests that among patients on the same current dose, the hazard decreases with longer continuous opioids use, possibly due to improved tolerance and/or healthy survivor effect. As a corollary, these results indicate that higher hazard for longer continuous duration of use (when not adjusted for current daily dose) may partly reflect higher daily doses of long-term users. Indeed, daily dose and continuous duration of use were strongly correlated: Pearson r=0.65.

The aforementioned non-linear effects of cumulative duration of opioid use are generally consistent with the results of flexible WCE analyses in Figures 7-4 and 7-5. The horizontal axis shows the number of days elapsed (t) since the exposure, and the vertical axis shows the corresponding estimated weights, reflecting the relative strength of the association between opioid use “t days ago” and the current hazard of opioid-related re-admissions/ED visits or death. The estimated weight functions for both (i) past use (Figure 7-4) and (ii) past log-transformed doses (Figure 7-5) suggest that their impact cumulates over the previous 40 or 50 days, when the estimated weights are positive. However, the WCE model for the past daily dose fits the data much better (by about 15 AIC points, Table 7-3) underscoring the importance of accounting for differences in dosage. The corresponding weight function indicates that most recent opioid doses have the highest impact on the current risk of adverse events whereas doses taken more than a month ago have only very minor effects.

Table 7-4 illustrates clinical implications of WCE results. The upper part of Table 7-4 shows how the adjusted hazard ratio (aHR), relative to no opioid use in the past 120 days, increases with increasing duration of recent use. Uninterrupted opioid use in the past 30 or 60 days is associated with important risks of adverse events or death (aHR: 4.86, 95% CI 1.56 – 6.67, and aHR: 6.68, 95% CI 2.07 – 12.0, respectively). The lower part of Table 7-4, based on the WCE model for log-transformed MME doses, shows that the aHRs associated with constant doses of 50-120 MME over the past 40 days, relative to no use, are very high, with even the lower 95% CI bounds indicating more than two-fold risk increases (e.g. for 50 MME: aHR: 5.92, 95% CI 2.46 - 14.1). Compared to users of low-dose opioids (25 MME), daily dose of 90 MME was associated with a 76% increased hazard (aHR of 1.76, 95% CI (1.33 – 2.32)) (Table 7-4).

7.6 Discussion

Advances in methods to accurately estimate the impact of opioid use are critical for improving guideline recommendations. [94] We assessed the associations between opioid dose and duration of use and the risk of potentially opioid-related adverse events by using novel flexible multivariable modeling techniques to account for the dynamic nature of opioid use, and their cumulative effects. We also considered alternative opioid exposure metrics and compared our results to conventional Cox MSM models.

These new analytic techniques offered additional insights regarding possible mechanisms linking opioid use to the risk of adverse events. The weight functions, obtained with the weighted cumulative exposure MSM modeling [217,218], indicated that most recent opioid use and doses have the highest impact on the current risk of adverse events with relatively weak effects of doses taken more than 30 days ago and no effects for exposures that occurred more than 50 days ago. This finding was corroborated by flexible modeling of non-linear (NL) effects of duration which indicated risk increases for up to 50-60 days of cumulative past opioid use. On the other hand, the best-fitting NL model for daily dose, showed no evidence of threshold, with the risk increasing continuously with increasing doses.

There is a paucity of observational research on how duration of opioid use is associated with potentially opioid-related adverse events. Most evidence is based on clinical trials which lasted

less than a year.[49] A 2017 Cochrane report on clinical trials found that opioid use beyond 90 days was associated with about three-fold and five-fold increases of risk of opioid dependence and opioid overdose, respectively. [18] A few observational studies have assessed opioids use in the first month following a hospitalization and found an increased risk of developing chronic opioid use with longer duration of initial prescription. [20,21,156] However, the design of these studies prevented accounting for longitudinal changes in opioids use and dose, which are expected for pain medication treatment, due to dynamic changes in patient's pain conditions. Consistent with our NL analyses for daily dose, previous observational studies have also demonstrated important dose-response relationships between opioids and adverse events such as fractures and opioid-related mortality. [2,39,42]

In considering the strengths of this study, we linked multiple data sources to harness detailed information on a multitude of potential confounders, in order to help improve the internal validity of our study. In addition, we utilized modern epidemiologic and analytic methods such as marginalized structural Cox models (Cox MSM) with inverse probability weighting. This allowed us to accurately model the associations of interest while considering the dynamic pattern of individual treatment regimens, and accounting for a patient's medical history, that might have partly affected their treatment changes, and medication taking behavior. Moreover, we applied a flexible spline-based methods, adapted for Cox MSM analyses [218], for modeling (i) cumulative effects of time-dependent opioid exposures, weighted by the recency of the exposure, as well as (ii) non-linear effects of opioid dose. [151]

Some limitations of our work should be recognized. In all analyses, we reconstructed prescription durations based on the pharmacist's records but since opioids are given on a *prn* basis, exposure measurement errors are possible. As in all observational studies, there is the risk of unmeasured confounding. However, by including only patients with at least one post-discharge opioid dispensation we reduce concerns about potential bias due to confounding by indication. Lastly, whereas our analyses failed to demonstrate further risk increases with cumulative duration of past opioid use continuing to increase beyond 100 days, the corresponding estimates were very imprecise. This issue requires further studies, possibly using

data sources from multiple healthcare systems, to replicate our findings in a larger cohort with longer follow-up.

7.7 Conclusion

In conclusion, we found an increased likelihood of harm when using opioids for prolonged periods and at higher doses, with the greatest risk associated with cumulative use in the past 60 days. Flexible modeling of recency-weighted cumulative opioid use/dose and non-linear effects of current dose allowed us to illustrate how careful analyses that account for dose, duration and timing of past exposures may improve the model's fit to data and enhance our understanding of the mechanism underlying potential adverse events of opioid exposure.

Table 7-1. Selected characteristics of patients who filled at least one opioid prescription in the three months' post-discharge

	Overall *(n = 3486)*	**Hospital Discharge Unit**	
		Internal Medicine *n = 392 (21.7%)*	***Surgery*** *n = 1119 (66.7%)*
Mean age (SD)	69.6 (14.9)	67.7 (16.8)	66.9 (11.9)
	N (%)	***N (%)***	***N (%)***
Male	2010 (57.7)	200 (51.0)	683 (61.0)
Length of hospital stay (≥ 6 days)	2930 (84.0)	351 (89.5)	875 (78.2)
Health Services Utilization: 1 Year Before Admission			
	Mean (SD)	***Mean (SD)***	***Mean (SD)***
Emergency department visits	8.4 (8.5)	15.3 (20.3)	4.4 (8.1)
Hospitalizations	0.8 (1.9)	0.9 (1.9)	0.7 (1.8)
Number of physicians prescribing opioids	0.6 (1.2)	1.9 (2.2)	0.5 (0.9)
Number of pharmacies dispensing opioids	0.4 (0.6)	0.9 (0.7)	0.4 (0.6)
Medication Use: 1 Year Before Admission			
	N (%)	***N (%)***	***N (%)***
Active Opioid Prescription at Admission	504 (14.5)	186 (47.4)	105 (9.4)
History of opioid use	1206 (34.6)	283 (72.2)	344 (30.7)
≥ 3 opioid dispensations	61 (15.6)	18 (1.6)	
History of long-acting opioids	104 (2.9)	89 (22.7)	35 (3.1)
	146 (4.2)		
History of methadone/buprenorphine	13 (0.4)	10 (2.6)	1 (0.1)
Pain Regimen at Discharge			
Opioids	1530 (43.9)	202 (51.5)	987 (88.2)
Non-opioid analgesics	2209 (63.4)	227 (57.9)	990 (88.5)
Comorbidities that may increase the risk of hospitalizations/ED visits			
Mental illness	511 (14.7)	74 (18.9)	132 (11.8)
Dementia	213 (6.1)	25 (6.4)	13 (1.2)
Substance & alcohol abuse	115 (3.3)	27 (6.9)	19 (1.7)
Pain Syndromes	1352 (38.8)	221 (56.4)	408 (36.5)
Cancer	1253 (35.9)	168 (42.9)	538 (48.1)

Table 7-2. Results from conventional marginal structural Cox models for the association between different opioid exposure metrics and risk of emergency department visits/re-admission or deaths.

Opioid Exposure Metric	**Average Starting Dose (MME) Mean (SD)**	**Average Daily Dose (MME) Mean (SD)**	**HR Stabilized Weights ***	**95% CI**	**AIC**
Current Opioid Use					
No	33.5 (19.3)	--	Ref	Ref	2611.3
Yes	41.2 (43.3)	57.1 (75.2)	1.71	1.21 – 2.43	
Cumulative Duration of Opioid Use					
1-30	33.7 (19.6)	41.3 (43.6)	Ref	Ref	2606.4
30-60	32.9 (24.7)	51.4 (71.5)	1.55	0.99 – 2.41	
60-90	38.4 (35.5)	62.6 (85.0)	2.39	1.34 – 4.29	
>90	44.9 (48.2)	72.5 (91.2)	2.61	1.59 – 4.27	
Continuous Duration of Opioid Use					
0	33.5 (19.3)	0	Ref	Ref	2611.4
1-30	36.1 (29.6)	41.5 (44.9)	1.08	0.52 – 2.23	
30-60	41.3 (44.4)	57.9 (79.6)	2.57	1.45 – 4.55	
>60	51.0 (59.9)	86.3 (104.6)	1.67	1.08 – 2.58	
MME Current Daily Dose (log-transformed)					
≤50 (log-transformed)	29.7		Ref	Ref	2588.2
50-90 (log-transformed)	33.4	__	2.37	1.42 – 3.93	
>90 (log-transformed)	44.8		4.84	2.94 – 7.99	

*The 95th percentile for the stabilized weight was 2.88 (mean =0.81, SD = 0.71). Covariates considered in the construction/calculation of the weights: 1) demographic characteristics: indicator for a patient randomized to the RightRx intervention group, age at admission, sex, copay status, 2) medical, prescription and healthcare use one-year before admission: unique number of dispensing pharmacies and prescribers, hospitalizations and emergency department visits, the receipt of radiotherapy and/or chemotherapy services, type of

cancer, history of mental health diagnoses, history of substance and/or alcohol abuse/dependence, targeted comorbidities which may increase someone's risk of opioid-related adverse events, history of chronic pain, previous opioid use, more than 3 opioid dispensations, previous use of psychotropic medications, 3) in-hospital characteristics: presence of an opioid-related reason for index admission, length of hospital stay, opioid administration during the index hospitalization, non-opioid pain medication administration, use of antidepressant and benzodiazepines, hospital unit discharged from (medical vs surgical) from, type of surgery (cardiac vs thoracic), 4) at discharge: receipt of an opioid prescription, prescribing reason (having had surgery, having anxiety or pain problems), 5) time-varying post-discharge characteristics: use of benzodiazepines, use of antidepressants, use of methadone/buprenorphine, cumulative number of physicians, cumulative number of dispensing pharmacies, recent discontinuation of opioid use, recent increases in opioid dose, recent add-on opioid therapy, updated targeted baseline medical comorbidities.

Table 7-3. Comparison of goodness of fit of conventional and flexible MSM models, with alternative time-varying opioid exposure metrics

Opioid Exposure Metric	**Statistical Model**	**AIC**	**P-value**
Current Use	Conventional Cox MSM	2611.3	
	Flexible TD MSM	2610.8	TD: 0.087
	Flexible WCE MSM	2591.4	
Cumulative Duration of Use	Conventional Cox MSM	2606.3	
	Flexible non-linear (NL) MSM	2584.0	NL: 0.000
	Flexible TD MSM	2609.6	TD: 0.007
	Flexible NL + TD MSM	2590.9	NL: 0.000, TD: 0.897
Continuous Duration of Use	Conventional Cox MSM	2611.4	
	Flexible non-linear (NL) MSM	2596.0	NL: 0.000
	Flexible TD MSM	2620.5	TD: 0.136
	Flexible NL + TD MSM	2595.6	NL: 0.000, TD: 0.079

MME Current Daily Opioid Dose (log-transformed)	Conventional Cox MSM	2588.2	
	Flexible non-linear (NL) MSM	2570.5	NL: 0.001
	Flexible TD MSM	2583.8	TD: 0.394
	Flexible NL + TD MSM	2577.7	NL: 0.007, TD: 0.928
	Flexible WCE MSM	2576.5	

Table 7-4. Results of weighted cumulative exposure (WCE) MSM Cox models: hazard ratio estimates for the association between specific *patterns of the past use and dosing regimens of opioid exposure* and opioid-related healthcare encounters or death *(95% CI)*

Duration of Recent Opioid Use (reference: no use)			
10 last -days	20-last days	30 last days	60- last days
1.47 (0.68 – 2.35)	2.72 (0.98 – 3.87)	4.86 (1.56 – 6.67)	6.68 (2.07 – 12.0)
Opioid Dose in the past 40 days			
50 MME (ref = 0) 5.92 (2.46 – 14.1)	90 MME (ref = 0) 7.69 (2.81 – 20.9)	120 MME (ref = 0) 8.75 (3.00 – 25.3)	90 MME (ref = 25 MME) 1.76 (1.33 – 2.32)

Figure 7-1. Non-linear effect of **cumulative duration of opioid use** and the risk of opioid-related emergency department visits, re-admissions or deaths.

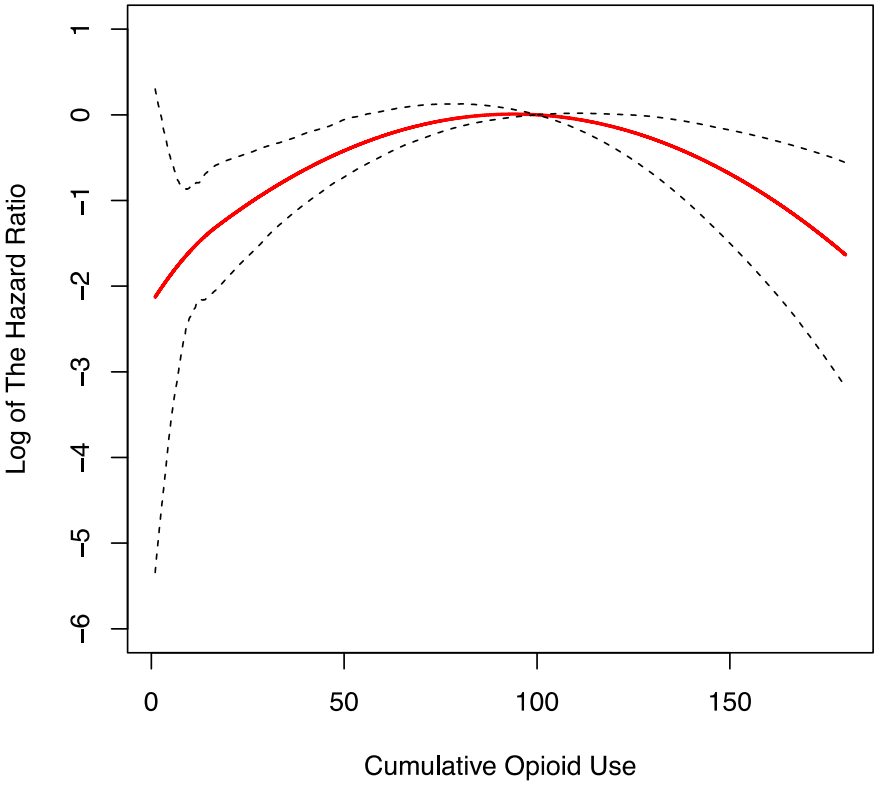


Figure 7-2. Non-linear effect of ***continuous opioid use*** and the risk of opioid-related emergency department visits, re-admissions or deaths.

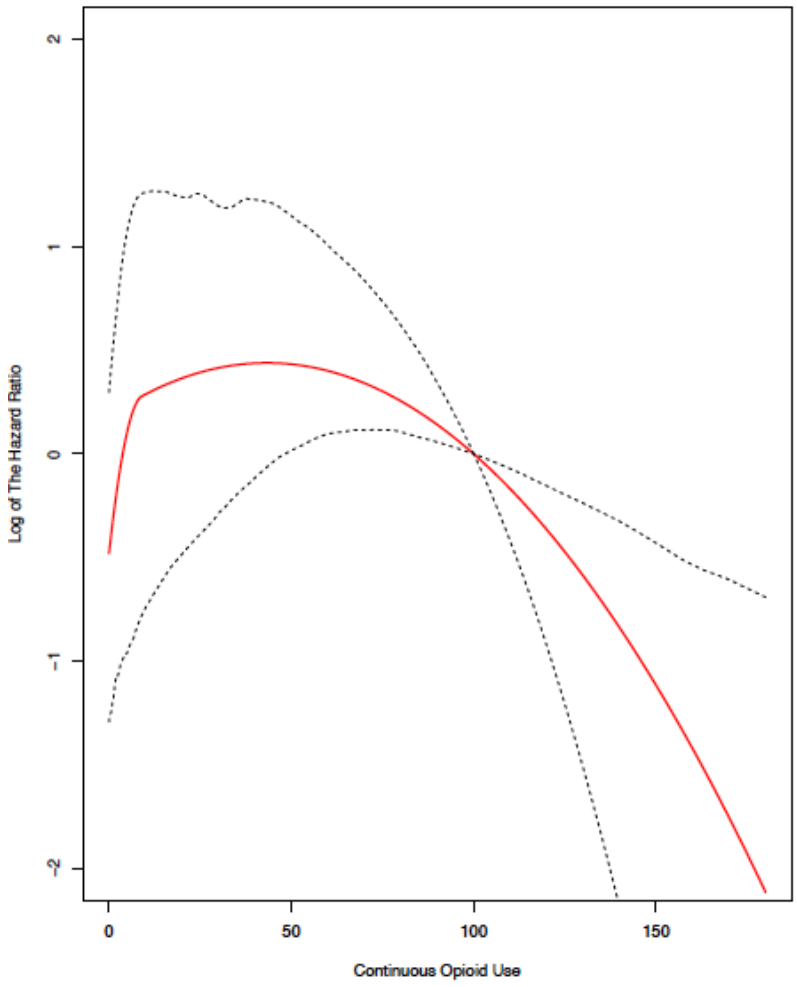


Figure 7-3. Non-linear effect of **current log-transformed daily opioid dose** and the risk of opioid-related emergency department visits, re-admissions or deaths.

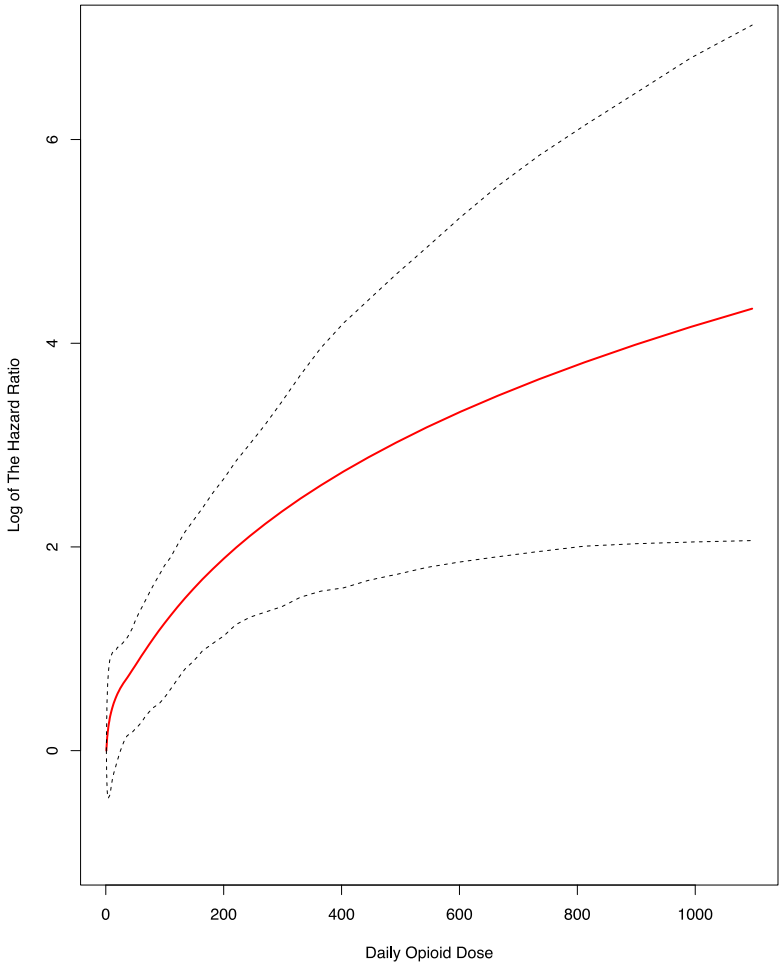


Figure 7-4. Estimated weight function for **current daily opioid use**.

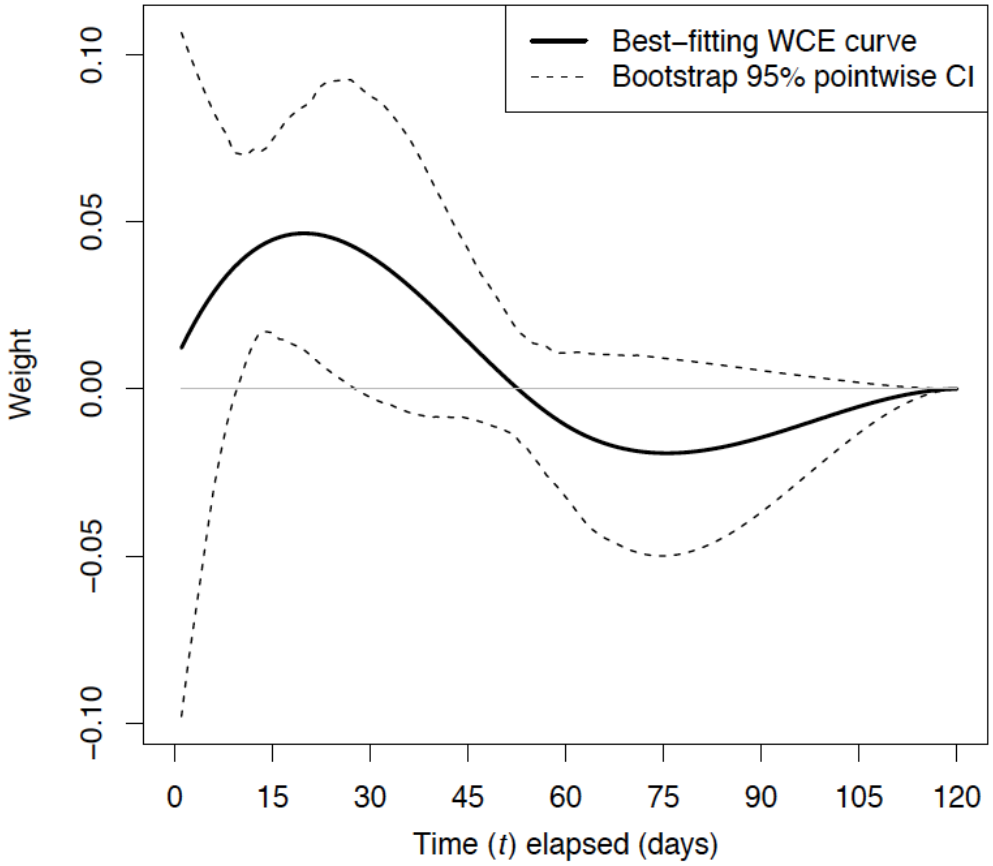
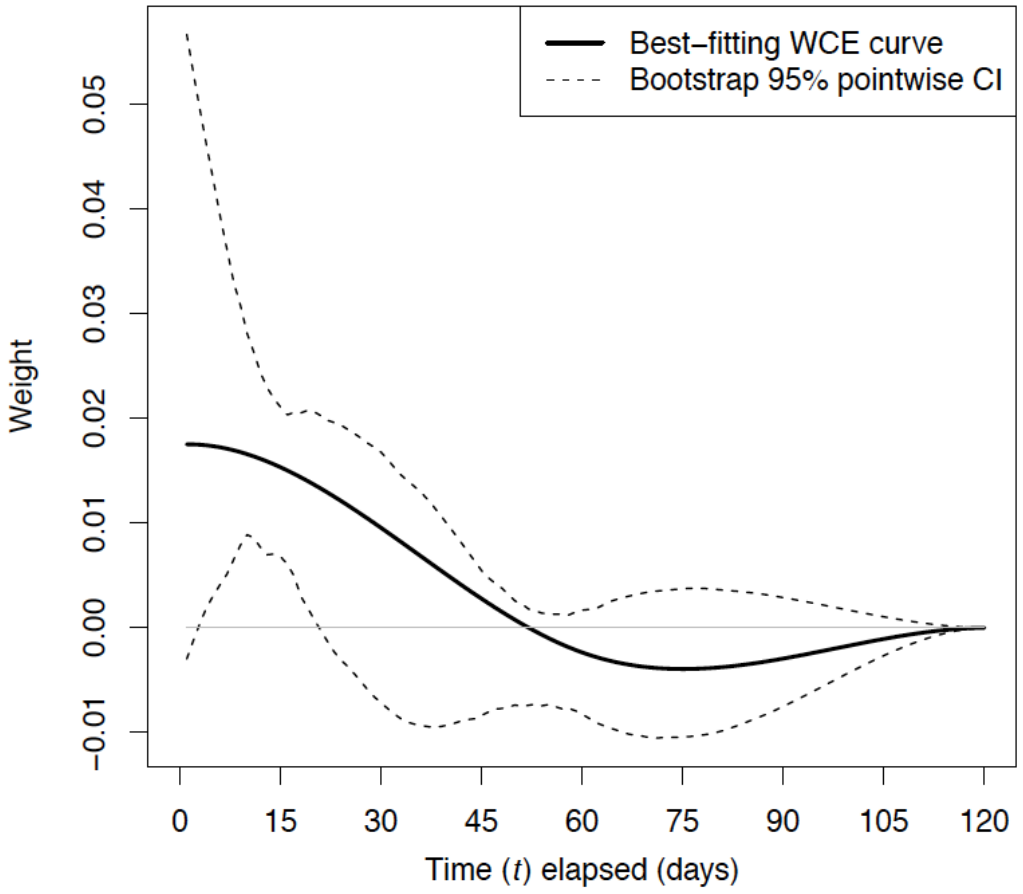


Figure 7-5. Estimated weight function for **current log transformed daily opioid dose.**



Appendix 7-A. Inclusion of Covariates and Their Assessment in Inverse Probability Treatment Weights Marginal Structural Models

Appendix 7-A.1. Description of available data on drug, patient, provider and system level characteristics

