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Title	Trends in utilization and cost of antipsychotics among older Ontarians from 2007 to 2013: the effects of the introduction of newer agents and changes in generic status: a Repeated Cross-Sectional Study
Authors	P.D. Foster BSc, X. Camacho MMath, S. Vigod MD MSc, Z. Yao MD MS, D.N. Juurlink MD PhD, J.M. Paterson MSc, M.M. Mamdani PharmD MA MPH, Diana Martins MSc, T. Gomes MHSc
Reviewer 1	Dr. A. Mark Clarfield
Institution	Soroka Hospital, Geriatrics, Medical School for International Health, Ben-Gurion University, Beer-sheva, Israel
General comments (author response in bold)	<p>Comments to the Author</p> <p>1) The issue of antipsychotic use in the elderly is an important one.  <b>We thank the reviewer for their comments.</b></p> <p>2) That being said, it is not immediately apparent from the findings what exactly the authors feel is their significance.  <b>We have attempted to clarify our conclusions with the following statements in the discussion section:</b>  <b>While prescribing preferences have shifted within the class as product availability has changed, atypical antipsychotics are increasingly a mainstay of geriatric psychiatry despite these safety concerns.</b>  <b>...despite a drop in atypical antipsychotic costs following the introduction of several generic formulations, expenditures related to these drugs are once again rising.</b></p> <p>3) The changes in the status of drugs (generic, new issues) during the study period is a bit confusing and needs clarification.  <b>The number of changes is indeed significant, and we believe that adding the following as a supplemental table may help resolve any ambiguity. See attached documents for properly formatted table.</b>  <b>Event Quarter Legend</b>  <b>Risperidone patent expiry 2006-Q3 Patent Expiry</b>  <b>Olanzapine patent expiry 2007-Q3 New Agent Introduced</b>  <b>Quetiapine patent expiry 2008-Q4</b>  <b>Paliperidone marketed 2009-Q3</b>  <b>Olanzapine rapid dissolve patent expiry 2010-Q1</b>  <b>Quetiapine extended release marketed 2010-Q4</b>  <b>Ziprasidone marketed 2010-Q3</b>  <b>Aripiprazole marketed 2011-Q4</b>  <b>Injectable paliperidone marketed 2012-Q1</b></p> <p>4) For those not familiar with the province of Ontario, I suggest adding a few details: size, population, % over 65, health budget, amount spent on drugs, coverage for seniors. I happen to have grown up in Ontario, but imagine that many readers of CMAJ will be from outside Canada and need some background. For my part I do not know the data on some of these suggested additions and it would help to give the article some context.  <b>Inserted text in bold: In 2010, the Ontario government, which at the time serviced a population of 13.2 million including nearly 2 million seniors with a health care budget of 46 billion Canadian dollars, reduced generic drug prices from 50% of the brand-name equivalent to 25% (13-15).</b></p> <p>5) Perhaps the most important focus relates to the line on p 11 (44-49) in the conclusion; a bit more on why doctors seem to be attracted to non-generics etc would be helpful.  <b>Inserted text: Possible reasons for this increase in use of newer agents include increased marketing of brand-name therapies and a relative paucity of third-party data concerning medium- to long-term risk of side effects (27-30).</b></p> <p>6) Has the use of the "new" anti-psychoics crowded out prescriptions of the "old" and what effect did the black box label have on doctors prescribing habits perhaps to go back to the "old" (not they are so safe either  <b>We have not addressed typical antipsychotic prescribing in this study; however, we agree that the effect of black box warnings on the observed shifts within the atypical antipsychotic class is of great interest. We have added the following comment to our discussion to address this possible relationship: Notably, risperidone and olanzapine were subject to safety warnings regarding their use in older individuals in 2002 and 2004, and a blanket statement urging caution in geriatric use of atypical antipsychotics followed in 2006; our data shows the corresponding decrease in risperidone and olanzapine prescribing countered by an increase in quetiapine, resulting in no observable net effect in use of this drug class (2).</b></p>
Reviewer 2	Dr. Colleen Maxwell
Institution	University of Waterloo, Pharmacy, Waterloo, Ontario
General comments (author response in bold)	<p>The paper would be strengthened with further consideration of the following issues:</p> <p>1. It would be helpful for the authors (in their Introduction) to expand on the possible reasons underlying the 'potential for rapid uptake of newer brand-name agents...' (pg. 5, lines 57-58).  <b>Prescriber preference for newer brand-name agents is a very complex subject, and we have added</b></p>

