

## Comprehensive Research Plan:

# Atypical antipsychotics for the behavioural and psychological symptoms of dementia in the elderly

## A Rapid Systematic Review and Network Meta-Analysis

George Wells, Shannon Kelly, Li Chen, Annie Bai, Amy Johnston, Becky Skidmore

October 9, 2014

## Background

Dementia is a syndrome characterized by a decline in cognitive capacities that results in impairment function but not in alertness or attention. Common types of dementia are Alzheimer's Disease, Lewy body dementia and vascular or frontotemporal dementia (1). It is largely seen in individuals later in life, and more specifically in populations aged 65 years or older where prevalence is estimated to be 9 to 13%.(2) A recent cohort study of Ontario, Canada home care clients revealed that as many as 22% had a diagnosis of dementia (3). Behavioural and psychological symptoms of dementia may include depression/dysphoria, anxiety, irritability/lability, agitation/aggression, apathy, aberrant motor behavior, sleep disturbance and appetite/eating disturbance, delusions and hallucinations, and disinhibition and elation/euphoria (4).

Significant financial, physical or emotional burden may accompany the care of people with dementia, and most forms have no known cure.(5) Drug and non-drug treatment of dementia focuses on maintenance of function and the well-being of patients and their caregivers.(1) A variety of drugs are used on and off-label for individuals with behavioural and psychological symptoms of dementia, yet clinicians continue to struggle to find the 'right' pharmacologic treatment. Atypical antipsychotics (AAP) are increasingly being used to control symptoms of dementia in both community and long-term care settings, however, the use of these medications is controversial given that benefit has not been definitely established and any perceived efficacy may need to be counterbalanced by a potential increase in adverse events. In addition, as many as eight of the nine AAPs licensed for use in Canada may be prescribed off-label to combat symptoms of dementia, and there is concern about the appropriate use of this class of drugs in this vulnerable population.

## Objectives

The objective of this review is to help policy makers and health professionals in Ontario make informed choices about the use of atypical antipsychotics in those with behavioural and psychological symptoms of dementia. We aim to summarize comparative data on the efficacy and safety of atypical antipsychotics in both community and long-term care settings.

## Research Questions

1. What is the efficacy and safety of atypical antipsychotics for the treatment of the behavioural and psychological symptoms of dementia in older adults?
2. Does the efficacy or safety of atypical antipsychotics differ in those who live in community settings when compared to those in long-term care?

## Inclusion Criteria

### Population

Older adults ( $\geq 65$  years of age) with behavioural and psychological symptoms of dementia.

### Intervention

Interventions included in this review are atypical (second generation) antipsychotics:

- Aripiprazole
- Asenapine
- Clozapine
- Lurasidone
- Olanzapine
- Paliperidone
- Quetiapine
- Risperidone
- Ziprasidone

### Comparator

Comparators included in this review are:

- Placebo
- Head-to-head comparisons of the interventions.
- Active-controlled trials comparing atypical antipsychotics to any other medication

Head-to-head studies are defined as any study that compares two or more atypical antipsychotics.

Active-control studies are those that compare an atypical antipsychotic to another drug.

### Outcomes:

#### Efficacy\*

- Behavioural and psychological symptoms of dementia
- Caregiver burden
- Global measures/Impression
- Use of rescue medication
- Cognition
- Activities of Daily Living

#### Safety

- Mortality (non-specific)
- Falls

- Extrapyramidal Symptoms (EPS)
- Weight change

### Studies Design:

Limited to randomized controlled trials. No controlled clinical trials.

Crossover studies must report data for the first treatment period prior to crossover in order to be included in the analysis for efficacy and harms.

### Subgroups:

Care setting (Community, hospital or long-term care (LTC))

For long-term care – study populations must be exclusively from LTC, or LTC residents must form a majority (>50%) of study participants.

### Exclusion Criteria:

- RCTs with < 10 participants;
- Studies not conducted in humans
- Additional criteria as stated in Exhibit 1.

