ODPRN ONTARIO DRUG POLICY RESEARCH NETWORK

Stakeholder Comments and Ontario Drug Policy Research Network (ODPRN) Response:

Atypical Antipsychotic Use for the Behavioural and Psychological Symptoms of Dementia in the Elderly

May 28th, 2015

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Executive Summary

COMMENT First paragraph: Suggest referencing Risperidone-restriction of the dementia indication (reference #56)

Response: *The statement: "Only risperidone is indicated for the symptomatic management of inappropriate behavior in patients with severe dementia of the Alzheimer type" is from the product monograph. The Health Canada warnings are discussed in greater detail in the body of the report..*

COMMENT Efficacy: If the atypical antipsychotics are all of equal efficacy, why would a payer opt to pick just one?

Response: *The reimbursement options presented including Limited Use and Exceptional Access Program, allow for choice for antipsychotic use.*

COMMENT Efficacy: for the statement "Overall, our network analysis found that there were no significant differences in the improvement of BPSD across the atypical antipsychotic agents (risperidone, quetiapine, olanzapine, aripiprazole) when compared to placebo". Does this mean each agent was equally effective or all agents were no more effective than placebo? If the latter, why use them at all?

Response: *Further analyses from the systematic review team was done after the stakeholder review. The paragraph has been revised:*

Heterogeneity of outcome measures may have limited our ability to find conclusive evidence within the drug class. Overall, our network meta-analyses found that there were no significant differences in the improvement of total BPSD or BPSD subscales for psychosis, aggression and agitation across atypical antipsychotic agents (namely: risperidone, quetiapine, olanzapine, aripiprazole) when compared to placebo among patients with dementia and BPSD. Additionally, in elderly patients with dementia and BPSD, none of the atypical antipsychotics showed significant symptom improvements when compared to each other or haloperidol. There were no significant differences amongst the atypical antipsychotics in the improvement of Global Measures/Impressions, Cognition, or Caregiver Burden outcomes when compared to placebo or any other active comparator. In contrast to our results, previous meta-analyses have found that select atypical antipsychotics may show some benefit in the management of behavioural symptoms of dementia, although their overall effect is small.[4] Differences between our results and published studies appear to be due to variations in methods of incorporation of subscales (e.g., Cohen-Mansfield Agitation Inventory (CMAI) - aggression subscale) into the analyses.

COMMENT Safety and tolerability: Suggest referencing statement pertaining to the advisory issued in February 2015.

Response: *The reference has been added.*

COMMENT Pharmacoeconomics: Is there an initiative underway to reduce antipsychotic use in LTC facilities by 15-30%?

Response: *Based on initiatives in other jurisdictions, in particular the NHS in UK and Centres for Medicare and Medicaid Services in the States, reductions of use of antipsychotics by 15-30% in long-term care facilities is suggested. More detailed information is available in the Environmental Report.*

COMMENT Reimbursement Options: The report on the Citizen's Panel results are of interest to the reader.

Response: *The report of the Citizen's Panel findings will be included in the final report.*

COMMENT Option 1, Rationale: Clarify whether "review" refers to the systematic review or the results of the network meta-analysis. Especially because review in the body of the report refers to the "drug class review"

Response: *This has been changed to: "Based on our network meta-analysis of efficacy and safety of the atypical antipsychotics in BPSD,…"*

COMMENT Option 1, Rationale, statement: "As well, data indicate limited efficacy…". Does this refer to the results of the network meta-analysis, or the systematic review.

Response: *This has been changed to: "As well, our network meta-analyses indicate limited efficacy of these agents in the management of BPSD.*

COMMENT Option 2: Recommend spelling out LU in text.

Response: *This has been changed as suggested.*

COMMENT Option 2, statement: …restricting their use via listing as Limited Use may result in interruption of care…

- I assume "limited Use" is at the commencement of a treatment rather than in the course of a treatment and therefore may cause a delay rather than an interruption. A delay may cause the team to consider more fully other options which is consistent with your report.

Response: *Thank you for your suggestion. This has been changed to "delay" rather than interruption.*

COMMENT Option 2 LU criteria: tried behavioural modification x 3 different options and Lewy body dementia ruled out. Also suggest including caregiver approval if required....and sign off acknowledging black box warnings.

Response: *Thank you for the suggestions. If OPDP wishes to pursue these restricted options, we will work with the stakeholders and clinicians to develop criteria for LU listing and EAP listing.*

COMMENT Reimbursement Options: I would support AAP being on limited use for patients over 65 years of age.

Response: *Thank you for your comment.*

COMMENT Option 3: Suggest spelling out EAP and adding to glossary.