	Description	Measurement	Timing of Measurement	Functional Form
Opioid-related Characteristics				
Opioid Dispensations				
ATC code	Anatomical Therapeutic Chemical Classification System code used to identify opioids and other concurrent medications that the patient is taking Opioids ATC Included: N02A, R05DA	RAMQ prescription claims.	In the community one year prior to admission and one year post-discharge	N/A
Dose	The daily amount of drug taken by patient will be calculated based on information about the number of tablets prescribed, strength and number of days' supply; daily dose will be converted to milligram morphine equivalents to facilitate comparisons across opioids.	From RAMQ prescription claims	In the community one year prior to admission and one year post-discharge	Continuous, categorical, time-varying
Duration	The days' supply on the drug claim as entered by the pharmacist	From RAMQ prescription claims	In the community one year prior to admission and one year post-discharge	Continuous, categorical, time-varying
Type of opioid	Type of opioid ingredient. E.g; Hydromorphone, oxycodone, morphine, fentanyl, etc.	From RAMQ prescription claims	One year post-discharge	Categorical, time-varying
Opioid Administration in Hospital				
ATC code	Anatomical Therapeutic Chemical Classification System code used to identify administered opioids	Hospital pharmacy	In hospital	Categorical
Opioid Prescription at Hospital Discharge				
Status of opioid medication	Continued or stopped from community, newly prescribed at discharge	From patient chart	At hospital discharge	Categorical, time-fixed

Reason for opioid prescribing	Pain-related including having had surgery as well as other diagnoses such as having insomnia or anxiety as recorder during the hospitalization	From patient chart	In-hospital	Categorical, time-fixed
Presence of a multi-modal pain management regimen	The opioid prescription at hospital discharge was part of multi-modal pain treatment regimen	From patient chart	At hospital discharge	Categorical, time-fixed
Patient-reported adherence to opioid prescription given at hospital discharge	Whether patient takes the medication as prescribed or deviated from the prescription posology (e.g.; medication taken less or more often than directed to patient due to pain complaints, complications, side-effects, etc.)	RAMQ prescription claims to determine whether opioid was filled post-discharge; Patient interview to assess if patients are taking the drugs as prescribed	30-days post-hospital discharge	Categorical, time-fixed
Opioid-related Characteristics				
Demographics				
Age		From patient chart	Admission to hospital	Continuous, time-varying
Sex	Male, Female	From patient chart	Admission to hospital	Binary, time-fixed
Drug insurance status	E.g.; Full copay, partial copay, no copay Serves as proxy for socio-economic status.	From RAMQ drug programs	Admission to hospital	Categorical, time-fixed
Co-Existing Illnesses				
History of mental health conditions	E.g.; Anxiety, depression, psychiatric diagnosis, mood disorder, and post-traumatic stress disorder	ICD-9 from RAMQ medical services and ICD-10 codes from hospitalization data	In community one year prior to admission, in hospital, post-discharge	Binary per condition, time-varying
Pain syndromes	E.g.; Chronic back pain, back and neck pain, back disorder, arthritis, migraine, headache, fibromyalgia, fracture	ICD-9 from RAMQ medical services and	In community one year prior to admission, in	Binary per condition, time-varying

		ICD-10 codes from hospitalization data	hospital, post-discharge	
Health conditions Associated with abuse	E.g.; Alcohol abuse, drug abuse	From patient chart. Also from RAMQ medical series and prescription claims	In community one year prior to admission, in hospital, post-discharge	Binary per condition, time-varying
Tobacco use	Patient-reported history of tobacco use	From hospital charts	At admission	Binary, time-fixed
Cancer diagnosis	E.g.; Metastatic, Non-metastatic, Lymphoma	ICD-9 from RAMQ medical services and ICD-10 codes from hospitalization data	In community one year prior to admission, in hospital, post-discharge	Binary per condition, time-varying
Other comorbidities	E.g.; Acute MI, cerebrovascular diseases, chronic kidney, COPD, diabetes, heart failure, hypertension, ischemic heart disease, liver, obesity	ICD-9 from RAMQ medical services and ICD-10 codes from hospitalization data	In community one year prior to admission, in hospital, post-discharge	Binary per condition, time-varying
Drug and Healthcare Utilization				
Use of potential interacting drugs increasing the risk of opioid misuse	E.g.; Selective serotonin reuptake inhibitors, other antidepressants, benzodiazepines, other antipsychotic drugs, central nervous system depressants, psychotropic medication	ATC codes, DIN, Generic Drug name used to extract information from RAMQ prescription claims, hospital data, patient chart.	In community one year prior to admission, in-hospital, post-discharge	Binary per drug, time-varying
Use of non-opioid pain medications	E.g.; NSAIDS, COX-2, Acetaminophen, Gabapentin, anti-migraine medications, muscle-relaxants, other anti-	ATC codes, DIN, Generic Drug name used to extract information	In community one year prior to admission, in-hospital, post-discharge	Binary per drug, time-varying

	inflammatories and anti-rheumatoid medications	from RAMQ prescription claims, hospital data, patient chart.		
Number of ED visits and hospitalizations	Total number of ED visits and hospitalizations	From RAMQ prescription claims and hospital data	One year prior to hospital admission & one year post-discharge	Categorical, continuous, time-varying
Measures of Care Continuity				
Number of physicians	Number of unique physicians that prescribed an opioid medication to a patient in the year post hospital admission	From RAMQ medical services	One year prior to hospital admission & one year post-discharge	Categorical, continuous, cumulative time-varying
Number of dispensing pharmacies	Number of unique pharmacies that a patient has opioid medications dispensed at in the one year post to hospital admission	From RAMQ medical services	One year prior to hospital admission & One year post-discharge	Categorical, continuous, cumulative time-varying
Other Patient Drug Behavior Characteristics				
Time since hospital discharge	The time elapsed between patent's hospital discharge and their first opioid dispensation	From RAMQ prescription claims and hospital data	One year post-discharge	Continuous, time-fixed
Discontinuation of opioid use	Recent discontinuation of opioid use in the past 2 weeks	From RAMQ medical services	One year post-discharge	Categorical, time-varying
Daily opioid dose increase	Recent increase in the daily opioid use in the past 2 weeks	From RAMQ medical services	One year post-discharge	Categorical, time-varying
Add-on opioid	Recent add-on of another opioid type in the past 2 weeks	From RAMQ medical services	One year post-discharge	Categorical, time-varying
In-hospital Characteristics				
Hospital patient is admitted to	Montreal General or Royal Victoria hospital	From hospital chart	Upon admission to the hospital	Binary, time-fixed
Hospital unit the patient is admitted to	Medical or surgical unit	From hospital chart	Upon admission to the hospital	Binary, time-fixed
Reason for index hospital admission	Reasons were classified as opioid-related if patient presented to the hospital for an opioid-related disorder, poisoning by opioids, or fractures.	From hospitalization data	During the hospital stay	Binary, time-fixed

Discharge Destination	Home community, long term care	Patient chart	Upon discharge	Binary, time-fixed
RightRx patients	Patients, who were part of the initial randomized controlled trial	Patient chart	Upon discharge	Binary, time-fixed

Appendix 7-B. Codes Used for Drug Classification and Rationale for Opioid Dose and Opioid Duration of Use Calculations.

Supplement Method 7-B.1.

ATC codes used to identify opioids: N02A (opioids), R05DA (opium alkaloids and derivatives)

Exclusions: Not all drug forms were included in the analyses. Only patches and tablets of these medications were kept. Injectable, liquid and rectal forms were excluded. Methadone and buprenorphine/naloxone combinations were kept to define subclinical patient populations but were excluded from all dosing/duration calculations as these medications are used to treat addiction and we want to focus on the association of duration/dose of opioids used for pain relief.

Supplement Method 7-B.2.

The daily dose of each opioid was calculated by first dividing the quantity of units dispensed by the prescription duration to determine the number of units per day, and then multiplying the number of units by the strength. To account for concurrent prescriptions, a subsequent dispensation was considered as an early refill if days of overlap were ≤30% of the previous dispensation duration. Otherwise, the opioids were considered to be taken simultaneously. Daily dose of each dispensation was converted to MME doses using the Center for Disease Control Opioid Morphine Equivalent Conversion Factor and the opioid doses determined to be concurrently dispensed were added together.

Appendix 7-B.1. Opioid Morphine Equivalent Conversion Factor [1]

Drug Name	Conversion Factor
Buprenorphine patch[2]	12.6
Buprenorphine tab or film	10
Butorphanol	7
Codeine	0.15
Dihydrocodeine	0.25
Fentanyl buccal or SL tablets, or lozenge/troche[3]	0.13
Fentanyl film or oral spray[4]	0.18
Fentanyl nasal spray[5]	0.16
Fentanyl patch[6]	7.2
Hydrocodone	1
Hydromorphone	4
Levorphanol tartrate	11
Meperidine hydrochloride	0.1
Methadone	3
Morphine	1
Nalbuphine	1
Opium	1
Oxycodone	1.5
Oxymorphone	3
Pentazocine	0.37
Tapentadol	0.4
Tramadol	0.1

[1] Centers for Disease Control and Prevention, Atlanta, GA, May 2014.

[2] The MME conversion factor for buprenorphine patches is based on the assumption that one milligram of parenteral buprenorphine is equivalent to 75 milligrams of oral morphine and that one patch delivers the dispensed micrograms per hour over a 24-hour day. Example: 5 ug/hr buprenorphine patch * 24 hrs = 120 ug/day buprenorphine = 0.12 mg/day buprenorphine = 9 mg/day oral morphine milligram equivalent. In other words, the conversion factor not accounting for days of use would be 9/5 or 1.8. However, since the buprenorphine patch remains in place for 7 days, we have multiplied the conversion factor by 7 (1.8 X 7 = 12.6). In this example, MME/day for four 5 µg/hr buprenorphine patches dispensed for use over 28 days would work out as follows: Example: 5 ug/hr buprenorphine patch * (4 patches/28 days) * 12.6 = 9 MME/day.

[3] The MME conversion factor for fentanyl buccal tablets, sublingual tablets, and lozenges/troche is 0.13. This conversion factor should be multiplied by the number of micrograms in a given lozenge/troche.

[4] The MME conversion factor for fentanyl film and oral spray is 0.18. This reflects a 40% greater bioavailability for films compared to lozenges/tablets and 38% greater bioavailability for oral sprays compared to lozenges/tablets.

[5] The MME conversion factor for fentanyl nasal spray is 0.16, which reflects a 20% greater bioavailability for sprays compared to lozenges/tablets.

[6] The MME conversion factor for fentanyl patches is based on the assumption that one milligram of parenteral fentanyl is equivalent to 100 milligrams of oral morphine and that one patch delivers the dispensed micrograms per hour over a 24 hour day. Example: 25 ug/hr fentanyl patch * 24 hrs = 600 ug/day fentanyl = 60 mg/day oral morphine milligram equivalent. In other words, the conversion factor not accounting for days of use would be 60/25 or 2.4. However, since the fentanyl patch remains in place for 3 days, we have multiplied the conversion factor by 3 (2.4 X 3 = 7.2). In this example, MME/day for ten 25 µg/hr fentanyl patches dispensed for use over 30 days would work out as follows: Example: 25 ug/hr fentanyl patch * (10 patches/30 days)* 7.2 = 60 MME/day.

Sources:

1) Centers for Medicare & Medicaid Services. Opioid Oral Morphine Milligram Equivalent (MME) Conversion Factors. https:\\www.cms.govMedicarePrescription-Drug-CoveragePrescriptionDrugCovContraDownloadsOpioid-Morphine-EQConversion-Factors-vFeb-.pdf. Accessed: September 5, 2019

2) Svendsen, K., Borchgrevink, P., Fredheim, O., Hamunen, K., Mellbye, A., & Dale, O. (2011). Choosing the unit of measurement counts: the use of oral morphine equivalents in studies of opioid consumption is a useful addition to defined daily doses. Palliative Medicine, 25(7), 725–732. http://doi.org/10.1177/0269216311398300

Supplement 7-B. 3.

Weighted cumulative duration of past use and weighted cumulative dose models were adjusted for the same time-fixed and time-varying covariates and using the same IPT weights as in more conventional MSM Cox analyses. In addition, to reduce the risk of residual confounding, we ran preliminary analyses to examine the possibility of non-linear and/or time-dependent relationships between the covariates and the log hazard using cubic splines, and tested if non-linearity improves the model's fit to data. [214] The same method permitted testing the proportional hazards assumption for the WCE exposure and – if it is rejected–estimating how the adjusted hazard ratio(s) for the WCE changed during the follow-up.

Supplement 7-B.4. Operational definitions of opioid use durations

Cumulative duration of past use assessed the long-term impact of opioids, where the effect on the outcome persisted upon discontinuation: defined as the total number of days exposed, calculated by summing the durations of all dispensations between cohort entry (first opioid dispensation) and a given day during the follow-up. Cumulative users represented patients who used opioids only when needed, thus accumulating use over time. On the other hand, we assessed continuous duration where the effect of opioids accumulated by dispensation supply but the risk returned to baseline after discontinuation. Continuous duration was defined similarly but was allowed to increase only during the periods of un-interrupted use and was reset to zero if there was a gap of >5 days between subsequent dispensations.

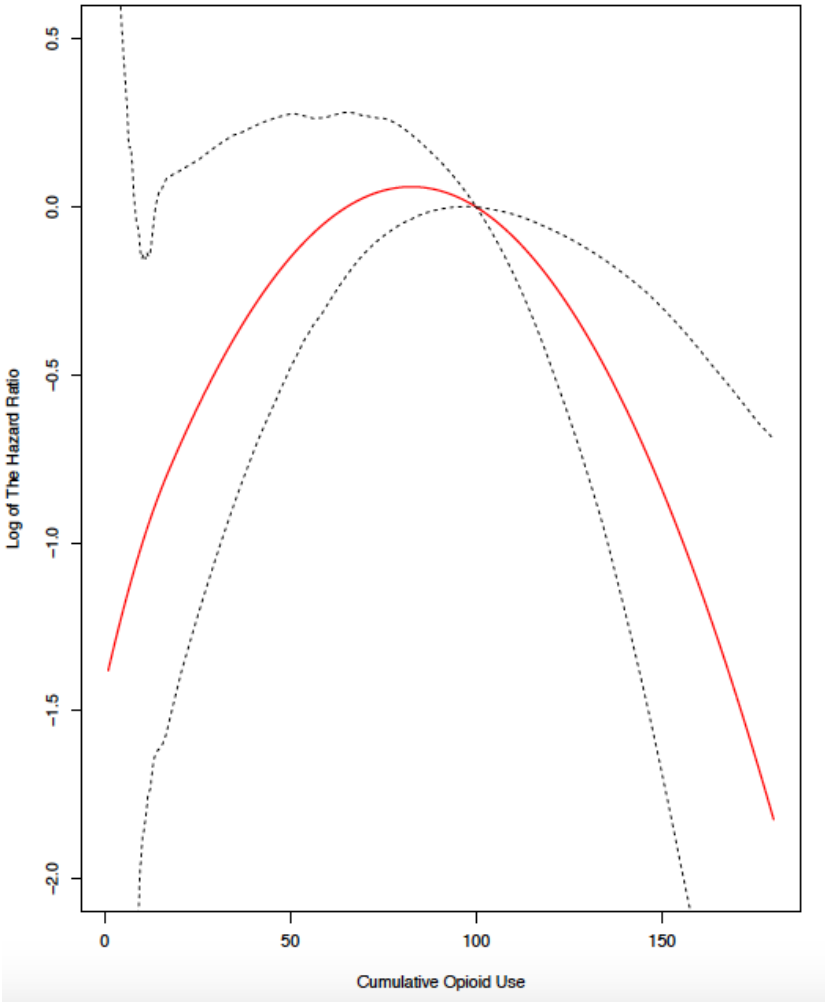
Appendix 7-C. Sensitivity analyses

Appendix 7-C.1. Comparison of goodness of fit in sensitivity analyses for flexible non-linear (NL) MSM additionally adjusting for the non-linear effect of MME current daily dose (log-transformed), with alternative time-varying opioid exposure metrics

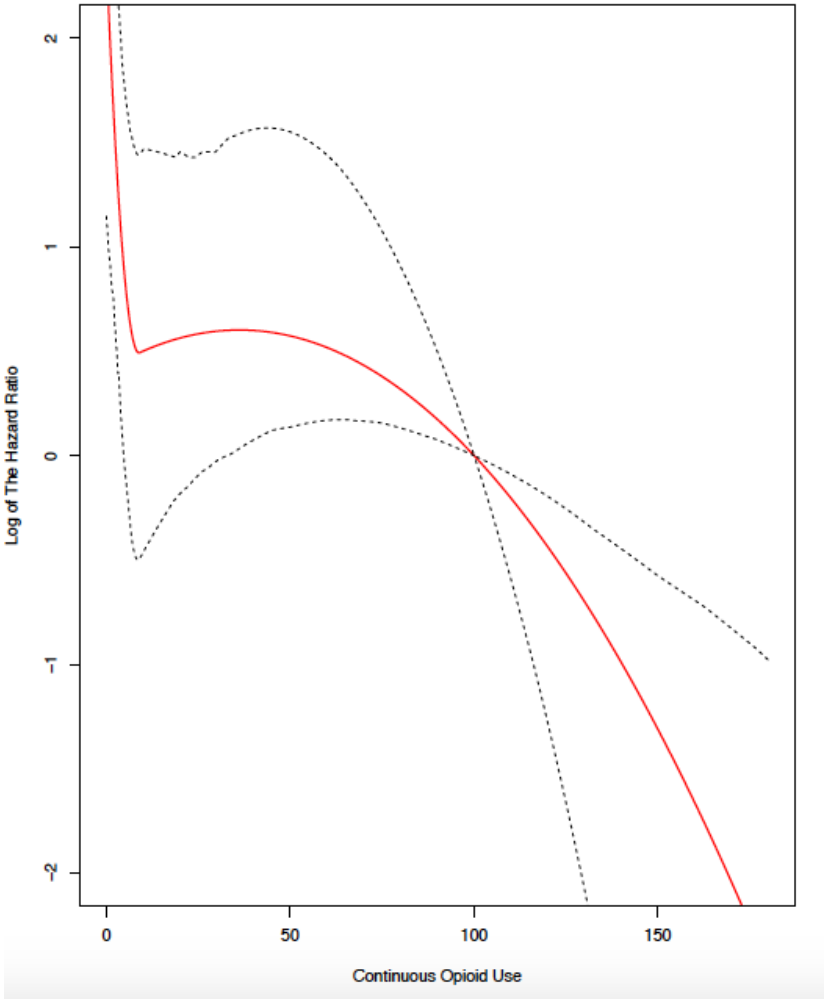
Opioid Exposure Metric	Statistical Model	AIC
Cumulative Duration of Use	Flexible non-linear (NL) MSM, no adjustment daily dose	2584.0
	Flexible non-linear (NL) MSM, with adjustment daily dose	2549.6

Continuous Duration of Use	Flexible non-linear (NL) MSM, no adjustment daily dose	2596.0
	Flexible non-linear (NL) MSM, with adjustment daily dose	2531.0

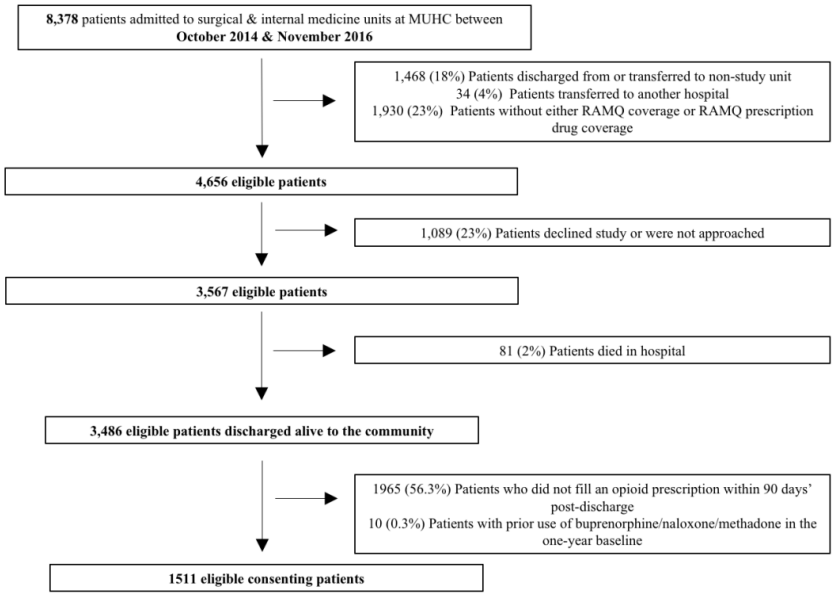
Appendix 7-C.1a. Non-linear effect of cumulative duration of opioid use and the risk of opioid-related emergency department visits, re-admissions or deaths, additionally adjusted for the non-linear effect current MME daily dose (log-transformed)



Appendix 7-C.2b. Non-linear effect of **continuous duration of opioid use** and the risk of opioid-related emergency department visits, re-admissions or deaths, additionally adjusted for the non-linear effect current MME daily dose (log-transformed)



Appendix 7-D. Flowchart of eligible patients.



8. Discussion

Opioids are an important part of any pain regimen [17,200], and one of the most commonly prescribed medications. [220] But when it comes to these drugs, where switching from one medication to another is common and multiple opioid products could be taken at the same time, not accounting for appropriate drug use and consumption patterns represents a challenge for adequately assessing opioid's effectiveness and appropriateness of use. [94,204] Understanding the risk associated with their use is, in turn, important for the development of evidence-based prescribing guidelines and helping practitioners manage their patients' pain. [70] The purpose of this Doctoral research program was to strengthen the evidence base of opioid safety research. The thesis focused on identifying potential modifiable determinants of opioid prescribing and potential medication errors at discharge as well as long-term opioid use among hospitalized patients in the period following hospital discharge. In addition, it assessed the impact of various opioid consumption profiles on patients' risk of acute post-discharge healthcare events. To achieve this goal, my program of research addressed four specific objectives, which were met through a series of four manuscripts. All manuscripts used data from a cluster-randomized trial on discharge medication reconciliation. We had a unique opportunity to link a variety of data sources. These included patient, demographic, administrative prescription and medical services claims, clinical information as well as patient-reported data derived from post-discharge interviews. Thus, we had a unique opportunity to link information on medication use prior to admission, during the hospitalization, medications prescribed at discharge, dispensed in the community post-discharge and patient-reported measures of consumption in the first one-month following the index hospitalization. As such, we were able to provide detailed patient information, which enhanced the findings of the study and positioned us well to explore the dynamic nature of opioid exposure using proper analytic techniques.

8.1 Summary of the main findings

The first manuscript titled "Incidence and Variables Associated with Inconsistencies in Opioid Prescribing at Hospital Discharge and Its Associated Adverse Drug Outcomes" described and estimated the incidence and variables associated with opioid-related medication errors at hospital discharge, an underexplored area, which we were able to further investigate given the wealth of clinical information available in the context of the electronic medication reconciliation trial. In

addition, it also determined the rates of adverse drug events and risk of ED visits, readmissions or death in the immediate post-discharge period. Overall, I found that rates of MEs were higher in handwritten prescriptions compared to the computer-based reconciliation discharge prescriptions (20.6% vs 1.2%). I also explored potential predictors associated with the receipt of an opioid prescription at discharge. The findings from this manuscript showed that computer-based prescriptions were associated with a 69% lower risk of opioid-related MEs (adjusted odds ratio [aOR]: 0.31, 95% CI: 0.14 – 0.65)) and 63% lower risk of receiving an opioid prescription. In addition, opioid-related MEs were associated with a two-fold increase in the risk of healthcare utilization in the 30-days post-discharge period (aOR: 2.32, 95% CI:1.24 – 4.32)). Given the importance of prescription opioids in the public health crisis of opioid-related mortality, the results from this manuscript highlighted the need of an accurate medication list and careful review of medications at transitions of care such as hospitalizations.

Patients may not only be newly exposed to opioids following their hospitalization but also continue opioid therapy beyond the expected duration of therapy. Manuscript 2 titled "Determinants for Long-Term Opioid Use in Hospitalized Patients" aimed to identify which patient, hospitalization and system level characteristics were also potential determinants of LTOT among hospitalized patients. This study found that 22.4% of the 1,551 study patients were classified as LTOT. I defined LTOT users as patients who had accumulated more than 60 days of use during the one year follow-up period. Using a Cox PH model, the main analyses identified drug copay status, being a previous LTOT user, having history of benzodiazepine use and initial opioid dispensation of > 90 MME as risk factors increasing the risk of LTOT one year following hospital discharge. As compared to medical patients, surgical patients, on the contrary, were associated with lower risk. I also found that longer duration of the initial opioid dispensation led to significantly high risk of subsequent LTOT among the previous pre-admission LTOT users, but the association remain insignificant for prior opioid-naïve patients. This study demonstrated that quantifying factors associated with the development of LTOT post-discharge is an important step in identifying and targeting patients who need more frequent clinical vigilance and better pain treatment strategy.

Manuscript 3 titled "Association of Opioid Consumption Profiles After Hospitalization with Risk of Adverse Health Care Events" aimed to strengthen the observational evidence on the risk of opioid-associated adverse outcomes and increases in duration and dose of opioid consumption.

In this paper, I conducted a cohort study to assess the risk of acute healthcare events such as opioid-related hospital admissions, emergency department visits or death associated with various patterns of opioid type, duration and dose. I also determined whether the risk was modified by treatment indication. I constructed several time-varying measures of opioid use including current use, daily dose, cumulative and continuous duration, and opioid type. I found that among those with at least one opioid dispensation within 90- day post' discharge, 16% (n = 241) experienced an opioid-related ED visit, re-admission or death. Results from marginal structural Cox PH models, one of the most advanced approaches to analyse longitudinal data with time-varying exposure in the presence of time-varying confounders, showed more than a two-fold increase in the risk of opioid-related adverse events associated with a cumulative opioid duration of > 90 days (adjusted hazard ratio (aHR) of 2.56 (95% CI:1.25 – 5.27), compared to 1-30 days. There was a three-fold increase in risk with a mean daily dose of ≥ 90 morphine milligram equivalent (MME), aHR of 3.24 (95% CI: 1.43-7.35) compared to users of ≤50 MME. The results highlight the importance of accounting for alternative opioid consumption patterns when quantifying the risk of adverse health care events or death. Findings also showed that treatment indications are also important to consider when quantifying the risk. Results of this study could be used to inform pain management policies or strategies aimed at preventing or attenuating opioid-related morbidity.

Manuscript 4 titled "Flexible modeling of opioid exposure provides new insights in its association with adverse outcomes" used novel methods of modelling time-varying exposures to better understand the mechanism behind opioid-related morbidity and mortality and opioid use. In this paper, I investigated how novel modelling techniques and the use of different methodological approaches to measure dynamic opioid exposures could improve our understanding of the how opioid-related adverse events may vary depending on the current and past opioid use. I used marginal structural Cox PH models and their flexible extensions, and a weighted cumulative exposure model to address the objectives for this study. I found that for each exposure metric, the flexible modelling improved the models' fit to data. Overall, the results indicate that both non-linear effects of continuous exposure metrics and weighted cumulative effects of past use or doses should be considered when assessing how the risks vary depending on the opioid exposure pattern. The estimated non-linear effect of cumulative opioid

duration shows that the risk of opioid-related adverse events increases gradually with total past exposure duration increasing to about 50-60 days of cumulative use. The results from the weighted cumulative exposure models suggested that the risk is mostly affected by use in the past 30 to 40 days, with doubling of risk for continuous exposure in the past month. This study allowed us to illustrate how careful analyses that account for dose, duration and timing of past exposures may improve the model's fit to data and enhance our understanding of the mechanism underlying potential adverse events of opioid exposure.

