Article details: 2014-0009	
Title	Quetiapine nation? 300% increase in quetiapine prescriptions by family physicians in Canada from 2005 to 2012
Authors	David Gomez MD PhD, Aziz S. Alali MD PhD(c), Barbara Haas MD PhD, Wei Xiong MSc, Homer Tien MD MSc, Avery B. Nathens MD PhD
Reviewer 1	Florian Naudet
Institution	INSERM, U669
General comments	I enjoyed this very simple paper which could play a key role in raising awareness of an important health issues in Canada which is probably the same in other countries. This is in the scope of CMAJ. I have just a small remark to say that the augmentation observed could occur because of a real augmentation in prescription but also because a change in coding the data in the database. But the add of other antipsychotics drugs give a part of the answer by controlling (partially) this phenomenon. Another limitation of the study is that the link with efficacy or safety data is not possible. Nevertheless, the striking data presented are simple (descriptive statistics are sufficient) and the discussion is insightful. I suggest to accept the paper without major revisions.
Reviewer 2	Declined to give name
Institution	Declined to give affiliation
General comments	The authors report a descriptive, cross-sectional study of second generation antipsychotic dispensing in Canada since 2005. Overall, this is an interesting question that could be a valuable contribution to the literature. However, I have several questions relating to the data sources used, the key objectives of the manuscript, and the organization of the interpretation and conclusions. Major Comments: 1. The introduction focuses on quetiapine, and so the assumption is that the entire study will be focused on this one drug. However, the first analysis reported describes the use of all second generation APs. More balance in the introduction would help set up the first piece of your manuscript. 2. Page 6, lines 17-39: There are no references provided for the information on the CDTI, and little detail on whether this has been validated, whether this is truly a representative sample, and how well the diagnoses are recorded. This is key to the validity of your findings, and therefore more detail on this database is warranted. 3. Pages 6/7 (Results): Although raw counts of prescriptions are listed, it would be more appropriate to include rates of use, adjusting for changing population size. Given that these medications are generally used in older populations, adjusting for the aging population in Canada would strengthen the results. 4. Page 7, Lines 50-60: The analysis restricted to women is not described in the methods, and it is unclear why this is included here, but not elsewhere (intro, methods or discussion) 5. Page 8, Lines 29-32: The statement that th**e "majority of recommendations for quetiapine were** for off-**label indications" appears to be true, however the data was not presented in the figures in a** way that makes this easy to determine. Currently, the figures are stratified by prescriber, and a separate figure is provided for each indication. Therefore, it is difficult to read across all figures to see which indications are most commonly cited for quetiapine (particularly because the scale of the y-axis changes substantially between figures). It might be more appropriate to change the figures so that each figure has a separate line for each indication, and a separate figure is generated for FPs, Psychiatrists, and Both. This could also be clarified on page 7, lines 32-37: the specific percentages for each of the indications should be listed here. 6. Page 8 Lines 51 **–** Page 11 line 30: The discussion is very long, and includes a great deal of information on the background evidence regarding quetiapine. Some of this could be incorporated into the introduction, or removed entirely. The discussion should tie in the results of the reported study in a more clear way, and should also report the strengths and weaknesses of the analysis. Minor comments: 1. Abstract, Page 2, line 36-41: crude numbers as well as % should be reported **– otherwise it isn't** clear which is prescribed most commonly (since only have relative increases) 2. Abstract, Page 3, Lines 1-5: The conclusion around the preferential increase in the use of quetiapine is true based on the result**s reported in the main text of the manuscript, but this isn't** clear enough in the results section in the abstract. A more succinct description of the relative market