Response: *This has been changed as suggested.*

COMMENT Option 3, statement: However, this option may lead the clinician to choose more readily available treatment options…

- I think that this refers to the situation where the physician may have tried other things, decided that drug therapy was the appropriate course of action, and now is driven to choose a more readily available treatment option compared to brand name atypical antipsychotics because of the EAP. Maybe it's as simple as clarifying that the change to EAP wouldn't impact whether or not to treat with medication, but may impact which drug treatment option gets chosen.

Response: *Thank you for your comment. The statement has been changed to: However, this option may lead the clinician to choose more readily accessible pharmacologic options that are available as General Benefit on the ODB formulary such as antidepressants, typical antipsychotics or genericized atypical antipsychotics…*

COMMENT Option 3, statement: …and have widespread use in the elderly (data from 2012: 72,488 users in community and 32,580 in long-term care).

- This statement is also made in Option 1 and 2, so could provide the numbers of users there as well).
- Maybe add "in Ontario" to 72,488 users in community and 32,580 in long-term care in Ontario

Response: *The sentence has been changed as suggested: "data from 2012: 72,488 users in community and 32,580 in long-term care in Ontario". As well, it has been added to the other two options as well.*

COMMENT Option 3, statement: "However it is unknown what proportion of these users have an underlying diagnosis of schizophrenia, bipolar disorder or depression. "

- Since reference to wide use among elderly is made in all three options, this statement could be made in the other sections too.

Response: *The sentence has been modified to provide clarity: "However, it is unknown what proportion of these users have an underlying diagnosis of schizophrenia, bipolar disorder or depression; therefore, it is difficult to estimate the number of eligible patients who would meet the EAP criteria for brand-name atypical antipsychotics."*
Please note that the descriptions of the options (previously under Formulary Modernization Options) have been removed from the final version of the report.

COMMENT Considerations for Other Recommendations, Recommendation 1, statement: "Although our review did not evaluate…"

- Does review refer to the drug class review, systematic review or network meta-analysis?

Response: *The sentence has been changed to provide clarity: "Although our drug class review did not evaluate…"*

COMMENT Recommendation 1: Statement: …"have engaged in initiatives that have been shown".

- I see you get to it here to some extent, but it does beg the question about the efficacy of these other initiatives and the next step would be to do a rigorous evaluation of these.... This is touched on in recommendation 2.

Response: *Thank you for your comment.*

COMMENT Recommendation 1: Statement: …"to reduce the rate of antipsychotic prescribing in dementia in long-term care facilities by 15-30%".

- We strongly support this. It would include workforce training in options, family education, public reporting. Priority could be given to transferring best practice from lowest prescribing LTC's to highest prescribing.
- Institutional staff numbers, appropriate training etc definitely would affect prescribing.

Response: *Thank you for your comment.*

Rationale for Review

COMMENT Statement: "Only risperidone is indicated for the symptomatic management of inappropriate behavior in patients with severe dementia of the Alzheimer type".

- Suggest referencing this with Reference 56 (Health Canada warning).

Response: *The statement: "Only risperidone is indicated for the symptomatic management of inappropriate behavior in patients with severe dementia of the Alzheimer type" is from the product monograph. The Health Canada warnings are discussed in greater detail in the body of the report. This statement has been referenced with the product monograph.*

COMMENT Statement: As part of the formulary modernization review, an evaluation of atypical antipsychotics for the management of elderly patients with behavioural and psychological symptoms of dementia (BPSD) was undertaken to provide policy recommendations for these products in Ontario.

- Good alignment. This section here aligns with what we say in the HQO theme report, but is more firm than the language we used

Response: *Thank you for your comment.*

Background Information

COMMENT Third paragraph, statement: Atypical antipsychotics have become the standard of care in the treatment of BPSD…"

- Use of "the standard" seems to imply best rather than most common. Could you consider "Common" and also insert "pharmacological" before care.

Response: *The sentence has been changed as suggested. "Atypical antipsychotics are used more commonly in the pharmacologic treatment of BPSD…"*

COMMENT Fourth paragraph, statement: Although many of the initial studies indicated a higher rate of mortality with atypical antipsychotics compared to typical antipsychotics[31], observational studies and meta-analyses have shown that typical antipsychotics are also associated with an increased risk of death.[32-34]

- For reference 31, I only read the abstract, but from what I read, this meta-analysis looked only at atypical compared to placebo not atypical compared to typical. Perhaps the wrong article was referenced?
- Compared to patients who used atypical? compared to patients who received placebo?
- Just want to point out that the referenced studies show the opposite. For example, the Wang (2005) study referenced showed that users of typical antipsychotics was the same or increased risk of death than atypical. The other referenced studies show Haloperidol having increased (compared to risperidone) risk of mortality.
- This section (in systematic review) describes the increased mortality risk better than in the Background Information section. Suggest editing the background info to better reflect this section.

