PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Multinational Comparison of New Antidepressant Use in Older Adults: A Cohort Study
AUTHORS	Tamblyn, Robyn; Bates, David; Buckeridge, David; Dixon, Will; Forster, Alan; Girard, Nadyne; Haas, Jennifer; Habib, Bettina; Kurteva, Siyana; Li, Jack; Sheppard, Therese

VERSION 1 - REVIEW

REVIEWER	Dr. Mary McHugh Angeles College U.S.A.
REVIEW RETURNED	24-Dec-2018

GENERAL COMMENTS	The correct name for this research design is "Retrospective Review of National or Regional medical database". Since the patients had already received care, this cannot reasonably be labeled as a prospective study.

REVIEWER	Andrea Berghold Institute for Medical Informatics, Statistics and Documentation, Medical University Graz, Austria
REVIEW RETURNED	30-Dec-2018

GENERAL COMMENTS	The authors aimed to estimate the rate and characteristics of antidepressant use in older adults in different countries using an international pharmacosurveillance network. They analyzed 6 databases (3 Administrative data, 3 EMR data) from 4 countries (Canada, USA, UK Taiwan). I think the authors explained well which datasets they used and which kind of data were available. For the analyses of these datasets descriptive statistics were used. Some small remarks: 1. In table 1 a summary of the depression guidelines are given – for Canada a guideline from 2016 is listed – how was the Canadian guideline during the timeperiod 2009-2014? 2. Result section – 1st paragraph: …Canada (26.8%) and Taiwan (23.4%) and – drop the last “and” 3. Result section – 5th paragraph: …the mean dose varied from 60% of (0.6) of – change to: the mean dose varied from 0.6 of

REVIEWER	BH Stricker Erasmus Medical Center Rotterdam, Netherlands
REVIEW RETURNED	06-Feb-2019

GENERAL COMMENTS	This manuscript concerns a comparison between antidepressant use in older adults in Canada, UK, USA, and Taiwan. According to the authors, there are remarkable differences in incidence and prevalence [not surprising considering the different guidelines] and a huge proportion was prescribed for the off-label indication chronic pain. If so, this raises important questions regarding the adequacy of antidepressant pharmacotherapy. Although the topic is not new, the size of the country-comparison is. 1. Essential in this descriptive study is the question whether identical measures were used and how the source populations are defined/selected. This is described in the methods but as the healthcare systems are different, it is unsure how this impacts the results. For instance, the role of the primary care physician in the USA is different from a GP in the UK. Also, the USA has health maintenance organizations which cover another socioeconomic population than Medicare. Also the databases are different. For instance, GP databases work with prescriptions but as there is often not a link to the pharmacy it is unclear if all prescriptions were filled. 2. The high percentage of the indication depression in Quebec suggests a healthcare/reimbursement flaw. 3. How can an incidence of 0.7% [UK] lead to a prevalence of 10% in a 5-year period ? 4. Why did the authors calculate age-adjusted rates and not sex- and age-adjusted. Prescribing antidepressant differs between the sexes and I do not find that back. 5. I guess lithium was also excluded [like MAO-inhibitors] 6. Is the study period 1st January 2009 through 31st December 2014 ? 7. Did the authors account for mortality during this period ? Was that complete ? 8. The prevalence ratios in table 4 assume that overlap of depression was with only one co-morbid condition. This seems unlikely. 9. It is unclear to me how the prevalence ratios in table 4 were calculated 10. The numbers in table 2 and 3 differ for Ontario. In table 2 the number of new users is 306,197 whereas it is 60,366 in table 3 11. 'The variation in approach in the use of antidepressants for depression and chronic pain in different countries creates the natural experiment that could generate unbiased evidence of potential harms and benefits'. [p.10; 4th para]. This overoptimistic statement should be explained. I disagree, it shows what a mess antidepressant prescribing is and what a burden for healthcare. The huge appendix can be deleted. Just mention that is available on request

VERSION 1 – AUTHOR RESPONSE

Reviewer's Comment	Response
Reviewer 1	
The correct name for this research design is "Retrospective Review of National or Regional medical	We have revised the description of our research design.