	share of the 2nd generation APs would help drive home this point. 3. Abstract: Page 5, lines 15-22. The objectives are not well described – in particular, the first objective regarding the relative rate of use of the 2nd generation APs is not listed here. 4. Method: Page 6, Lines 1-3: You mention that IMS can identify the specialty of the prescriber. How do they handle prescribers with multiple specialties who may change their type of practice over time? 5. Methods: Page 6, Line 10: Need a reference for the statement regarding the % of prescriptions reported by IMS. 6. Results: Page 6, line **58: In the sentence " increased by only 37% over the same time interval", the number e.g. "from 1.2 to 1.5 million prescriptions" would be informative.** 7. Results: Page 7, Line 1-6: It is written that the number of prescriptions for quetiapine surpassed those of the other medications in 2012, however according to Figure 1, this occurred in 2007. **8. Page 7, Lines 10 and 22: The word "Rate" should be removed since you're not really reporting** rates here. 9. Interpretation: Page 8, line 25: the ratio of 2:1 or the breakdown of quetiapine by specialty **doesn't appear to be reported in the results section. This should be in the results to warrant** discussion in the interpretation section. 10. Page 8, Lines 39-41: These percentages were not reported in the result**s, and so shouldn't be** introduced in the interpretation section. 11. Page 11, Lines 44-**49: The sentence ending in "fasting glucose and insulin, and TSH" needs a** reference. 12. Page 11, Lines 34-51: This concluding paragraph makes recommendations around the monitoring of patients on quetiapine, however that was not the objective or key finding of this study. The study conclusions should focus on what this specific research question adds to the literature.
Reviewer 3	Marie Tournier
Institution	SMBD Jewish General Hospital, Center for clinical epidemiology and community studies
General comments	This is a very interesting and well-written paper on a hot topic: the dramatic increase in the prescription of the second-generation antipsychotics, with coming Public Health consequences. The manuscript is strong and committed, based on unequivocal data. Regulatory agencies will be able to correct tendencies towards over-prescription. Some minor comments in order to improve the understanding of the manuscript: Methods p 6: The outcomes should be more clearly described. What is the definition of a dispensed prescription? Is there a notion of number of days with treatment? Can subjects be included several times? In the same way, are diagnoses associated with recommendations recorded for each subject or for each prescription? p 6, line 22: I do not understand this sentence. Which quarter? Discussion p10, line 17: Authors should explain the results: What are the clinical consequences of the observed sleep changes? Are they significative?
Reviewer 4	Barbara Mintzes
Institution	Centre for Health Services and, Policy Research
General comments	General comments: This is a very interesting and alarming analysis, as it highlights a prescribing trend that is likely to be leading to greater harm than benefit. I have some comments that are mainly relevant to how the methods and results are explained and discussed in the text, and very little related to the analysis itself – this seems very straightforward and the figures are clear and well-presented. Methods (relevant to abstract and methods section) It should be clearer under the methods that the IMS Brogan data were used for total quantity of prescriptions and proportions per specialty; CDTI is a sample used to estimate the proportion for specific diagnoses. The sample size for the latter should be noted. Please add 95% confidence intervals for all estimates based on the sample. Background: Given that the acronym SGA is only used twice, I would just include this in full – it is easier to read a text with as few acronyms as possible. **Paragraph 1: please briefly define 'second-generation antipsychotic' (e.g. antipsychotics first** marketed after xx date or joint mechanism of action, whichever is relevant) and state there which