Note: Studies will not be excluded based on the outcomes that are reported. All studies that meet the requirements for population, intervention, comparator and study design will be formally included in the review, however, data will only be extracted for those studies reporting outcomes of interest.

## Methods

The strategy for building and analyzing the evidence base for the efficacy and safety of atypical antipsychotics in older adults with behavioural and psychological symptoms of dementia consists of two fundamental steps\*:

- (1) The ideal method to address the research questions would be a **systematic review and meta-analysis of the available randomized evidence** in the published and grey literature following the methods and procedures outlined in the Cochrane Handbook for Systematic Reviews for Interventions(6). In order to meet the rigorous timelines of the review process, we propose to search broadly for a comprehensive, well-conducted, recent (within 5 years) evidence synthesis that meets the PICO requirements laid out in our inclusion criteria. If we are able to **update an existing high-quality systematic review of the available randomized evidence, we will build onto the studies included in the existing review**. A new literature search will capture studies published from the date of the last literature search to present.

A potentially eligible systematic review will be assessed for quality using AMSTAR(7), and the focus will be on the comprehensiveness of the literature search of the SR and thoroughness of the article selection for the inclusion of all eligible articles. Regarding the literature search, the search strategy

itself will need to be available and our experienced information scientist(s) will interrogate the search to provide insight into its comprehensiveness. If the search passes this critical stage, then the quality of the selection of the titles and abstract and then the articles will be investigated. Information on the process (e.g. 2 independent review authors) and scrutiny of the excluded articles will be used in this assessment, and only if this information is available and meets expectations will the articles from this SR be considered in the review process and the PDFs of the articles imported into DistillerSR, an online tool used to create efficiency in the literature screening and data extraction processes.

Articles identified in an existing SR will be subjected *de novo* to the usual SR processes, namely: data abstraction by two independent review authors (or extraction by one reviewer with checking by a second) and quality assessment. These methods and procedures will be identical to those followed for the articles identified in the updated literature search, and the information on the articles from these two sources will be combined in generating the table of characteristics (with design elements and PICO elements), the risk of bias tables (at the article and review level) and the analysis datasets for pair wise MA and NMA.

NOTE: If we do not locate an evidence synthesis that meets our requirements, we will conduct a **rapid systematic review of the efficacy and safety outcomes prioritized in the PICO**. The rapid systematic review will provide a summary of the best available evidence published in the previous five years, including health technology assessments, systematic reviews and meta-analyses and randomized controlled trials. Searches will be conducted in the same comprehensive manner on both databases and grey literature with only date limitations applied.

- (2) A **Bayesian network meta-analysis of randomized evidence** will be conducted for each of the efficacy outcomes specified *a priori*. The methods and procedures to be followed are those developed by the Canadian Collaboration for Drug Safety, Effectiveness and Network Meta-Analysis (ccNMA), funded by the Drug Safety and Effectiveness Network (DSEN) of the Canadian Institute of Health Research.

\* Input from interested stakeholders made available through evidence submission packages to ODPRN will also be considered.

## Systematic Review Methods Overview

The specific steps for the systematic review are as follows:

### Electronic Search Strategy

The literature search (or update of the literature search) will be conducted by a professional Information Scientist (IS). If an existing evidence synthesis is located, the IS will utilize the existing search strategy to provide an update to the literature search. Databases and grey literature will be searched from the date of the last literature search to present. All citations will be imported into an electronic database

(EndNote X7)

If a de novo rapid systematic review is required, literature search strategies for efficacy and safety will be developed using medical subject headings (MeSH) and text words related to the population, interventions and comparators specified in the PICO statement. Searches will use validated filters for RCTs. All studies will be included regardless of publication status (i.e., unpublished studies) and year of publication. A limited grey-literature search will be carried out by searching the websites of health technology assessment and related agencies, professional associations, and other specialized databases (following CADTH “Grey Matters Light”)(available at: [http://www.cadth.ca/media/is/cadth\\_Handout\\_greymatters\\_light\\_e.pdf](http://www.cadth.ca/media/is/cadth_Handout_greymatters_light_e.pdf)).