database". Since the patients had already received care, this cannot reasonably be labeled as a prospective study.	
Reviewer 2	
In table 1 a summary of the depression guidelines are given – for Canada a guideline from 2016 is listed – how was the Canadian guideline during the time period 2009-2014?	This is a good point. We have switched the description in Table 1 to the 2009 guidelines, which are not as clear as the 2016 guidelines but in light of the study time period are more appropriate to cite
Result section – 1st paragraph: …Canada (26.8%) and Taiwan (23.4%) and – drop the last "and"	We have modified the text according to the reviewer's suggestion.
Result section – 5th paragraph: …the mean dose varied from 60% of (0.6) of – change to: the mean dose varied from 0.6 of	We have modified the text according to the reviewer's suggestion.
Reviewer 3	
This manuscript concerns a comparison between antidepressant use in older adults in Canada, UK, USA, and Taiwan. According to the authors, there are remarkable differences in incidence and prevalence [not surprising considering the different guidelines] and a huge proportion was prescribed for the off-label indication chronic pain. If so, this raises important questions regarding the adequacy of antidepressant pharmacotherapy. Although the topic is not new, the size of the country-comparison is.	We agree
Essential in this descriptive study is the question whether identical measures were used and how the source populations are defined/selected. This is described in the methods but as the healthcare systems are different, it is unsure how this impacts the results. For instance, the role of the primary care physician in the USA is different from a GP in the UK. Also, the USA has health maintenance organizations which cover another socioeconomic population than Medicare. Also the databases are different. For instance, GP databases work with prescriptions but as there is often not a link to the pharmacy it is unclear if all prescriptions were filled.	In the discussion, we outline important aspects of the respective health systems that may influence the incidence of antidepressant use and choice of therapy (second paragraph). In the second last paragraph we outlined other differences, such as those outlined by the reviewer, that may influence incidence and prevalence. We have added the issue of measurement using prescription vs dispensing data which will influence estimates of incidence of prevalence because of primary non-adherence. Our own studies have estimated that the incidence of primary non-adherence with antidepressants is approximately 37% (Tamblyn et al. Ann Intern Med. 2014;160(7)).
The high percentage of the indication depression in Quebec suggests a healthcare/reimbursement flaw.	In the third paragraph of the interpretation, we explained why the Montreal/Quebec City cohort would have double the prevalence of depression compared to other jurisdictions. This is because the EMR used by these physicians is the only one in the jurisdictions studied to require the physician, for each prescription written, to document the treatment indication from drug-specific health problem lists. The selected treatment indications are added to the patient's problem list, and the treatment history is documented for each health problem (Tamblyn et al. JAMIA. 2006;13(2). The validity of these data has been documented (Eguale et al. Drug Safety. 2010;33(7)).
How can an incidence of 0.7% [UK] lead to a prevalence of 10% in a 5-year period?	Thank you for picking this up as there was an error in the denominator used in this calculation, as the numerator was based on the 10% sample we obtained

	from the total population of elderly. To avoid confusion, we have revised this table to only include statistics from the random samples for Ontario, Montreal and the United Kingdom.
Why did the authors calculate age-adjusted rates and not sex- and age-adjusted. Prescribing antidepressant differs between the sexes and I do not find that back.	We have added sex standardized rates.
I guess lithium was also excluded [like MAO-inhibitors]	Yes
Is the study period 1st January 2009 through 31st December 2014 ?	Yes. We have added this detail to the methods section.
Did the authors account for mortality during this period? Was that complete ?	For the statistics shown in Table 1, a person was included in the denominator if they were alive at the start of the follow-up period. For the analysis of treatment episodes (Table 6A & B), the individual had to have a full 48 months of follow-up, and be alive during this period.
The prevalence ratios in table 4 assume that overlap of depression was with only one co-morbid condition. This seems unlikely.	We agree, but the purpose of this table was to identify the likelihood for each co-morbid condition being associated with depression, as it may influence choice of therapy.
It is unclear to me how the prevalence ratios in table 4 were calculated	The prevalence ratio was calculated as the prevalence of the health problem of interest among depressed individuals, divided by the prevalence of the health problem among non-depressed individuals. For example, in table 4, the prevalence of alcohol/drug abuse among depressed individuals is 450/7,484 = 0.06, whereas among non-depressed individuals it is (1,989 - 450) / (60,366 – 7,484) = 0.029. The prevalence ratio is therefore 0.06/0.029 = 2.1. We have included a description of how prevalence ratios were calculated in the analysis section of the methods.
The numbers in table 2 and 3 differ for Ontario. In table 2 the number of new users is 306,197 whereas it is 60,366 in table 3	Due to privacy issues, we were required to take random samples of the population in Ontario, Montreal and the United Kingdom. To avoid confusion, we have revised Table 1 to only include incidence and prevalence in the sample.
'The variation in approach in the use of antidepressants for depression and chronic pain in different countries creates the natural experiment that could generate unbiased evidence of potential harms and benefits'. [p.10; 4th para]. This overoptimistic statement should be explained. I disagree, it shows what a mess antidepressant prescribing is and what a burden for healthcare.	We have decided to delete this sentence.
The huge appendix can be deleted. Just mention that is available on request	We have made this change.