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Title	**Frequency and cost of potentially inappropriate prescriptions for older adults: an analysis of 9 provincial drug plan claims**
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Reviewer 1	Dr. Ching-Wen Chien,
Institution	National Yang-Ming University, Taipei, Taiwan
General comments (author response in bold)	Three major drawbacks which lead a rejection of this paper: 1. the authors just report how serious IM is across different providences which does not contribute to existing knowledge about IM among elderly. 2. There are so many factors which uniquely confound with IM among elderly, such as knowledge toward side-effects of drugs of each benefitialry, are not discussed in this paper. 3. Assessment of factors contributing to IM should use research method such as multilevel regression since differences in IM across different providences are nested in different groups of elderly. A plain description in the paper can be used to discussed deeper issues of differences among elderly Canadian people. Besides, this is a cross-sectional study, there are no follow-ups to validate the results of this paper. **We respectfully disagree with this assessment. Ours is the first Canadian study to quantify the cost of potentially inappropriate prescriptions in Canada, and it does so not just for one province but for 9 using best available data and methods. In addition to being a contribution to Canadian dialogue regarding related policies and practices, it will be a valued contribution to the global literature on the cost of potentially inappropriate prescribing.** **Ours is not a study of determinants of potentially inappropriate prescribing; however, as relevant to the potential implications of this study, we have described the complexity of influences on prescribing practices.** **Again, ours is not a study of determinants of potentially inappropriate prescribing. It is an analysis of the extent and cost of such prescribing across Canada. Trends in potentially inappropriate prescribing in Canada have not been dramatic in recent years – neither for the better nor for the worse. As such, 2013 is a reasonable – indeed, the best available – snapshot of current practices and costs.**
Reviewer 2	Ingrid Sketris, Professor
Institution	College of Pharmacy, Dalhousie University, Halifax NS
General comments (author response in bold)	This paper discusses an important topic –the cost of potentially inappropriate prescribing in older persons in Canada which has not been well studied. I have provided some general comments and then more specific comments. **We are grateful for the detailed comments. Many stem from our omission of full methodological details owing to the need to keep the text as brief as possible. We have included the STROBE checklist and have edited the paper to more explicitly state that we used the methods described in detail in CIHI's report "Drug Use Among Seniors on Public Drug Programs in Canada, 2012" (reference 12 of the original version). Readers interested in the finer details concerning methods used can find them there.** General comments 1. Beers 2012 may be formally called American Geriatrics Society (AGS) Beers the first time **This has been corrected to the American Geriatrics Society's 2012 version of the Beers Criteria for potentially inappropriate medication use in older adults.** Methods 3. The authors could consider checking the RECORD statement and the STROBE statement to ensure that all relevant items are documented. **Have considered the statements and have included the STROBE checklist as an appendix.** A few specific comments follow: Population studied 5. Provide further information on the population. Did any of the databases include individuals living in nursing home and/or homes for special care? If so, can you provide the percent in each province? Specify if enrollee or claimant (at least one claim reimbursed in the 2013 fiscal year) is used for the denominator. For example, a person could pay premium and enroll in program and have no claims. When describing seniors pharmacare drug plan features by province, refer to a source for further information on the details and note that some plans also have premiums. Provinces have different age and sex structures. Consider referring to a source for this information and consider providing age/sex standardized rates of potentially inappropriate use.

