Author’s response to reviews

Title: Prescribing trends of antipsychotics in youth receiving income assistance: results from a retrospective population database study

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Version: 2 Date: 18 March 2013

Author’s response to reviews: see over
March 17, 2013

Dear BMC Psychiatry Editorial team:

Here are our responses and revised paper based on the astute and excellent feedback of the reviewers. We look forward to your correspondence.

Kind regards,

Andrea Murphy on behalf of all authors

Response to reviewers’ feedback

Review one: Irene Eriksson

Major compulsory revisions:

1. Comments on the Abstract

a) The background is scarce and does not state the purpose of the study.

We changed the background to:

Antipsychotic (AP) utilization is increasing internationally in youth. We aimed to characterize AP prescribing in a population of low-income youth in Nova Scotia.

b) The results section: the statements "Antipsychotic use doubled over the study period" and "males received more APs" are ambiguous.

We understand the reviewer’s point and deleted this statement. Further elaboration on the statement would put us beyond the word count. The next statement adequately describes the trends in AP use for the purpose of the abstract.

We changed the males statement to be:

“.... and 66% of all AP users were male.”

c) The conclusions: “This study raises questions about antipsychotic prescribing given the wide range of diagnoses, doses, duration and psychotropic co-prescribing for all ages, even those under 5 years old.” This study describes the use in patients <=25 only, hence, “all ages” is misleading.
We have changed the last statement to read:

This study raises questions about antipsychotic prescribing in those 25 years of age and under given the wide range of diagnoses, doses, duration and psychotropic co-prescribing.

2. Comments on the Background

“We aimed to characterize various aspects of AP prescribing (e.g. indication/diagnoses, prescriber type, antipsychotic type, etc.)” is vague. Be specific about the purpose of the study.

We are assuming that the reviewer is requesting more details regarding what we characterized so we listed the pertinent information from our analyses more specifically. We also adjusted this sentence as a result of comments from a minor revision request.

Here is the new statement:

Using a retrospective population database design, we aimed to characterize AP prescribing by prevalence, drug, dose, duration, indication/diagnoses, prescriber type, psychotropic co-prescribing, morbidity, and mortality in a population of low income youth in Nova Scotia.

3. Comments on the Methods

a) The inclusion and exclusion criteria for the study cohort are not provided.

We have changed the first sentence to read:

The cohort in this retrospective population based study of prescription drug claims from October 1st, 2000 (2000Q3) to September 30, 2007 (2007Q2) included all Pharmacare beneficiaries 25 years of age or younger receiving Community Services in Nova Scotia, Canada.

b) This is a database-based study and it is essential that authors provide a very clear description of each database used.

We have provided a link to the databases used to facilitate this process for readers. In this way, they can see the kinds of information that are included in each data set. We have added this sentence at the end of the “Patients - cohort and databases” section:

Specific details of the databases used are available at http://metadata.phru.dal.ca.

c) It would help if the authors explain the purpose of identifying “long-term users”. Also, it should be clear from reading the methods section what analyses were performed (and why) for this sub group only.

This group was used to examine psychotropic co-prescribing and non-psychiatric comorbidity in those with longer exposure to antipsychotics.
d) The definitions of incident and prevalent prescriptions are unclear. Did the authors use a 6 months interval prior to October 1, 2000 to identify any dispensation of antipsychotic medications that might have occurred prior to the study period?

*We clarified this to be:*

*Incident prescription of an AP was defined as the first recorded AP prescription during the observation period of October 1st, 2000 to September 30, 2007. It excluded those individuals with AP prescriptions in the 6 months prior to October 1, 2000. In each quarter, a prevalent user was an individual for whom an AP prescription was dispensed. The Pharmacare program reimburses a maximum of 100 days of dispensed medication at each prescription fill.*

e) In the “Identification of diagnoses” section – consider adding a graphical representation of the algorithm used to identify diagnoses attributable to antipsychotic medication use.

*We made a new figure (Figure 1) for this request. As such, all other figures in the document have been relabeled.*

### 4. Statistical Analyses

a) I recommend that the description of time series analyses is assessed by a statistician experienced in conducting this type of analysis.

*We will defer to the editorial team if they would like us to request a third party review of the statistical analyses.*

*In our acknowledgement section, we state:*

*“Shakhawat Hossain and Yan Wang of the Population Health Research Unit worked individually with the research team as data and statistical analysts.”*

*The time series analyses was conducted individually by both S. Hossain and Y. Wang. Shakhawat Hossain is a statistician and at the time of our research, was a database analyst employed at PHRU and not part of the investigative team. He provided the statistical consultations for these specific analyses and the details on the analyses that were incorporated into the manuscript. Here is Dr. Hossain’s current bio http://ion.uwinnipeg.ca/~shossain/*.

b) I noted that the Results section provides the results of some survival analyses, but the authors do not mention these analyses in the statistical analyses section.