**a brief comment on brand name drugs being marketed with favourable side effect profiles, including reference to several more in-depth studies of this phenomenon and possible explanations.**

2. The rationale (and relative strengths vs. limitations) behind the particular approach in calculating the denominator for the rates is a little unclear (at least in terms of other possible options here) — some further comment on this is warranted.  
**We calculated rates as the number of individuals who used each atypical antipsychotic, divided by the total number of people who were eligible for drug coverage and alive in each quarter. In our opinion, this is the appropriate denominator as our denominator reflects the pool of individuals who are eligible for our study and who are eligible for drug coverage to receive an antipsychotic through the ODB. We are unaware of any other potential alternative denominators given our study design and objectives, and therefore have not made any changes in response to this comment.**

3. There are some potentially interesting factors that were not examined in the current analyses - despite the likely availability of relevant data (e.g., how did utilization trends vary by age group; sex; and, in particular, by setting [community vs. LTC]?).  
**We agree that these are of great interest and have deferred further investigation in hopes of keeping this particular study concise.**

4. Some caution is warranted regarding the scale used for some of the axes in the Figures (particularly the y-axis in Figure 2 - which is somewhat misleading in terms of the magnitude of change observed).  
**We thank the reviewer for pointing this out. We have changed the range of our y-axis to go from 10 to 30 users per 1000 seniors. We believe that this achieves a balance of not overstating the shifts in prescribing patterns, while still allowing the reader to view the statistically significant change in trends that occurred at the end of 2009. If the editors would prefer us to make further changes to the figure to reflect this, we would be happy to do so.**

5. The cost findings are a little difficult to follow in the text of the Results section and it might be helpful to present these data in Table format.  
**Table 1: Total quarterly costs and cost per user of atypical antipsychotics at start and end of study period**

Atypical Antipsychotic	First Quarter, 2007	First Quarter, 2013
Total Cost	\$10,993,284	\$8,518,981
% Overall Costs	217.74%	137.58%
Risperidone	\$2,201,115	\$2,061,866
Olanzapine	\$5,815,987	\$1,890,328
Quetiapine	\$2,976,182	\$3,365,143
Paliperidone	\$394,855	\$953.76
Ziprasidone	\$65,639	\$362.64
Aripiprazole	\$741,151	\$349.60

6. The first sentence of the Discussion seems a little misleading given the rather modest increase observed in rates (specifically, the phrase, "...large shifts in atypical antipsychotic prescribing...").  
**Thank you for pointing out the ambiguity in our description of the large shifts within the drug class. We have added the following comment on the modest overall change in use for clarity: Over the study period, we found large shifts in atypical antipsychotic prescribing preferences and drug costs among seniors in Ontario, and a modest overall increase in the rate of atypical antipsychotic prescribing following the introduction of new brand name agents to the public drug formulary.**

7. The Discussion should be expanded to include further comment on the possible reasons for the trends observed for the older atypical agents (particularly the increase observed for quetiapine vs. decline observed for the other 2 agents in Figure 1).  
**We agree with the reviewer, and in response to this comment and comments by the earlier reviewer, we have inserted text into our discussion to explain the shifts away from risperidone and olanzapine prescribing towards quetiapine.**  
**Inserted text: Notably, risperidone and olanzapine were subject to safety warnings regarding their use in older individuals, and a blanket statement urging caution in geriatric use of atypical antipsychotics followed; our data shows the corresponding decrease in risperidone and olanzapine prescribing countered by an increase in quetiapine, resulting in no observable net effect in use of this drug class (2).**

8. It would also be helpful for the authors to elaborate on the limitations of their analyses and data in their study limitation section (e.g., in terms of absence of data regarding appropriateness [of use] and other factors potentially underlying prescribing preferences and utilization trends).  
**We have expanded our limitations section to reflect some of the other data limitations that the reviewer outlines above.**  
**Inserted text: Second, we assessed overall patterns of use and not patient information such as diagnoses and prescription information such as dose or length of use; therefore we are unable to draw conclusions regarding the appropriateness of the observed prescribing habits, nor the clinical reasoning underlying the observed preferences for certain agents.**