8.2 Main Contributions

Substantive contributions

Manuscript 1 contributed to the area of reported medication errors associated with opioid medications at transitions in care and its impact on patient health and potentially preventable adverse patient outcomes. Different types of medication-related errors were considered such as omissions, duplications and unintended dose changes. None of the previously conducted studies had the advantage of integrating multiple data sources, and most used either only prescriptions written at discharge or pharmacy claims to determine the status of the discharge prescription. In addition, we were able to incorporate information and report the extent of patient harms from the resulting opioid errors. The finding that, those patients whose prescription was finalized with the electronic medication reconciliation software had lower risk of having a medication error associated with their opioid medication, highlights the effectiveness of successful medication reconciliation to improve safety of opioid prescribing.

In manuscript 2, I identified several risk factors of LTOT following a hospitalization. The risk for continued opioid use has been considered as a central component of quality care assessment. These findings, thus, may help physicians and healthcare practitioners to identify and target patients who need more frequent clinical vigilance and better pain treatment strategy. For example, the finding initial opioid duration plays a greater role in the development of LTOT, especially for previous opioid users, suggests that limiting and selecting an optimal initial opioid duration may be particularly important to reduce the risk of subsequent opioid use. Moreover, initial dose was associated with increased risk of LTOT for both opioid-naïve and previous

LTOT users. As such, initial opioid exposure characteristics may help flag patients who might be at a greater risk of later developing LTOT.

Methodological contributions

Importance of time-varying drug exposures: a correct treatment episodes' construction (exposure quantification) is fundamental to avoid bias in treatment effect estimates. In Manuscript 3 and 4, we used one of the most advanced approaches, which exist, to address the magnitude and complexity of the exposure and properly modelled time-varying confounders, cumulative exposure and overlapping prescriptions. The findings and methodological approaches in these studies helped to advance our understanding of the impact of opioid use on the risk of opioid-related adverse effects and healthcare use, and are critical for improving guideline recommendations. Manuscript 4 demonstrated how novel flexible multivariable modeling techniques to account for the dynamic nature of opioid use, and their cumulative effects are important and offer additional insights regarding possible mechanisms linking opioid use to the risk of adverse events.

The design of these studies adequately accounted for longitudinal changes in opioids use and dose, which are expected for pain medication treatment, due to dynamic changes in patient's pain conditions. The work from these two objectives demonstrated valuable considerations when constructing and quantifying opioid exposure: 1) considering the non-linear effect of cumulative opioid exposure is important to assess the optimal duration of opioid use that minimizes the risk of adverse events, and 2) the benefits of taking into account the recency of past exposure when quantifying the impact of total duration of past use and total cumulative dose. Manuscripts 3 and 4 also showed that it is feasible to address methodological issues arising from complex exposure definitions and application of proper statistical methods for time-varying covariates. Finally, this thesis demonstrated a feasible approach for linking a variety of data sources: dispensing pharmacy records, in-hospital medical records, detailed information on opioid prescriptions written at hospital discharge and interviews with patients in the post-discharge period, in order to enhance the validity of studies by accounting for a wealth of confounders

8.3 Implications for physicians and policy makers

Physicians should be made aware of the increased risk of opioid-related adverse effects associated with specific opioid consumption patterns. This knowledge is particularly relevant for hospitalized patients where opioids are prescribed for acute pain during hospitalization and continued at discharge, increasing the risk for long-term opioid use. Practitioners should adjust opioid duration and dose for patients who are transitioning from acute postoperative to chronic pain. Results from this program of research could inform pain management strategies and prescribing guidelines. Effective management of pain symptoms and timely identification of patients at risk of long-term opioid use could prevent opioid-related adverse events, mitigate its effects and reduce the burden on the healthcare system. Treatment of chronic pain has become a central component of quality improvement efforts. [53] As such, researchers should incorporate criteria to identify long-term opioid therapy to build and strengthen the evidence around safe and appropriate use of prescription opioids. The quality of care could also be improved through integration of risk stratification algorithms into routine follow-up, flagging high-risk patients for more frequent clinical vigilance. The information from this thesis could help guide physician decision-making around opioid duration, dose and type of opioid used or providing patients with other alternatives to treat their pain. The results of this thesis could be used to inform development of more accurate risk stratification algorithms that could be implemented in clinical practice. Policy efforts should also be targeted at the implementation of feasible methods to audit opioid-related medication discrepancies in medications at hospital discharge in pharmacies and feed the data back to hospitals.

8.4 Final conclusions and future directions

This thesis found that hospitalized medical patients, previous LTOT, having previously used benzodiazepines and having an initial post-discharge opioid dispensation of >90 MME were associated with an increased risk of receiving an opioid prescription at discharge and becoming a long-term opioid user in the one year post-discharge. These results could be used to help stratify patients who are at high-risk of continuing opioids beyond guideline recommendations and inform policies and intervention programs to curb excessive opioid prescribing. The thesis also provided evidence of increased risk of opioid-related adverse events with prolonged opioid duration and high doses. The results of the final study also provided a methodological insight

into the mechanism underlying potential adverse events of opioid exposure by assessing the impact of recency of exposure on the risk of acute healthcare events. The results from my doctoral work generated important scientific knowledge for the development of effective prevention strategies to minimize long-term opioid dependency and reduce the risk of opioid-related morbidity among the vulnerable population of hospitalized medical and surgical patients. Future research using data from multiple health care systems is required to replicate these findings in larger population cohorts and provide greater generalizability. In addition, studies should try to incorporate data on opioid medications obtained through diversion or other illicit means. More work is needed to explore whether accumulation of opioid use post-discharge is a reflection of over-prescription by some in-hospital or community prescribers or of patent drug-seeking behavior.

Finally, development of pharmacodynamics tolerance with increasing duration of exposure, due to adaptive changes in the brain, is a prominent feature of opioids. [192,221] It is possible that some of the opioid users in our study developed some degree of tolerance, with its strength likely varying depending on the opioid type, dose and, in particular, the duration of exposure. Developed tolerance and drug dependence could also affect the physicians' prescribing decisions, patients' consumption patterns and adherence to the prescribed treatment. [173,222] Our databases did not provide any information that would allow us to measure tolerance. For these reasons, future pharmacoepidemiological and clinical studies should attempt to assess how tolerance depends on the exposure patterns and affects, in turn, the risk of opioid-related adverse events.

Appendix 8. Copy of published articles included in the thesis.

ScienceDirect

Contents lists available at sciencedirect.com
Journal homepage: www.elsevier.com/locate/jval

Themed Section: Opioid Misuse: A Global Crisis

Incidence and Variables Associated With Inconsistencies in Opioid Prescribing at Hospital Discharge and Its Associated Adverse Drug Outcomes

Siyana Kurteva, BSc, Bettina Habib, MSc, MScPH, Teresa Moraga, MSc, Robyn Tamblyn, BScN, MSc, PhD

ABSTRACT

Objectives: Opioid-related medication errors (MEs) can have a significant impact on patient health and contribute to opioid misuse. The objective of this study was to estimate the incidence of and variables associated with the receipt of an opioid prescription and opioid-related MEs (omissions, duplications, or dose changes) at hospital discharge. We also determined rates of adverse drug events and risks of emergency department visits, readmissions, or death 30 days and 90 days post discharge associated with MEs.

Methods: A cohort of hospitalized patients discharged from the McGill University Health Centre between 2014 and 2016 was assembled. The impact of opioid-related MEs was assessed in a propensity score–adjusted logistic regression models. Multivariable logistic regression was used to determine characteristics associated with MEs and discharge opioid prescription.

Results: A total of 1530 (43.9%) of 3486 patients were prescribed opioids, of which 13.4% (n = 205) of patients had at least 1 opioid-related ME. Rates of MEs were higher in handwritten prescriptions compared to the electronic reconciliation discharge prescription group (20.6% vs 1.2%). Computer-based prescriptions were associated with a 69% lower risk of opioid-related MEs (adjusted odds ratio: 0.31, 95% confidence interval: 0.14-0.65) as well as 63% lower risk of receiving an opioid prescription. Opioid-related MEs were associated with a 2.3 times increased risk of healthcare utilization in the 30 days postdischarge period (adjusted odds ratio: 2.32, 95% confidence interval: 1.24-4.32).

Conclusions: Opioid-related MEs are common in handwritten discharge prescriptions. Our findings highlight the need for computer-based prescribing platforms and careful review of medications during critical periods of care such as hospital transitions.

Keywords: opioids, opioid prescribing, transitions in care, hospital discharge, medication reconciliation.

VALUE HEALTH. 2021; 24(2):147–157

Introduction

Opioid use is associated with both fatal and nonfatal adverse effects. In the United States, rates of opioid-related hospitalizations increased by 64% between 2005 and 2014.[1] In addition to patient-related factors that may increase one's risk of opioid misuse,[2] errors associated with high-risk medications also heighten the risk of harm.[3] Opioid medications represent a high-risk class of drugs[3] that have been shown to be associated with the highest rate of reported medication errors (MEs).[2,4] Opioid-related MEs could have a significant impact on patient health and may result in potentially preventable adverse patient outcomes and contribute to the prescription opioid misuse crisis.[5,6]

Transitions in care represent a particularly high-risk period in the patient pathway.[7–9] Previous studies have found between 1.2 and 5.3 MEs per patient in transitions from hospital discharge to the community.[7,10,11] The literature on predictors of MEs and discrepancies shows that higher age, polypharmacy, patient sex, and specific medical interventions are associated with increased likelihood of MEs.[12–14] Nevertheless, the occurrence of and specific predictors of opioid-related errors during these care transitions is an underexplored area, which warrants further investigation. Inadequate communication of changes in medication at the time of discharge is a well-established problem, and hospital physicians may discontinue or initiate opioids without fully knowing a patient's medication history, including their history of opioid use before hospitalization.[15–19] Moreover, the hospitalization itself may inadvertently be a risk factor whereby opioids are prescribed for acute pain during hospitalization and inadvertently continued at discharge, increasing the risk for chronic use.[20,21]

Medication reconciliation, introduced as a potential solution to identifying and reducing MEs, could be used as an intervention to

reduce opioid MEs and associated preventable harm.[22-24] A recent systematic review quantifying the burden of opioid MEs in adult oncology settings highlighted the lack of research on opioid error incidence, type, and patient impact.[25,26] The objective of this study was to estimate the incidence of opioid-related MEs (omissions, duplications, or dose changes) at transitions in care, and associated rates of adverse drug events and risk of emergency department (ED) visits, readmissions, or death in the 30 and 90 days postdischarge. In addition, we also explored potential predictors associated with (1) the receipt of an opioid prescription, and (2) having an opioid-related ME at hospital discharge.

Methods

Setting

The study took place within the context of a cluster-randomized trial on discharge medication reconciliation conducted at the McGill University Health Centre (MUHC).[27] The MUHC is an over 1000-bed quaternary care teaching hospital in Montreal (Canada) that operates within the universal healthcare plan of the province of Quebec (RAMQ). This plan covers all necessary medical care and includes prescription drug insurance for registrants aged 65 years and older, income security recipients, and those not insured through their employer. Ethics approval was provided by the MUHC Research Ethics Board. Privacy Commissioner approval was obtained to link clinical and administrative data from the Commission d'accès à l'information du Quebec.

Participants

A prospective cohort of hospitalized patients discharged from medical and surgical units of the MUHC between October 2014 and November 2016 was followed for up to 90 days postdischarge. To be eligible for the original trial and for this study, patients had to be 18 years or older at admission and admitted from the community or transferred from another hospital, with at least 1 year of continuous provincial healthcare and prescription drug coverage before hospital admission.

Data Sources

Multiple sources of data were assembled and linked to address the objectives of the proposed study. For each patient, demographic, clinical, healthcare service use, and prescription claims data were retrieved from the admission note and provincial healthcare administrative databases (RAMQ medical services and prescription claims data) in the year before and following the hospitalization for which the patient was enrolled. The RAMQ prescription claims database covers approximately 50% of all Quebec residents, including medicare registrants who are 65 years of age and older, income security recipients, and those not insured through their employer. The RAMQ medical services database covers 100% of residents. Dates of admission and discharge, admitting and discharge unit, patient demographics, health problems at admission and discharge, and major procedures (surgeries, treatment interventions) were retrieved from the MED-ECHO hospitalization database. Physical findings, laboratory results, diagnoses, and medications taken at admission and in hospital as well as those prescribed at discharge were abstracted from the MUHC Data Warehouse. Data on hospital discharge experiences and adverse drug events were obtained via telephone interview 30 days postdischarge with trained interviewers, and adverse drug event occurrence was adjudicated by 2 reviewers using the Leape-Bates method.[5,28,29] This is one of the only data sources in the world that links information on medication use before admission and during the hospital stay and medications prescribed at discharge and dispensed in the community postdischarge.

Outcomes

Opioid Medications Administered in Hospital

We used the Anatomical Therapeutic Chemical Classification System (ATC) code used to search the in-hospital pharmacy databases and identify opioids (ATC included N02A and, R05DA) and other concurrent medications such as benzodiazepines, antidepressants, and analgesics that the patient was administered while in the hospital.

Opioid Prescriptions at Discharge

The status of opioid prescriptions at hospital discharge was ascertained using patients' charts (handwritten prescriptions) and the electronic reconciliation software (electronic prescriptions). For patients whose prescription was finalized using the RightRx software, opioid discharge prescriptions were grouped by reconciliation action: stop, modify, continue from the community, and new prescription. For patients who left the hospital with a paper discharge prescription, we determined the opioid status based on what was indicated in the patient's chart. Patients were considered to have left the hospital with an opioid prescription when the status of the opioid medication was continued, modified, or newly prescribed. Patients with multimodal analgesia were defined as those who were prescribed an opioid medication at discharge with at least 1 other analgesic agent.[30]

MEs at Discharge

Three different types of medication-related errors were considered as part of our main outcome: omissions, duplications, and unintended dose changes. An unintended error of omission was defined as a drug that was in the community drug list that was not prescribed at discharge and for which there was no documented evidence of having been stopped in the medical chart. On the other hand, an unintended therapy duplication was defined as 1 drug with an active prescription in the community drug list and a second drug in the same 4-digit ATC[31] in the discharge prescription, where there was no evidence in the medical chart that the community drug had been stopped, or that it was to be intentionally continued. Omissions and therapy duplication errors were further classified into 2 categories depending on whether they were owing to a reconciliation error or a history error. For example, an omission that was considered as owing to reconciliation error was defined as a drug that was in the community drug list that was prescribed at discharge but for which there was no documented evidence of the status in the medical chart (continued, prescribed, stopped, or modified). An unintended dose change was defined as a 25% or more increase or decrease in the prescribed dose of a community medication that was not documented in the medical chart as a change. To calculate the difference in dose between community drugs and those prescribed at discharge, the strength, quantity, and duration of community-based medications were used to calculate daily dose for all opioid medications. Refer to the Appendix for full conceptualization of definitions for MEs (see Appendix in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.07.015).

Medication-related error definitions were based on information on medications dispensed in the 3 months before hospitalization, from RAMQ, medications listed at hospital admission indicating whether or not the patient is taking the drug, drugs at discharge, as well as status of drugs at discharge. The community

Table 1. Baseline characteristics of the 3486 patients and of 1511 patients who filled an opioid prescription within 90 days of hospital discharge.

	Overall (n = 3486)	Opioid prescription at discharge	
		No n = 1956 (56.1%)	Yes n = 1530 (43.9%)
Mean age (SD)	69.6 (14.9)	71.8 (15.5)	66.6 (13.7)
	N (%)	N (%)	N (%)
Male	2010 (57.7)	1083 (55.4	927 (60.6)
Surgical discharge units	1677 (48.1)	417 (21.3)	1260 (82.3)
Electronic reconciliation used	1464 (42.0)	893 (45.6)	571 (37)
Length of hospital stay (≥6 days)	2930 (84.0)	1689 (86.3)	1241 (81.1)
Health services utilization: 1 year before admission	Mean (SD)	Mean (SD)	Mean (SD)
Emergency department visits	8.4 (8.5)	9.9 (15.1)	6.2 (14.1)
Hospitalizations	0.8 (1.9)	0.78 (2.2)	0.7 (1.5)
Physician visits	10.9 (14.5)	11.3 (17.2)	10.4 (11.4)
Number of prescribing physicians	4.2 (3.4)	4.5 (3.4)	3.9 (3.2)
Number of physicians prescribing opioids	0.6 (1.2)	0.6 (1.1)	0.7 (1.3)
Number of dispensing pharmacies	1.4 (0.9)	1.4 (0.9)	1.4 (0.8)
Number of pharmacies dispensing opioids	0.4 (0.6)	0.39 (0.6)	0.4 (0.6)
Active prescriptions at admission	9.8 (10.1)	10.6 (11.0)	7.1 (8.2)
	N (%)	N (%)	N (%)
Active opioid prescription at admission	504 (14.5)	272 (13.9)	232 (15.2)
Radiotherapy	215 (6.2)	70 (3.6)	145 (9.5)
Chemotherapy	262 (7.5)	77 (3.9)	185 (12.1)
Medication use: 1 year before admission	N (%)	N (%)	N (%)
History of opioid use	1206 (34.6)	670 (34.2)	536 (35.0)
≥3 opioid dispensations	104 (2.9)	49 (2.5)	55 (3.6)
History of long-acting opioids	146 (4.2)	60 (3.1)	86 (5.6)
Opioid dispensation within previous 30 days	666 (19.1)	353 (18.1)	313 (20.5)
History of methadone/buprenorphine	13 (0.4)	0 (0)	13 (0.9)
History of benzodiazepine use	1088 (31.2)	638 (32.6)	450 (29.4)
History of antidepressant use	706 (20.3)	431 (22.0)	275 (17.9)
SSRIs	336 (9.6)	220 (11.2)	116 (7.6)
SNRIs	167 (4.8)	96 (4.9)	71 (4.6)
TCAs	34 (1.0)	20 (1.0)	14 (0.9)
Other	189 (5.4)	108 (5.5)	81 (5.3)
History of analgesic use	1068 (30.6)	735 (37.6)	589 (38.5)
Acetaminophen	775 (22.2)	463 (23.7)	312 (20.4)
NSAIDS	563 (16.2)	257 (13.1)	306 (20.0)
COX-2	271 (7.8)	107 (5.5)	107 (6.9)
Targeted comorbidities	N (%)	N (%)	N (%)
Mental illness	511 (14.7)	315 (16.1)	196 (12.8)
Depression	190 (5.5)	113 (5.8)	77 (5.0)
Anxiety	261 (7.5)	138 (7.1)	123 (8.0)
Bipolar disorders	165 (4.8)	131 (6.7)	34 (2.2)
Dementia	213 (6.1)	179 (9.2)	34 (2.2)
Substance and alcohol abuse	115 (3.3)	76 (3.9)	39 (2.6)
Pain syndromes	1352 (38.8)	748 (38.2)	604 (39.5)
Neck and back pain	334 (9.6)	172 (8.8)	162 (10.6)
Arthritis and joint pain	1272 (36.5)	704 (35.9)	568 (37.1)
Cancer	1253 (35.9)	658 (43.0)	595 (30.4)
Digestive	309 (8.9)	144 (7.7)	165 (10.8)
Lung	488 (14.0)	156 (7.9)	332 (21.7)
Breast cancer	274 (7.9)	154 (7.9)	120 (7.8)
Urologic	248 (7.1)	126 (6.4)	122 (7.9)

continued on next page

Table 1. Continued

	Overall (n = 3486)	Opioid prescription at discharge	
		No n = 1956 (56.1%)	Yes n = 1530 (43.9%)
Unspecified cancer	88 (2.5)	51 (2.6)	37 (2.4)
Other comorbidities that may increase the risk of hospitalizations/ED visits	N (%)	N (%)	N (%)
Cardiovascular diseases	1817 (52.1)	849 (55.5)	968 (49.5)
Cerebrovascular diseases	334 (9.6)	222 (11.3)	112 (7.3)
Pneumonia	338 (9.7)	231 (11.8)	107 (6.9)
Chronic obstructive pulmonary disease	751 (21.5)	448 (22.9)	303 (19.8)
Renal disease	364 (10.4)	266 (13.6)	98 (6.4)
Diabetes	791 (22.7)	488 (24.9)	303 (19.8)
Primary reasons for the hospitalization	N (%)	N (%)	N (%)
Cancer	388 (11.2)	93 (4.7)	295 (19.3)
Cardiovascular	1047 (30.1)	439 (22.4	608 (39.7)
Respiratory	532 (15.3)	391 (20.0)	141 (9.2)
Urinary infections	173 (4.5)	139 (7.1)	34 (2.2)
Other infections	110 (3.2)	91 (4.7)	19 (1.2)
Injection poisonings	59 (1.7)	40 (20.4)	19 (1.2)
Digestive	256 (7.4)	188 (9.6)	68 (4.4)
Blood and immune system	73 (2.1)	49 (2.5)	24 (1.6)
Musculoskeletal	121 (3.5)	51 (2.6)	70 (4.6)
Alcohol-related	47 (1.3)	46 (2.4)	1 (<0.1)
Fractures and injuries	98 (2.8)	41 (2.1)	57 (3.7)
Endocrine and metabolic	84 (2.4)	70 (3.6)	14 (0.9)
Skin	82 (2.4)	72 (3.7)	10 (0.6)
Other*	372 (10.7)	258 (13.2)	113 (73.8)
In-hospital medication use	N (%)	N (%)	N (%)
Antidepressants	628 (18.0)	401 (20.5)	227 (14.8)
Opioids	2509 (72.0)	997 (50.9)	1512 (98.8)
Benzodiazepines	2278 (65.4)	1036 (52.9)	1242 (81.2)
Analgesics	1813 (52.0)	634 (32.4)	1179 (77.1)

COX-2 indicates cyclo-oxygenase-2; ED, emergency department; NSAID, nonsteroidal anti-inflammatory drug; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.
*Other: nausea, dizziness, vomiting, swelling.

drug list generated using the RAMQ prescription claims data for each patient was considered the gold standard, because these records identify over 40% more medications than are noted in the ED chart.[32]

Adverse Drug Events (ADEs)

We used information from patient interviews conducted postdischarge to assess the presence of ADEs, defined as the presence of a new health problem or worsening of a preexisting condition that could be medication-related. Information from patients' self-reported symptoms and medications dispensed following hospital discharge was collected and independently rated using the Leape-Bates adverse drug event classification. ADEs were further classified as definitely/probably preventable to definitely/probably not preventable using the same categories to classify probability. These categorizations were previously described elsewhere.[27]

ED Visits, Hospital Readmissions, Death Postdischarge

The outcome was a combined measure of an ED visit, hospital readmission, or death in the 30 days postdischarge and was ascertained using the RAMQ provincial medical services claims databases and the Ministry of Health and Social Services discharge abstract database. This approach ensured that all ED visits and readmissions are included, not just those occurring at the MUHC. In addition, we also explored the potential long-term impact of opioid-related MEs by determining rates of healthcare utilization in the 90-day postdischarge period.

Variables Potentially Associated With the Receipt of an Opioid Prescription at Discharge, MEs, and Adverse Outcomes

Potential risk factors for receiving an opioid prescription at discharge and factors associated with MEs were identified from

the literature. In addition, variables associated with increased risk of healthcare utilization were also considered. This included patient demographics, coexisting comorbidities that may increases one's risk of receiving an opioid prescription at discharge, healthcare utilization in the 1 year before the hospitalization, and patients' medications dispensed in the 1 year before the admission as well as in-hospital use of medications.

Analysis

Descriptive statistics were used to summarize and characterize the study cohort including patient demographics, coexisting comorbidities (using the *International Classification of Diseases, Ninth Revision* classification), drug and healthcare utilization in the 1 year before hospitalization, diagnoses recorded at hospital admission as indicated in patients' admission notes (using *International Classification of Diseases, Tenth Revision* classification), medications administered in the hospital, as well as characteristics of medications prescribed for pain at hospital discharge. Generalized estimating equation extension of multivariable logistic regression with an exchangeable correlation structure was used to estimate the independent association among medical history, patient- and medication-related characteristics, and the receipt of an opioid prescription at discharge, while accounting for clustering of opioid prescriptions within in-hospital physicians.[33] A separate model was also fitted to explore potential variables associated with having at least 1 of the abovementioned medication-related errors. The 2 models included all variables, selected a priori based on the literature and not on statistical significance. The incidence of opioid-related MEs was estimated, overall, by type of error, and by type of prescription (electronic vs handwritten). The rates of ADEs and healthcare encounters were estimated and stratified by the presence or absence of an opioid medication–related error at discharge. A propensity score–adjusted logistic regression model was used to assess the risk of ED visits, readmission, or death associated with opioid-related MEs in the 30 and 90 days postdischarge. The same exploratory variables as in the generalized estimating equation model were used in building the propensity score model.

Results

Overall, 3486 patients were discharged alive from study units; 57.7% were male and the mean age was 69.6 (SD = 14.9) (Table 1). Among the 1530 patients (43.9%) prescribed an opioid at discharge, 82.3% were prescribed to surgical patients and the rate of opioid prescriptions for surgical patients was 73%. Patients with or without an opioid prescription at discharge shared similar characteristics, except that patients prescribed an opioid were more likely to have received opioids, benzodiazepines, and analgesics during their hospital stay. Overall, most patients were opioid-naïve with 65% (n = 2280) having had no history of opioid use in the 1 year before their admission and 72% having been administered an opioid during their stay. More than half of the patients prescribed an opioid at discharge received a handwritten prescription. Overall, patients who received an opioid at discharge (n = 1530) had, on average, 10.5 medications (SD = 5.0) with a mean number of changes in the community medications of 7.5 (SD = 4.9) (Table 2).

Figure 1 shows the flowchart of patients with an opioid prescription at discharge, according to use before admission and after discharge. Interestingly, there was an equal split of discharge opioid prescriptions comparing previous users of opioids and opioid-naïve patients. Among patients who did not receive an opioid prescription at discharge, almost one-third (22%) of patients with history of opioid use and 12% of opioid-naïve patients had an opioid dispensed in the community 30 days following the hospitalization. More than two-thirds of patients filled their opioid prescription within 7 days postdischarge (n = 1070, 69.9%) (Table 2) with an overall rate of opioid dispensations of 74.6% during the follow-up period of 30 days postdischarge.

