Overall Comprehensive Research Plan:

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

October 9, 2014

A. Introduction

Atypical antipsychotics are indicated primarily for the treatment of bipolar disorder and schizophrenia. However, they are used off-label (except for risperidone which is officially indicated for patients with severe dementia) for the management of behavioural and psychological symptoms of dementia in the elderly. There are nine atypical antipsychotics available in Canada: aripiprazole, asenapine, clozapine, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone.

The objective of the antipsychotic use in the elderly drug class review is to provide evidence-informed recommendations for the use of atypical antipsychotics in the elderly through the publicly funded drug program in Ontario. This comprehensive review will include:
- systematic review of the literature,
- cost-effectiveness and reimbursement-based analyses, and drug utilization studies using administrative claims data from Ontario and across Canada,
- environmental scans of national and international drug policies,
- contextualization of the available evidence and experience from other regions, with consideration given to health equity,
- qualitative analyses of perspectives of patients, pharmacists and prescribers,
- identification of barriers to, and enablers of, successful policy implementation,
- recommendation of potential drug reimbursement models.

B. Research Questions

Patient population and inclusion criteria
- Patients 65 years of age and older
- Diagnosis of dementia
- Subgroup analysis: where possible, the review will consider age, gender, socioeconomic status and geographic location (e.g. urban/rural)

Drugs of interest
- aripiprazole, asenapine, clozapine, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone
- all dosage forms (including oral, injectable)

Comparator(s)
- Typical antipsychotics (i.e., chlorpromazine, flupentixol, fluphenazine, haloperidol, loxapine, methotrimeprazine, periciazine, perphenazine, pimozide, pipotiazine, prochlorperazine, thioproperazine, thiothixene, trifluoperazine, zuclopenthixol)
- Antidepressants used as active comparator (e.g., sertraline, trazodone, citalopram)

Proposal	Research unit	Research question(s)
Patient and Healthcare Professional Perspectives	Qualitative Research Program	What is the perceived effectiveness of atypical antipsychotics? What is the impact of atypical antipsychotics on perceived quality of life? What is the experience of patients using atypical antipsychotics regarding access of these drugs? What is the experience of prescribing/dispensing these drugs? To what extent are the policy recommendations feasible and acceptable?
Systematic Reviews and Network Meta-Analyses	Systematic Review Unit	What is the efficacy and safety of atypical antipsychotics for the treatment of the behavioural and psychological symptoms of dementia in older adults? Does the efficacy or safety or atypical antipsychotics differ in those who live in community settings when compared to those in long-term care?
Environmental Scan and Barriers to Implementation; Local and Historical Context	Formulary Modernization Unit	How are atypical antipsychotics currently being funded in public programs in Canada as well as internationally, with an emphasis on accessibility in the elderly? What mechanisms are in place to maximize access while minimizing costs? How successful are these mechanisms in achieving a cost-access balance?
Costs and Utilization Trends	Pharmacoepidemiology Unit	• To examine national and provincial trends in use of antipsychotics in the elderly across Canada • To perform cross provincial comparisons of the trends in antipsychotic use in the elderly • To describe characteristics of elderly patients prescribed publically-funded antipsychotics in Ontario • To investigate the patterns of use of antipsychotics medications among elderly patients with dementia in Ontario • To summarize any observational studies evaluating the safety and effectiveness of antipsychotics in elderly patients
Health Equity	All units	Does sex/gender, age, geographical location (e.g., rural vs. urban) or socioeconomic status play an important role in any of the analyses described?
Reimbursement-based Economics	Pharmacoeconomics Program	What is the current evidence for the cost-effectiveness of atypical antipsychotics versus typical antipsychotics and antidepressants in the management of behavioural and psychological symptoms of dementia in the elderly? Based on a de novo economic model, what is the cost-effectiveness of atypical antipsychotics versus typical antipsychotics and antidepressants in the management of behavioural and psychological symptoms of dementia in the elderly? What is the economic impact of alternative policies for reimbursing atypical antipsychotics versus typical antipsychotics and antidepressants in the management of behavioural and psychological symptoms of dementia in the elderly?