Response: *Thank you for your comments. The sentence has been revised: "Studies have shown an increased rate of mortality with atypical antipsychotics compared to placebo. More recent observational studies and meta-analyses have shown that typical antipsychotics are associated with an increased risk of death compared to atypical antipsychotics. However, comparative safety within the antipsychotic drug class and measures of level of risk have largely been inconclusive due challenges with residual*

confounding and selection bias that is inherent in observational studies of this population.[32;47] In general, there is conflicting evidence to support differences between atypical and typical antipsychotics, aside from extrapyramidal symptoms. [48-53]"

COMMENT Public plan reimbursement of atypical antipsychotics in Canada, Statement: All typical antipsychotics are available as General Benefit on the ODB formulary. All typical antipsychotics (with the exception of zuclopenthixol) are listed on the ODB formulary as General Benefits.

- Repeated sentence.

Response: *Thank you for your comment. This first sentence has been deleted.*

COMMENT Objective, statement: Final policy recommendations for will be released…

- Needs to be edited.

Response: *Thank you for your suggestion; the final report will be changed.*

Qualitative Team

COMMENT Interesting read...especially the qualitative unit work.

Response: *Thank you for your comment.*

COMMENT Statement: Trends in AAP prescription in dementia care

- For clarity this needs to be spelled out first, then abbreviated. To this point the full term has been used, seems odd here

Response: *This has been changed to atypical antipsychotics.*

COMMENT Statement: Although there are many initiatives to decrease the use of antipsychotics, clinician and nursing participants believed that atypical antipsychotics are not overused in dementia care in Ontario.

- I find this statement disturbing. Is this perceived by clinicians to be non-problematic? If it is, where will any change leadership come from? what about public concern? what about Ontario as over prescribing when compared to other provinces? Could it be reworded?

Response: *Thank you for your comment; please note that this statement is derived from the interviews of the stakeholders, and may not be reflective of current evidence. We have changed this paragraph to read:*

- *Participants perceived that there are significant efforts that are being made to encourage optimal use of antipsychotics. In general, most participants believed that there is a place for atypical antipsychotics in dementia care and it was their opinion that these medications are not grossly miss-used in every setting across Ontario. However, they acknowledged that there are occasions where atypical antipsychotic use could be avoided or monitored more carefully.*

Pharmacoepidemiology Team

COMMENT Recommendation 2: Engage in further research (from Executive Summary)
Statement: "However, use of these agents in the community setting is substantial, with over 55% of

total expenditures for atypical antipsychotics originating from the community."

- Can we determine if this treatment was started in hospital. It may give focus to reduction interventions?

Response: *Unfortunately, we do not have information on medications dispensed in hospital and so we are unable to determine this.*

Current utilization across Canada

COMMENT Statement: Prescriptions for antipsychotics to elderly patients in Canada have increased by nearly 32% over the past 4 years, from 2,912,013 prescriptions dispensed in the last quarter of 2009 to 3,912,013 prescriptions dispensed by the second quarter of 2014 (See Exhibit 2).

- This stands in remarkable contrast to my preceding comment. 32% increase but no problem????

Response: *There are two very different sources of information for these statements. The data provided in the Qualitative Research Team's section is the perspective of the interviewees, whereas the data provided in the pharmacoepidemiology section is from prescription claims information.*

COMMENT Statement: By the second quarter of 2014, Ontario's rate of antipsychotic prescribing to elderly patients was 592 prescriptions dispensed per 1,000 eligible population, which was higher than rates in all provinces except for New Brunswick and Quebec.

- I think in general, there should be a bit more detail on how you are counting numerators and denominators. I know just a little about this, but it is enough to make me ask questions about what exactly is being measured.
- For example, with this sentence - it could mean that one person had a large number of prescriptions, or that others were on the drug only periodically. I realize from a cost perspective, they are still filled - but from the perspective of understanding care - it needs more detail

Response: *We agree that this only gives the reader as sense of the total volume of drug dispensed at population level, however because IMS cannot provide data at the individual level, we have no way of knowing whether one person has a large number of prescriptions or many people have a small number of prescriptions. Later in our report, when we have access to this patient-level data, we have provided further detail on how these medications are dispensed at an individual level (i.e. Exhibits 8, 9and 18 for the Pharmacoepidemiology Report (mean dose dispensed/user)).*

COMMENT Exhibit 2: Have you shared these results with Quebec?