	Further details are now provided, with citations regarding variations in drug plan design. **We now explain that there are small differences in the age profile of provincial populations over age 65 and of the age profile of public drug plan beneficiaries who are age 65 and older. We also now explain that age standardization changed province-specific measures of overall rates of use of potentially inappropriate prescriptions by less than one third of one percentage point (results not reported).** Data sources and analysis Provide more information on the NPDUIS database. If the WHO ATC system was used to classify drugs, provide the version and the level i.e. 4th level. **We have added a line to explain, "Drugs in the NPDUIS database were classified using the 5th level of the 2013 version of the World Health Organization ATC classification system."** The methods state "relevant fields in the NPDUIS database." Please specify these and how they were used. For example how was dosage calculated? If the directions field was used how PRN was dosing handled? Provide further information on how prescribed daily dose calculated-only for oral formulations? Provide further information on how duration calculated-what was considered a single course and how were to gaps in therapy handled. **We measured total costs of prescriptions using total cost accepted amount in the NPDUIS dataset, including ingredient cost and dispensing fees. Daily dose was calculated as the quantity dispensed multiplied by the strength per unit (e.g. 20mg/tab*100 tabs) divided by number of days' supply. We did not use the dosing direction field (it is not available in NPDUIS).** **Owing the word limits, we were unable to provide full methodological details in the submission. We have edited the paper to more explicitly state that we used the methods described in detail in CIHI's report "Drug Use Among Seniors on Public Drug Programs in Canada, 2012" (reference 12 of the original version). Readers interested in the finer details concerning methods used can find them there.** Note if the proportion is calculated as cumulative, so that some persons contributed only a part of a year as in and out migration from the drug plan occurs and death occurs. Was there a way to capture if pharmacare was the insurer of first or last resort which will influence the cost of the claim? For amount paid, was this the amount submitted by the pharmacy and approved and does this capture both that paid by public plan and that paid by claimant towards deductible, but not the amount a patient pays above the maximum allowable cost for specific drugs? **We have added text to show that the period prevalence data reported in this NPDUIS analysis is consistent with recent, more detailed analyses of gold-standard data that accounts for residency, deaths, and all payer types.** **Correct, amount paid was the approved amount.** How were dosage forms handled? For example for estrogens, the oral formulation is on Beers list whereas topical formulations are considered appropriate. **Owing the word limits, we were unable to provide full methodological details in the submission. We have edited the paper to more explicitly state that we used the methods described in detail in CIHI's report "Drug Use Among Seniors on Public Drug Programs in Canada, 2012" (reference 12 of the original version). Readers interested in the finer details concerning methods used can find them there.** Were there specific exclusions e.g. Clobazam which is primarily used for epilepsy. **Clobazam was excluded as per the CIHI methods for implementing Beers Criteria in Canada. The new appendix lists dugs included. We have edited the paper to more explicitly state that we used the methods described in detail in CIHI's report "Drug Use Among Seniors on Public Drug Programs in Canada, 2012" (reference 12 of the original version). Readers interested in the finer details concerning methods used can find them there.** Be explicit as to how the proportion of patients receiving drugs on the Beers list was calculated for each drug in an appendix. In the methods it is stated all prescriptions meeting Beers criteria based on drug dose and duration were identified as potentially inappropriate. Consider providing data on dose and duration. This may be relevant for specific drugs. For example, while many consider amitriptyline to be inappropriate in all cases for older persons, some guidelines recommend low dose amitriptyline for neuropathic pain, especially in those individuals who have failed other agents. Benzodiazepines are sometimes prescribed short term (e.g. before certain procedures), whereas chronic use is more problematic and it would be useful to know the duration of therapy.