C. Specific Proposals

The Drug Class Review is comprised of five different reviews, namely the Qualitative Research Unit, Systematic Review Unit, Pharmacoepidemiology Unit, Environment Scan/local and historical context and Pharmacoeconomics Unit. Further information on each of the proposals is provided below.

1. Qualitative Review Unit

Objectives:

- To explore factors related to the experience of atypical antipsychotics prescription, dispensing and use in elders with dementia
- To determine the social acceptability of reimbursement policy recommendations for atypical antipsychotics.

Study Questions:

- What is the perceived effectiveness of atypical antipsychotics?
- What is the impact of atypical antipsychotics on quality of life?
- What is the experience of patients/caregivers using atypical antipsychotics regarding access of these drugs?
- What is the experience of prescribing/dispensing these drugs?
- To what extent are the policy recommendations feasible and acceptable?

Phase 1: Exploration of factors affecting the dispensing and utilization of drugs within the drug class of interest

Study Design – This phase will use a qualitative framework approach to guide the data collection and analysis processes. One-on-one interviews and accompanying field notes will be the primary and secondary data sources, respectively.
Study Population – Identified stakeholders for the atypical antipsychotics drug class review include 1) patients over the age of 65 with dementia and/or their family members; 2) primary care physicians (PCPs) and long-term care (LTC) physicians; 3) nursing and support staff; 4)geriatricians; 5) health navigators including discharge planners and community care access centres (CCAC) staff; 6) pharmacists.
Methods – A purposive sampling approach using a convenience sample will be used in order to elicit the specific perceptions and opinions of those who will be involved in or affected by drug policy decisions. Clinicians will be recruited through circles of contact, professional networks and snowball recruitment. Publicly available contact information will also be searched to develop contact lists. An ODPRN member or study coordinator will make contact with clinicians by phone, e-mail or fax. Patients will be recruited through circles of contact. A patient recruitment flyer will also be sent to participating clinicians who agree to distribute the flyer to patients. Patient networks will be used to send recruitment notices by e-mail. General calls for recruitment of all eligible groups will be placed in professional newsletters, e-blasts and social media (Twitter, Facebook).

We will aim to recruit 6 to 8 participants from each identified stakeholder group and 20-25 patients, which may be sufficient to reach saturation amongst homogenous groups of participants.
Outcomes:

- Experiences of the disease condition and of taking atypical antipsychotics
- Experiences accessing atypical antipsychotics
- Experiences treating patients with and dispensing atypical antipsychotics
- Perceived safety and effectiveness of atypical antipsychotics
- Perceived barriers to access and health equity issues
- Any unanticipated issues related to atypical antipsychotics

Phase 2: Assessment of the social acceptability of recommended policy actions related to the drug class of interest

Study Design – RAND Appropriateness Method and Survey

Study Population – Representatives of the general public; stakeholder groups (i.e. among the 6 groups described in Phase 1 above); patient advocacy groups; topic-specific interest groups; and industry

Methods – Members of the general public will be recruited to participate in a meeting/webinar to rate or prioritize a series of questions, discuss these questions, then re-rate and prioritize them. An online survey will also be distributed to assess aspects of social acceptability, including affordability, accessibility, and appropriateness. Survey analysis will include descriptive statistics (e.g., mean, standard deviation, median) and thematic content analysis for open-ended questions.

Outcomes -The primary outcome of interest is the feasibility and acceptability of draft recommendations

2. Systematic Review Unit

Study Questions:

- What is the efficacy and safety of atypical antipsychotics for the treatment of the behavioural and psychological symptoms of dementia in older adults?

- Does the efficacy or safety or atypical antipsychotics differ in those who live in community settings when compared to those in long-term care?