Response: *We share these results through public posting on our website. As well, when appropriate, we have also reached out and communicated with other provinces for additional feedback.*

Trends in Provincially-funded Antipsychotic Products in Ontario

COMMENT Statement: In Ontario, the rate of atypical antipsychotics has increased by 214% and the rate of typical has decreased by 43% between the Q1 2000 and Q4 2013.

- Does this warrant a comment? it is clearly an overall increase in use. this is said a few times, but the difference in the increase and decrease are striking.

Response: *We believe that the large increase in atypical antipsychotics is warranted. By specifying the decrease in typical antipsychotics we are able to demonstrate that this isn't entirely replacement of typical antipsychotics with atypical antipsychotics. We have added a sentence to this effect in the*

report.

COMMENT Statement: In Ontario, rates of both typical and atypical antipsychotic use in the elderly are substantially higher in the LTC setting.

- What do you mean by use? is this prescriptions filled or actually taking the drug?

Response: *All data reported in these analyses are based on prescriptions filled. We are unable to determine whether someone actually took the drug – this is a common limitation to observational research in this area. We have added this as a limitation in our report.*

COMMENT Statement: In the community setting, the rates of atypical antipsychotic use have increased over time (7 per 1,000 eligible in Q1-2000 to 22 per 1,000 eligible in Q4-2013). This rate has continually increased over each quarter in this time period.

- Were you able to derive any findings from the international review? They do not seem to be reported.

Response: *From an international perspective, we reviewed the public plan listings in Australia, New Zealand and in some select US jurisdictions. We did not review the literature on rates of antipsychotic use in these international jurisdictions.*

COMMENT Exhibit 3: Vertical axis does not seem to be labelled correctly (remove the second of)

Response: *Thank you for pointing this out – this has been corrected.*

COMMENT Exhibit 3: What is meant by users?

Response: *Users are individuals who received at least one prescription for an atypical antipsychotic over the quarter. We have clarified this in the methods section of our report.*

Characteristics of elderly antipsychotic users in Ontario

COMMENT Statement: …72,488 community and 32,580 LTC users over the age of 65…

- Is users referring to dwelling people or Ontarians?

Response*: Thank you for pointing this out – it was an error in the sentence. This has been fixed in the revised report to read: In 2013, 72,488 community-dwelling elderly and 32,580 LTC residents over the age of 65 were users of provincially-funded AP in Ontario*

COMMENT Statement: The average age of users was higher in LTC compared to community (84.3 and 77.4, respectively).

- This is probably more reflective of the age distributions in each setting. perhaps you could add a line " this is consistent with the expected age distribution in the two settings."

Response: *We have added a line similar to this in the revised report.*

COMMENT Statement: In both settings, those treated with typical antipsychotics were sicker…

- Compared to those treated with atypical or untreated?

Response: *Thank you for pointing this out – we have clarified that this is compared to those treated with atypical antipsychotics.*

COMMENT Statement: … more likely to have visited a hospital in the past year, but less likely to have seen a specialist.

- Is this any specialist?

Response: *This refers to psychiatrists, geriatricians or neurologists. This is detailed in the footnote of Exhibit 18.*

Patterns of Antipsychotic use

COMMENT Statement: …and one year after initiation of therapy close to half in both the community and LTC still remained on therapy.

- Does this exclude people who died? should it?

Response: *These percentages are obtained from a Kaplan-Meier analysis that takes into account censoring on death. The sentence has been amended to:*
Approximately half of new antipsychotic users persisted on therapy for at least one year (50-60%), with 35-40% of new users discontinuing therapy and the remaining 5-10% dying within one year of follow-up.

Systematic Review Team

COMMENT Safety and tolerability, statement: Published product monographs warn of increased risk of death in the elderly population with dementia

- Is this compared to placebo? typical?

Response: *The product monographs "Black Box Warning" warn of increased risk of death in the elderly population with dementia compared to placebo. The sentence has been changed.*

COMMENT Exhibit 5: For the footnote, this is the wrong set of outcomes I believe. Should be safety outcomes.

Response: *Thank you; the footnote has been changed to four safety outcomes.*

Recommendations for Consideration

Key considerations, efficacy

COMMENT I am a layperson and when I read these bullet points, I ask myself, why use them at all? is this a fair question?

Response: *Further analyses and comments have been provided by the systematic review team (see above). As well, it is noted under Recommendation #1, that: "In some patients, a combination of various treatments (including pharmacological and non-pharmacological) are needed for management of BPSD.*

Key considerations, pharmacoeconomics

COMMENT Savings here could be invested in further quality initiatives around polypharmacy.

Response: *Thank you for your comment. No changes have been made to the monograph.*