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Title	Medication use and its impact on older adult high-cost healthcare users: protocol for the population-based matched cohort HiCOSTT study
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Reviewer 1	Giulio DiDiodato
Institution	Critical Care Medicine, Royal Victoria Regional Health Centre, Barrie, Ont.
General comments (author response in bold)	<p>I want to commend the investigators on a well written proposal.</p> <p>As i understand the proposal, the investigators' main hypotheses are that the transition into an elderly high cost healthcare user (HCU) class may be associated with high medication costs and antecedent medication use. By using patient level data available from fiscal years 2010 to 2014, incident / prevalent HCUs will be identified in fiscal 2013, and compared to 3 controls matched for age, sex, and residence region. A combination of standardized differences and logistic regression analyses will be used to test the primary and secondary hypotheses.</p> <p>Questions:</p> <p>1) It would seem that the patient's antecedent healthcare expenditure class would be associated with their likelihood of transition to an HCU class. For example, would a patient whose antecedent healthcare expenditures were in the 90th-94.9th percentile not be more likely to find themselves in the HCU in the following year compared to someone in the lowest 10th percentile? However, it does not appear that the controls are matched on this antecedent variable. Can you explain why this would not be an important matching variable?</p> <p>Thank you for the feedback. A study of Ontario HCUs (Wodchis et al. CMAJ 2016; 188(3): 182-8) has previously looked at antecedent healthcare expenditure class and HCU transition. Of those patients in the 90-94th cost percentile in FY2009, only 13.7% were in the > 95% cost percentile the next year and 48.4% were in the < 90th cost percentile in both of the following two years.</p> <p>We have considered several additional matching variables related to specific HCU strata. After reviewing data from previous studies of HCUs, we decided not to proceed with them in favour of not losing an excess number of people due to matching. We are not focused on any particular HCU subtype (outside of those that are older adults) and this is an exploratory study to look for patterns or factors deserving of further study. We believe that our matching criteria is a compromise between controlling for regional differences in health provision and the excess loss of individuals due to matching. We will be using regression techniques to adjust for the other confounding factors that may contribute to future HCU status.</p> <p>The investigators provided an example of an absolute value for HCU of approximately \$8000, which would be the equivalent of a 3 day stay in an Ontario ICU. It would seem to me that there are several categories of HCUs; those with an acute life-threatening illness that requires a one-off expensive intervention such as an admission to an ICU or those with a new cancer diagnosis requiring both surgery and chemo-/chemoimmunotherapy versus those with poorly controlled/decompensated chronic illnesses requiring frequent hospitalizations</p>

	<p>such as COPD/CHF patients. I can see how antecedent medication use might be associated with the transition of the second group of HCUs but i can't really see how it would be associated with the first HCU group as these would most likely have abrupt transitions into an HCU group as opposed to a gradual transition that would be expected in the second group? This is an extension of the first question i posted. I wonder if patients should be stratified according to the type of transition to HCUs, however one might define these levels?</p> <p>We agree that there are several subtypes of HCUs. Stratification based on the type of HCU transition is both complex to operationalize and also goes beyond the scope of our intended study. Focus on a more specific HCU subtypes may be the subject of future studies.</p> <p>We believe that medication could play a role in both abrupt and more gradual HCU transitions (e.g. abrupt transition could be caused by new use of high cost biologic, non-adherence to antiresorptive therapy leading to catastrophic hip fracture, etc).</p> <p>3) Another question relates to the association between the timing of medication initiation and time to transition to HCU. Would it not be more informative to determine the time to HCU transition from the time that these drugs/drug classes were started? Would this not better define a temporal relationship between medication use and HCU transition, and strengthen the overall association between these variables? It is difficult to understand how the investigators will be able to demonstrate, without consideration of how long a patient has been on medications, the association between medication use with an HCU transition? I think the duration of medication treatment would need to be included in the analysis in some way, perhaps through an interaction term in the logistic regression model or as another variable in the assessment of baseline differences in the matched cohort?</p> <p>We agree with the reviewer that the timing and duration of medication may be a factor in time to HCU transition. As explained above, we are using an already defined cohort and dataset for this study. Unfortunately, we do not have the data available to uniformly incorporate the actual date of first prescription for all drugs of interest (e.g. if it occurred outside our study window). We have added this as a study limitation in the manuscript. In attempt to strengthen the case for any associations found between specific medication use and HCU transition, we will be incorporating the duration of medication use within our study window into the regression analysis to assess the association based on increasing exposure to the drug(s) of interest. This description has been added to the analysis section.</p>
Reviewer 2	Kieran Quinn
Institution	Department of Medicine, University of Toronto, Toronto, Ont.
General comments (author response in bold)	<p>This protocol for a retrospective population-based matched cohort study of incident high-cost users in FY2013 (those in the top 5% of measured healthcare costs who were not high-cost users in FY2012) proposes to estimate the relative financial and clinical contributions of prescription medications on healthcare system expenditures and the development of incident HCU status in older adults.</p> <p>This study is important and timely because publicly reimbursed spending on prescription medication (which is particularly relevant for all adults >65 years who medications are paid for in Ontario) currently accounts for nearly 16% of health spending and continues to rise. There is definite novelty in that the specific types</p>