The proportion of patients with at least 1 opioid-related ME was 13.4% (n = 205), with the incidence of omission errors (40.0%) and unintended dose change errors (44.4%) being the highest, followed by therapy duplication errors (15.6%) (Table 2). Of the dose change errors made, 68.1% were a decrease in the dose of the opioid. The overall rate of MEs in handwritten prescriptions was higher than electronic prescriptions (20.6% vs 1.2%). There were no duplication or omission errors among patients where the medication reconciliation software was used for their discharge prescription.

Overall, 27.9% (n = 427) of all patients with an opioid prescription at discharge, regardless of the presence of an opioid-related ME, had an acute health service encounter (ED visits, hospitalization) or died in the 30-day follow-up period (Table 3). Of the 62 ADEs, 82.2% were adjudicated by reviewers as definitely preventable and 4.8% as definitely or probably not preventable. Patients with an opioid-related ME had slightly higher rates of adverse drug events (5.4% vs 3.9%) and more than 3 times the number of hospital readmissions (23.4% vs 8.5%) in the 30 days postdischarge. Similarly, they had higher rates of the composite outcomes of visiting the ED, being readmitted, or dying within 30 days or 90 days of hospital discharge. Results from propensity score–adjusted logistic regression models showed that patients with opioid-related MEs were 2.32 times more likely to have a re admissions 30 days postdischarge compared to patients without MEs (adjusted odds ratio [aOR]: 2.32, 95% confidence interval [CI]: 2.32 [1.24-4.32]) (Table 3). Other healthcare encounters during the 30- or 90-day postdischarge follow-up period showed increased risk associated with MEs in crude analyses, but the associations were no longer significant in propensity score–adjusted analyses (Table 4).

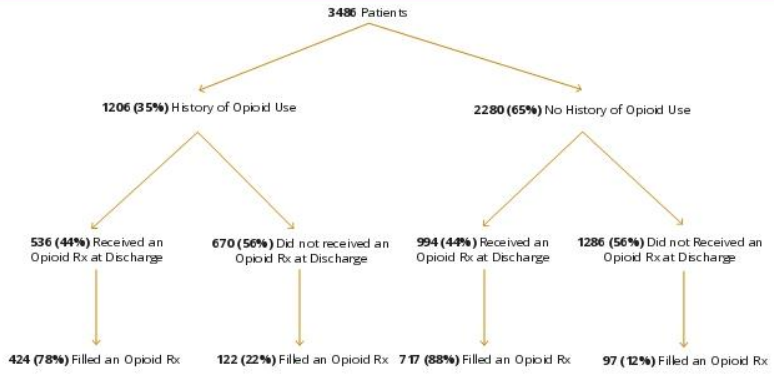
A number of characteristics were associated with an increased risk of receiving an opioid prescription at discharge (Table 5). First, patients ages 35 to 64 had a 38% increase in the likelihood of being given an opioid upon leaving the hospital (aOR 1.38, 95% CI: 1.07-1.76), while the age group of 64 to 79 had more than a 2 times higher risk of receiving an opioid (aOR 2.19, 95% CI:1.47-3.24). Having been admitted for thoracic surgery (aOR 4.53, 95% CI: 3.17-6.48), having received chemotherapy in the 1 year before admission (aOR 2.17, 95% CI: 1.15-4.08), and having a diagnosis for a pain syndrome (aOR 1.27, 95% CI: 1.03-1.57) were all associated with increased likelihood of receiving a prescription for opioids. The presence of an active opioid prescription at discharge (aOR 1.72, 95% CI: 1.22-2.44) and having been administered an opioid in the hospital also showed a positive association with having an opioid prescription at discharge (aOR 17.9, 95% CI: 11.0-29.3). Similarly, receiving an analgesic medication in the hospital as well as at discharge were both associated with an increased risk of being given an opioid medication upon hospital discharge (aOR 1.43, 95% CI: 1.14-1.82 and aOR 6.51, 95% CI: 4.57-9.25, respectively). Finally, patients with more than 10 medications prescribed at discharge and more than 10 changes made to their discharge medication list were also more likely to be given an opioid as part of their discharge drug regimen (aOR 1.92, 95% CI:1.37-2.69 and 1.48, 95% CI: 1.09-2.03, respectively). Variables associated with a decreased risk of receiving an opioid at discharge were having a computerized discharge prescription (aOR 0.37, 95% CI: 0.28-0.49), having more than 1 ED visit in the 1 year preadmission (aOR 0.72,

Table 2. Characteristics of discharge prescription for patients who received an opioid at discharge according to previous history of opioid use.

	Overall n = 1530	Electronic reconciliation software	
		Not used (n = 959, 63%)	Used (n = 571, 37%)
Surgical units	1260 (82.3)	775 (61.5)	485 (38.5)
Overall medications	Mean (SD)	Mean (SD)	Mean (SD)
Number of medications prescribed	10.6 (5.0)	9.5 (5.2)	12.4 (4.1)
Number of changes in community medications	7.5 (4.9)	5.8 (4.7)	10.3 (3.7)
Number of new medications	5.5 (3.2)	4.4 (2.9)	7.3 (2.8)
Number of stopped medications	1.4 (2.6)	0.9 (2.6)	2.3 (2.1)
Number of unintended dose changes	0.5 (1.0)	0.5 (0.9)	0.7 (1.0)
Opioid medications	N (%)	N (%)	N (%)
Medication-related errors	205 (13.4)	198 (20.6)	7 (1.2)
Type of medication-related errors			
Omission*	82 (40.0)	82 (41.4)	0
Status of medication discrepancy			
Omission—reconciliation error	38 (46.3)	38 (46.3)	0
Omission—history error	44 (54.7)	44 (54.7)	0
Duplication†	32 (15.6)	32 (16.1)	0
Status of medication discrepancy			
Duplication—reconciliation error	15 (46.9)	15 (46.9.)	0
Duplication—history error	17 (53.1)	17 (53.5)	0
Unintended dose changes‡	91 (44.4)	84 (42.4)	7 (100)
Dose increases	29 (31.9)	22 (26.2)	7 (100)
Dose decreases	62 (68.1)	62 (73.8)	0
Type of pain regimen at discharge	N (%)	N (%)	N (%)
Unimodal pain regimen	144 (9.4)	128 (13.3)	16 (2.3)
Opioid multimodal regimen	1390 (90.8)	834 (86.9)	556 (97.4)
Opioid dispensations postdischarge	N (%)	N (%)	N (%)
Filled an opioid prescription within 7 days	1070 (69.9)	669 (69.8)	401 (70.2)
Filled an opioid prescription within 30 days	1141 (74.6)	721 (75.2)	420 (73.6)

*Error of omission was defined as a drug that was in the community drug list that was not prescribed at discharge and for which there was no documented evidence of having been stopped in the medical chart.
†Therapy duplication was defined as one drug with an active prescription in the community drug list and a second drug in the same 4-digit Anatomic Therapeutic Class[29] in the discharge prescription, where there was no evidence in the medical chart that the community drug had been stopped, or that it was to be intentionally continued.
‡Unintended dose change was defined as a 25% or more increase or decrease in the prescribed dose of a community medication that was not documented in the medical chart as a change.

Figure 1. Flowchart of patients with an opioid prescription at discharge, according to use prior to admission and after discharge.



Rx, prescription.

Table 3. Number of adverse drug events in the 30-day postdischarge period according to opioid-related medication error patients with an opioid prescription at discharge.

	Overall n = 1530	Opioid-related medication error	
		Yes (n = 205, 13.3%)	No (n = 1325, 86.6%)
Adverse drug event	62 (4.1)	11 (5.4)	51 (3.8)
Definitely preventable	51 (82.2)	8 (72.7)	43 (84.3)
Probably preventable	8 (12.9)	3 (1.4)	5 (9.8)
Definitely/probably not preventable	3 (4.8)	0 (0)	3 (5.9)

Table 4. Results from propensity score–adjusted model of the association of having an opioid-related medication error at hospital discharge compared to no medication error and patients' healthcare utilization in the 30 and 90 days postdischarge.

	Overall (n = 1530)	Patients with MEs (n = 205, 13.3%)	Patients without MEs (n = 1325, 86.6%)	Crude OR, 95% CI	PS-adjusted OR,* 95% CI
Healthcare encounters 30 days postdischarge	N (%)	N (%)	N (%)		
ED visits	397 (25.1)	79 (38.5)	318 (24.0)	1.54 (1.20-1.98)	1.18 (0.69-1.82)
Readmission to hospital	161 (10.2)	48 (23.4)	113 (8.5)	1.96 (1.46-2.65)	2.32 (1.24-4.32)
ED visit, readmission, death	427 (27.9)	87 (42.4)	340 (25.7)	1.55 (1.21-1.98)	1.23 (0.76-1.98)
Healthcare encounters 90 days postdischarge	N (%)	N (%)	N (%)		
ED visits	643 (42.0)	119 (58.0)	524 (39.5)	1.59 (1.25-2.01)	1.10 (0.70-1.72)
Readmission to hospital	254 (16.0)	71 (34.6)	183 (13.8)	1.86 (1.44-2.41)	1.10 (0.66-1.84)
ED visit, readmission, death	674 (44.1)	127 (61.9)	547 (41.3)	1.64 (1.29-2.10)	1.05 (0.67-1.65)

CI indicates confidence interval; ED, emergency department; ME, medication error; OR, odds ratio; PS, propensity score.
*Variables considered in the construction/calculation of the propensity score of having an opioid-related medication error (omission, duplication, dose changes): (1) demographic characteristics: indicator for a patient randomized to the RightRx intervention group, age at admission, sex; (2) medical, prescription, and healthcare use 1 year before admission: number of dispensing pharmacies and prescribers, hospitalizations and emergency department visits, the receipt of radiotherapy and/or chemotherapy services, history of cancer diagnoses, mental health diagnoses, substance and/or alcohol abuse/dependence, respiratory diseases, cardiovascular and cerebrovascular diseases, diabetes, previous use of psychotropic medications; (3) in-hospital characteristics: hospital unit discharged from (medical vs surgical) from, length of hospital stay, opioid administration during the index hospitalization, nonopioid pain medication administration, use of antidepressant and benzodiazepines, having a nonopioid medication prescribed at discharge, total number of medications prescribed at discharge, and the total number of changes (news, stopped, dose changes) made to medications at discharge.

95% CI: 0.62-0.85), previous history of analgesics (aOR 0.74, 95% CI: 0.58-0.96), and being administered an antidepressant in the hospital (aOR 0.60, 95% CI: 0.46-0.79).

Regarding the potential predictors of opioid-related MEs, the only variable associated with a higher risk was having an active opioid prescription at admission (aOR 5.15, 95% CI: 3.03-8.78). On the contrary, having the discharge prescription finalized with the electronic reconciliation software was associated with a 69% lower risk of having an ME for an opioid medication (aOR 0.31, 95% CI: 0.14-0.65). Albeit associations being nonsignificant, older ages were also positively associated with increased risk of MEs related to opioid prescriptions.

Discussion

Our study showed that almost 1 in every 2 hospitalized patients left the hospital with an opioid prescription, with more than 80% of these prescriptions given to patients discharged from surgical units. Moreover, most patients with an opioid discharge prescription were opioid-naive before admission. Most patients filled their opioid prescription in the 30-day postdischarge period with 11% of patients with no discharge opioid prescription filling prescriptions from community physicians in the 30 days postdischarge. As such, findings from our study should be viewed as a reflection of either a communication gap between inpatient and community-based care teams or potentially gaps in access to care, because patients who experience acute pain after discharge but cannot reach their hospital-based team will reach out to a primary care provider for relief. Moreover, similarly to other studies looking at overall predictors of opioid prescription at discharge, in this cohort of hospitalized patients, we found that older patients, patients undergoing specific medical interventions such as thoracic surgery, and patients with diagnoses for pain syndromes were all at a higher risk of receiving an opioid prescription at discharge.[34-36] In addition, higher number of medications and medication changes prescribed at hospital discharge were also associated with a higher likelihood of receiving an opioid medication at discharge, findings not previously investigated elsewhere.

In addition, we found that using an electronic medication software was associated with a substantially lower risk of having an ME associated with an opioid-related ME as well as with receiving an opioid prescription at discharge, which is in accordance with previous literature on the effectiveness of successful medication reconciliation to prevent MEs.[10,37]

Most studies, which look at the amount of opioid prescriptions given at hospital discharge, focus largely on the surgical group of patients,[38,39] and they estimate that the proportion of patients with an opioid prescription at discharge ranges from 6%, in Dutch patients, to 82% in US patients, for the same type of surgeries.[40] Multiple comparison studies demonstrated persistent and striking

Table 5. Exploratory analyses of potential predictors of receiving an opioid prescription and having an opioid-related medication error at discharge.

Variable	Adjusted OR (95% CI) Opioid prescription	Adjusted OR (95% CI) Opioid-related medication error*
Patient level		
Demographics		
Age, years		
18-35	Reference	Reference
35-64	1.38 (1.07-1.76)	1.38 (0.87-2.18)
65-79	2.19 (1.47-3.24)	1.59 (0.81-2.98)
80+	0.32 (0.16-0.59)	2.37 (0.48-11.5)
Sex		
Male	Reference	Reference
Female	0.92 (0.76-1.10)	0.94 (0.62-1.42)
Hospital unit discharge from		
Internal medicine	Reference	Reference
Cardiac surgery	0.67 (0.42-1.09)	0.41 (0.15-1.01)
Thoracic surgery	4.53 (3.17-6.48)	0.30 (0.12-0.72)
Electronic reconciliation used		
No	Reference	Reference
Yes	0.37 (0.28-0.49)	0.31 (0.14-0.65)
Length of hospital stay		
<6 days	Reference	Reference
≥6 days	1.03 (0.77-1.36)	0.61 (0.34-1.10)
Health services utilization: 1 year before admission		
Emergency department visits		
0	Reference	Reference
1+	0.72 (0.62-0.85)	1.41 (0.81-2.46)
Hospitalizations		
0	Reference	Reference
1+	1.01 (0.88-1.16)	1.12 (0.74-1.69)
Radiotherapy		
No	Reference	Reference
Yes	1.37 (0.85-2.21)	1.57 (0.89-2.77)
Chemotherapy		
No	Reference	Reference
Yes	2.17 (1.15-4.08)	0.84 (0.54-1.29)
Medication use: 1 year before admission		
Active opioid prescription at admission		
No	Reference	Reference
Yes	1.72 (1.22-2.44)	5.15 (3.03-8.78)
History of opioid use		
No	Reference	Reference
Yes	1.22 (0.88-1.66)	NA†
History of benzodiazepine use		
No	Reference	Reference
Yes	1.02 (0.78-1.32)	0.88 (0.48-1.63)
History of antidepressant use		
No	Reference	Reference
Yes	0.81 (0.61-1.07)	0.98 (0.51-1.88)
History of analgesic use		
No	Reference	Reference
Yes	0.74 (0.58-0.96)	0.98 (0.51-1.89)
Targeted comorbidities		
Mental illness		
No	Reference	Reference
Yes	1.17 (0.81-1.66)	1.12 (0.65-1.91)
Pain syndromes		
No	Reference	Reference
Yes	1.27 (1.03-1.57)	0.91 (0.55-1.49)

continued on next page

Table 5. Continued

Variable	Adjusted OR (95% CI) Opioid prescription	Adjusted OR (95% CI) Opioid-related medication error*
Cancer diagnoses		
No	Reference	Reference
Yes	1.12 (0.90-1.39)	1.02 (0.63-1.66)
In-hospital medication use		
Antidepressants		
No	Reference	Reference
Yes	0.60 (0.46-0.79)	1.06 (0.58-1.96)
Opioids		
No	Reference	Reference
Yes	17.9 (11.0-29.3)	0.71 (0.23-2.17)
Benzodiazepines		
No	Reference	Reference
Yes	0.88 (0.12-1.15)	0.79 (0.43-1.45)
Analgesics		
No	Reference	Reference
Yes	1.43 (1.14-1.82)	1.38 (0.85-2.26)
Pain medicine injection		
No	Reference	Reference
Yes	1.18 (0.86-1.62)	1.42 (0.88-2.29)
Medications prescribed at discharge		
Analgesics		
No	Reference	Reference
Yes	6.51 (4.57-9.25)	1.51 (0.83-2.74)
Total number of medications prescribed at discharge		
0-4	Reference	Reference
5-6	0.98 (0.76-1.26)	0.72 (0.32-1.62)
7-9	0.92 (0.69-1.22)	0.74 (0.39-1.42)
10+	1.92 (1.37-2.69)	1.10 (0.48-2.53)
Total number of medication changes at discharge		
0-4	Reference	Reference
5-6	0.78 (0.56-1.08)	0.69 (0.42-1.17)
7-9	0.70 (0.49-0.98)	0.71 (0.43-1.21)
10+	1.48 (1.09-2.03)	1.07 (0.57-1.99)

CI indicates confidence interval; OR, odds ratio.
*The model was fitted only among patients who had received an opioid prescription at discharge (n = 1530).
†This variable was not included in the model exploring variables potentially predicating medication discrepancies owing to sparseness of data. Since the conceptualization of the main variable of opioid-related medication errors relied on information of the previous history of patient's opioid use, all patients with/without a medication error were previous users of opioids and by definition, there is no patient who was opioid-naïve and had a discrepancy in their opioid medication written at discharge.

differences between North America, and particularly the United States, and other countries in their opioid prescribing practices.[41,42] Our estimates are close to the ones found in the United States, with 73% of surgical patients in our cohort having received an opioid prescription at discharge. Research within the United States has also shown that the quantity and the number of dispensed opioids has increased over time,[43–45] suggesting that many are receiving opioids that are most likely not needed at all for adequate relief. It has been argued that overprescribing of opioids after surgery could lead to increased risk of adverse outcomes and adverse opioid-related behaviors such as prescription opioid misuse, opioid diversion, and new or unintended prolonged opioid use.[43,46,47] Although we cannot comment on the causal link between opioid exposure and these outcomes, we did observe high rates of ED visits, readmissions, or deaths in the 1 month postdischarge for patients with an opioid prescription at discharge. We also noticed that these rates were almost twice as high in patients with opioid-related MEs such as therapy omissions, duplications, or dose changes, and while for most statistically insignificant, the associations of opioid-related MEs pointed to an increased risk of healthcare utilization compared to no MEs. Multiple interventions have been proposed to minimize opioid prescribing at the provider, system, and patient level.[48–51] Future research should further explore whether accumulation of opioid use postdischarge is a reflection of overprescription by some in-hospital or community prescribers or of patient drug-seeking behavior.

Our results for opioid-related medication errors found that most errors occurred in handwritten prescriptions, which reflects results from previously published studies.[22,26,52–55] Nevertheless, most of these studies, which looked at differences in rates of MEs between electronic and handwritten prescriptions, focused largely on any medication-related errors,[52,54,55] or separated them in high- and low-risk groups.[54] Our findings reflect those of other studies,[5,22,55,56] which showed that MEs could be prevented using computer-generated prescriptions, as we observed a very low rate of opioid-related MEs in the groups of patients who received an electronic opioid prescription at discharge. Errors in prescriptions written by hand are largely introduced because of inaccurate medication reconciliation at the time of discharge or incomplete retrieval of the community medications list at the time of hospital

admission. Given the importance of prescription opioids in the public health crisis of opioid-related mortality, our findings highlight the need for an accurate medication list and careful review of medications at transitions of care such as hospitalization. Policy efforts should be targeted at the implementation of feasible methods to audit errors in pharmacies and feed the data back to hospitals.[56]

The strength of this study is its ability to link data on medication use before admission and during the hospitalization as well as to integrate information on patient discharge prescriptions and dispensations postdischarge to comprehensively describe opioid-related MEs and quantify ADEs in the community. Most of what is known about the incidence and types of medication-related errors uses different, single-focus, and narrow definitions of medication-related errors, which made comparison across these studies difficult.[26] Another recent study that looked at errors in opioid prescription for adult outpatients analyzed prescriptions as error-related if they deviated from best-practice guidelines, had incorrect dates or medication frequencies, and lacked information on pill quantity.[55] None of these studies had the advantage of integrating multiple data sources, and most used either only discharge prescriptions or pharmacy claims to determine the status of discharge prescriptions. In addition, none of these studies reported the extent of patient harms from the resulting opioid errors. In this study, we compared profiles of patients who received a discharge opioid prescription and further provided information on the type of errors that may occur at transitions in care as well as the occurrence of adverse drug-related events and healthcare encounters.

Some limitations of our work merit emphasis. This is a descriptive study and as such, results should be interpreted with caution. First, we reported rates of ADEs across patients with and without opioid-associated ME and therefore, no causality should be inferred for these associations. Moreover, there is a potential for recall bias as measurement of information on adverse events was collected through self-reported interviews with patients. Third, we reported the risk of healthcare utilization such as ED visits, readmission, and death up to 3 months postdischarge associated with an opioid-related ME and, while we used a propensity score to adjust for a number of patient and medical characteristics, confounding could still be a problem. Lastly, we did not build a predictive model but rather explored potential variables associated with the presence of a discharge opioid prescription and medication-related errors based on substantive knowledge and not statistical significance. Thus, our results should be considered as hypothesis-generating rather than definitive and reported associations should be further investigated in future studies.

Conclusion

In conclusion, we found a 13.4% rate of errors in opioid prescriptions written for hospitalized adults and, in this sample, almost exclusively present in handwritten prescriptions. A significant number of these errors were owing to reconciliation errors or history errors. The utilization of computer-based prescribing and medication reconciliation software has the potential to improve the safety of opioid and medication prescribing, especially during critical periods of care such as hospital discharge after surgery.

Supplemental Material

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2020.07.015.

Article and Author Information

Accepted for Publication: July 25, 2020

Published Online: November 10, 2020

doi: https://doi.org/10.1016/j.jval.2020.07.015

Author Affiliations: Department of Epidemiology and Biostatistics, McGill University, Montreal, Canada (Kurteva, Tamblyn); Clinical and Health Informatics Research Group, Department of Medicine, McGill University, Montreal, Canada (Kurteva, Habib, Moraga, Tamblyn); Department of Medicine, McGill University Health Center, Montreal, Canada (Tamblyn).

Correspondence: Siyana Kurteva, Clinical & Health Informatics Research Group, Department of Medicine, McGill University, 1140 Pine Ave W, Montreal, Quebec, Canada, H3A 1A3. Email: siyana.kurteva@mail.mcgill.ca

Author Contributions: *Concept and design*: Kurteva, Habib, Tamblyn
Acquisition of data: Tamblyn
Analysis and interpretation of data: Kurteva, Habib, Moraga, Tamblyn
Drafting of the manuscript: Kurteva
Critical revision of the paper for important intellectual content: Kurteva, Habib, Moraga, Tamblyn
Statistical analysis: Kurteva
Obtaining funding: Tamblyn
Administrative, technical, or logistic support: Moraga
Supervision: Tamblyn

Conflict of Interest Disclosures: The authors reported no conflicts of interest.

Funding/Support: This work was supported by the CIHR Drug Safety and Effectiveness Program and the McGill Internal Medicine Burke Scholarship (doctoral awards held by Siyana Kurteva).

Role of the Funder/Sponsor: The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

REFERENCES

1. Trends in the rate of opioid-related hospitalizations. Agency for Healthcare Research and Quality. https://www.ahrq.gov/opioids/map/index.html. Accessed May 2019.
2. Manias E, Williams A, Liew D, Rixon S, Braaf S, Finch S. Effects of patient-, environment- and medication-related factors on high-alert medication incidents. *Int J Qual Health Care*. 2014;26(3):308–320.
3. Institute for Safe Medication Practices. ISMP List of High-Alert Medications in Community/Ambulatory Healthcare. https://www.ismp.org/sites/default/files/attachments/2017-11/highAlert-community.pdf. Accessed May 12, 2020.
4. Silva M, Rosa MB, Franklin BD, Reis AM, Anchieta LM, Mota JA. Concomitant prescribing and dispensing errors at a Brazilian hospital: a descriptive study. *Clinics (Sao Paulo)*. 2011;66(10):1691–1697.
5. 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.
6. Kwan JL, Lo L, Sampson M, Shojania KG. Medication reconciliation during transitions of care as a patient safety strategy: a systematic review. *Ann Intern Med*. 2013;158(5 Pt 2):397–403.
7. Kersten H, Hvidsten LT, Gloersen G, Wyller TB, Wang-Hansen MS. Clinical impact of potentially inappropriate medications during hospitalization of acutely ill older patients with multimorbidity. *Scand J Prim Health Care*. 2015;33(4):243–251.
8. Forster AJMH, Peterson JF, Gandhi TK, Bates DW. Adverse drug events occurring following hospital discharge. *J Gen Intern Med*. 2005;20(4):317–323.
9. Boockvar K, Fishman E, Kyriacou C, 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.
10. Mekonnen AB, Abebe TB, McLachlan AJ, Brien JA. Impact of electronic medication reconciliation interventions on medication discrepancies at hospital transitions: a systematic review and meta-analysis. *BMC Med Inform Decis Mak*. 2016;16:112.
11. Redmond P, Grimes TC, McDonnell R, Boland F, Hughes C, Fahey T. Impact of medication reconciliation for improving transitions of care. *Cochrane Database Syst Rev*. 2018;8:CD010791.
12. Picone DM, Titler MG, Dochterman J, et al. Predictors of medication errors among elderly hospitalized patients. *Am J Med Qual*. 2008;23(2):115–127.