*Thank you for pointing this out. We added the following to the methods (second last sentence):*

*We conducted a Cox proportional hazards regression to model survival, controlling for age and gender. Kaplan-Meier survival curves were generated.*
5. The Results section

a) The authors should be careful with implying that “over one-third of antipsychotic treatments were started during an inpatient stay”. In my opinion the manuscript does not provide information to arrive at such statement.

We deleted the latter half of the sentence and it now reads:

Hospital discharge diagnostic information was used as the source 36% of attributable diagnoses.

b) In “Doses prescribed”: “Dosing of olanzapine appeared to be higher than dosing of the other SGAs likely as a reflection of its greater use in the treatment of psychosis.” - the “likely as a reflection of its greater use in the treatment of psychosis.” should be in the Discussion.

The latter half of the sentence noted above was deleted and now reads:

Dosing of olanzapine was higher than dosing of the other SGAs.

c) In “Duration”: consider using a table to report the “median (IQR) duration of AP use”.

We considered this prior to our initial submission but decided that the information was brief enough to be presented in a short paragraph.

Minor Essential Revisions
1. Incomplete sentences and sentences that appear to contain fragments:

a) “We designed as a mixed methods study with the first phase consisting of a retrospective population database study, which is reported here.”

We have adjusted this sentence and the one immediately following (which is a sentence included as a major revision comment above):

We conducted a mixed methods study with two phases with an initial quantitative phase followed by a qualitative phase. Using a retrospective population database design, we aimed to characterize AP prescribing by prevalence, drug, dose, duration, indication/diagnoses, prescriber type, psychotropic co-prescribing, morbidity, and mortality in a population of low income youth in Nova Scotia.

b) “The maximum allowable number of days for Pharmacare reimbursement is 100 days supply.”

This sentence was changed to:

The Pharmacare program reimburses a maximum of 100 days of dispensed medication at each prescription fill.
c) "The hierarchy includes priorities assigned based on the databases from the diagnosis was extracted (i.e. the source), the provider type, and the diagnoses."

*We changed the sentence and also made reference to the figure that was recommended.*

The hierarchy included which database the diagnosis came from, the provider type (e.g. psychiatrist vs general practitioner), and the diagnoses itself (e.g. psychosis vs conduct disorder) (Figure 1).

d) “Information about the type of prescriber of the was available for 52% of incident antipsychotic prescriptions.”

*We changed this to:*

Prescriber type was available for 52% of incident antipsychotic prescriptions.

e) “It is apparent from our study, and the work of others, [2, 14] the use of SGA agents in younger age strata are used at an increasing rate.”

*We changed this to:*

The prevalent use of SGAs in younger age strata in our study is similar to others.[2, 14]

f) “Our findings contextualized with the current literature demonstrate that there is a need for capacity building in clinical areas in which these agents are used and with a research enterprise to enhance our understanding of appropriate use and whether targeted interventions are needed to alter current practices.”

*This last statement in the conclusion has been changed to:*

The cumulative body of research regarding antipsychotic use in youth demonstrates that there are gaps in knowledge regarding safe and effective use of these agents. Translation and implementation of knowledge to inform policy and practice towards appropriate use is needed.


*This was changed in the text and figure titles.*

3. “Patient location” – same as place of residence?

*We changed this to patient residence.*

4. “International Classification of Diseases (ICD) codes were used to determine
diagnoses of encrypted unique patient identifiers.” – this is an example of a sentence that needs to be revised for clarity.

We changed this sentence and combined it with the sentence following. It now reads:

*International Classification of Diseases (ICD) 9 and 10 codes were used for diagnostic information from the MSI Physician Billings database and CIHI DAD, respectively.*

5. “Multi-counting was avoided by only counting the first time the ICD code appeared for each unique identifier.” – this is a technical detail that can be omitted.

We deleted the sentence.

6. “Mean prescribed daily doses were calculated for each AP using Pharmacare claims and the days supplied field.” – unclear. By “Pharmacare claims” do you mean a certain variable or the whole database?