and costs of prescription medications in HCU is not well understood. In short, these descriptive population-based studies are much needed to further the quality of care for this vulnerable population.

Overall, I believe this study to be relevant and interesting, but would benefit from further clarity in defining its intended objectives, along with some of its methods. For example, the authors indicate that their primary objectives are to determine the “clinical and financial contributions of prescription medications to healthcare expenditures and the development of incident HCU status in older adults”. There are 3 issues with this statement as I see it:

- 1) the language chosen infers causality;
- 2) I am unclear as to what specific outcomes they wish to measure. Table 1 outlines these outcomes much clearer, and I would suggest using some of its language specifically in the objective statement; and
- 3) the authors propose 4 measures for the co-primary outcomes. It may be easier to follow if the authors chose 1 (or 1 from each financial and clinical measure) as their primary outcome(s).

I believe the manuscript could be improved with further clarity and by addressing the following issues:

Thank you for the feedback. We have amended the language of our study objectives to avoid inferring causality:

“A better understanding of the multi-morbidity and medication use in older adults high-cost healthcare users (HCUs) is needed to inform health interventions and policies. This study’s main objectives are to determine the financial contribution of medications to HCU expenditures and explore whether potentially inappropriate prescribing is associated with incident HCU development.”

Based on the feedback, we amended the abstract methods section to describe the outcomes with greater clarity. We have amended Table 1 to clarify that there are only two co-primary outcomes as described in the text.

How did the authors choose which confounders to match on? HCUs are a heterogenous group, and may be conceptually grouped in 6 phenotypes (children with complex needs; nonelderly disabled adults: adults <65 y old with physical or cognitive disability; frail elderly individuals; patients with major complex chronic conditions; patients with less severe but multiple chronic conditions; patients with terminal illness (eg, advanced cancer) or near end of life – see Figueroa and Jha JAMA Int Med 2018). Why not stratify by these groups, or restrict the study sample to the phenotypes of specific interest?

The commentary by Figueroa and colleagues outlines general observations made about high-need patients all ages in the US context. We agree that there are several HCU subtypes, and they may be the same in Ontario as outlined by Figueroa.

To focus our study, we have restricted our evaluation to the older adult HCU subtype and more specifically, to those that are incident HCUs (in contrast to most studies that have focused on prevalent or persistent HCUs). We also want to specifically explore the impact of medications without making assumptions of their financial contributions and clinical impact in older adult HCU subgroups in the Canadian context.

Please refer to our response to Comment #19 re: decisions regarding

matching.