13. Hias J, Van der Linden L, Spriet I, et al. Predictors for unintentional medication reconciliation discrepancies in preadmission medication: a systematic review. *Eur J Clin Pharmacol*. 2017;73(11):1355–1377.
14. Lee KP, Nishimura K, Ngu B, Tieu L, Auerbach AD. Predictors of completeness of patients' self-reported personal medication lists and discrepancies with clinic medication lists. *Ann Pharmacother*. 2014;48(2):168–177.
15. Beaton A, O'Leary K, Thorburn J, Campbell A, Christey G. Improving patient experience and outcomes following serious injury. *N Z Med J*. 2019; 132(1494):15–25.
16. Naylor MD, Kurtzman ET, Pauly MV. Transitions of elders between long-term care and hospitals. *Policy Polit Nurs Pract*. 2009;10(3):187–194.
17. Yemm R, Bhattacharya D, Wright D, Poland F. What constitutes a high quality discharge summary? A comparison between the views of secondary and primary care doctors. *Int J Med Education*. 2014;5:125–131.
18. Newnham H, Barker A, Ritchie E, Hitchcock K, Gibbs H, Holton S. Discharge communication practices and healthcare provider and patient preferences, satisfaction and comprehension: a systematic review. *Int J Qual Health Care*. 2017;29(6):752–768.
19. Ozavci G, Bucknall T, Woodward-Kron R, et al. A systematic review of older patients' experiences and perceptions of communication about managing medication across transitions of care. *Res Social Adm Pharm*. 2020. S1551-7411(19)31089-7.
20. Fregoso G, Wang A, Tseng K, Wang J. Transition from acute to chronic pain: evaluating risk for chronic postsurgical pain. *Pain Physician*. 2019; 22(5):479–488.
21. Glare P, Aubrey KR, Myles PS. Transition from acute to chronic pain after surgery. *Lancet*. 2019;393(10180):1537–1546.
22. Seidling HM, Faller CK, Thalheimer M, Bruckner T, Haefeli WE. Formal prescribing errors are substantially reduced in electronic prescribing and after teaching sessions [article in German]. *Deutsche Med Wochenschr (1946)*. 2016;141(1):e1–e7.
23. Abdellatif ABJ, Barajas ER, et al. Assuring medication accuracy at transitions in care. *Jt Comm J Qual Patient Saf*. 2007;33(7):450–453.
24. Institute for Healthcare Improvement. *How-to Guide: Prevent Adverse Drug Events by Implementing Medication Reconciliation*. Cambridge, MA: Institute for Healthcare Improvement; 2011.
25. Heneka N. Quantifying the burden of opioid medication errors in adult oncology and palliative care settings: a systematic review. *Palliat Med*. 2016;30(6):520–532.
26. Heneka N, Shaw T, Rowett D, Phillips JL. Quantifying the burden of opioid medication errors in adult oncology and palliative care settings: a systematic review. *Palliat Med*. 2016;30(6):520–532.
27. Tamblyn R, Abrahamowicz M, Buckeridge DL, et al. Effect of an electronic medication reconciliation intervention on adverse drug events: a cluster randomized trial. *JAMA Netw Open*. 2019;2(9):e1910756.
28. Leape LL, Bates DW, Cullen DJ, et al. Systems analysis of adverse drug events. ADE Prevention Study Group. *JAMA*. 1995;274(1):35–43.
29. Nebeker JR, Barach P, Samore MH. Clarifying adverse drug events: a clinician's guide to terminology, documentation, and reporting. *Ann Intern Med*. 2004;140(10):795–801.
30. Memtsoudis SG, Poeran J, Zubizarreta N, et al. Association of multimodal pain management strategies with perioperative outcomes and resource tilization: a population-based study. *Anesthesiology*. 2018; 128(5):891–902.
31. WHO Collaborating Centre. ATC/DDD Index 2018. https://www.whocc.no/atc_ddd_index/. Accessed August 6, 2018.
32. Tamblyn R, Poissant L, Huang A, et al. Estimating the information gap between emergency department records of community medication compared to on-line access to the community-based pharmacy records. *J Am Med Inform Assoc*. 2014;21(3):391–398.
33. Zeger SL, Liang KY, Albert PS. Models for longitudinal data: a generalized estimating equation approach. *Biometrics*. 1988;44(4):1049–1060.
34. Chaudhary MA, Schoenfeld AJ, Harlow AF, et al. Incidence and predictors of opioid prescription at discharge after traumatic injury. *JAMA Surg*. 2017;152(10):930–936.
35. Chaudhary MA, Scully R, Chowdhury R, et al. Patterns of use and factors associated with early discontinuation of opiates after major trauma. *J Am Coll Surg*. 2016;223(4 suppl 1):S114–S115.
36. Luo X, Pietrobon R, Hey L. Patterns and trends in opioid use among individuals with back pain in the United States. *Spine (Phila Pa 1976)*. 2004;29(8):884–890. discussion 891.
37. Salanitro AH, Osborn CY, Schnipper JL, et al. Effect of patient- and medication-related factors on inpatient medication reconciliation errors. *J Gen Intern Med*. 2012;27(8):924–932.
38. Neuman MD, Bateman BT, Wunsch H. Inappropriate opioid prescription after surgery. *Lancet*. 2019;393(10180):1547–1557.
39. Hill MV, McMahon ML, Stucke RS, Barth Jr RJ. Wide variation and excessive dosage of opioid prescriptions for common general surgical procedures. *Ann Surg*. 2017;265(4):709–714.
40. Lindenhovius AL, Helmerhorst GT, Schnellen AC, Vrahas M, Ring D, Kloen P. Differences in prescription of narcotic pain medication after operative treatment of hip and ankle fractures in the United States and The Netherlands. *J Trauma*. 2009;67(1):160–164.
41. Gomes T, Juurlink D, Moineddin R, et al. Geographical variation in opioid prescribing and opioid-related mortality in Ontario. *Healthc Q*. 2011;14(1):22–24.
42. Morden NE, Munson JC, Colla CH, et al. Prescription opioid use among disabled Medicare beneficiaries: intensity, trends, and regional variation. *Med Care*. 2014;52(9):852–859.
43. Chen EY, Marcantonio A, Tornetta 3rd P. Correlation between 24-hour predischarge opioid use and amount of opioids prescribed at hospital discharge. *JAMA Surg*. 2018;153(2):e174859.
44. Volkow ND, McLellan TA. Curtailing diversion and abuse of opioid analgesics without jeopardizing pain treatment. *JAMA*. 2011;305(13):1346–1347.
45. Inciardi JA, Surratt HL, Kurtz SP, Cicero TJ. Mechanisms of prescription drug diversion among drug-involved club- and street-based populations. *Pain Med*. 2007;8(2):171–183.
46. Brat GA, Agniel D, Beam A, et al. Postsurgical prescriptions for opioid naive patients and association with overdose and misuse: retrospective cohort study. *BMJ*. 2018;360:j5790.
47. Pizzi LT, Toner R, Foley K, et al. Relationship between potential opioid-related adverse effects and hospital length of stay in patients receiving opioids after orthopedic surgery. *Pharmacotherapy*. 2012;32(6):502–514.
48. Bruehl S, Apkarian AV, Ballantyne JC, et al. Personalized medicine and opioid analgesic prescribing for chronic pain: opportunities and challenges. *J Pain*. 2013;14(2):103–113.
49. Saunders KW, Shortreed S, Thielke S, et al. Evaluation of health plan interventions to influence chronic opioid therapy prescribing. *Clin J Pain*. 2015;31(9):820–829.
50. Finnell JT, Twillman RK, Breslan SA, Schultz J, Miller L. The role of continuing medical education in increasing enrollment in prescription drug monitoring programs. *Clin Ther*. 2017;39(9):1896–1902.e2.
51. Liu S, Gnjidic D, Nguyen J, Penm J. Effectiveness of interventions on the appropriate use of opioids for noncancer pain among hospital inpatients: a systematic review. *Br J Clin Pharmacol*. 2020;86(2):210–243.
52. Kenawy AS, Kett V. The impact of electronic prescription on reducing medication errors in an Egyptian outpatient clinic. *Int J Med Inform*. 2019;127:80–87.
53. Mohan P, Sharma AK, Panwar SS. Identification and quantification of prescription errors. *Med J Armed Forces India*. 2014;70(2):149–153.
54. Hitti E, Tamim H, Bakhti R, Zebian D, Mufarrij A. Impact of internally developed electronic prescription on prescribing errors at discharge from the emergency department. *West J Emerg Med*. 2017;18(5):943–950.
55. Bicket MC, Kattail D, Yaster M, Wu CL, Pronovost P. An analysis of errors, discrepancies, and variation in opioid prescriptions for adult outpatients at a teaching hospital. *J Opioid Manag*. 2017;13(1):51–57.
56. Singer A, Duarte Fernandez R. The effect of electronic medical record system use on communication between pharmacists and prescribers. *BMC Fam Pract*. 2015;16:155.

JAMA Network Open

Original Investigation | Health Policy

Association of Opioid Consumption Profiles After Hospitalization With Risk of Adverse Health Care Events

Siyana Kurteva, BSc; Michal Abrahamowicz, PhD; Tara Gomes, PhD; Robyn Tamblyn, PhD

Abstract

IMPORTANCE Although better pain management has guided policies for opioid use over the past few decades, evidence is limited regarding how patterns of use are associated with the risk of potentially avoidable opioid-related adverse events.

OBJECTIVE To estimate the risk of harms associated with opioid dose and duration of use, and to ascertain whether the risk is modified by treatment indication and age.

DESIGN, SETTING, AND PARTICIPANTS This ad hoc cohort study followed up patients who were enrolled in a cluster randomized trial of medication reconciliation between October 1, 2014, and November 30, 2016, 12 months after they were discharged from the McGill University Health Centre in Montreal, Quebec, Canada. To be eligible for this study, patients needed to have filled at least 1 opioid prescription 3 months after discharge. Patients with a history of using methadone or buprenorphine were excluded. Data analyses were performed between February 1, 2019, and February 28, 2020.

EXPOSURES Time-varying measures of opioid use included current use, daily morphine milligram equivalent (MME) dose, cumulative and continuous use duration, and type of ingredients in prescription opioids used. Hospitalization records, dispensed prescriptions records, and postdischarge interviews were used to evaluate adherence to the opioid prescriptions after discharge.

MAIN OUTCOMES AND MEASURES Opioid-related emergency department visits, hospital readmissions, or all-cause death. Outcomes were ascertained using provincial medical services claims and hospitalization databases.

RESULTS Of 3486 participants in the cluster randomized trial (mean [SD] age of 69.6 [14.9] years; 2010 men [57.7%]), 1511 patients were included in this ad hoc cohort study. Among those with at least 1 opioid dispensation, 241 patients (15.9%) experienced an opioid-related emergency department visit, hospital readmission, or death. Results from marginal structural Cox proportional hazards regression models showed more than a 2-fold increase in the risk of opioid-related adverse events associated with a cumulative use duration of more than 90 days (adjusted hazard ratio, 2.56; 95% CI, 1.25-5.27) compared with 1 to 30 days. A 3-fold risk increase was found with a mean daily dose higher than 90 MME (adjusted hazard ratio, 3.51; 95% CI, 1.58-7.82) compared with 90 MME or lower.

CONCLUSIONS AND RELEVANCE This study found an association between risk of adverse health care events and higher opioid doses and longer treatment duration. This finding can inform policies for limiting opioid duration and dose to attenuate the risk of avoidable morbidity.

JAMA Network Open. 2021;4(5):e218782. doi:10.1001/jamanetworkopen.2021.8782

Key Points

Question Is the risk of opioid-related emergency department visit, hospital admission, or death associated with the prescribed opioid dose and duration of use?

Findings In this cohort study of 1511 patients who were discharged from an academic hospital, both cumulative opioid use duration of more than 90 days and daily opioid dose higher than 90 morphine milligram equivalents were associated with increased risk of opioid-related adverse events.

Meaning Results of this study suggest that practitioners need to focus on adjusting pain management strategies for patients who are transitioning from acute postoperative to chronic pain and that policies should limit opioid use duration and doses to minimize opioid-related morbidity.

+ Invited Commentary

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Introduction

Over the past 20 years, opioid prescribing and average prescription volumes continued to increase in the United States and Canada.[1,2] Opioids remain the main treatment for cancer pain, as recommended by the World Health Organization.[3] However, substantial increases in prescriptions for chronic noncancer pain have also been documented. In the 2010s in North America, opioid use increased by nearly 100%,[4] with acute pain being the most common indication.[5,6] These patterns in prescription opioids have been accompanied by higher rates of opioid-related morbidity and mortality.[4,7] Nonfatal opioid-related outcomes have been reported in older adults, even when the drugs were used as directed.[8,9] Furthermore, the long-term benefits are uncertain given that even short-term use may lead to greater predisposition to adverse events.[10] Longer trials have shown less pain relief with opioids, possibly because of pain tolerance or opioid-induced hyperalgesia.[11] This response may play a role in an escalation in the dose and potency of opioids, which subsequently may be associated with higher risk for adverse reactions. Yet, no opioid trial has followed up patients for longer than 6 months,[12] and most observational studies have examined only the association between the initial dose of opioid prescriptions and the duration of subsequent use.[13-15]

For many patients, their first opioid exposure follows a hospitalization, making this group a high-priority population for investigation. Inadequate postdischarge communication of hospital-initiated changes in medication among community-based practitioners is a well-established problem.[16] Consequently, community physicians may continue prescribing opioids started in the hospital for acute pain relief because they have no information on the treatment indication or the expected therapy duration. Thus, the prescribing practices during hospitalization may have implications for the increase in opioid consumption and its related adverse outcomes.

In this cohort study, we aimed to estimate the risk of harms associated with opioid dose and duration of use. We also aimed to ascertain whether the risk is modified by treatment indication and age.

Methods

Ethics approval for this study was obtained from the McGill University Health Centre (MUHC) Research Ethics Board. Some patients provided written informed consent, whereas others provided verbal consent on the telephone. Privacy Commissioner permission to link clinical and administrative data was obtained from the Commission d'Accès à l'Information du Quebec. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.[17]

Design, Setting, Participants, and Data Sources

We followed up a prospective cohort of patients 12 months after their discharge from a medical or surgical unit. These patients were enrolled in a cluster randomized trial of medication reconciliation at the MUHC between October 1, 2014, and November 30, 2016.[18] The MUHC is a quaternary care teaching hospital with more than 1000 beds in Montreal, Canada, that operates within the universal health care system of the province of Quebec (Régie de l'Assurance Maladie du Québec [RAMQ]). The RAMQ plan covers all hospitalizations, essential medical care, and drug insurance for registrants who are aged 65 years or older, are recipients of income security, and are not insured through their employer (approximately 50% of the Quebec population).

To be eligible for the original cluster randomized trial, patients had to be aged 18 years or older at admission, have been admitted from the community or transferred from another hospital, and have had at least 1 year of previous continuous provincial health care coverage. To be included in the present ad hoc study, patients needed to have filled at least 1 opioid prescription in the 90 days after discharge. We excluded patients with a history of using methadone hydrochloride or buprenorphine

hydrochloride, which are prescribed to treat opioid addiction.[19] eFigure 2 in the Supplement shows the patient selection for the study.

We linked multiple data sources. Demographic, clinical, health care use, and prescription claims data were retrieved from admission notes and from RAMQ medical services and prescription claims in the year before and after the index hospitalization. Data on admission and discharge dates, units, and diagnoses as well as major procedures were retrieved from the hospitalization database. Medications at admission, in hospital, and prescribed at discharge were abstracted from the MUHC Data Warehouse. Information on hospital discharge experiences was obtained through telephone interviews 30 days after discharge.

Postdischarge Opioid Use

Opioid use 1 year after discharge was measured using RAMQ pharmacy claims. For each prescription filled, the drug identification number, strength, dispensing date and quantity, prescription duration, and prescribing physician are documented in these claims. Drug identification numbers that were mapped to Anatomical Therapeutic Chemical codes N02A and R05DA were used to identify opioids (eMethods 1 in the Supplement). On each day, an individual was classified as having an active prescription or not. A 5-day grace period was added to the end of each dispensation given that opioids were often prescribed on a use-as-needed basis, and patients were likely to take some unused pills for a few days after the prescription ended. eMethods 2 and eTable 6 in the Supplement describe the opioid daily dose calculations.[20] We also constructed time-varying binary indicators of recent opioid discontinuation, dose increases, and opioid add-on therapy.

This study was unique in that administratively derived measures of opioid exposure were supplemented with information on the patient's medication-use behavior. This information was extracted from interviews 30 days after discharge to construct a series of time-invariant indicators that identified patients who filled a prescription and (1) continued using it, (2) started using it but stopped, or (3) never used it.

Outcomes, Potential Modifiers of Harms, and Covariates

Outcome was defined as the time from the first opioid dispensation to the earliest of the first opioid-related emergency department (ED) visit, hospital readmission, or death from any cause in the year after discharge. Outcomes were ascertained using RAMQ medical services claims and hospitalization databases, which identified all ED visits and readmissions to any hospital. An adverse event was considered opioid-related if the diagnosis indicated opioid abuse, opioid dependence, and/or opioid poisoning and/or any of the more common adverse effects of opioids,[21] including constipation, nausea, vomiting, dizziness,[22-26] or fractures.[27-30] We combined all possible opioid-related adverse effects because only 3 patients (0.2%) were diagnosed with opioid abuse, dependence, and/or poisoning and because medication-related adverse events are underascertained in the ED.[31] eTables 1 to 5 in the Supplement list the *International Classification of Diseases, Ninth Revision, Clinical Modification*, and *International Statistical Classification of Diseases, Tenth Revision, Clinical Modification* codes we used.

We assessed potential modifiers of harms associated with opioid use, stratified by age (<64 years vs ≥64 years) and treatment indication, categorized as (1) cancer-related pain, (2) postsurgical pain management, or (3) other chronic pain problems. Medical records were used to identify treatment indication.

Potential risk factors for long-term opioid use included patient demographic characteristics (age, sex, and drug insurance status), coexisting illnesses (history of mental health conditions, pain syndromes, substance and/or alcohol use disorder, tobacco use, cancer diagnoses, and other comorbidities), and drug and health care use 1 year before hospitalization (opioid misuse; nonopioid pain medications; and number of ED visits, hospitalizations, physicians seen, and dispensing pharmacies). We also assessed the reason for hospital admission, in-hospital administration of opioids, the reason for opioid prescribing at discharge, whether a multimodal pain management

regimen was prescribed, and discharge destination.[11,37] To measure health care fragmentation associated with low quality of care and increased adverse outcomes or opioid-seeking behavior associated with greater dependence,[33,34] we created time-varying covariates, updated daily during follow-up, for the cumulative numbers of distinct prescribers and dispensing pharmacies after discharge.

Statistical Analysis

Descriptive statistics were used to summarize patient, practitioner, and health care system characteristics. For all main analyses, we relied on time-to-event methods. Specifically, we used multivariable marginal structural Cox proportional hazards regression models (MSM Cox)[35,36] to identify the association between time-varying opioid use and the risk of the outcome. Cohort entry was the date of the first opioid dispensation within 3 months after hospital discharge. Patients were followed up until their first opioid-related ED visit, hospital readmission, death, or end of follow-up. We temporarily censored patients during hospitalizations that were unrelated to opioid use. Because of the uncertainty regarding the association of opioid consumption patterns with adverse events, we constructed alternative time-varying metrics of opioid use, which were updated daily during the 1-year follow-up period: (1) current use (no or yes), (2) cumulative use duration (1-30, >30-60, >60-90, and >90 days), (3) continuous use duration (0, 1-30, >30-60, and >60 days), (4) daily dose in morphine milligram equivalent (MME; ≤90 or >90), and (5) type of ingredient in prescription opioids used (codeine sulfate, morphine sulfate, oxycodone hydrochloride, hydromorphone hydrochloride, fentanyl citrate, or multiple opioid products) (eTable 7, eFigure 1, and eMethods 3 in the Supplement).[37]

All MSM Cox models included the same potential confounders, including time-invariant baseline variables and time-varying covariates, that were selected according to statistical and clinical significance. To account for time-varying potential confounders that could also be affected by previous opioid exposure, we used psychotropic medication use, targeted comorbidities, and cumulative numbers of prescribers and dispensing pharmacies to estimate stabilized time-varying inverse probability treatment weights[38,39] for opioid exposure. To estimate the inverse probability treatment weights, separately for each 10-day time interval during the 1-year follow-up, we used a series of multivariable logistic models,[39] and to avoid unstable estimates, we truncated at the 95th percentile of their distribution.[40] We used the robust sandwich covariance estimator to calculate SEs, while accounting for the inverse probability treatment weights.[41] To ascertain whether the risk of opioid-related harms was modified by treatment indication or age, we used Wald tests of the respective 2-way interactions at 2-sided $\alpha = .05$.

All MSM Cox models were implemented with SAS, version 9.4 (SAS Institute Inc). Data analyses were performed between February 1, 2019, and February 28, 2020.

Sensitivity Analyses

First, to account for potential long-term opioid use before study entry, we recreated the cohort in 2 sensitivity analyses, excluding patients with 1 or more opioid dispensations from the first analysis and those with 3 or more opioid dispensations from the second analysis, during the baseline period. Second, in separate sensitivity analyses, we restricted the outcome to either opioid-related ED visit, hospital readmission, or death. We also conducted sensitivity bias analyses in which we tested an interaction term between the main exposure and the adherence measure constructed from patient interviews to identify the extent to which the potential nonadherence to opioid prescriptions could have affected the estimated association. Third, to account for the differences in severity of opioid-related adverse effects, in 2 additional sensitivity analyses, we categorized the outcomes into fracture or dizziness and nausea or constipation.

Additional sensitivity analyses were performed to ascertain the extent to which selected, statistically significant results could reflect potential bias from unmeasured confounders.[42] The analyses involved (1) simulating a potential confounder with prespecified associations (odds ratios)

Table 1. Baseline Characteristics of Patients Who Filled an Opioid Prescription Within 90 Days of Hospital Discharge, Stratified by Discharge Unit

Characteristic	Trial cohort, No. (%)	Follow-up cohort, No. (%) (n = 1511)	
		Discharged from medical unit	Discharged from surgical unit
All patients	3486	392 (25.9)	1119 (74.1)
Age, mean (SD), y	69.6 (14.9)	67.7 (16.8)	66.9 (11.9)
Female	1476 (42.3)	192 (49.0)	436 (39.0)
Male	2010 (57.7)	200 (51.0)	683 (61.0)
Length of hospital stay, ≥6 d	2930 (84.0)	351 (89.5)	875 (78.2)
Health care use 1 y before admission, mean (SD)			
ED visits	8.4 (8.5)	15.3 (20.3)	4.4 (8.1)
Hospitalizations	0.8 (1.9)	0.9 (1.9)	0.7 (1.8)
Physician visits	10.9 (14.5)	14.0 (16.3)	9.9 (8.4)
No. of prescribing physicians	4.2 (3.4)	6.3 (4.4)	3.6 (2.4)
No. of physicians prescribing opioids	0.6 (1.2)	1.9 (2.2)	0.5 (0.9)
No. of dispensing pharmacies	1.4 (0.9)	1.6 (0.9)	1.4 (0.8)
No. of pharmacies dispensing opioids	0.4 (0.6)	0.9 (0.7)	0.4 (0.6)
Active prescriptions at admission	9.8 (10.1)	14.3 (14.1)	6.6 (6.5)
Radiotherapy	215 (6.2)	77 (19.6)	133 (11.9)
Chemotherapy	262 (7.5)	83 (21.2)	176 (15.7)
Medication use 1 y before admission			
Active opioid prescription at admission	504 (14.5)	186 (47.4)	105 (9.4)
History of opioid use	1206 (34.6)	283 (72.2)	344 (30.7)
≥3 opioid dispensations	104 (2.9)	61 (15.6)	18 (1.6)
History of long-acting opioid use	146 (4.2)	89 (22.7)	35 (3.1)
History of methadone or buprenorphine use	13 (0.4)	10 (2.6)	1 (0.1)
History of benzodiazepine use	1088 (31.2)	175 (44.6)	336 (30.0)
History of antidepressant use	706 (20.3)	133 (33.9)	208 (18.6)
History of nonopioid pain medication use	1068 (30.6)	243 (61.9)	406 (36.3)
In-hospital medication use			
Antidepressants	628 (18.0)	112 (28.6)	153 (13.7)
Opioids	2509 (72.0)	307 (78.3)	1113 (99.5)
Benzodiazepines	2278 (65.4)	196 (50.0)	997 (89.1)
Analgesics	3161 (90.7)	168 (43.1)	942 (84.2)
Pain regimen at hospital discharge			
Opioids	1530 (43.9)	202 (51.5)	987 (88.2)
Nonopioid analgesics	2209 (63.4)	227 (57.9)	990 (88.5)
Targeted comorbidities that may increase the risk of hospitalizations or ED visits			
History of mental illness	511 (14.7)	74 (18.9)	132 (11.8)
Dementia	213 (6.1)	25 (6.4)	13 (1.2)
Substance and/or alcohol use disorder	115 (3.3)	27 (6.9)	19 (1.7)
Pain syndromes	1352 (38.8)	221 (56.4)	408 (36.5)
Cancer diagnosis	1253 (35.9)	168 (42.9)	538 (48.1)
Other comorbidities that may increase the risk of hospitalizations or ED visits			
Cardiovascular diseases	1398 (40.1)	154 (39.3)	657 (58.7)
Cerebrovascular diseases	334 (9.6)	49 (12.5)	69 (6.2)
Pneumonia	338 (9.7)	46 (11.7)	63 (5.6)
COPD	751 (21.5)	102 (26.0)	236 (21.1)
Kidney disease	364 (10.4)	53 (13.5)	41 (3.7)
Diabetes	791 (22.7)	92 (23.5)	223 (19.9)

Abbreviations: COPD, chronic obstructive pulmonary disease; ED, emergency department.

(eTable 16 in the Supplement). Analyses that restricted the outcomes to either fracture-related or other opioid-related ED visits or hospital readmissions showed consistent results (eTable 17 in the Supplement).

Discussion

We assessed the association between long-term opioid use patterns (represented by time-varying measures of current daily use, daily MME dose, cumulative and continuous use duration, and type of opioid ingredient) and opioid-related adverse events or death. We found increased risks with daily dose as well as with cumulative and continuous use duration. There were also variations in the magnitude of risk when considering different treatment indications. The results highlight the importance of accounting for alternative opioid consumption patterns when quantifying the risk of adverse health care events or death. Although much of the literature considers 90 days as a threshold for safe opioid use,[14,45,46] in this study, we provided risk estimates for multiple duration

Table 2. Characteristics of Prescription Opioids Dispensed, Stratified by Ingredient Type and Potency[20,44]

Ingredient (molecule)[a]	MME conversion factor	Patients who filled at least 1 type of opioid ingredient, No. (%)[b]	Days' supply of initial dispensation, mean (SD)	Dose of initial dispensation, mean (SD), MME	Patients who filled ≥2 opioid prescriptions, No. (%)	Patients who filled ≥1 type of opioid ingredients, No. (%)
Codeine sulfate	0.15	215 (14.2)	13.2 (10.1)	19.9 (12.4)	201 (93.5)	11 (5.1)
Morphine sulfate	1	244 (16.1)	10.4 (8.3)	27.4 (27.2)	226 (92.6)	159 (65.2)
Oxycodone hydrochloride	1.5	1044 (69.1)	8.6 (6.3)	35.3 (17.7)	610 (58.4)	441 (42.2)
Hydromorphone hydrochloride	4	689 (45.6)	9.8 (7.4)	31.8 (26.0)	594 (86.2)	180 (6.1)
Fentanyl citrate	7.2	109 (7.2)	22.5 (11.3)	137.2 (121.5)	108 (99.1)	16 (14.7)
Methadone hydrochloride	NA	44 (2.9)	NA	NA	37 (84.1)	33 (75.0)
Total No. of patients[c]	NA	1511	NA	NA	950 (62.8)	595 (39.4)

Abbreviations: MME, morphine milligram equivalent; NA, not applicable.

[a] Only the tablet and patch forms of these medications were considered.

[b] A given patient can be in more than 1 category as the patient fills multiple types of opioid ingredients.

[c] This total is not equivalent to the sum of patients in each opioid ingredient category.