We have changed this. It now reads:

*Mean prescribed daily doses were calculated for each AP using the days supplied field.*

7. In statistical analyses: “Age categories for claimants were divided 0-5, 6-10, 11-15, 16-20, and 21-25.” Sentence can be omitted as the age stratification will be obvious from the tables.

We deleted the sentence.

8. Recommendations for the tables/figures:

a) Table 3 reports a mix of numbers, with percentages calculated using inconsistent denominators. I tried to think of alternative ways of presenting these data – please see attachment.

Thank you for your suggestions. We reviewed the information and in attempts to add clarity we changed our table.

b) Table 4 – please provide the units for the dose

We changed this to be “mean mg dose (SD)” in the left column, second row of the table.

c) Figure 5 – a table might be better for reporting these data

Thank you for the suggestion. We considered this and prefer the figure.

d) Figure 6 – consider reporting proportions instead of counts

We changed this figure.
Reviewer two:

Reviewer: Andrew Bulloch

Major revisions:

1. The procedure to define the most attributable diagnoses for Pharmacare prescriptions needs further explanation. This was based on literature and clinical experience. Perhaps some examples would clarify exactly how this occurs. This is a critical issue.

   We have modified the Identification of diagnosis subheading in our methods section. Directly addressing this concern are the following changes:

   The addition of Figure 1, which is a flow diagram of how the diagnostic hierarchy for identifying the most attributable diagnosis

   Re-written components of this subheading to make it more clear how the attributable diagnoses were determined. For example, “... A diagnostic hierarchy was applied to cases in which more than one diagnosis occurred during this time period to determine the most attributable diagnosis for AP use. The hierarchy included which database the diagnosis came from, the provider type (e.g. psychiatrist vs. general practitioner), and the diagnoses itself (e.g. psychosis vs. conduct disorder) (Figure 1). For databases, CIHI-DAD diagnoses received priority over MSI diagnoses. For example, if two diagnoses were received around the time of the incident AP prescription and one diagnosis was from a mental health related hospitalization (i.e., CIHI DAD) and another from a general practitioner per the MSI database, the hospitalization diagnosis was designated as the most attributable to AP use. ...”

2. Fig 4 is very briefly described. Are there trends re the age groups? If not say so.

   We have modified the 2nd and 3rd sentences to more clearly indicate no changes in dosing were observed: “Average dose per age group was shown not to change or to decrease somewhat per antipsychotic over this period. Figure 5 shows the mean overall olanzapine-equivalent dose per age group for each antipsychotic.”

3. Ditto re Fig 5. Some disorders stand out, as pointed out, whereas others are remarkably similar...any other trends?

   Time trends regarding duration of use were not formally investigated. No changes were made to the manuscript.

4. Ditto re Fig 6!

   Time trends regarding co-prescribed psychotropics were also not specifically analyzed. No changes were made to the manuscript.
5. The reviews in CJP (Dec 2012) in this area should be cited and integrated into the text.

*In our discussion (2nd para, 2nd sentence) we now reference the review of epidemiological studies published by Patten et al (Dec 2012). We have added some points regarding the similarities of this work to ours and have also taken the opportunity to reference the Pringsheim paper again.*

**Minor revisions: A few points of clarification would aid the reader:**

1. Re Table 2, the codes are for Bipolar I, why was Bipolar II excluded?

   All types of bipolar disorder were included. ICD-9 codes 296.8 and 296.9 are typically used to identify non-bipolar I disorder diagnoses (e.g., bipolar II and bipolar NOS). All forms of bipolar disorder are covered in ICD-10 by code F31, which we also included.

2. Figures: it is hard to discern one shade of line from another. Different types of broken lines could be used, or color if the journal is agreeable. Perhaps the journal can assist here. Similar comment re bars eg in Fig 3.

   *The figures use different colours that are well contrasted from each other and also from a white background. We wonder if the reviewer was using a printed copy from a black and white printer when completing the review. We have left the figures’ colours unchanged. If you would like us to change the figures such that they can be differentiated using a black and white printed copy please let us know.*

3. The legend for Fig 2, although obvious, needs explanation (“FGA” etc)

   *We have added the following to the legend: FGA: first generation antipsychotics; OLZ: olanzapine; QTP: quetiapine; RSP: risperidone*

4. Costs section: how do they compare to inflation?

   *We prefer to leave this section as is. We only report costs for the purpose of sharing information. We have intentionally avoided any health economic overtures as this was not intended to provide any form of economic analysis.*

5. Discussion: first two paragraphs are very wordy and somewhat speculative...could be shortened.

   *The initial paragraph has been reduced by about 50%. The second paragraph was also simplified slightly.*