How do the authors intend on determining the “quality of prescribing” of medications? Simply “cross-referencing” medication classes to co-morbid conditions seems insufficient given the complexity of clinical decision making in the use of medications, especially in medically complex individuals. One strategy may be to select 3-5 specific drug classes that are potentially high risk in older adults (see Quinn et al JGIM 2019), and not comment on their appropriateness or quality. Alternatively, I have seen authors use guidelines to determine “appropriateness” (Vaughn Annals of Int Med 2019). For example, in Table 3, the authors support the use of ASA as a “high-quality” medication, but the recent ASPREE Trial (and other evidence) raises the question of benefit in older adults without secondary indications.

We have added the following text and references to provide greater clarity and justification for our chosen approach:

“Previous studies have highlighted the existence of important prescribing practice gaps and the use of potential prescribing omissions and inappropriate medication use as quality indicators of pharmacologic care in older adults.(23–25) Suboptimal prescribing and use of statins (<30%) and bisphosphonates (<50%) in those with a history of cerebrovascular disease and osteoporosis respectively are two examples.(23,24) In a similar fashion, the prevalent use of specific medication classes will be compared with the relevant diagnoses of patients within these cohorts to explore potential quality improvement areas for prescribing and the financial implications of current drug utilization by (1) HCUs vs. non-HCUs and (2) HCUs pre- vs. post-HCU designation.”

In a similar strategy to the reviewer’s own mentioned study, we have selected drug classes that expert consensus groups have identified as those commonly prescribed or omitted inappropriately in older adults due to evidence suggesting high risk of harm outweighing benefit or vice versa (e.g. START/STOPP, Beers Criteria). Similar to the study by Higashi et al, Ann Int Med 2004, we will be exploring whether the prevalent usage rates point towards the need for further evaluation when compared to the prevalence of specific conditions with indications for those specific drugs. Logistic regression analyses evaluating the association between use of specific medication classes and HCU development will only be conducted in individuals who have conditions for which those specific drugs might be indicated.

The co-primary outcomes measure cost in the one year after index, but the authors do not describe how they intend to address the competing risk of bias for those who die within this time period. For example, 2 seemingly identical individuals will have substantial differences in their expenditure and prescription medications if one dies within 2 months and the other survives.

Please refer to our response to Comment #12 above.9

The authors propose the importance of their study may be to “identify high-cost drugs suited for reference-based drug pricing reimbursement” but do not appear to measure specific medications suitable for this in their listed outcome measures.

We state that “we seek to identify opportunities to improve the quality of

care and prevent HCU development”. Reference-based drug pricing is listed as one potential policy that knowledge users may choose to further explore based on the data, but there may be others. We believe that studying additional details relevant to reference-based pricing, including specific targets, will be the topic of a follow-up study.

The use of ADGs is reliant upon ICD-9 and 10 coding that comes from acute care databases. The accuracy of physician diagnoses in outpatient insurance claims has been demonstrated to be unreliable. I am concerned about the authors methods to identify diagnostic clusters that will limit detection to those who have interacted with acute care, and by the associated costs of acute care may bias the exposure groups. The best approach to address this limitation may be to restrict the study sample to specific diagnoses that are reliable measured in outpatient settings in administrative data that fall within the above phenotypes.

We have ensured that the limitations of the ICD and billing codes (and thus ACG system) are described in the limitations section of the manuscript.

Given the exploratory study objectives, we are examining many co-morbidities and deriving each from the best data available to us. When available, the ICES-derived chronic disease cohorts (which have been chart validated in primary care) will be used. Johns Hopkins Expanded Diagnosis Clusters (EDCs) are being used when an ICES-derived cohort is not available.

The EDCs are groupings of diagnostic codes that describe the same or related medical condition; as such they help to account for differences in coding behaviour between practitioners. Since the EDCs are derived from the ACG system, they are also based on both inpatient and ambulatory health data. The ADGs (also based on the same ACG system) are being used in our study as means to measure level of comorbidity and illness severity across the cohort (which is heterogeneous).

Abstract:

- Please clarify the objective statement with the specific primary outcomes to be measured.