	drugs are included. **Paragraph 2: The sentence on 'bipolar mania and depression' is unclear as it can be read either to be** another way of saying bipolar disorder (I assume the intended meaning) but can also be read as **'bipolar, mania, and dep**ression (e.g. 3 conditions). You could clarify by putting in single quotes if this is the indication. Please list the indications separately in Canada and in the US. The last sentence is unclear, as manufacturers apply for a new indication is in a specific jurisdiction – there are no global applications. Please explain (internal company decision released in the business press?) The background information requires mention of two highly relevant issues: - court cases in the US over illegal off-label promotion of second generation antipsychotic drugs; - recommendations against prescribing to the elderly with dementia, because of evidence of increased mortality. Additionally, a bulletin was published in British Columbia assessing effectiveness in the treatment of insomnia, and with data on frequency of use in BC for lower doses, used to treat insomnia. This should be referenced in the background and should inform the discussion, as quetiapine was found to be the 9th most frequently prescribed drug in BC, and the majority of prescriptions were at a dose used off-label for insomnia. Therapeutics Initiative. Is use of quetiapine for sleep evidence-based? Therapeutics Letter 79. Sept-Dec 2010. Available at: www.ti.ubc.ca Methods – continued from above: - IMS Brogan Canadian Compuscript database: do data on numbers of prescriptions also provide information on prescription duration? If not, how did you address this issue? Are numbers of prescriptions reported per month? Per year? - CDTI - line 20, page 6 should start as a new paragraph and the first sentence should state which of your analyses were based on CDTI data (e.g. helpful to start with the last sentence so the reader understands the distinction between this database and the Compuscript one. - please explain representative sample (weighted to be representative by age, sex, duration of practice, specialty? random sampling used to invite participants?) Results: - please state a denominator for CDTI data (total # of encounters included – is this for 652 physicians for all of the included years?) - as noted above, 95% CI should be provided in the text when results are reported based on CDTI data - the text of results needs at least one line that includes numbers for aripiprazole, ziprasidone, clozapine and paliperidone. They only appear in methods and figures; the reader needs at least a **statement that less than xx% of prescriptions were for these products, therefore the focus is on…** - it would be useful to know something about the age distribution of off-label use for sleep, anxiety and mood, as well as sex ratios, as this is highly relevant to the concern about use in the elderly (e.g. on page 7) Interpretation: - The first line needs to clarify that this is an increase compared with other second generation antipsychotics - **the second line is no doubt true but some readers will consider 'mood disorders' to be an approved** use because of the approval of use in MDD if other treatments have failed; you should add clarification for this sentence (perhaps the combined % for sleep and anxiety and any indication **that most 'mood disorders' use is off**-label, which is probably the case but needs to be established); when mood disorders are discussed on page 9, please again note what this diagnosis means versus refractory MDD. - **the 22% 'other indications' is very interesting –** what were those ? As this is much more than the 5% for sleep disturbances, the most frequent ones warrant discussion. - line 51 onwards on page 8, and top of page 9: the discussion of indications is confusing. As these **are Canadian data, 'on-label' use is for Canadian indications. The US approved indications are** irrelevant. If, however, US indications are thought to be influential this should be discussed separately in terms of whether or not the uses you found to be widespread are approved in the US. - for the top paragraph page 9 on the Komossa systematic review, please report outcomes that indicate drug benefits on a scale shown to be meaningful for patients. Response is not necessarily **relevant if it is a 50% decline over previous levels. The NNT of 11 reported for 'discontinuation due to adverse effects' versus placebo is confusing. Is this an NNH? Or did more patients discontinue on** placebo? - anxiety disorders, line 39-40: what measures indicated clinical benefit? It would be useful to have

	these results reported as NNT and NNH similar to results above. - **last paragraph: it isn't clear if these reports are based on the same denominator as yours (e.g.** 108,000 recommendations out of same total?); otherwise this is a very interesting and important paragraph. - for evidence on use as a hypnotic, see also the TI bulletin listed above. - on page 10, lines 39 – 46: an open label uncontrolled trial cannot provide a reliable or valid indication of the effectiveness of a drug treatment for sleep; I would suggest deleting this if you are reviewing the data on effectiveness. - **lines 22 to 25, page 11: I'd suggest adding dry mouth as a frequent anticholinergic effect (often** ignored but important for quality of life and dental/ oral health). Lines 41-42, page 11: The suggestion that clinicians adhere to published monitoring guidelines for off-label use could be read to be the major recommendation, as this is the final paragraph. It seems inconsistent with the text above. If you believe, as seems to be stated above, that quetiapine should not be used for anxiety and sleep disturbances in the absence of convincing evidence of benefit, particularly given the serious potential for harm, a statement to that effect is needed (and would flow from the content). The point about monitoring could be made at an earlier point if desired, so it does not look like the paper is concluding by recommending to use, but monitor.
Author response	Reviewer: 1 Comments to the Author I have just a small remark to say that the augmentation observed could occur because of a real augmentation in prescription but also because a change in coding the data in the database. But the add of other antipsychotics drugs give a part of the answer by controlling (partially) this phenomenon. Another limitation of the study is that the link with efficacy or safety data is not possible. Nevertheless, the striking data presented are simple (descriptive statistics are sufficient) and the discussion is insightful. I suggest to accept the paper without major revisions. Thank you for your comment. There were no changes in the coding of the database over the time interval we studied. Reviewer: 2 Comments to the Author The authors report a descriptive, cross-sectional study of second generation antipsychotic dispensing in Canada since 2005. I have several questions relating to the data sources used, the key objectives of the manuscript, and the organization of the interpretation and conclusions. Major Comments: 1. The introduction focuses on quetiapine, and so the assumption is that the entire study will be focused on this one drug. However, the first analysis reported describes the use of all second generation APs. More balance in the introduction would help set up the first piece of your manuscript. We have modified the introduction (final paragraph) to provide details of why we analyzed all SGAs, which was to provide a contrast to quetiapine. The story is more compelling when we contrast use to other drugs. 2. Page 6, lines 17-39: There are no references provided for the information on the CDTI, and little detail on whether this has been validated, whether this is truly a representative sample, and how well the diagnoses are recorded. This is key to the validity of your findings, and therefore more detail on this database is warranted. We have added a reference for this. 3. Pages 6/7 (Results): Although raw counts of prescriptions are listed, it would be more appropriate to include rates of use, adjusting for changing population size. Given that these medications are generally used in older populations, adjusting for the aging population in Canada would strengthen the results. We do not have information from Compuscript on the ages of the individuals receiving these prescriptions, so I do not think assumptions can be made regarding the age distribution of use. The CDTI data suggest that the majority of prescriptions are for depression, anxiety, psychosis and sleep disturbances, which are present in people of all ages.