	We have added text to the methods section; further details are in the appendix and citations mentioned in response to comment #8 above. Note where there is a Canadian modification of Beers list, if any. For example the Beers list specifies glyburide. The Canadian diabetes guidelines note that hypoglycemia is a concern with glyburide and glimepiride has less hypoglycemia than glyburide whereas the lowest risk is with gliclazide. Table 3 notes glibenclamide which is also known as glyburide. **See response to comment #8.** Provide information on program used for analysis e.g. SAS version. **Revised accordingly.** Describe how missing data handled. **Records with invalid patient or drug identification codes were excluded.** Consider providing age/sex standardized rates of cost per enrollee per year when comparing across provinces. **We now explain that there are small differences in the age profile of provincial populations over age 65 and of the age profile of public drug plan beneficiaries who are age 65 and older. We also now explain that age standardization changed province-specific measures of overall rates of use of potentially inappropriate prescriptions by less than one third of one percentage point (results not reported).** Be more explicit on how $75 per capita was determined. Consider if you want to conduct a sensitivity analysis for example related to drugs which may be considered inappropriate only under certain conditions. What was the source of the denominator that was used for Canadians over 65? Was this the spending from the public sector so that there could be additional spending on potentially inappropriate drugs by the private sector or cash paying patients? **We have edited relevant lines to make it clear that the $75 result is from high-data-coverage provinces. We discuss how private payment for prescriptions not covered by public plans would render this figure an conservative estimate of the total.** Include date of ethics approval and REB number. **Feb 2014 (renewed in 2015 and 2016); H11-02273.** Results Consider providing specific information on inappropriate type, dose and duration. Strategies to optimize prescribing may differ among these areas. **An interesting suggestion for future study and reporting.** For the drugs in Table 3 are there provincial formulary differences and if so, consider providing in an online appendix. **We mention the significant formulary differences in the rest of the study.** Interpretation Why do you think the cost estimate was considerably lower in Canada than in Ireland? **We now elaborate on how addition to differences stemming from differences in health system design and prescribing practices, differences in the study findings may stem from facts that study of potentially inappropriate medication use in Ireland focused on a slightly older population and used diagnostic information to identify cases of potentially inappropriate medication use that we could not identify with data available for our study.** Why was the rate of potentially inappropriate prescriptions in PEI considerably lower than other provinces? Do individuals in PEI living in nursing homes not subsidized by government have their prescriptions covered by the public plan? **We don't know why PEI is lower. Same has been found in previous studies. PEI residents in private nursing homes are covered under the seniors' drug plan.**

	Consider discussing the chronic disease gradient and socioeconomic gradient across provinces which can influence the number of diseases and the number of drugs per pharmacare beneficiary. Canadian provinces vary in the rate of chronic diseases and the per capita income. Others have shown variation in potentially inappropriate use by socioeconomic gradient. (Hughes et al 2016, Cooper et al 2016) **Noted. There is a vast literature that could be cited on the myriad influences on likelihood of PIM use. However, owing to space constraints, we have chosen not to place emphasis on variations across regions or to attempt to explain them through conjectures about possible health and social differences by province.** Are there specific drug classes accounting for differences in the provinces? Were formulary considerations or the differences in special drug programs likely to influence this difference? **Though we do not produce province-specific rates, we tested for differences and found that leading drug types were generally similar for all provinces with the notable exception of zopiclone (as described in the text).** Limitations The authors note that the NPDUIS data is not linked to electronic health records in primary care or hospital records. There are some therapeutic areas where this is more problematic and these could be highlighted e.g. the use of antipsychotics may be appropriate for schizophrenia and behavioral issues not responding to alternative nonpharmacological and pharmacologic therapies. **We have revised the text to better explain the limitations of the data and the inability to implement diagnostic-dependent Beers criteria.** The duration of therapy is not reported and it is not known the prevalence of individuals receiving a single prescription vs chronic therapy. (Ble et al 2016) **We cite prior work (Drug Use Among Seniors on Public Drug Programs in Canada, 2012 – referenced in our study) concerning rates of chronic use of Beers List drugs in question.** Samples and nonprescription medications were not included (e.g. ASA is on the Beers List) **We explain that, like most comparable studies, our analysis pertains to prescription-only drugs.** Combinations not considered (e.g. two benzodiazepines) **True. However, sensitivity analyses from one of our author's more detailed studies of BC data indicate that this is not a major flaw in the methods used with the NPDUIS data.** Comment further on the frail elderly. The evidence in the Beers criteria is particularly weak for this subgroup as often excluded from clinical trials and there may be many more drugs for which the risk may outweigh benefit such as statins for specific population and antihypertensive for patients where the blood pressure is too tightly controlled that are not picked up by the Beers criteria used in this study. (Lang et al 2016). **We agree that there may be other medications that are of potential risk to frail elderly. Time and space constraints have meant that we cannot explore alternative criteria for measuring potentially inappropriate medication use. For comparability to most of the related literature (in Canada and abroad), we've stuck with the Beers list.** Give information on potential magnitude of prescriptions written and not filled and non-adherence. **This is an interesting idea but we feel it would amount to informed speculation at best because there are few (if any) CRNA estimates that are age- and drug-specific.** Conclusion Consider including discussion regarding Australia's Medicine Wise in interpretation section and also the UK's use of quality outcomes framework and the Pharmacy Quality Alliance in the US which assist in improving prescribing. **We hope the mention of NPS MedicineWise in the conclusion section would suffice.** <u>Table 1</u> Include the sample size in each province and then the share covered by NPDUIS with information where the sample size comes from e.g. Stats Canada and year. Be clear if beneficiaries who reside in long term care facilities are excluded.