As best as we could within the abstract word limits, we have modified the objective statement for greater clarity of the outcomes to be measured:

“This study’s main objectives are to determine the financial contribution of medications to HCU expenditures and explore whether potentially inappropriate prescribing is associated with incident HCU development.”

- Please add more detail to clarify the outcome measures described in the methods

We have added detail in the method sections for greater clarity:

“Average annual medication costs (at individual level) and the ratio of medication to total healthcare costs (at population level) will be examined over the HCU transition period and compared to non-HCUs. Potential quality improvement areas for prescribing will be explored by analyzing chronic conditions and the use of medications with a strong evidence base for either clinical benefit or risk of harms outweighing benefits in older adults with these diagnoses. Logistic regression will be conducted to explore the relationship between these medication classes and incident HCU status.”

- Please avoid language inferring causality in the Interpretation section.
We have accordingly modified the verbs used in this section. The results will “explore” (rather than “determine”) whether medications “may be” triggers (rather than “are”).

Introduction

- Are healthcare costs truly unsustainable? Costs are rising, and “unsustainability” is certainly common fodder, but it may not be true depending on the rate of growth of our GDP. See Dhalla CMAJ 2007

Thank you for the insightful comment. Healthcare sustainability is certainly one of debate. In the 2007 article mentioned, Dr. Dhalla proposes that sustainability should be assessed on the basis of GDP. According to a recent OECD report, health spending is rising faster than economic growth in all OECD countries and will become unaffordable without reform. In the absence of effective cost-containment policies, OECD projections show public spending on health and long-term care is reaching 9% of GDP by 2030, and as much as 14% by 2060. This report is referenced in the manuscript.

- Is the quality of evidence surrounding the interventions to reduce healthcare use and expenditure low based on the authors application of the GRADE criteria? There does not appear to be a reference supporting this determination.

The citation of our work supporting this statement is referenced in the manuscript (i.e. Lee et al. J Am Geriatr Soc. 2018). In this review, we applied the GRADE criteria to the studies that we found.

- On page 4, lines 3-4 - Is polypharmacy associated with increased rates of inappropriate prescribing? Suggest revising this statement.

Yes, there is evidence from multiple studies to suggest that polypharmacy is associated with increased rates of inappropriate prescribing (both potentially inappropriate medications [PIMs] and potentially inappropriate omissions [PPOs]). We have added an additional reference to support this statement in the manuscript.

Methods

- It would be helpful to provide more detail on how costs are measured given that they come from multiple sectors (e.g. outpatient visits, medications, acute care) in order to determine that a patient falls within the top 5% threshold.

Since we are limited by word count restrictions, we have cited the reference that explains the costing methodology in detail for readers (Wodchis WP, Bushmeneva K, Nikitovic M, McKillop I. Guidelines on person-level costing using administrative databases in Ontario. 2013;1(May):1–71.)

- What is the proposed matching strategy used – with or without replacement? This has implications for the planned statistical analysis.

We have clarified this in the text. We are using matching without replacement since we do not anticipate a shortage of potential matched controls and it is preferable to keep them independent for the analysis.

- At what study point will the “baseline characteristics” be collected? In FY2012? Or the beginning of FY2013? Or some other date?
This has been clarified in the manuscript. The baseline characteristics are assessed at the time of the index date.

Interpretation

- Sorry to be repetitive, but on p.11 line 52 the authors propose to identify a gap in appropriate and cost-effective use of prescription medications. The study does not appear to measure either.
- Strengths are very well written.
- There are methods to infer medication adherence based on refills. I refer the authors to work by Dr. David Juurlink in this regard to define “continuous users”.
We have amended the text based on the feedback for greater clarity: “This study’s data will... explore whether there are possible quality improvement areas for prescribing amongst older adult HCUs.”
Please refer to our response to Comment #26 on the rationale to our approach on exploring potential prescribing quality issues.

Figures

- Excellent figure. Very clearly outlines design and is visually appealing.
Thank you for the feedback.