### Eligibility and Study Selection:

Studies will be selected and assessed for eligibility de novo whether they were previously included in an existing systematic review that is being updated or through a structured literature search.

Selection eligibility criteria will be applied to each title and abstract by two independent review authors in a standardized manner using electronic tools customized to the project in DistillerSR. Any uncertainties will be resolved by discussion and consensus with a third review author. All studies that meet the selection criteria will be obtained in full-text format. The eligibility criteria (Exhibit 1) will then be applied, and a final decision will be made for inclusion. The reviewers will not be blinded as to the study authors or centre of publication prior to study selection because this can complicate the review process and only weak evidence suggests that this would improve the results.

*Exhibit 1: Eligibility criteria for full-text article screening*

CATEGORY	INCLUSION	EXCLUSION
<b>Databases</b>	OVID Medline, Embase, Cochrane, PsychINFO  Others potentially based on IS input	Other databases not recommended by IS
<b>Grey Literature</b>	Clinicaltrials.com, Health Canada and US Food and Drug Administration Center for Drug Evaluation and Research website for medical and statistical reviews of individual drug products, CADTH Grey Matters Light.	Other grey literature sources
<b>Languages</b>	English	None

CATEGORY	INCLUSION	EXCLUSION
<b>Populations</b>	<p>Humans only</p> <p>Adults ≥ 65 years of age years* with behavioural and psychological symptoms of dementia.</p> <p>*It is possible that RCTs will include a broader age group of dementia patients. In this case, RCTs will meet the population inclusion criteria if the mean age of participants is ≥ 65.</p>	<p>Animal Studies</p> <p>Psychosis or psychiatric symptoms unrelated to the behavioural and psychological symptoms of dementia</p> <p>Other psychiatric conditions.</p> <p>Population included in study arms with a mean age under 65.</p>
<b>Study Design</b>	<p>Randomized controlled trials (RCT), Health Canada, US Food and Drug Administration reports of RCTs, labels and warnings</p> <p>Crossover RCTs must report first period treatment results for efficacy. If not, they will be formally included but no study data will be analyzed.</p>	<p>Any other publications that have no original data.</p>
<b>Interventions</b>	<p>As specified in the PICO statement</p>	<p>All interventions or comparators not explicitly identified in the PICO.</p> <p>Behavioural or non-drug interventions</p> <p>Complex interventions where interventions and comparators are only one component of many.</p>
<b>Duration</b>	<p>All</p>	<p>No exclusions on study duration.</p>
<b>Outcomes</b>	<p>Any – Inclusion decisions for primary studies will not be made based on the outcomes reported.</p> <p>Studies reporting the safety and efficacy outcomes identified in the study protocol will be analyzed.</p>	<p>No exclusions based on outcome reporting</p>

## Data Extraction and Management

All information will be extracted using standardized data extraction forms, which will be developed, piloted, and modified as necessary. Data will be extracted by a single review author, and checked for accuracy by a second independent review author. The following data will be extracted from included RCTs:

1. Study characteristics (Design, duration, setting, funding);
2. Population Characteristics (Age, sex, diagnosis, key baseline characteristics as specified by expert consensus);

3. Eligibility criteria (inclusion and exclusion);
4. Study medications:
  - a. Interventions (dose, durations, route of administration)
  - b. Comparators (dose, durations, route of administration)
  - c. Concomitant medications
5. Numbers screened, eligible, enrolled, lost-to-follow-up, withdrawals;
6. Methods of outcome ascertainment; and,
7. Results for each outcome.

The original, primary publication for each unique RCT included will be used for data extraction, except where multiple publications for a single RCT are found. Multiple publications for a unique RCT (e.g. supplemental online appendices, FDA or HC data, companion publications) will be handled by extracting the most recently adjudicated data for each outcome specified a priori.

### Quality Assessment

We will assess internal validity of included studies using the Cochrane Collaboration's tool for assessing risk of bias(8).