Table 3. Characteristics of First Opioid Prescription Filled in the 90-Day Postdischarge Period

Characteristic	Overall	Opioid prescription at discharge?	
		Yes	No
All patients	1511	1163 (76.9)	348 (23.0)
Opioid prescription filled			
Within first 7 d	1228 (81.3)	1050 (90.3)	178 (51.2)
Within first 30 d	1360 (90.0)	1118 (96.1)	242 (69.5)
MME dose dispensed			
Mean (SD)	34.9 (28.6)	34.9 (23.6)	34.8 (40.9)
Median (IQR)	29.1 (20.0-41.7)	30.0 (21.0-41.7)	25.0 (16.0-40.9)
MME dose dispensed			
≤90	1467 (97.1)	1137 (97.8)	330 (94.8)
>90	44 (2.9)	26 (2.2)	18 (5.2)
Type of opioid ingredients dispensed			
Codeine	47 (3.1)	21 (1.8)	26 (7.5)
Morphine	68 (4.5)	33 (2.8)	35 (10.1)
Oxycodone	952 (63.0)	814 (69.9)	138 (39.7)
Hydromorphone	419 (27.7)	286 (24.6)	133 (38.2)
Fentanyl	22 (1.5)	7 (0.6)	15 (4.3)
Combination opioid products dispensed	308 (20.4)	209 (17.9)	99 (28.5)
Combination nonopioid products dispensed	1300 (86.0)	999 (85.9)	301 (86.5)

Abbreviations: IQR, interquartile range; MME, morphine milligram equivalent.

categories of up to and beyond 90 days to illustrate how the risk of adverse events may vary with short-term and long-term use patterns.

Observational research into extended opioid treatment duration and associated adverse events is scant, with most of the evidence coming from clinical trials with a duration of less than a year and previous observational studies examining only the initial opioid prescription duration.[14,47,48] Regarding the risks of opioid use duration, results of the current study are similar to the findings of a 2017 Cochrane Reviews summary.[12] In this study, the nonsignificant findings and wide CIs for continuous use beyond 90 days could be a reflection of low statistical power given that only a few patients had long, uninterrupted use during the 1-year follow-up. However, it has been previously documented that just as patients developed tolerance to the analgesic properties of opioids, they also developed the capacity to tolerate adverse outcomes.[49] In this study, mean opioid doses started

Table 4. Risk of Adverse Events for Opioid Exposure Metrics in Marginal Structural Cox Proportional Hazards Regression Models

Opioid exposure metric	No. of adverse events[a]	Person-years	Incidence rate (95% CI)[b]	Risk of ED visits, hospital readmissions, or death, adjusted HR (95% CI)[c,d]	Risk of ED visits or hospital readmissions, adjusted HR (95% CI)[e]	Risk of death, adjusted HR (95% CI)
Current use						
No	128	1102.7	116.1 (96.8-138.0)	1 [Reference]	1 [Reference]	1 [Reference]
Yes	113	233.4	484.2 (399.0-582.1)	1.71 (1.04-2.82)	2.00 (0.98-4.10)	1.56 (0.79-3.04)
Cumulative use duration, d						
1-30	123	973.3	126.4 (105.0-150.8)	1 [Reference]	1 [Reference]	1 [Reference]
>30-60	44	181.1	242.9 (176.6-326.2)	1.55 (0.95-2.52)	1.47 (0.69-3.14)	1.61 (0.86-3.03)
>60-90	24	56.6	423.7 (271.5-630.4)	2.45 (1.18-5.09)	1.05 (0.22-3.92)	3.45 (1.41-8.47)
>90	50	125.1	399.8 (296.7-527.0)	2.56 (1.25-5.27)	2.07 (0.70-6.07)	2.89 (1.11-7.59)
Continuous use duration, d						
0	128	1102.7	116.1 (96.8-138.0)	1 [Reference]	1 [Reference]	1 [Reference]
1-30	63	132.0	477.3 (366.7-610.6)	1.79 (1.00-3.22)	2.10 (0.72-5.86)	1.66 (0.84-3.29)
>30-60	26	32.4	801.5 (523.5-1174.3)	3.73 (1.83-7.60)	5.19 (1.56-17.2)	3.10 (1.28-7.54)
>60	24	68.9	348.1 (223.1-517.9)	0.86 (0.37-1.96)	0.91 (0.32-2.49)	0.81 (0.26-2.47)
Daily MME dose						
≤90	207	1302.2	158.9 (138.0-182.1)	1 [Reference]	1 [Reference]	1 [Reference]
>90	34	33.9	1003.1 (694.7-1401.7)	3.51 (1.58-7.82)	1.06 (0.30-2.78)	5.84 (2.12-16.09)
Type of opioid ingredient used						
Codeine	4	13.5	296.9 (80.9-760.2)	1 [Reference]	1 [Reference]	1 [Reference]
Morphine	19	18.1	1047.5 (630.7-1635.8)	4.04 (1.02-15.9)	1.81 (0.28-11.6)	9.36 (1.18-73.9)
Oxycodone	16	78.8	202.9 (115.9-329.5)	1.48 (0.35-6.25)	0.67 (0.10-4.27)	2.98 (0.33-27.0)
Hydromorphone	45	87.2	515.8 (376.3-690.2)	2.62 (0.64-10.7)	1.06 (0.18-6.41)	6.74 (0.83-54.6)
Fentanyl	11	15.3	718.7 (358.8-1286.0)	2.93 (0.57-15.0)	0.43 (0.03-6.01)	8.67 (0.87-86.1)
Multiple opioid products	18	20.4	883.3 (523.5-1396.0)	6.36 (1.42-28.4)	4.74 (0.69-32.4)	9.94 (1.01-98.3)

Abbreviations: ED, emergency department; HR, hazard ratio; MME, morphine milligram equivalent.

[a] The event counts are for the composite outcome of ED visits, readmissions, and/or death.

[b] Incidence rate is reported as 1000 per year.

[c] Covariates considered in the calculation of the inverse probability treatment weights were as follows: (1) demographic characteristics (ie, indicator for a patient randomized to the RightRx intervention group, age at admission, sex, and copay status); (2) medical, prescription, and health care use 1 year before admission (ie, unique number of dispensing pharmacies and prescribers, hospitalizations and ED visits, receipt of radiotherapy and/or chemotherapy services, type of cancer, history of mental health diagnoses, history of substance and/or alcohol abuse or dependence, targeted comorbidities that may increase someone's risk of opioid-related adverse events, history of chronic pain, previous opioid use, more than 3 opioid dispensations, and previous use of psychotropic medications); (3) in-hospital characteristics (ie, presence of an opioid-related reason for index admission, length of hospital stay, opioid administration during the index hospitalization, nonopioid pain medication administration, use of antidepressants and benzodiazepines, hospital unit discharged from [medical vs surgical], and type of surgery [cardiac vs thoracic]); (4) at-discharge characteristics (ie, receipt of an opioid prescription; prescribing reason such as having had surgery, having anxiety, or pain problems); (5) time-varying postdischarge characteristics (ie, use of benzodiazepines, use of antidepressants, use of methadone or buprenorphine, cumulative number of physicians, cumulative number of dispensing pharmacies, recent discontinuation of opioid use, recent increases in opioid dose, recent add-on opioid therapy, and updated targeted baseline medical comorbidities). The 95th percentile for the stabilized weight was 2.88 (mean [SD] = 0.81 [0.71]).

[d] The Akaike information criteria for the models were 2562.3 with current use, 2557.6 with cumulative use duration, 2548.1 with continuous use duration, 2535.5 with MME daily dose, and 2548.1 with type of opioid ingredient used.

[e] Additional censoring weights were included to account for competing risk by death. Same covariates as those included in the treatment weights were used for the censoring weights.

with both relevant opioid exposure and occurrence of the outcome and (2) rerunning the multivariable analyses with additional adjustment for the simulated confounder.[43]

Results

Among the 3486 participants in the original cluster randomized trial, including 2010 men (57.7%) and 1476 women (42.3%) with a mean (SD) age of 69.6 (14.9) years (**Table 1**), 1511 were followed up in the current study. Most patients underwent surgery (1119 [74.1%]), and 392 (25.9%) received care in the medical unit. At hospital discharge, 202 of 392 patients (51.5%) from the medical unit and 987 of 1119 patients (88.2%) from the surgical unit received an opioid prescription. A list of the prescriptions dispensed by type of opioid ingredient and potency is provided in **Table 2**.[20,44] Among the 348 patients who did not receive an opioid prescription at discharge, 178 (51.2%) filled an opioid prescription in the 7 days after discharge (**Table 3**). Fewer surgical than medical patients used opioids before admission (344 of 1119 [30.7%] vs 283 of 392 [72.2%]). Overall, 168 of all patients from the medical unit (42.9%) and 538 of all patients from the surgical unit (48.1%) had documented cancer diagnoses in the year before hospitalization and/or at hospital discharge. In the year after discharge, 241 patients (15.9%) had an opioid-related ED visit or hospitalization or died. The most frequent potentially opioid-related adverse events were fractures (219 [51.8%]), nausea and vomiting (66 [15.6%]), and dizziness (78 [18.4%]). Additional results from descriptive analyses and main models are shown in eTables 8 to 17 in the Supplement.

Current opioid use, which identified patients as having an active prescription on a given day during the follow-up period, was associated with a 71% increased risk of opioid-related adverse events (adjusted hazard ratio [AHR], 1.71; 95% CI, 1.04-2.82) (**Table 4**). Compared with shorter cumulative exposure of 1 to 30 days, longer past use of more than 60 to 90 days (AHR, 2.45; 95% CI, 1.18-5.09) and more than 90 days (AHR, 2.56; 95% CI, 1.25-5.27) were both associated with a 2-fold increase in risk of adverse events. Uninterrupted continuous use for up to 60 days was associated with a 3-fold increased risk of opioid-related adverse health care events (AHR, 3.73; 95% CI, 1.83-7.60) compared with patients who were not current opioid users. In contrast, for a few patients who exceeded 60 days of continuous use, no evidence of an increased risk of adverse events was found (AHR, 0.86; 95% CI, 0.37-1.96).

The risk of opioid-related adverse events or death was 3 times higher for a current daily dose higher than 90 MME (AHR, 3.51; 95% CI, 1.58-7.82) vs 90 MME or lower. Among different types of opioid ingredients, only morphine showed statistically significant risk increase (AHR, 4.04; 95% CI, 1.02-15.9) compared with codeine, albeit with wide CIs (Table 4). We found 2 statistically significant interactions between surgery and current opioid use (AHR, 3.35; $P = .003$) and between surgery and more than 90 days of opioid use (AHR, 7.80; $P = .002$). Among patients discharged from the surgical unit, both current use (AHR, 3.35; 95% CI, 1.82-6.85) and cumulative use duration of more than 90 days (AHR, 7.80; 95% CI, 3.20-13.1) were associated with statistically significant increased risk of opioid-related adverse events or death. In contrast, both associations were not statistically significant for patients discharged from the medical unit. The interaction between cumulative opioid use duration of more than 90 days and a cancer diagnosis was also significant (eTable 13 in the Supplement). Results of interaction analyses by age and treatment indication are in eTables 12 and 13 in the Supplement.

Excluding previous opioid users slightly changed the results (eTables 9 and 10 in the Supplement). The absence of an interaction between adherence and current use ($P = .99$) could be attributed to excellent adherence: in the first month after discharge, 90% of patients (n = 1360) reported using their dispensed opioids as prescribed, only 12% (n = 169) discontinued their initial dispensation, and 5% (n = 70) filled their prescription but never started using it. In bias sensitivity analyses, patients with a daily opioid dose higher than 90 MME remained at a significantly increased risk of opioid-related adverse health care events, even after adjusting for a moderately strong unobserved confounder, with an odds ratio of 2 for both exposure (higher dose) and outcome

to plateau by the greater than 90-day threshold and did not escalate with increasing duration beyond 90 days of use (eTable 13 in the Supplement), which suggests that these patients potentially transitioned into long-term users.

We noted an increased risk of adverse events with daily doses higher than 90 MME. Previous studies have also demonstrated an association of opioid dose with adverse events, such as increased risks of fractures, road trauma, and opioid-related mortality.[7,50-53] Saunders et al[50] showed that a daily opioid dose higher than 50 MME was associated with a 2-fold increase in the risk of fractures. Similar to our study, work by Ishida et al[54] found high doses to be associated with risks for all adverse outcomes. The present study showed that use by most patients in this cohort did not exceed the recommended maximum dose of 90 MME,[32] and yet their risk of adverse events was still high vs the risk of patients who were not exposed to opioids.

Existing data on the rates of morbidity and mortality as a function of drug potency among commonly prescribed opioids are somewhat conflicting.[55-58] However, because of the relatively small sample size and overlapping CIs in this study, our comparisons of the risks associated with different prescription opioids were inconclusive, even if the results suggested that morphine users may be at higher risk of a composite outcome and death.

Results of this study can inform pain management policies or strategies aimed at preventing or attenuating opioid-related morbidity. Practitioners need to adjust opioid use duration and opioid doses for patients who are transitioning from acute postoperative to chronic pain.

Strengths and Limitations

This study has some strengths. It used multiple data sources, which enhanced the internal validity of the study by providing detailed covariate information to adjust for confounders and account for potential mediators. Most of what is known about extended opioid treatment and associated adverse events is based on different and arbitrary definitions.[59-62] In this study, we compared various time-varying opioid use metrics to provide further insights into the mechanism behind the development of opioid-related events.[37,63]

This study has some limitations. In the data analyses, we used prescription duration as recorded by pharmacists. Because opioids are given on an as-needed basis, exposure mismeasurement is possible. However, we expect the resulting exposure misclassification to be nondifferential and thus to bias the estimates toward the null. As in all observational studies, this study had the potential for unmeasured confounding and confounding by indication. Our decision to include only patients with at least 1 opioid dispensation after discharge (excluding never users) and to select as a comparator those patients on short-term or low-dose opioids reduces concerns about potential bias from confounding by indication. Moreover, a consistent limitation across all claims-based studies, including this study, is the inability to account for opioid medications that were obtained through diversion or other illicit means. However, a study conducted in a similar cohort of universally covered patients in the province of Quebec found older adults to be less likely to experience an opioid prescription–associated overdose death and to seek outpatient prescriptions compared with younger people. Most patients in this study cohort were 64 years of age or older; thus, we expected illicit use to have little implication for the main findings.[64] In this study, the choice of a broader outcome may be prone to confounding. However, we explored the amount of hidden bias from a simulated confounder necessary to alter the conclusion that patients with higher daily opioid doses have a higher risk of opioid-related adverse events, and the association was robust. Future research using data from multiple health care systems is required to replicate these findings in larger population cohorts and provide greater generalizability.

Conclusions

In this cohort study, we found that using opioids for prolonged duration and at high doses was associated with increased risk of opioid-related adverse events or death. These results can inform

policies or strategies for minimizing the harms and risks associated with opioid-related morbidity. Opioid use duration and opioid doses may need to be adjusted for patients who are transitioning from acute postoperative to chronic pain.

ARTICLE INFORMATION

Accepted for Publication: March 12, 2021.

Published: May 18, 2021. doi:10.1001/jamanetworkopen.2021.8782

Corresponding Author: Siyana Kurteva, BSc, Clinical and Health Informatics Research Group, Department of Medicine, McGill University, 1140 Pine Ave W, Montreal, QC H3A 1A3, Canada (siyana.kurteva@mail.mcgill.ca).

Author Affiliations: Department of Epidemiology and Biostatistics, McGill University, Montreal, Quebec, Canada (Kurteva, Abrahamowicz, Tamblyn); Clinical and Health Informatics Research Group, Department of Medicine, McGill University, Montreal, Quebec, Canada (Kurteva, Tamblyn); Institute of Health Policy Management and Evaluation, Toronto, Ontario, Canada (Gomes); Li Ka Shing Knowledge Institute, St Michael's Hospital, Toronto, Ontario, Canada (Gomes); ICES, Toronto, Ontario, Canada (Gomes, Tamblyn); McGill University Health Centre, Montreal, Quebec, Canada (Tamblyn).

Author Contributions: Ms Kurteva and Dr Tamblyn had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Kurteva, Tamblyn.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Kurteva, Tamblyn.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Kurteva, Abrahamowicz.

Obtained funding: Kurteva, Tamblyn.

Administrative, technical, or material support: Tamblyn.

Supervision: Tamblyn.

Conflict of Interest Disclosures: Dr Gomes reported receiving grants from the Ontario Ministry of Health outside the submitted work. No other disclosures were reported.

Funding/Support: This study was supported by a Kuok Scholarship (Ms Kurteva), a grant from the Canadian Institutes of Health Research-Drug Safety and Effectiveness Cross-Disciplinary Training Program (Ms Kurteva), a Burke Scholarship from the Faculty of Medicine at McGill University (Ms Kurteva), and a doctoral award from the Fonds de Recherché du Québec-Santé (Ms Kurteva).

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

REFERENCES

1. Fischer B, Gooch J, Goldman B, Kurdyak P, Rehm J. Non-medical prescription opioid use, prescription opioid-related harms and public health in Canada: an update 5 years later. *Can J Public Health*. 2014;105(2):e146-e149. doi:10.17269/cjph.105.4143

2. Gomes T, Mamdani MM, Dhalla IA, Paterson JM, Juurlink DN. Opioid dose and drug-related mortality in patients with nonmalignant pain. *Arch Intern Med*. 2011;171(7):686-691. doi:10.1001/archinternmed.2011.117

3. World Health Organization. WHO guidelines for the pharmacological and radiotherapeutic management of cancer pain in adults and adolescents. Accessed March 30, 2020. https://apps.who.int/iris/handle/10665/279700

4. Dhalla IAPN, Persaud N, Juurlink DN. Facing up to the prescription opioid crisis. *BMJ*. 2011;343:d5142. doi:10.1136/bmj.d5142

5. Habib ASKM, Kertai MD, Cooter M, Greenup RA, Hwang S. Risk factors for severe acute pain and persistent pain after surgery for breast cancer: a prospective observational study. *Reg Anesth Pain Med*. 2019;44(2):192-199. doi:10.1136/rapm-2018-000040

6. Buvanendran A, Della Valle CJ, Kroin JS, et al. Acute postoperative pain is an independent predictor of chronic postsurgical pain following total knee arthroplasty at 6 months: a prospective cohort study. *Reg Anesth Pain Med*. 2019;rapm-2018-100036. doi:10.1136/rapm-2018-100036

7. Volkow NDFT, Frieden TR, Hyde PS, Cha SS. Medication-assisted therapies—tackling the opioid-overdose epidemic. *N Engl J Med*. 2014;370(22):2063-2066. doi:10.1056/NEJMp1402780

8. Bayoumi I, Dolovich L, Hutchison B, Holbrook A. Medication-related emergency department visits and hospitalizations among older adults. *Can Fam Physician*. 2014;60(4):e217-e222.

9. Frood J, Paltser G. Types of opioid harms in Canadian hospitals: comparing Canada and Australia. *Healthc Q*. 2019;22(2):10-12. doi:10.12927/hcq.2019.25912

10. Calcaterra SL, Yamashita TE, Min SJ, Keniston A, Frank JW, Binswanger IA. Opioid prescribing at hospital discharge contributes to chronic opioid use. *J Gen Intern Med*. 2016;31(5):478-485. doi:10.1007/s11606-015-3539-4

11. Busse JW, Craigie S, Juurlink DN, et al. Guideline for opioid therapy and chronic noncancer pain. *CMAJ*. 2017;189(18):E659-E666. doi:10.1503/cmaj.170363

12. Els C, Jackson TD, Kunyk D, et al. Adverse events associated with medium- and long-term use of opioids for chronic non-cancer pain: an overview of Cochrane Reviews. *Cochrane Database Syst Rev*. 2017;10:CD012509. doi:10.1002/14651858.CD012509

13. Deyo RA, Hallvik SE, Hildebran C, et al. Association between initial opioid prescribing patterns and subsequent long-term use among opioid-naïve patients: a statewide retrospective cohort study. *J Gen Intern Med*. 2017;32(1):21-27. doi:10.1007/s11606-016-3810-3

14. Shah A, Hayes CJ, Martin BC. Factors influencing long-term opioid use among opioid naive patients: an examination of initial prescription characteristics and pain etiologies. *J Pain*. 2017;18(11):1374-1383. doi:10.1016/j.jpain.2017.06.010

15. Hadlandsmyth K, Lund BC, Mosher HJ. Associations between initial opioid exposure and the likelihood for long-term use. *J Am Pharm Assoc (2003)*. 2019;59(1):17-22. doi:10.1016/j.japh.2018.09.005

16. Tamblyn R, Huang AR, Meguerditchian AN, et al. Using novel Canadian resources to improve medication reconciliation at discharge: study protocol for a randomized controlled trial. *Trials*. 2012;13:150. doi:10.1186/1745-6215-13-150

17. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol*. 2008;61(4):344-349. doi:10.1016/j.jclinepi.2007.11.008

18. Tamblyn R, Abrahamowicz M, Buckeridge DL, et al. Effect of an electronic medication reconciliation intervention on adverse drug events: a cluster randomized trial. *JAMA Netw Open*. 2019;2(9):e1910756. doi:10.1001/jamanetworkopen.2019.10756

19. Fhima A, Henrion R, Lowenstein W, Charpak Y. [Two-year follow-up of an opioid-user cohort treated with high-dose buprenorphine (Subutex)]. *Ann Med Interne (Paris)*. 2001;152(suppl 3):1S26-1S36.

20. Svendsen K, Borchgrevink P, Fredheim O, Hamunen K, Mellbye A, Dale O. Choosing the unit of measurement counts: the use of oral morphine equivalents in studies of opioid consumption is a useful addition to defined daily doses. *Palliat Med*. 2011;25(7):725-732. doi:10.1177/0269216311398300

21. Vigilance Santé. Drugs database and pharmaceutical software for health professionals and pharmacists. Accessed November 30, 2020. https://www.vigilance.ca

22. Gregorian RS Jr, Gasik A, Kwong WJ, Voeller S, Kavanagh S. Importance of side effects in opioid treatment: a trade-off analysis with patients and physicians. *J Pain*. 2010;11(11):1095-1108. doi:10.1016/j.jpain.2010.02.007

23. Kalso E, Edwards JE, Moore AR, McQuay HJ. Opioids in chronic non-cancer pain: systematic review of efficacy and safety. *Pain*. 2004;112(3):372-380. doi:10.1016/j.pain.2004.09.019

24. Manchikanti L, Ailinani H, Koyyalagunta D, et al. A systematic review of randomized trials of long-term opioid management for chronic non-cancer pain. *Pain Physician*. 2011;14(2):91-121. doi:10.36076/ppj.2011/14/91

25. Uribe AA, Stoicea N, Echeverria-Villalobos M, et al. Postoperative nausea and vomiting after craniotomy: an evidence-based review of general considerations, risk factors, and management. *J Neurosurg Anesthesiol*. 2019. doi:10.1097/ANA.0000000000000667

26. Jamison RN, Dorado K, Mei A, Edwards RR, Martel MO. Influence of opioid-related side effects on disability, mood, and opioid misuse risk among patients with chronic pain in primary care. *Pain Rep*. 2017;2(2):e589. doi:10.1097/PR9.0000000000000589

27. Buckeridge D, Huang A, Hanley J, et al. Risk of injury associated with opioid use in older adults. *J Am Geriatr Soc*. 2010;58(9):1664-1670. doi:10.1111/j.1532-5415.2010.03015.x

28. Rubenstein LZ. Falls in older people: epidemiology, risk factors and strategies for prevention. *Age Ageing*. 2006;35(suppl 2):ii37-ii41. doi:10.1093/ageing/afl084

29. Rubenstein LZ, Josephson KR. Falls and their prevention in elderly people: what does the evidence show? *Med Clin North Am*. 2006;90(5):807-824. doi:10.1016/j.mcna.2006.05.013

30. Coluzzi F, Pergolizzi J, Raffa RB, Mattia C. The unsolved case of "bone-impairing analgesics": the endocrine effects of opioids on bone metabolism. *Ther Clin Risk Manag*. 2015;11:515-523. doi:10.2147/TCRM.S79409

31. Hohl CM, Small SS, Peddie D, Badke K, Bailey C, Balka E. Why clinicians don't report adverse drug events: qualitative study. *JMIR Public Health Surveill*. 2018;4(1):e21. doi:10.2196/publichealth.9282

32. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain—United States, 2016. *JAMA*. 2016;315(15):1624-1645. doi:10.1001/jama.2016.1464

33. Dyer O. Canada's prescription opioid epidemic grows despite tamperproof pills. *BMJ*. 2015;351:h4725. doi:10.1136/bmj.h4725

34. Chou R, Gordon DB, de Leon-Casasola OA, et al. Management of Postoperative Pain: A Clinical Practice Guideline From the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. *J Pain*. 2016;17(2):131-157. doi:10.1016/j.jpain.2015.12.008

35. Hernán MABB, Brumback B, Robins JM. Marginal structural models to estimate the causal effect of zidovudine on the survival of HIV-positive men. *Epidemiology*. 2000;11(5):561-570. doi:10.1097/00001648-200009000-00012

36. Xiao Y, Abrahamowicz M, Moodie EE. Accuracy of conventional and marginal structural Cox model estimators: a simulation study. *Int J Biostat*. 2010;6(2):13. doi:10.2202/1557-4679.1208

37. Abrahamowicz M, Beauchamp ME, Sylvestre MP. Comparison of alternative models for linking drug exposure with adverse effects. *Stat Med*. 2012;31(11-12):1014-1030. doi:10.1002/sim.4343

38. Cole SR Sr, Hernán MA, Margolick JB, Cohen MH, Robins JM. Marginal structural models for estimating the effect of highly active antiretroviral therapy initiation on CD4 cell count. *Am J Epidemiol*. 2005;162(5):471-478. doi:10.1093/aje/kwi216

39. Cole SR, Hernán MA. Constructing inverse probability weights for marginal structural models. *Am J Epidemiol*. 2008;168(6):656-664. doi:10.1093/aje/kwn164

40. Xiao Y, Moodie EEM, Abrahamowicz M. Comparison of approaches to weight truncation for marginal structural Cox models. *Epidemiol Methods*. 2013;2(1):1-20.