	I have included the population data for Canada at the start and end years of our study, to contrast the rate of growth of the Canadian population with the rate of growth of prescriptions for the medications. 4. Page 7, Lines 50-60: The analysis restricted to women is not described in the methods, and it is unclear why this is included here, but not elsewhere (intro, methods or discussion) I have deleted the analysis restricted to women from the paper. 5. Page 8, Lines 29-**32: The statement that the "majority of recommendations for quetiapine were** for off-**label indications" appears to be true, however the data was not** presented in the figures in a way that makes this easy to determine. Currently, the figures are stratified by prescriber, and a separate figure is provided for each indication. Therefore, it is difficult to read across all figures to see which indications are most commonly cited for quetiapine (particularly because the scale of the y-axis changes substantially between figures). It might be more appropriate to change the figures so that each figure has a separate line for each indication, and a separate figure is generated for FPs, Psychiatrists, and Both. This could also be clarified on page 7, lines 32-37: the specific percentages for each of the indications should be listed here. We have changed the figures as suggested, with all 4 diagnoses appearing on a single graph, one for psychiatrists and one for family physicians/general practitioners. 6. Page 8 Lines 51 – Page 11 line 30: The discussion is very long, and includes a great deal of information on the background evidence regarding quetiapine. Some of this could be incorporated into the introduction, or removed entirely. The discussion should tie in the results of the reported study in a more clear way, and should also report the strengths and weaknesses of the analysis. We have shortened and modified the discussion, incorporating the feedback of all reviewers. Minor comments: 1. Abstract, Page 2, line 36-41: crude numbers as well as % should be reported – **otherwise it isn't** clear which is prescribed most commonly (since only have relative increases) I have added this information to the abstract. 2. Abstract, Page 3, Lines 1-5: The conclusion around the preferential increase in the use of **quetiapine is true based on the results reported** in the main text of the manuscript, **but this isn't** clear enough in the results section in the abstract. A more succinct description of the relative market share of the 2nd generation APs would help drive home this point. Please see response above. 3. Introduction: Page 5, lines 15-22. The objectives are not well described – in particular, the first objective regarding the relative rate of use of the 2nd generation APs is not listed here. I have added this information to the final paragraph of the introduction. 4. Method: Page 6, Lines 1-3: You mention that IMS can identify the specialty of the prescriber. How do they handle prescribers with multiple specialties who may change their type of practice over time? IMS identifies the primary specialty of the prescriber. I do not think having multiple specialties is an issue for the vast majority of physicians, though this may be problematic for a minority of prescribers. 5. Methods: Page 6, Line 10: Need a reference for the statement regarding the % of prescriptions reported by IMS. A reference for this statement has been added. **6. Results: Page 6,** line 58: In the sentence " increased by only 37% over the same time interval", **the number e.g. "from 1.2 to 1.5 million prescriptions" would be informative.** I have added this information. 7. Results: Page 7, Line 1-6: It is written that the number of prescriptions for quetiapine surpassed