### Assessment of Reporting Bias

Reporting bias will be assessed by use of funnel plots, as well as bias indicators (e.g. Egger, Harbord-Egger), for each outcome.

### Data Synthesis

Data will first be summarized descriptively. A meta-analysis will be undertaken using fixed- or random-effects models when data are available, sufficiently similar, and of sufficient quality. The effect sizes for the identified dichotomous outcomes will be expressed in terms of risk ratio (RR) or odds ratio (OR). In the case of rare events, the Peto odds ratio will be used. For continuous outcomes (e.g., quality of life), the effect size will be expressed in terms of the mean difference (MD) and standardized mean difference (SMD). Pair wise meta-analyses will be conducted using RevMan or R. Absolute differences in the important benefits and harms, absolute mean difference, and relative percent change from baseline will be included in a summary of findings table.

### Assessment of Heterogeneity

The results will be assessed for both clinical and methodological diversity. Clinical diversity will be assessed by checking that the participants, interventions, and comparators are not too different from each other such that combining them is not appropriate. Methodological diversity will be assessed by checking that the studies are similar in terms of study design and risk of bias.

Once it has been established that the studies are minimally diverse and that it makes sense to pool them together in a meta-analysis, an assessment of the statistical heterogeneity will be undertaken by examining the forest plot and result of the I<sup>2</sup> statistic (forest plots provide a visual sense of heterogeneity, and the I<sup>2</sup> statistic indicates the presence of statistical heterogeneity). If the effects observed across trials are inconsistent and vary to a large extent (e.g., I<sup>2</sup> > 50%), the results will be

explored to assess whether the differences can be explained by some clinical or methodological feature.

Inconsistency that cannot be reduced by pre-specified subgroup or meta-regression analyses will lead to an overall estimate with less confidence when interpreting the inference from the meta-analysis.

In this case, a more conservative random-effects model approach would be used so that the uncertainty of the single effect estimate is reflected by wider confidence intervals.

### **Subgroup Analysis:**

Outcomes will be assessed in the identified subgroup (community or long term care setting) in the populations of adults  $\geq 65$  with behavioural or psychological symptoms of dementia. The subgroup were selected to confirm clinically sound hypotheses and as few subgroups as possible were pre-specified and justified against the criteria proposed by Sun et al.; wherein the greater the number of criteria that are satisfied for each subgroup and outcome, the more plausible is the hypothesized subgroup effect (9, 10).

### **Sensitivity Analysis**

Sensitivity analysis will be conducted based on aspects of the PICO statement and study methodology to examine the robustness of the results to the risk of bias and the influence of other variables. In particular, the results of studies at low risk of bias will be compared to those from studies at higher risk of bias; if the results differ substantively, the conclusions of the review will be based on analyses of studies at low risk of bias only. Published literature(Xu, 2013) also suggests that sensitivity analysis based on funding may be appropriate to consider(11).

### **Grading of Evidence**

To help in the understanding of the strength of the evidence included in the review, grading of the evidence for each major outcome will be considered using The 'Grading of Recommendation Assessment Development and Evaluation' (GRADE) approach(12).

### **Bayesian Network Meta-Analysis Methods**

Bayesian network meta-analyses will be conducted using WinBUGS software (MRC Biostatistics Unit, Cambridge, UK) (13, 14). The use of a Bayesian network meta-analysis offers several advantages, including:

1. Drugs have not been compared directly with each other in a large number of studies, and Bayesian network meta-analysis permits combination of all head-to-head, active and placebo-controlled evidence; and
2. The number of individual pair-wise comparisons between the pharmacological treatments for dementia is large, given the large number of available treatment options. As a result, summary effect estimates against a common comparator are likely to be of greater utility for clinical and policy decisions. Further, we will also construct graphical aids to assist in decision making.