41. Robins JM, Hernán MA, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology*. 2000;11(5):550-560. doi:10.1097/00001648-200009000-00011

42. Greenland S. Basic methods for sensitivity analysis of biases. *Int J Epidemiol*. 1996;25(6):1107-1116. doi:10.1093/ije/25.6.1107

43. Pilote L, Abrahamowicz M, Rodrigues E, Eisenberg MJ, Rahme E. Mortality rates in elderly patients who take different angiotensin-converting enzyme inhibitors after acute myocardial infarction: a class effect? *Ann Intern Med*. 2004;141(2):102-112. doi:10.7326/0003-4819-141-2-200407200-00008

44. Centers for Medicare & Medicaid Services. Opioid oral morphine milligram equivalent (MME) conversion factors. Accessed September 5, 2019. https://www.cms.gov/Medicare/Prescription-Drug-Coverage/PrescriptionDrugCovContra/Downloads/Oral-MME-CFs-vFeb-2018.pdf

45. Glare P, Aubrey KR, Myles PS. Transition from acute to chronic pain after surgery. *Lancet*. 2019;393(10180):1537-1546. doi:10.1016/S0140-6736(19)30352-6

46. Neuman MD, Bateman BT, Wunsch H. Inappropriate opioid prescription after surgery. *Lancet*. 2019;393(10180):1547-1557. doi:10.1016/S0140-6736(19)30428-3

47. Busse JW, Wang L, Kamaleldin M, et al. Opioids for chronic noncancer pain: a systematic review and meta-analysis. *JAMA*. 2018;320(23):2448-2460. doi:10.1001/jama.2018.18472

48. Miller NS, Greenfeld A. Patient characteristics and risks factors for development of dependence on hydrocodone and oxycodone. *Am J Ther*. 2004;11(1):26-32. doi:10.1097/00045391-200401000-00008

49. Thompson AR, Ray JB. The importance of opioid tolerance: a therapeutic paradox. *J Am Coll Surg*. 2003;196(2):321-324. doi:10.1016/S1072-7515(02)01800-8

50. Saunders KW, Dunn KM, Merrill JO, et al. Relationship of opioid use and dosage levels to fractures in older chronic pain patients. *J Gen Intern Med*. 2010;25(4):310-315. doi:10.1007/s11606-009-1218-z

51. Gomes T, Mamdani MM, Dhalla IA, Cornish S, Paterson JM, Juurlink DN. The burden of premature opioid-related mortality. *Addiction*. 2014;109(9):1482-1488. doi:10.1111/add.12598

52. Bohnert AS, Valenstein M, Bair MJ, et al. Association between opioid prescribing patterns and opioid overdose-related deaths. *JAMA*. 2011;305(13):1315-1321. doi:10.1001/jama.2011.370

53. Gomes T, Redelmeier DA, Juurlink DN, Dhalla IA, Camacho X, Mamdani MM. Opioid dose and risk of road trauma in Canada: a population-based study. *JAMA Intern Med*. 2013;173(3):196-201. doi:10.1001/2013.jamainternmed.733

54. Ishida JH, McCulloch CE, Steinman MA, Grimes BA, Johansen KL. Opioid analgesics and adverse outcomes among hemodialysis patients. *Clin J Am Soc Nephrol*. 2018;13(5):746-753. doi:10.2215/CJN.09910917

55. Dasgupta N, Kramer ED, Zalman MA, et al. Association between non-medical and prescriptive usage of opioids. *Drug Alcohol Depend*. 2006;82(2):135-142. doi:10.1016/j.drugalcdep.2005.08.019

56. Murphy DL, Lebin JA, Severtson SG, Olsen HA, Dasgupta N, Dart RC. Comparative rates of mortality and serious adverse effects among commonly prescribed opioid analgesics. *Drug Saf*. 2018;41(8):787-795. doi:10.1007/s40264-018-0660-4

57. Centers for Disease Control and Prevention, National Center for Health Statistics. Number and age-adjusted rates of drug-poisoning deaths involving opioid analgesics and heroin: United States, 2000–2014. National Vital Statistics System, Mortality File. Accessed March 20, 2020. https://www.cdc.gov/nchs/data/health_policy/AADR_drug_poisoning_involving_OA_Heroin_US_2000-2014. pdf

58. Volkow ND, McLellan TA, Cotto JH, Karithanom M, Weiss SR. Characteristics of opioid prescriptions in 2009. *JAMA*. 2011;305(13):1299-1301. doi:10.1001/jama.2011.401

59. Mosher HJ, Jiang L, Vaughan Sarrazin MS, Cram P, Kaboli PJ, Vander Weg MW. Prevalence and characteristics of hospitalized adults on chronic opioid therapy. *J Hosp Med*. 2014;9(2):82-87. doi:10.1002/jhm.2113

60. Miller M, Barber CW, Leatherman S, et al. Prescription opioid duration of action and the risk of unintentional overdose among patients receiving opioid therapy. *JAMA Intern Med*. 2015;175(4):608-615. doi:10.1001/jamainternmed.2014.8071

61. Coutinho AD, Gandhi K, Fuldeore RM, Landsman-Blumberg PB, Gandhi S. Long-term opioid users with chronic noncancer pain: assessment of opioid abuse risk and relationship with healthcare resource use. *J Opioid Manag*. 2018;14(2):131-141. doi:10.5055/jom.2018.0440

62. Chang HY, Kharrazi H, Bodycombe D, Weiner JP, Alexander GC. Healthcare costs and utilization associated with high-risk prescription opioid use: a retrospective cohort study. *BMC Med*. 2018;16(1):69. doi:10.1186/s12916-018-1058-y

63. Tamblyn R, Abrahamowicz M, du Berger R, McLeod P, Bartlett G. A 5-year prospective assessment of the risk associated with individual benzodiazepines and doses in new elderly users. *J Am Geriatr Soc*. 2005;53(2):233-241. doi:10.1111/j.1532-5415.2005.53108.x

64. Fuller C. *The Association Between Non-Concordance with the Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain and Opioid Overdose Death in Quebec*. Thesis. McGill University; 2015. Accessed November 10, 2020. https://escholarship.mcgill.ca/concern/theses/j6731696b

SUPPLEMENT.

eTable 1. ICD-9-CM and ICD-10-CM Codes for Opioid Abuse
eTable 2. ICD-9-CM Codes for Opioid Dependence
eTable 3. ICD-9-CM Codes for Adverse Effects of Opioids
eTable 4. ICD-9-CM Codes for Opioid Poisoning
eTable 5. ICD-9-CM Codes for Other Most Commonly Occurring Adverse Events Associated With Opioid Use
eMethods 1. ATC Codes Used to Identify Opioids: N02A (Opioids), R05DA (Opium Alkaloids and Derivatives)
eMethods 2. Daily Dose Calculation
eTable 6. Opioid Morphine Equivalent Conversion Factor
eTable 7. Description of Available Data on Drug, Patient, Provider and System Level Characteristics
eFigure 1. Operational Definitions of Opioid Use Duration
eMethods 3. Operational Definitions of Opioid Use Durations
eTable 8. Overall Characteristics of the Opioid Prescriptions Dispensed by Patients According to Opioid Type and Potency
eTable 9. Sensitivity Analyses Excluding Patients With More Than Three Opioids Dispensations in the One Year Before Initial Hospital Admission (Final Cohort N=1468)
eTable 10. Sensitivity Analyses Excluding Patients With an Opioids Dispensation in the One Year Before Initial Hospital Admission (Final Cohort N = 884)

References

1. Fischer B, Gooch J, Goldman B, Kurdyak P, Rehm J. Non-medical prescription opioid use, prescription opioid-related harms and public health in Canada: an update 5 years later. *Canadian journal of public health = Revue canadienne de sante publique.* 2014;105(2):e146-149.
2. Gomes T MM, Dhalla IA, Cornish S, et al. The burden of premature opioid-related mortality. Addiction 2014; 109: 1482-8.
3. Canadian Institute for Health Information. Pan-Canadian trends in the prescribing of opioids, 2012 to 2016. . *Ottawa, ON: CIHI.* 2017.
4. International Narcotics Control Board. Narcotic drugs: estimated world requirements for 2004, statistics for 2002. New York: United Nations; 2004.
5. International Narcotics Control Board. Availability of internationally controlled drugs: ensuring adequate access for medical and scientific purposes. New York: United Nations; 2016.
6. Portenoy RK, Ahmed E. Principles of opioid use in cancer pain. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2014;32(16):1662-1670.
7. Volkow ND FT, Hyde PS, Cha SS. Medication-assisted therapies – tackling the opioid-overdose epidemic. N Engl J Med 2014; 370: 2063-6.
8. Dhalla IA PN, Juurlink DN. Facing up to the prescription opioid crisis. BMJ 2011; 343: d5142.
9. Center for Disease Control and Prevention NCfHS, National Vital Statistics System, Mortality File. Number and Age-Adjusted Rates of Drug-poisoning Deaths Involving Opioid Analgesics and Heroin: United States, 2000–2014. Atlanta: Center for Disease Control and Prevention; 2015. Available at https://www.cdc.gov/nchs/data/health_policy/AADR_drug_poisoning_involving_OA_Heroin_US_2000-2014. pdf.
10. Gomes Tara T. Contributions of prescribed and non-prescribed opioids to opioid related deaths: population based cohort study in Ontario, Canada. *BMJ, The.*362.
11. British Columbia Coroners Service. Fentanyl-Detected Illicit Drug Overdose Deaths January 1, 2012 to December 31, 2017.Office of the Chief Coroner, 2018.
12. Allen MJ, Asbridge MM, Macdougall PC, Furlan AD, Tugalev O. Self-reported practices in opioid management of chronic non-cancer pain: a survey of Canadian family physicians. *Pain research & management.* 2013;18(4):177-184.
13. Boudreau Denise D. Trends in long-term opioid therapy for chronic non-cancer pain. *Pharmacoepidemiology and drug safety.*18(12):1166-1175.
14. Depelteau A, Racine-Hemmings F, Lagueux E, Hudon C. Chronic pain and frequent use of emergency department: A systematic review. *The American journal of emergency medicine.* 2019.
15. Habib AS KM, Cooter M, Greenup RA, Hwang S. Risk factors for severe acute pain and persistent pain after surgery for breast cancer: a prospective observational study. Regional anesthesia and pain medicine. 2019;44(2):192-199.
16. Buvanendran A DVC, Kroin JS, et al. Acute postoperative pain is an independent predictor of chronic postsurgical pain following total knee arthroplasty at 6 months: a prospective cohort study. Regional anesthesia and pain medicine. 2019.

17. Busse JW, Craigie S, Juurlink DN, et al. Guideline for opioid therapy and chronic non-cancer pain. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne.* 2017;189(18):E659-e666.
18. Els C, Jackson TD, Kunyk D, et al. Adverse events associated with medium- and long-term use of opioids for chronic non-cancer pain: an overview of Cochrane Reviews. *The Cochrane database of systematic reviews.* 2017;10:Cd012509.
19. Deyo RA, Hallvik SE, Hildebran C, et al. Association Between Initial Opioid Prescribing Patterns and Subsequent Long-Term Use Among Opioid-Naïve Patients: A Statewide Retrospective Cohort Study. *J Gen Intern Med.* 2017;32(1):21-27.
20. Shah A, Hayes CJ, Martin BC. Factors Influencing Long-Term Opioid Use Among Opioid Naive Patients: An Examination of Initial Prescription Characteristics and Pain Etiologies. *The journal of pain : official journal of the American Pain Society.* 2017;18(11):1374-1383.
21. Hadlandsmyth K, Lund BC, Mosher HJ. Associations between initial opioid exposure and the likelihood for long-term use. *Journal of the American Pharmacists Association : JAPhA.* 2019;59(1):17-22.
22. Fernandes K, Martins D, Juurlink D, et al. High-Dose Opioid Prescribing and Opioid-Related Hospitalization: A Population-Based Study. *PloS one.* 2016;11(12):e0167479.
23. Pasricha SV, Tadrous M, Khuu W, et al. Clinical indications associated with opioid initiation for pain management in Ontario, Canada: a population-based cohort study. *Pain.* 2018;159(8):1562-1568.
24. Liu Y, Logan JE, Paulozzi LJ, Zhang K, Jones CM. Potential misuse and inappropriate prescription practices involving opioid analgesics. *The American journal of managed care.* 2013;19(8):648-658.
25. Gomes T, Mamdani MM, Dhalla IA, Paterson JM, Juurlink DN. Opioid dose and drug-related mortality in patients with nonmalignant pain. *Archives of internal medicine.* 2011;171(7):686-691.
26. Dunn KM, Saunders KW, Rutter CM, et al. Opioid prescriptions for chronic pain and overdose: a cohort study. *Annals of internal medicine.* 2010;152(2):85-92.
27. Gomes T, Juurlink DN. Opioid Use and Overdose: What We've Learned in Ontario. *Healthcare quarterly (Toronto, Ont).* 2016;18(4):8-11.
28. Fielden JM, Scott S, Horne JG. An investigation of patient satisfaction following discharge after total hip replacement surgery. *Orthopedic nursing.* 2003;22(6):429-436.
29. Coleman EA, Parry C, Chalmers S, Min S. The care transitions intervention: Results of a randomized controlled trial. *Archives of internal medicine.* 2006;166(17):1822-1828.
30. Canadian Institute for Health Information. . *National Health Expenditure Trends, 1975 to 2019 2019.*
31. Fischer B GJ, Goldman B, et al. Non-medical prescription opioid use, prescription opioid-related harms and public health in Canada: an update 5 years later. Can J Public Health 2014; 105: el146-9.
32. Mann C. Reducing nonurgent use of emergency departments and improving appropriate care in appropriate settings. Baltimore (MD): Department of Health and Human Services, Centers for Medicare and Medicaid Services; 2014.
33. Coben JH, Davis SM, Furbee PM, Sikora RD, Tillotson RD, Bossarte RM. Hospitalizations for poisoning by prescription opioids, sedatives, and tranquilizers. *American journal of preventive medicine.* 2010;38(5):517-524.

34. Canadian Institute for Health Information, Canadian Centre on Substance Abuse. Hospitalizations and Emergency Department Visits Due to Opioid Poisoning in Canada. Ottawa, ON: CIHI; 2016.
35. Tremblay Éric D, Jean-Marc. Portrait de l'usage des opioïdes chez les personnes couvertes par le régime public d'assurance médicaments du Québec. *Institut national d'excellence en santé et en services sociaux (INESSS), Québec.* 2018:79.
36. Ishida JH, McCulloch CE, Steinman MA, Grimes BA, Johansen KL. Opioid Analgesics and Adverse Outcomes among Hemodialysis Patients. *Clinical journal of the American Society of Nephrology : CJASN.* 2018;13(5):746-753.
37. Chou R, Deyo R, Devine B, et al. The Effectiveness and Risks of Long-Term Opioid Treatment of Chronic Pain. *Evidence report/technology assessment.* 2014(218):1-219.
38. Vowles KE, McEntee ML, Julnes PS, Frohe T, Ney JP, van der Goes DN. Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis. *Pain.* 2015;156(4):569-576.
39. Saunders KW, Dunn KM, Merrill JO, et al. Relationship of opioid use and dosage levels to fractures in older chronic pain patients. *J Gen Intern Med.* 2010;25(4):310-315.
40. Miller Matthew M. Opioid analgesics and the risk of fractures in older adults with arthritis. *Journal of the American Geriatrics Society.*59(3):430-438.
41. Miller M, Barber CW, Leatherman S, et al. Prescription Opioid Duration of Action and the Risk of Unintentional Overdose Among Patients Receiving Opioid Therapy. *JAMA Internal Medicine.* 2015;175(4):608-615.
42. Bonhert AS VM, et al. Association between opioid prescribing and opioid overdose-related deaths. JAMA.2011; 305: 1315-1321.
43. Gomes T, Khuu W, Craiovan D, et al. Comparing the contribution of prescribed opioids to opioid-related hospitalizations across Canada: A multi-jurisdictional cross-sectional study. *Drug and alcohol dependence.* 2018;191:86-90.
44. Chou R, Gordon DB, de Leon-Casasola OA, et al. Management of Postoperative Pain: A Clinical Practice Guideline From the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. *The journal of pain : official journal of the American Pain Society.* 2016;17(2):131-157.
45. Jena AB, Goldman D, Weaver L, Karaca-Mandic P. Opioid prescribing by multiple providers in Medicare: retrospective observational study of insurance claims. *BMJ (Clinical research ed).* 2014;348:g1393.
46. Dyer. Canada's prescription opioid epidemic grows despite tamper proof pills. 2015.
47. Gomes T, Redelmeier DA, Juurlink DN, Dhalla IA, Camacho X, Mamdani MM. Opioid dose and risk of road trauma in Canada: a population-based study. *JAMA Intern Med.* 2013;173(3):196-201.
48. Els C, Jackson TD, Kunyk D, et al. Adverse events associated with medium- and long-term use of opioids for chronic non-cancer pain: an overview of Cochrane Reviews. *Cochrane Database of Systematic Reviews.* 2017(10).
49. Busse JW, Wang L, Kamaleldin M, et al. Opioids for Chronic Non-cancer Pain: A Systematic Review and Meta-analysis. *Jama.* 2018;320(23):2448-2460.
50. Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain--United States, 2016. *Jama.* 2016;315(15):1624-1645.

51. Brummett CM WJ, Goesling J, Moser S, Lin P, Englesbe MJ, Bohnert ASB, Kheterpal S, Nallamothu BK. New Persistent Opioid Use After Minor and Major Surgical Procedures in US Adults. JAMA Surg.2017;152(6):e170504.
52. Calcaterra SL YT, Min SJ, Keniston A, Frank JW, Binswanger IA. Opioid Prescribing at Hospital Discharge Contributes to Chronic Opioid Use. J Gen Intern Med. 2016;31(5):478-485.
53. Karmali RN, Bush C, Raman SR, Campbell CI, Skinner AC, Roberts AW. Long-term opioid therapy definitions and predictors: A systematic review. *Pharmacoepidemiology and drug safety.* 2020;29(3):252-269.
54. Beaton A, O'Leary K, Thorburn J, Campbell A, Christey G. Improving patient experience and outcomes following serious injury. *The New Zealand medical journal.* 2019;132(1494):15-25.
55. Naylor MD, Kurtzman ET, Pauly MV. Transitions of elders between long-term care and hospitals. *Policy, politics & nursing practice.* 2009;10(3):187-194.
56. Yemm R, Bhattacharya D, Wright D, Poland F. What constitutes a high quality discharge summary? A comparison between the views of secondary and primary care doctors. *International journal of medical education.* 2014;5:125-131.
57. Newnham H, Barker A, Ritchie E, Hitchcock K, Gibbs H, Holton S. Discharge communication practices and healthcare provider and patient preferences, satisfaction and comprehension: A systematic review. *International Journal for Quality in Health Care.* 2017;29(6):752-768.
58. Ozavci G, Bucknall T, Woodward-Kron R, et al. A systematic review of older patients' experiences and perceptions of communication about managing medication across transitions of care. *Research in social & administrative pharmacy : RSAP.* 2020.
59. Tamblyn R HA, Meguerditchian A, et al. Using Novel Canadian Resources to Improve Medication Reconciliation at Discharge: Study Protocol For a Randomized Controlled Trial. Trials 2012; 13:150.
60. Fregoso G, Wang A, Tseng K, Wang J. Transition from Acute to Chronic Pain: Evaluating Risk for Chronic Postsurgical Pain. *Pain physician.* 2019;22(5):479-488.
61. Glare P, Aubrey KR, Myles PS. Transition from acute to chronic pain after surgery. *Lancet (London, England).* 2019;393(10180):1537-1546.
62. Brummett CM, Waljee JF, Goesling J, et al. New Persistent Opioid Use After Minor and Major Surgical Procedures in US Adults. *JAMA surgery.* 2017:e170504.
63. Calcaterra SL, Yamashita TE, Min SJ, Keniston A, Frank JW, Binswanger IA. Opioid Prescribing at Hospital Discharge Contributes to Chronic Opioid Use. *Journal of general internal medicine.* 2016;31(5):478-485.
64. Clarke H, Soneji N, Ko DT, Yun L, Wijeysundera DN. Rates and risk factors for prolonged opioid use after major surgery: population based cohort study. *BMJ (Clinical research ed).* 2014;348:g1251.
65. Habib AS, Kertai MD, Cooter M, Greenup RA, Hwang S. Risk factors for severe acute pain and persistent pain after surgery for breast cancer: a prospective observational study. *Regional anesthesia and pain medicine.* 2019;44(2):192-199.
66. Johnson SP, Chung KC, Zhong L, et al. Risk of Prolonged Opioid Use Among Opioid-Naive Patients Following Common Hand Surgery Procedures. *The Journal of hand surgery.* 2016.

67. Mosher HJ, Hofmeyer BA, Hadlandsmyth K, Richardson KK, Lund BC. Predictors of Long-Term Opioid Use After Opioid Initiation at Discharge From Medical and Surgical Hospitalizations. *Journal of hospital medicine.* 2018;13(4):243-248.
68. Sun EC, Darnall BD, Baker LC, Mackey S. Incidence of and Risk Factors for Chronic Opioid Use Among Opioid-Naive Patients in the Postoperative Period. *JAMA Intern Med.* 2016;176(9):1286-1293.
69. Thornton JD, Dwibedi N, Scott V, et al. Predictors of Transitioning to Incident Chronic Opioid Therapy Among Working-Age Adults in the United States. *American health & drug benefits.* 2018;11(1):12-21.
70. Ray GT, Bahorik AL, VanVeldhuisen PC, Weisner CM, Rubinstein AL, Campbell CI. Prescription opioid registry protocol in an integrated health system. *The American journal of managed care.* 2017;23(5):e146-e155.
71. Alghnam S, Castillo R. Traumatic injuries and persistent opioid use in the USA: findings from a nationally representative survey. *Injury prevention : journal of the International Society for Child and Adolescent Injury Prevention.* 2017;23(2):87-92.
72. Fritz JM, King JB, McAdams-Marx C. Associations Between Early Care Decisions and the Risk for Long-term Opioid Use for Patients With Low Back Pain With a New Physician Consultation and Initiation of Opioid Therapy. *The Clinical journal of pain.* 2018;34(6):552-558.
73. Sun EC, Dixit A, Humphreys K, Darnall BD, Baker LC, Mackey S. Association between concurrent use of prescription opioids and benzodiazepines and overdose: retrospective analysis. *BMJ (Clinical research ed).* 2017;356:j760.
74. Dunn LK, Yerra S, Fang S, et al. Incidence and Risk Factors for Chronic Postoperative Opioid Use After Major Spine Surgery: A Cross-Sectional Study With Longitudinal Outcome. *Anesth Analg.* 2018;127(1):247-254.
75. Jones JD, Mogali S, Comer SD. Polydrug abuse: a review of opioid and benzodiazepine combination use. *Drug and alcohol dependence.* 2012;125(1-2):8-18.
76. Park TW, Saitz R, Ganoczy D, Ilgen MA, Bohnert AS. Benzodiazepine prescribing patterns and deaths from drug overdose among US veterans receiving opioid analgesics: case-cohort study. *BMJ (Clinical research ed).* 2015;350:h2698.
77. Gomes T, Murray R, Kolla G, Leece P, Bansal S, Besharah J, Cahill T, Campbell T, Fritz A, Munro C, Toner L, Watford J on behalf of the Ontario Drug Policy Research Network, O ce of the Chief Coroner for Ontario and Ontario Agency for Health Protection and Promotion (Public Health Ontario). Changing circumstances surrounding opioid-related deaths in Ontario during the COVID-19 pandemic. Toronto, ON: Ontario Drug Policy Research Network; 2021.
78. Manias E, Williams A, Liew D, Rixon S, Braaf S, Finch S. Effects of patient-, environment- and medication-related factors on high-alert medication incidents. *International journal for quality in health care : journal of the International Society for Quality in Health Care.* 2014;26(3):308-320.
79. Institute For Safe Medication Practices. *ISMP List of High-Alert Medications in Community/Ambulatory Healthcare* https://wwwismporg/sites/default/files/attachments/2017-11/highAlert-communitypdf. Accessed 12 May, 2020.

80. Chen EY, Marcantonio A, Tornetta P, 3rd. Correlation Between 24-Hour Predischarge Opioid Use and Amount of Opioids Prescribed at Hospital Discharge. *JAMA surgery.* 2018;153(2):e174859.
81. Brat GA, Agniel D, Beam A, et al. Postsurgical prescriptions for opioid naive patients and association with overdose and misuse: retrospective cohort study. *BMJ (Clinical research ed).* 2018;360:j5790.
82. Pizzi LT, Toner R, Foley K, et al. Relationship between potential opioid-related adverse effects and hospital length of stay in patients receiving opioids after orthopedic surgery. *Pharmacotherapy.* 2012;32(6):502-514.
83. Chaudhary MA, Schoenfeld AJ, Harlow AF, et al. Incidence and Predictors of Opioid Prescription at Discharge After Traumatic Injury. *JAMA surgery.* 2017;152(10):930-936.
84. Chaudhary MA, Scully R, Chowdhury R, et al. Patterns of Use and Factors Associated with Early Discontinuation of Opiates after Major Trauma. *Journal of the American College of Surgeons.* 2016;223(4, Supplement 1):S114-S115.
85. Luo X, Pietrobon R, Hey L. Patterns and trends in opioid use among individuals with back pain in the United States. *Spine.* 2004;29(8):884-890; discussion 891.
86. Silva M, Rosa MB, Franklin BD, Reis AM, Anchieta LM, Mota JA. Concomitant prescribing and dispensing errors at a Brazilian hospital: a descriptive study. *Clinics (Sao Paulo, Brazil).* 2011;66(10):1691-1697.
87. 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.
88. Kwan JL, Lo L, Sampson M, Shojania KG. Medication reconciliation during transitions of care as a patient safety strategy: a systematic review. *Annals of internal medicine.* 2013;158(5 Pt 2):397-403.
89. Picone DM, Titler MG, Dochterman J, et al. Predictors of medication errors among elderly hospitalized patients. *American journal of medical quality : the official journal of the American College of Medical Quality.* 2008;23(2):115-127.
90. Hias J, Van der Linden L, Spriet I, et al. Predictors for unintentional medication reconciliation discrepancies in preadmission medication: a systematic review. *European journal of clinical pharmacology.* 2017;73(11):1355-1377.
91. Lee KP, Nishimura K, Ngu B, Tieu L, Auerbach AD. Predictors of completeness of patients' self-reported personal medication lists and discrepancies with clinic medication lists. *The Annals of pharmacotherapy.* 2014;48(2):168-177.
92. Mekonnen AB, Abebe TB, McLachlan AJ, Brien JA. Impact of electronic medication reconciliation interventions on medication discrepancies at hospital transitions: a systematic review and meta-analysis. *BMC medical informatics and decision making.* 2016;16(1):112.
93. Salanitro AH, Osborn CY, Schnipper JL, et al. Effect of patient- and medication-related factors on inpatient medication reconciliation errors. *J Gen Intern Med.* 2012;27(8):924-932.
94. Ranapurwala SI, Naumann RB, Austin AE, Dasgupta N, Marshall SW. Methodologic limitations of prescription opioid safety research and recommendations for improving the evidence base. *Pharmacoepidemiology and drug safety.* 2019;28(1):4-12.
95. Edlund MJ, Martin BC, Russo JE, DeVries A, Braden JB, Sullivan MD. The role of opioid prescription in incident opioid abuse and dependence among individuals with

chronic non-cancer pain: the role of opioid prescription. *The Clinical journal of pain.* 2014;30(7):557-564.
96. Paulozzi LJ, Zhang K, Jones CM, Mack KA. Risk of adverse health outcomes with increasing duration and regularity of opioid therapy. *Journal of the American Board of Family Medicine : JABFM.* 2014;27(3):329-338.
97. Ishida Julie HJ. Opioid Analgesics and Adverse Outcomes among Hemodialysis Patients. *Clinical Journal of the American Society of Nephrology.* 2018;13(5):746-753.
98. Miller Matthew M. Prescription opioid duration of action and the risk of unintentional overdose among patients receiving opioid therapy. *JAMA Internal Medicine.*175(4):608-615.
99. Liberman JS, Samuels LR, Goggins K, Kripalani S, Roumie CL. Opioid Prescriptions at Hospital Discharge Are Associated With More Postdischarge Healthcare Utilization. *Journal of the American Heart Association.* 2019;8(3):e010664.
100. Schlosser MJ, Korwek KM, Dunn R, Poland RE. Reduced post-operative opioid use decreases length of stay and readmission rates in patients undergoing hip and knee joint arthroplasty. *Journal of orthopaedics.* 2020;21:88-93.
101. Miller JA, Derakhshan A, Lubelski D, et al. The impact of preoperative depression on quality of life outcomes after lumbar surgery. *The spine journal : official journal of the North American Spine Society.* 2015;15(1):58-64.
102. Desai K, Carroll I, Asch SM, et al. Utilization and effectiveness of multimodal discharge analgesia for postoperative pain management. *The Journal of surgical research.* 2018;228:160-169.
103. Gomes T, Juurlink D, Moineddin R, et al. Geographical variation in opioid prescribing and opioid-related mortality in Ontario. *Healthcare quarterly (Toronto, Ont).* 2011;14(1):22-24.
104. Franklin GM, Rahman EA, Turner JA, Daniell WE, Fulton-Kehoe D. Opioid use for chronic low back pain: A prospective, population-based study among injured workers in Washington state, 2002-2005. *The Clinical journal of pain.* 2009;25(9):743-751.
105. Thornton JDJD. Predictors of Transitioning to Incident Chronic Opioid Therapy Among Working-Age Adults in the United States. *American Health Drug Benefits.*11(1):12-21.
106. Shah A, Hayes CJ, Martin BC. Characteristics of Initial Prescription Episodes and Likelihood of Long-Term Opioid Use - United States, 2006-2015. *MMWR Morbidity and mortality weekly report.* 2017;66(10):265-269.
107. Deyo RA, Hallvik SE, Hildebran C, et al. Association Between Initial Opioid Prescribing Patterns and Subsequent Long-Term Use Among Opioid-Naive Patients: A Statewide Retrospective Cohort Study. *J Gen Intern Med.* 2017;32(1):21-27.
108. Tamblyn R, Abrahamowicz M, Buckeridge DL, et al. Effect of an Electronic Medication Reconciliation Intervention on Adverse Drug Events: A Cluster Randomized Trial. *JAMA Netw Open.* 2019;2(9):e1910756.
109. Leape LL, Bates DW, Cullen DJ, et al. Systems analysis of adverse drug events. ADE Prevention Study Group. *Jama.* 1995;274(1):35-43.
110. Nebeker JR, Barach P, Samore MH. Clarifying adverse drug events: a clinician's guide to terminology, documentation, and reporting. *Annals of internal medicine.* 2004;140(10):795-801.