	those of the other medications in 2012, however according to Figure 1, this occurred in 2007. Sorry this sentence was worded poorly. I have changed it as suggested. **8. Page 7, Lines 10 and 22: The word "Rate" should be removed since you're not really re**porting rates here. Changed as suggested. 9. Interpretation: Page 8, line 25: the ratio of 2:1 or the breakdown of quetiapine by specialty **doesn't appear to be reported in the** results section. This should be in the results to warrant discussion in the interpretation section. I have deleted this from the interpretation section. 10. Page 8, Lines 39-**41: These percentages were not reported in the results, and so shouldn't be** introduced in the interpretation section. I have deleted this from the interpretation section. 11. Page 11, Lines 44-**49: The sentence ending in "fasting glucose and insulin, and TSH" needs a** reference. I have added a reference. 12. Page 11, Lines 34-51: This concluding paragraph makes recommendations around the monitoring of patients on quetiapine, however that was not the objective or key finding of this study. The study conclusions should focus on what this specific research question adds to the literature. I have added a concluding paragraph appropriate to the results of the study. Reviewer: 3 Comments to the Author Some minor comments in order to improve the understanding of the manuscript: Methods p 6: The outcomes should be more clearly described. What is the definition of a dispensed prescription? Is there a notion of number of days with treatment? Can subjects be included several times? In the same way, are diagnoses associated with recommendations recorded for each subject or for each prescription? Dispensed prescriptions are filled prescriptions. I have added this in brackets. Number of days on treatment is not included in this database. A single subject can be included several times if they are taking multiple antipsychotics. Diagnoses for each subject are recorded for each drug recommendation made. p 6, line 22: I do not understand this sentence. Which quarter? Per quarter means four times yearly. I have added this in brackets. Discussion p10, line 17: Authors should explain the results: What are the clinical consequences of the observed sleep changes? Are they significative? We have removed this paragraph at the request of another reviewer. Reviewer: 4 Comments to the Author I have some comments that are mainly relevant to how the methods and results are explained and discussed in the text, and very little related to the analysis itself – this seems very straightforward and the figures are clear and well-presented.

	Methods (relevant to abstract and methods section) It should be clearer under the methods that the IMS Brogan data were used for total quantity of prescriptions and proportions per specialty; CDTI is a sample used to estimate the proportion for specific diagnoses. The sample size for the latter should be noted. Please add 95% confidence intervals for all estimates based on the sample. I have modified the initial description of these databases to make this clearer. 95% confidence intervals for the estimates are not available. IMS does not share this information with researchers. Background: Given that the acronym SGA is only used twice, I would just include this in full – it is easier to read a text with as few acronyms as possible. Changed as suggested. **Paragraph 1: please briefly define 'second-generation antipsychotic' (e.g. antipsychotics first** marketed after xx date or joint mechanism of action, whichever is relevant) and state there which drugs are included. This information has been added. **Paragraph 2: The sentence on 'bipolar mania and depression' is unclear as it can be read either to be** another way of saying bipolar disorder (I assume the intended meaning) but can also be read as **'bipolar, mania, and depression (e.g. 3 conditions). You could clarify by putting in single quotes if** this is the indication. Changed to make clearer. Please list the indications separately in Canada and in the US. The last sentence is unclear, as manufacturers apply for a new indication is in a specific jurisdiction – there are no global applications. Please explain (internal company decision released in the business press?) The indications are the same in Canada and the US, so I think the sentence is phrased appropriately. The last sentence means that the application for anxiety indications was retracted everywhere around the globe, not that they made a global application. I have attempted to clarify. The background information requires mention of two highly relevant issues: - court cases in the US over illegal off-label promotion of second generation antipsychotic drugs; - recommendations against prescribing to the elderly with dementia, because of evidence of increased mortality. I agree these are important issues, but with the word limitation of 2500 words I do not feel I can fit this in. Additionally, a bulletin was published in British Columbia assessing effectiveness in the treatment of insomnia, and with data on frequency of use in BC for lower doses, used to treat insomnia. This should be referenced in the background and should inform the discussion, as quetiapine was found to be the 9th most frequently prescribed drug in BC, and the majority of prescriptions were at a dose used off-label for insomnia. Therapeutics Initiative. Is use of quetiapine for sleep evidence-based? Therapeutics Letter 79. Sept-Dec 2010. Available at: www.ti.ubc.ca We have added this reference to our Background section. Methods – continued from above: - IMS Brogan Canadian Compuscript database: do data on numbers of prescriptions also provide information on prescription duration? If not, how did you address this issue? Are numbers of prescriptions reported per month? Per year? We did not evaluate prescription duration. The numbers reported are the number of prescriptions per year. - CDTI - line 20, page 6 should start as a new paragraph and the first sentence should state which of your analyses were based on CDTI data (e.g. helpful to start with the last sentence so the reader

understands the distinction between this database and the Compuscript one.