We will conduct a Bayesian network meta-analysis. The essential methods for conducting the Bayesian mixed treatment comparison are summarized in Exhibit 2. Both fixed- and random-effects network meta-analyses will be conducted. Model fit for Bayesian analyses will be based on the Deviance Information Criterion (DIC) and comparison of residual deviance to number of unconstrained data points (15-18). Selection of the model/measure will depend on the outcome of interest and the availability of data. Heterogeneity across trials in terms of patient characteristics, trial methodologies, and treatment protocols will be carefully assessed. To further investigate heterogeneity, subgroup analyses and meta-regressions (17, 18) will be conducted to explore the effect of various characteristics including but not limited to the variables considered for the subgroup and sensitivity analyses. We will also perform analyses including removal of studies from the network of therapies that were not scored as being of high quality. We will formally (18) and informally assess consistency between direct and indirect evidence by comparing direct estimates obtained from pair-wise meta-analysis with estimates from the Bayesian network meta-analysis(16, 17). Model diagnostics including trace plots and the Brooks-Gelman-Rubin statistic will be assessed to ensure model convergence. At least two chains will be fit in WinBUGS for each analysis, each employing at least 40,000 iterations, with a burn-in of at least 20,000 iterations(14, 16).(Exhibit 2)

### **Timeline and Deliverables**

On acceptance of this proposal, work will commence. The systematic review, meta-analysis, and Bayesian network meta-analysis will be completed in approximately 12 weeks to 16 weeks. Any re-analyses and a revised final report will be available 4 weeks after receipt of stakeholder reviews.

We will provide a written censored report to ODPRN detailing methods adopted, results, discussion and key outcome highlights within 16 weeks of study protocol approval. Outcome data required for economic evaluation will also be provided to the ODPRN pharmacoeconomics team at approximately 12 weeks.

*Exhibit 2: Methods for Bayesian mixed treatment comparison*

- Bayesian NMAs will be conducted for outcomes pre-specified in the DSEN request, following careful assessment of heterogeneity across trials in terms of subject characteristics, trial methodologies, and treatment protocols.
- The effect estimate chosen (e.g., relative risk) will depend on the outcome of interest and availability of data.
- For reference case network meta-analyses, appropriate comparators will be considered and some comparators may be stratified by dose.
- Both fixed and random-effects models will be conducted; model selection will be based on the Deviance Information Criterion (DIC) and residual deviance.
- R (R Foundation for Statistical Computing, Vienna, Austria) and WinBUGS (MRC Biostatistics Unit, Cambridge, UK) will be used for Bayesian network meta-analyses according to the routine which accommodates evidence structures which may consist of multi-arm trials as developed at the Universities of Bristol and Leicester ([www.bris.ac.uk/cobm/research/mpes/](http://www.bris.ac.uk/cobm/research/mpes/)).
- Specific therapy(ies) will be identified as the reference group for all Bayesian network meta-analyses.
- Posterior densities for unknown parameters will be estimated using Markov Chain Monte Carlo (MCMC) methods.
- Basic parameters will be assigned non-informative or vague prior distributions; more informative priors will be considered after evaluation of the information base and clinical expert advice.
- Point estimates and 95% credible intervals will be used to summarize findings.
- The probability of a comparator being optimal will be estimated for each outcome based on the proportion of MCMC simulations in which its relative measure of effect was best.
- The mean rank for each comparator will also be calculated.
- Consistency between direct and indirect evidence will be formally assessed using back-calculation and node splitting techniques.
- Graphical methods and numerical summaries will be developed for presenting results from network meta-analysis.
- Model diagnostics will also include trace plots and the Brooks-Gelman-Rubin statistic (reference) to assess and ensure model convergence.
- Two chains will be fit in WinBUGS for each analysis, each usually employing  $\geq 20,000$  iterations, with a burn-in of  $\geq 20,000$  iterations.
- Provided sufficient data is available to inform the evidence network, meta-regression and/or sub-groups analyses will be conducted to adjust for key demographic, medical, and study design characteristics to test the robustness of reference case analyses.
- In other sensitivity analyses, studies will be removed from the network that are of poor methodological quality, study design, etc.
- Examine whether novel agent effects are present and estimate their magnitude of effect .

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