111. Trends in the Rate of Opioid-Related Hospitalizations. Content last reviewed May 2019. Agency for Healthcare Research and Quality R, MD., https://www.ahrq.gov/opioids/map/index.html.
112. Kersten H, Hvidsten LT, Gloersen G, Wyller TB, Wang-Hansen MS. Clinical impact of potentially inappropriate medications during hospitalization of acutely ill older patients with multimorbidity. *Scandinavian journal of primary health care.* 2015;33(4):243-251.
113. Forster AJ MH, Peterson JF, Gandhi TK, Bates DW. Adverse Drug Events Occurring Following Hospital Discharge. Journal of general internal medicine. 2005;20(4):317-323.
114. Boockvar K FE, Kyriacou C, 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. Archives of internal medicine. 2004;164(5):545-550.
115. Mekonnen AB, Abebe TB, McLachlan AJ, Brien JA. Impact of electronic medication reconciliation interventions on medication discrepancies at hospital transitions: a systematic review and meta-analysis. *BMC medical informatics and decision making.* 2016;16:112.
116. Redmond P, Grimes TC, McDonnell R, Boland F, Hughes C, Fahey T. Impact of medication reconciliation for improving transitions of care. *The Cochrane database of systematic reviews.* 2018;8:Cd010791.
117. Seidling HM, Faller CK, Thalheimer M, Bruckner T, Haefeli WE. [Formal prescribing errors are substantially reduced in electronic prescribing and after teaching sessions]. *Deutsche medizinische Wochenschrift (1946).* 2016;141(1):e1-7.
118. Abdellatif A BJ, Barajas ER, et al. Assuring Medication Accuracy at Transitions in Care. Joint Commission Journal on Quality and Patient Safety. 2007;33(7):450-453.
119. How-to Guide: Prevent Adverse Drug Events by Implementing Medication Reconciliation. Cambridge MIfHI.
120. Heneka Nicole N. Quantifying the burden of opioid medication errors in adult oncology and palliative care settings: A systematic review. *Palliative Medicine: The Research Journal of the EAPC - A Multiprofessional Journal.* 2016;30(6):520-532.
121. Heneka N, Shaw T, Rowett D, Phillips JL. Quantifying the burden of opioid medication errors in adult oncology and palliative care settings: A systematic review. *Palliative medicine.* 2016;30(6):520-532.
122. Memtsoudis SG, Poeran J, Zubizarreta N, et al. Association of Multimodal Pain Management Strategies with Perioperative Outcomes and Resource Utilization: A Population-based Study. *Anesthesiology.* 2018;128(5):891-902.
123. ATC/DDD Index 2018. 2018; https://www.whocc.no/atc_ddd_index/. Accessed August 6, 2018.
124. Tamblyn R, Poissant L, Huang A, et al. Estimating the information gap between emergency department records of community medication compared to on-line access to the community-based pharmacy records. *Journal of the American Medical Informatics Association : JAMIA.* 2014;21(3):391-398.
125. Zeger SL, Liang KY, Albert PS. Models for longitudinal data: a generalized estimating equation approach. *Biometrics.* 1988;44(4):1049-1060.
126. Neuman MD, Bateman BT, Wunsch H. Inappropriate opioid prescription after surgery. *Lancet (London, England).* 2019;393(10180):1547-1557.

127. Hill MV, McMahon ML, Stucke RS, Barth RJ, Jr. Wide Variation and Excessive Dosage of Opioid Prescriptions for Common General Surgical Procedures. *Annals of surgery.* 2017;265(4):709-714.
128. Lindenhovius AL, Helmerhorst GT, Schnellen AC, Vrahas M, Ring D, Kloen P. Differences in prescription of narcotic pain medication after operative treatment of hip and ankle fractures in the United States and The Netherlands. *The Journal of trauma.* 2009;67(1):160-164.
129. Morden NE, Munson JC, Colla CH, et al. Prescription opioid use among disabled Medicare beneficiaries: intensity, trends, and regional variation. *Medical care.* 2014;52(9):852-859.
130. Volkow ND, McLellan TA. Curtailing diversion and abuse of opioid analgesics without jeopardizing pain treatment. *Jama.* 2011;305(13):1346-1347.
131. Inciardi JA, Surratt HL, Kurtz SP, Cicero TJ. Mechanisms of prescription drug diversion among drug-involved club- and street-based populations. *Pain medicine (Malden, Mass).* 2007;8(2):171-183.
132. Bruehl S, Apkarian AV, Ballantyne JC, et al. Personalized medicine and opioid analgesic prescribing for chronic pain: opportunities and challenges. *The journal of pain : official journal of the American Pain Society.* 2013;14(2):103-113.
133. Saunders KW, Shortreed S, Thielke S, et al. Evaluation of Health Plan Interventions to Influence Chronic Opioid Therapy Prescribing. *The Clinical journal of pain.* 2015;31(9):820-829.
134. Finnell JT, Twillman RK, Breslan SA, Schultz J, Miller L. The Role of Continuing Medical Education in Increasing Enrollment in Prescription Drug Monitoring Programs. *Clinical therapeutics.* 2017;39(9):1896-1902.e1892.
135. Liu S, Gnjidic D, Nguyen J, Penm J. Effectiveness of interventions on the appropriate use of opioids for non-cancer pain among hospital inpatients: A systematic review. *British journal of clinical pharmacology.* 2020;86(2):210-243.
136. Kenawy AS, Kett V. The impact of electronic prescription on reducing medication errors in an Egyptian outpatient clinic. *International journal of medical informatics.* 2019;127:80-87.
137. Mohan P, Sharma AK, Panwar SS. Identification and quantification of prescription errors. *Medical Journal Armed Forces India.* 2014;70(2):149-153.
138. Hitti E, Tamim H, Bakhti R, Zebian D, Mufarrij A. Impact of Internally Developed Electronic Prescription on Prescribing Errors at Discharge from the Emergency Department. *The western journal of emergency medicine.* 2017;18(5):943-950.
139. Bicket MC, Kattail D, Yaster M, Wu CL, Pronovost P. An analysis of errors, discrepancies, and variation in opioid prescriptions for adult outpatients at a teaching hospital. *Journal of opioid management.* 2017;13(1):51-57.
140. Singer A, Duarte Fernandez R. The effect of electronic medical record system use on communication between pharmacists and prescribers. *BMC family practice.* 2015;16:155.
141. Campbell CI, Weisner C, Leresche L, et al. Age and gender trends in long-term opioid analgesic use for non-cancer pain. *American journal of public health.* 2010;100(12):2541-2547.
142. Kurteva S AM, Beauchamp ME, Tamblyn R. Flexible modeling of opioid exposure provides new insights in its association with adverse outcomes. *[Prepared for journal submission]*.

143. Herzig SJ, Calcaterra SL, Mosher HJ, et al. Safe Opioid Prescribing for Acute Non-cancer Pain in Hospitalized Adults: A Systematic Review of Existing Guidelines. *Journal of hospital medicine.* 2018;13(4):256-262.
144. Khalid L, Liebschutz JM, Xuan Z, et al. Adherence to prescription opioid monitoring guidelines among residents and attending physicians in the primary care setting. *Pain medicine (Malden, Mass).* 2015;16(3):480-487.
145. Kahl LK, Stevens MW, Gielen AC, McDonald EM, Ryan L. Characteristics of opioid prescriptions for discharged pediatric emergency department patients with acute injuries. *Journal of investigative medicine : the official publication of the American Federation for Clinical Research.* 2019;67(6):1024-1027.
146. Borgundvaag B, McLeod S, Khuu W, Varner C, Tadrous M, Gomes T. Opioid prescribing and adverse events in opioid-naive patients treated by emergency physicians versus family physicians: a population-based cohort study. *CMAJ open.* 2018;6(1):E110-e117.
147. Deepmala D, Franz L, Aponte C, Agrawal M, Jiang W. Identification of provider characteristics influencing prescription of analgesics: a systematic literature review. *Pain practice : the official journal of World Institute of Pain.* 2013;13(6):504-513.
148. Dhalla IA, Mamdani MM, Gomes T, Juurlink DN. Clustering of opioid prescribing and opioid-related mortality among family physicians in Ontario. *Canadian family physician Medecin de famille canadien.* 2011;57(3):e92-96.
149. Ringwalt C, Gugelmann H, Garrettson M, et al. Differential prescribing of opioid analgesics according to physician specialty for Medicaid patients with chronic non-cancer pain diagnoses. *Pain research & management.* 2014;19(4):179-185.
150. Kragh Andersen P, Pohar Perme M, van Houwelingen HC, et al. Analysis of time-to-event for observational studies: Guidance to the use of intensity models. *Statistics in medicine.* 2021;40(1):185-211.
151. Abrahamowicz M, MacKenzie TA. Joint estimation of time-dependent and non-linear effects of continuous covariates on survival. *Statistics in medicine.* 2007;26(2):392-408.
152. Sylvestre MP, Beauchamp ME, Kyle R, Abrahamowicz M. (2018). WCE: Weighted Cumulative Exposure Models. R package, version 1.0.2. https://cran.r-project.org/package=WCE.
153. Frank R. Targeting the opioid drug crisis: a Health and Human Services initiative. Health Affairs Blog. April 3, 2015 (http://healthaffairs.org/blog/2015/04/03/targeting-the-opioid-drug-crisis-a-health-and-human-services-initiative).
154. Department of Health and Human Services Behavioral Health Coordinating Committee. Addressing prescription drug abuse in the United States: current activities and future opportunities. 2014 (https://www.cdc.gov/drugoverdose/pdf/hhs_prescription_drug_abuse_report_09.2013.pdf.).
155. Colburn JL, Jasinski DR, Rastegar DA. Long-term opioid therapy, aberrant behaviors, and substance misuse: comparison of patients treated by resident and attending physicians in a general medical clinic. *J Opioid Manag.* 2012;8(3):153-160.
156. Miller M, Barber CW, Leatherman S, et al. Prescription opioid duration of action and the risk of unintentional overdose among patients receiving opioid therapy. *JAMA Intern Med.* 2015;175(4):608-615.

157. HEDIS. NCQA Updates Quality Measures for HEDIS® 2019. https://wwwncqaorg/news/ncqa-updates-quality-measures-forhedis-2019. Accessed November 25, 2020.
158. Centers for Disease Control and Prevention. Quality Improvement and Care Coordination: Implementing the CDC Guideline for Prescribing Opioids for Chronic Pain. 2018. National Center for Injury Prevention and Control.
159. Von Korff MR. Long-term use of opioids for complex chronic pain. *Best practice & research Clinical rheumatology.* 2013;27(5):663-672.
160. Goesling J, Moser SE, Zaidi B, et al. Trends and predictors of opioid use after total knee and total hip arthroplasty. *Pain.* 2016;157(6):1259-1265.
161. Rosenbloom BN, McCartney CJL, Canzian S, Kreder HJ, Katz J. Predictors of Prescription Opioid Use 4 Months After Traumatic Musculoskeletal Injury and Corrective Surgery: A Prospective Study. *The journal of pain : official journal of the American Pain Society.* 2017.
162. Anciano Granadillo V, Cancienne JM, Gwathmey FW, Werner BC. Perioperative Opioid Analgesics and Hip Arthroscopy: Trends, Risk Factors for Prolonged Use, and Complications. *Arthroscopy : the journal of arthroscopic & related surgery : official publication of the Arthroscopy Association of North America and the International Arthroscopy Association.* 2018;34(8):2359-2367.
163. Pugely AJ, Bedard NA, Kalakoti P, et al. Opioid use following cervical spine surgery: trends and factors associated with long-term use. *The spine journal : official journal of the North American Spine Society.* 2018;18(11):1974-1981.
164. Fuller C. The association between non-concordance with the Canadian Guideline for Safe and Effective Use of Opioids in Chronic Non-Cancer Pain and opioid overdose death in Quebec. *McGill University* 2014;Montreal, Quebec, Canada.
165. Tauchi R, Kawakami N, Tsuji T, et al. Evaluation of thoracic factors after scoliosis surgery in patients with both scoliosis and pectus excavatum. *European spine journal : official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society.* 2018;27(2):381-387.
166. Bayoumi I, Dolovich L, Hutchison B, Holbrook A. Medication-related emergency department visits and hospitalizations among older adults. *Canadian family physician Medecin de famille canadien.* 2014;60(4):e217-222.
167. Frood J, Paltser G. Types of Opioid Harms in Canadian Hospitals: Comparing Canada and Australia. *Healthcare quarterly (Toronto, Ont).* 2019;22(2):10-12.
168. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. *International journal of surgery (London, England).* 2014;12(12):1495-1499.
169. Fhima A, Henrion R, Lowenstein W, Charpak Y. [Two-year follow-up of an opioid-user cohort treated with high-dose buprenorphine (Subutex)]. *Annales de medecine interne.* 2001;152 Suppl 3:Is26-36.
170. Svendsen K, Borchgrevink P, Fredheim O, Hamunen K, Mellbye A, Dale O. Choosing the unit of measurement counts: The use of oral morphine equivalents in studies of opioid consumption is a useful addition to defined daily doses. *Palliative medicine.* 2011;25(7):725-732.

171. Vigilance Santé. Drugs database and pharmaceutical software for health professionals and pharmacists. . *Available: wwwvigilanceca/* (accessed November 30, 2020).
172. Gregorian RS, Jr., Gasik A, Kwong WJ, Voeller S, Kavanagh S. Importance of side effects in opioid treatment: a trade-off analysis with patients and physicians. *The journal of pain : official journal of the American Pain Society.* 2010;11(11):1095-1108.
173. Kalso E, Edwards JE, Moore RA, McQuay HJ. Opioids in chronic non-cancer pain: systematic review of efficacy and safety. *Pain.* 2004;112(3):372-380.
174. Manchikanti L, Ailinani H, Koyyalagunta D, et al. A systematic review of randomized trials of long-term opioid management for chronic non-cancer pain. *Pain physician.* 2011;14(2):91-121.
175. Uribe AA, Stoicea N, Echeverria-Villalobos M, et al. Postoperative Nausea and Vomiting After Craniotomy: An Evidence-based Review of General Considerations, Risk Factors, and Management. *Journal of neurosurgical anesthesiology.* 2019.
176. Jamison RN, Dorado K, Mei A, Edwards RR, Martel MO. Influence of opioid-related side effects on disability, mood, and opioid misuse risk among patients with chronic pain in primary care. *Pain reports.* 2017;2(2):e589.
177. Buckeridge D, Huang A, Hanley J, et al. Risk of injury associated with opioid use in older adults. *Journal of the American Geriatrics Society.* 2010;58(9):1664-1670.
178. Rubenstein LZ. Falls in older people: epidemiology, risk factors and strategies for prevention. *Age and ageing.* 2006;35 Suppl 2:ii37-ii41.
179. Rubenstein LZ, Josephson KR. Falls and their prevention in elderly people: what does the evidence show? *The Medical clinics of North America.* 2006;90(5):807-824.
180. Coluzzi F, Pergolizzi J, Raffa RB, Mattia C. The unsolved case of "bone-impairing analgesics": the endocrine effects of opioids on bone metabolism. *Therapeutics and clinical risk management.* 2015;11:515-523.
181. Hohl CM, Small SS, Peddie D, Badke K, Bailey C, Balka E. Why Clinicians Don't Report Adverse Drug Events: Qualitative Study. *JMIR public health and surveillance.* 2018;4(1):e21.
182. Hernan MA BB, Robins JM. Marginal structural models to estimate the causal effect of zidovudine on the survival of HIV-positive men. Epidemiology (Cambridge, Mass). 2000;11(5):561-570.
183. Xiao Y, Abrahamowicz M, Moodie EE. Accuracy of conventional and marginal structural Cox model estimators: a simulation study. *Int J Biostat.* 2010;6(2):Article 13.
184. Abrahamowicz M, Beauchamp ME, Sylvestre MP. Comparison of alternative models for linking drug exposure with adverse effects. *Statistics in medicine.* 2012;31(11-12):1014-1030.
185. Cole SR HM, Margolick JB, Cohen MH, Robins JM. Marginal structural models for estimating the effect of highly active antiretroviral therapy initiation on CD4 cell count. American journal of epidemiology. 2005;162(5):471-478.
186. Cole S, and Hernan, M. Constructing Inverse Probability Weights for Marginal Structural Models. American Journal of Epidemiology. 2008; 168: 656–664.
187. Xiao Y, Moodie EEM, Abrahamowicz M. Comparison of Approaches to Weight Truncation for Marginal Structural Cox Models. 2013;2(1):1.
188. Robins JM, Hernán MA, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology (Cambridge, Mass).* 2000;11(5):550-560.

189. Greenland S. Basic methods for sensitivity analysis of biases. *International journal of epidemiology.* 1996;25(6):1107-1116.
190. Pilote L, Abrahamowicz M, Rodrigues E, Eisenberg MJ, Rahme E. Mortality rates in elderly patients who take different angiotensin-converting enzyme inhibitors after acute myocardial infarction: a class effect? *Annals of internal medicine.* 2004;141(2):102-112.
191. Miller NS, Greenfeld A. Patient characteristics and risks factors for development of dependence on hydrocodone and oxycodone. *American journal of therapeutics.* 2004;11(1):26-32.
192. Thompson AR, Ray JB. The importance of opioid tolerance: a therapeutic paradox. *Journal of the American College of Surgeons.* 2003;196(2):321-324.
193. Dasgupta N, Kramer ED, Zalman MA, et al. Association between non-medical and prescriptive usage of opioids. *Drug and alcohol dependence.* 2006;82(2):135-142.
194. Murphy DL, Lebin JA, Severtson SG, Olsen HA, Dasgupta N, Dart RC. Comparative Rates of Mortality and Serious Adverse Effects Among Commonly Prescribed Opioid Analgesics. *Drug safety.* 2018;41(8):787-795.
195. Volkow ND, McLellan TA, Cotto JH, Karithanom M, Weiss SR. Characteristics of opioid prescriptions in 2009. *Jama.* 2011;305(13):1299-1301.
196. Mosher HJ, Jiang L, Vaughan Sarrazin MS, Cram P, Kaboli PJ, Vander Weg MW. Prevalence and characteristics of hospitalized adults on chronic opioid therapy. *Journal of hospital medicine.* 2014;9(2):82-87.
197. Coutinho Anna DA. Long-term opioid users with chronic non-cancer pain: Assessment of opioid abuse risk and relationship with healthcare resource use. *Journal of opioid management.* 2018;14(2):131-141.
198. Chang Hsien-Yen HY. Healthcare costs and utilization associated with high-risk prescription opioid use: a retrospective cohort study. *BMC Medicine.*16(1).
199. Tamblyn R, Abrahamowicz M, du Berger R, McLeod P, Bartlett G. A 5-year prospective assessment of the risk associated with individual benzodiazepines and doses in new elderly users. *Journal of the American Geriatrics Society.* 2005;53(2):233-241.
200. Daubresse M, Chang HY, Yu Y, et al. Ambulatory diagnosis and treatment of nonmalignant pain in the United States, 2000-2010. *Medical care.* 2013;51(10):870-878.
201. Belzak L, Halverson J. The opioid crisis in Canada: a national perspective. *Health promotion and chronic disease prevention in Canada : research, policy and practice.* 2018;38(6):224-233.
202. Mosher HJ HB, Hadlandsmyth K, Richardson KK, Lund BC. Predictors of Long-Term Opioid Use After Opioid Initiation at Discharge From Medical and Surgical Hospitalizations. Journal of hospital medicine. 2018;13(4):243-248.
203. Musich S, Wang SS, Slindee L, Kraemer S, Yeh CS. Characteristics associated with transition from opioid initiation to chronic opioid use among opioid-naive older adults. *Geriatric nursing (New York, NY).* 2018.
204. Pazzagli L, Linder M, Zhang M, et al. Methods for time-varying exposure related problems in pharmacoepidemiology: An overview. *Pharmacoepidemiology and drug safety.* 2018;27(2):148-160.
205. Tamblyn R, Abrahamowicz M, Buckeridge DL, et al. Effect of an Electronic Medication Reconciliation Intervention on Adverse Drug Events: A Cluster Randomized Trial. *JAMA Network Open.* 2019;2(9):e1910756-e1910756.

206. Pergolizzi V GC, Passik S, et al. Dynamic Risk Factors in the misuse of opioid analgesics. Journal of Psychosomatic Research. 2012.
207. Dufour I, Chouinard MC, Dubuc N, Beaudin J, Lafontaine S, Hudon C. Factors associated with frequent use of emergency-department services in a geriatric population: a systematic review. *BMC geriatrics.* 2019;19(1):185.
208. Hauser W, Bock F, Engeser P, Tolle T, Willweber-Strumpfe A, Petzke F. Long-term opioid use in non-cancer pain. *Deutsches Arzteblatt international.* 2014;111(43):732-740.
209. Hauser W, Schubert T, Scherbaum N, Tolle T. Long-term opioid therapy of non-cancer pain : Prevalence and predictors of hospitalization in the event of possible misuse. *Schmerz (Berlin, Germany).* 2018.
210. Grosen K, Olesen AE, Gram M, et al. Predictors of opioid efficacy in patients with chronic pain: A prospective multicenter observational cohort study. *PloS one.* 2017;12(2):e0171723.
211. Reyes-Gibby CC, Anderson KO, Todd KH. Risk for Opioid Misuse Among Emergency Department Cancer Patients. *Academic emergency medicine : official journal of the Society for Academic Emergency Medicine.* 2016;23(2):151-158.
212. Xiao Y AM, Moodie EEM. Accuracy of conventional and marginal structural Cox model estimators: a simulation study. The International Journal of Biostatistics 2010 Feb;6(2):Article 13.
213. Cox, D.R. (1972). Regression models and life-tables (with discussion). J. R. Statist. Soc. Ser. B, 34, 187–202.
214. Wynant W, Abrahamowicz M. Impact of the model-building strategy on inference about nonlinear and time-dependent covariate effects in survival analysis. *Statistics in medicine.* 2014;33(19):3318-3337.
215. Benedetti A, Abrahamowicz M, Leffondré K, Goldberg MS, Tamblyn R. Using Generalized Additive Models to Detect and Estimate Threshold Associations. *The international journal of biostatistics.* 2009;5(1).
216. Abrahamowicz M, Bartlett G, Tamblyn R, du Berger R. Modeling cumulative dose and exposure duration provided insights regarding the associations between benzodiazepines and injuries. *Journal of clinical epidemiology.* 2006;59(4):393-403.
217. Sylvestre MP, Abrahamowicz M. Flexible modeling of the cumulative effects of time-dependent exposures on the hazard. *Statistics in medicine.* 2009;28(27):3437-3453.
218. Xiao Y, Abrahamowicz M, Moodie EEM, Weber R, Young J. Flexible Marginal Structural Models for Estimating the Cumulative Effect of a Time-Dependent Treatment on the Hazard: Reassessing the Cardiovascular Risks of Didanosine Treatment in the Swiss HIV Cohort Study. *Journal of the American Statistical Association.* 2014;109(506):455-464.
219. Danieli C, Cohen S, Liu A, et al. Flexible Modeling of the Association Between Cumulative Exposure to Low-Dose Ionizing Radiation From Cardiac Procedures and Risk of Cancer in Adults With Congenital Heart Disease. *American journal of epidemiology.* 2019;188(8):1552-1562.
220. Kuehn BM. Opioid prescriptions soar: increase in legitimate use as well as abuse. *Jama.* 2007;297(3):249-251.
221. Morgan MM, Christie MJ. Analysis of opioid efficacy, tolerance, addiction and dependence from cell culture to human. *British journal of pharmacology.* 2011;164(4):1322-1334.

222. Colvin LA, Bull F, Hales TG. Perioperative opioid analgesia-when is enough too much? A review of opioid-induced tolerance and hyperalgesia. *Lancet (London, England).* 2019;393(10180):1558-1568.