Tables

- Table 1: very nicely organized and clear to understand
Thank you for the feedback.

- Table 2: can the authors discuss and reference the validity of some of these datasets?
We have included additional information and references in Table 2 to support the validity of these datasets (in particular the ODB and ICES-derived chronic disease cohorts). For more detailed data, we have also provided a reference to the online ICES data dictionary in the main text.

- Table 3: why were these specific medications chosen? References 19 and 20 do not speak to the prevalence of their use or costs in a publicly funded healthcare system like Ontario.
We have added a clarifying statement: “We choose these classes as high-priority medications based on review of expert consensus guidelines on potentially inappropriate prescribing in older adults (i.e. START/STOPP, Beers Criteria), Canadian deprescribing guidelines, and previous studies of potentially inappropriate prescribing and high cost medication use in Ontario.”
As per the reviewer’s suggestion, we have also included additional references that provide data on the prevalence of their use and costs in a Canadian context.

Reviewer 3	Jennifer Davis
Institution	Centre for Clinical Epidemiology and Evaluation, VCH Research Institute, The

	University of British Columbia, Vancouver, BC
General comments (author response in bold)	<p>I read this well-written paper assessing the medication use and impact amongst older adults HCU's with great interest! The authors have conducted an interesting study ascertaining the contribution of clinical and financial prescription medications to healthcare system expenses and incident HCU status. A clear strength of this paper is looking at incident HCU status.</p> <p>I include the following minor comments/suggestions below:</p> <p>Thank you for the feedback.</p> <p>Abstract</p> <p>Background: Can the authors please provide a statement of some of the health complications of high cost users (i.e., what are some of the health consequences of HCU's that are most common)?</p> <p>Since the editor requested that we keep this section to 2 sentences (comment #3), we have added a statement in the background section of the main text instead in order to incorporate this feedback:</p> <p>“These individuals are often characterized by frequent hospitalization, co-morbid mental illness, socio-economic challenges, and increased mortality risk.”</p> <p>Methods: For the regression analysis, can the authors please state their dependent variable and the potential categories of independent variables they will examine?</p> <p>We have modified the abstract. The abstract lists the dependent variable (i.e. incident HCU status) and the main independent variables (i.e. use of the pre-specified list of medication classes). We have also added more details about the selection of these medication classes:</p> <p>“Potential quality improvement areas for prescribing will be explored by analyzing chronic conditions and the use of medications with a strong evidence base for either clinical benefit or risk of harms outweighing benefits in older adults with these diagnoses. Logistic regression will be conducted to explore the relationship between these medication classes and incident HCU status.”</p> <p>We are constrained by the abstract word limit to add more detailed info, but it is explained in more depth in the Data Analysis section of the manuscript.</p> <p>Methods: Can the authors please state what type of regression they intend to perform?</p> <p>We have modified the abstract to specify logistic regression.</p> <p>Introduction</p> <p>Page 4: Can the authors please continue their thoughts on why old adults may be the most important HCU subpopulation to target? Is there a system level approach in Ontario for HCU tracking?</p> <p>We have added more detail as per the reviewer's suggestion:</p> <p>“Older adults aged ≥65 years arguably represent the most important HCU sub-population to target. They account for the largest proportion of HCUs and this age group incurs the greatest median healthcare expenditures amongst HCUs.(9,10) In Ontario, 5% of older adult HCUs account for 44% of</p>

total healthcare expenditures by older adults”

To our knowledge, there is no system-level approach in Ontario for HCU tracking.

Methods

Could the authors comment on why the data are from 2013/2014 rather than more recent data? I appreciate that these data may not have been available from more recent years.

Please refer to our response to Comment #8.

In the statistical analysis section, could the authors comment on how missing data will be handled for any of the variables collected?

We have added a statement regarding missing data:

“Missing data for any covariates will be reported as separate categories. Since our sample size is expected to be large, we will use pairwise deletion unless missing data is greater than 5% and an independent statistician recommends multiple imputation.(21)”