This has been changed as suggested.

- please explain representative sample (weighted to be representative by age, sex, duration of practice, specialty? random sampling used to invite participants?)

The sample of physicians is representative by specialty and geographically.

Results:
- please state a denominator for CDTI data (total # of encounters included – is this for 652 physicians for all of the included years?)

We do not have an appropriate denominator for this data.

- as noted above, 95% CI should be provided in the text when results are reported based on CDTI data

IMS does not provide 95% CIs for the data to researchers.

- the text of results needs at least one line that includes numbers for aripiprazole, ziprasidone, clozapine and paliperidone. They only appear in methods and figures; the reader needs at least a **statement that less than xx% of prescriptions were for these products, therefore the focus is on…**

I have added that the remaining antipsychotics accounted for less than 20% of prescriptions.

- it would be useful to know something about the age distribution of off-label use for sleep, anxiety and mood, as well as sex ratios, as this is highly relevant to the concern about use in the elderly (e.g. on page 7)

We did not analyze data on age distributions.

Interpretation:
- The first line needs to clarify that this is an increase compared with other second generation antipsychotics

This has been changed.

- **the second line is no doubt true but some readers will consider 'mood disorders' to be an approved** use because of the approval of use in MDD if other treatments have failed; you should add clarification for this sentence (perhaps the combined % for sleep and anxiety and any indication **that most 'mood disorders' use is off**-label, which is probably the case but needs to be established); when mood disorders are discussed on page 9, please again note what this diagnosis means versus refractory MDD.

I have changed this to "quetiapine's expanded use is mostly due to an increase in prescribing by GPs for non-**psychotic disorders"**

- **the 22% 'other indications' is very interesting –** what were those ? As this is much more than the 5% for sleep disturbances, the most frequent ones warrant discussion.

We have taken this information out as recommended by another reviewer.

- line 51 onwards on page 8, and top of page 9: the discussion of indications is confusing. As these **are Canadian data, 'on-label' use is for Canadian indications. The US approved indications are** irrelevant. If, however, US indications are thought to be influential this should be discussed separately in terms of whether or not the uses you found to be widespread are approved in the US.

I have removed the US indication information.

- for the top paragraph page 9 on the Komossa systematic review, please report outcomes that indicate drug benefits on a scale shown to be meaningful for patients. Response is not necessarily **relevant if it is a 50% decline over previous levels. The NNT of 11 reported for 'discontinuation due to adverse effects' versus placebo is confusing. Is this an NNH? Or** did more patients discontinue on placebo?

In response to the reviewer's feedback regarding the findings of Komossa et al on page 9, we have

	modified the paraphraph in two ways. We have added a sentence to indicate the difference in scores between quetiapine and placebo as measured by the familiar Hamilton Depression Rating Scale. We also clarified the NNT and NNH attributions to the dichotomous outcomes included (response, remission, and discontinuation due to adverse effects). - anxiety disorders, line 39-40: what measures indicated clinical benefit? It would be useful to have these results reported as NNT and NNH similar to results above. We have similarly provided comparative quantitative results that indicate how quetiapine compares with placebo and with antidepressants in the treatment of anxiety. - **last paragraph: it isn't clear if these reports are based on the same denominator as yours (e.g.** 108,000 recommendations out of same total?); otherwise this is a very interesting and important paragraph. The referenced paper used the same database, the CDTI. - on page 10, lines 39 – 46: an open label uncontrolled trial cannot provide a reliable or valid indication of the effectiveness of a drug treatment for sleep; I would suggest deleting this if you are reviewing the data on effectiveness. The data from the open label study has been deleted. - **lines 22 to 25, page 11: I'd suggest adding dry mouth as a frequent anticholinergic effect (often** ignored but important for quality of life and dental/ oral health). I have added dry mouth. Lines 41-42, page 11: The suggestion that clinicians adhere to published monitoring guidelines for off-label use could be read to be the major recommendation, as this is the final paragraph. It seems inconsistent with the text above. If you believe, as seems to be stated above, that quetiapine should not be used for anxiety and sleep disturbances in the absence of convincing evidence of benefit, particularly given the serious potential for harm, a statement to that effect is needed (and would flow from the content). The point about monitoring could be made at an earlier point if desired, so it does not look like the paper is concluding by recommending to use, but monitor. We have added a final paragraph to support the content of the paper.