	Done. Table 3 In Beers list was the drug potentially appropriate but not at the specific dose or duration-if so note? **As noted in the methods, we identify only those cases where type, dose and duration criteria are satisfied. The CIHI cation contains further methodological details.** In Note pharmacists' professionals fees not dispensing fees **Some program databases refer to these as dispensing fees, others professional fees.** In this table can you disaggregate proportion inappropriate drug, vs dose vs duration? **Most drugs with a dose or duration criteria have either a dose or a duration criteria, not both.** For this table, note where there were differences in formulary coverage of some agents e.g. Zopiclone. Also was zopiclone only considered inappropriate if as in the 2012 Beers list the prescription has a greater than 90 day duration? **We could not account for Zopiclone use in provinces that do not cover it. This is mentioned in the study limitations. As per the CIHI methods, only 90+ days of therapy were flagged as inappropriate.** Specific comments Page 3 of 17 Abstract Line 11 prescriptions-add s **Revised accordingly.** Line 17 prescriptions-add s **Revised accordingly.** Page 4 of 17 Introduction Line 22 Can lead to unnecessary emergency department visits and hospitalizations as well as morbidity and increased risk of death and increased risk of institutionalization for community dwelling older adults **For parsimony, we have left this as "unnecessary hospitalizations as well as increase the risk of death." There are a number of other outcomes also correlated - - point of the line here was to provide some motivation but not necessarily to delineate all associated outcomes.** Line 26: Prescribers are not just physicians but also nurse practitioners, dentists, pharmacists and others. **Noted but don't think it is necessary to edit text given the initiative discussed in the section is physician-led.** Page 5 of 17 /Line 14: These data cover the dispensing and cost… use by patient is not known **Revised accordingly.** Page 6 of 17: Dispensing fee now referred to as pharmacists' professional fee **Noted but not changed as both terms are commonly used.** Page 7 of 17: Line 36-Consider terminology "meeting" or potentially inappropriate as defined by Beers list

	Revised accordingly. Page 8 of 17: Line 19 purchased replaced by dispensed and reimbursed for **Have rephrased to "prescriptions for Beers List drugs filled by"** Line 28 –direct drug costs incurred by the public sector? **Total direct cost for eligible prescriptions, as costs toward deductibles are included, as are patient contributions in terms of co-payments/co-insurance.** Line 46 Drug type dose or duration… did not have to meet all three? **Not all drugs on the Beers List have a dose or duration criteria. Those with additional criteria typically have either a dose or duration criteria.** Page 10 of 17: Line 47 not linked to electronic ambulatory health records (more than medical-patients may be seen by nurse practitioner etc.) **The text of this paragraph has been edited.** Line 50-not able to adjust for allergies, contraindications, previous therapeutic failures, palliative state and diagnosis which may…. **The text of this paragraph has been edited.** Page 11 of 17 Line 28: Considerable use-not really measuring use… prescriptions dispensed or patients received medications **Text edited to "evidence of frequent dispensations and considerable cost of..."**