PICO (Population, interventions, comparator, outcomes)

Population	Older adults (≥ 65 years of age) with behavioural and psychological symptoms of dementia.
Interventions	Atypical antipsychotics (aripiprazole, asenapine, clozapine, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone)
Comparator	Placebo, head-to-head comparisons of interventions, active-controlled trials comparing atypical antipsychotics to any other medication
Outcomes: Efficacy	Behavioural and psychological symptoms of dementia, caregiver burden, global measures/impression, use of rescue medication, cognition, activities of daily living
Outcomes: Safety	Mortality (non-specific), falls, extrapyramidal symptoms, weight change

Notes: Efficacy and safety outcome lists may be truncated if we identify many studies for inclusion, as this is a rapid review. We may not perform a meta-analysis (or network meta-analysis) on

all of these outcomes and will work with all stakeholders to select the most important efficacy outcomes and safety outcomes with sufficient data to conduct network meta-analysis. Prior to conducting network meta-analysis, we will ensure that all factors are considered as this analysis only is valid when homogenous studies and patient populations are included.

Methods

For efficacy and safety, RQ1 and RQ2 will be answered using a stepped approach. First, we will search for a well-conducted, recent (last 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.

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.

3. Pharmacoepidemiology Unit

Analysis 1 – National and provincial trends in antipsychotic drug use

Study question: To examine national and provincial trends of antipsychotic use and costs among public drug plan beneficiaries over the past 5 years
Short description of analysis: We will examine trends in antipsychotic drug use between 2009 and September 2014.

Analysis 2 – Cross-provincial changes in prescribing of antipsychotics in public drug programs

Study question: to examine cross-provincial changes in prescribing of antipsychotics in specific jurisdictions across Canada
Short description of analysis: We will examine changes in antipsychotic prescriptions dispensed in Alberta, Saskatchewan, Manitoba, Ontario, New Brunswick, Nova Scotia, PEI and British Columbia between January 2000 and December 2012.

Analysis 3 – Characteristics of elderly patients prescribed antipsychotics in Ontario

Study question: To characterize elderly patients prescribed antipsychotics in Ontario
Short description of analysis: We will look at descriptive characteristics (January 2012-December 2013), including age, gender, socioeconomic status, proportion of patients with diagnosed dementia, number of patients treated with multiple antipsychotic concurrently, of hospitalizations and emergency room visits, various comorbidity measures, stratified by age, long-term care or community dwelling and antipsychotic (atypical or typical)

Analysis 4 – Investigate the patterns of use for newly initiated antipsychotic medications among elderly patients with dementia in Ontario

Study questions: To describe patterns of use for elderly patients with dementia newly initiated on antipsychotic medications

Short description of analysis: We will look at all publically-funded beneficiaries of Ontario age 66 and older who initiated antipsychotic medication over the study period.

Analysis 5 – Summarize observational studies evaluating the comparative effectiveness and safety of antipsychotic use in the elderly

Study questions: To review population-based studies investigating comparative effectiveness and/or safety of antipsychotics in the elderly

Short description of analysis: A review of observational studies will be done investigating effectiveness or safety of antipsychotics in the elderly.

4. Pharmacoeconomic Unit

Research Questions

- What is the current evidence for the cost-effectiveness of atypical antipsychotics versus typical antipsychotics and antidepressants in the management of behavioural and psychological symptoms of dementia in the elderly?
  Based on a de novo economic model, what is the cost-effectiveness of atypical antipsychotics versus typical antipsychotics and antidepressants in the management of behavioural and psychological symptoms of dementia in the elderly?
- What is the economic impact of alternative policies for reimbursing atypical antipsychotics versus typical antipsychotics and antidepressants in the management of behavioural and psychological symptoms of dementia in the elderly?

Methods

RQ1   Systematic Review of Published Economic Evaluations

We will conduct a review of the available literature on the cost-effectiveness of atypical antipsychotics versus atypical antipsychotics versus typical antipsychotics and antidepressants in the management of behavioural and psychological symptoms of dementia in the elderly.

RQ2   De Novo Economic Model

We will develop a new economic model assessing the cost effectiveness of atypical antipsychotics versus atypical antipsychotics versus typical antipsychotics and antidepressants in the management of behavioural and psychological symptoms of dementia in the elderly.

RQ3   Reimbursement Based Economic Assessment

We will develop a model which will identify the optimal policy relating to reimbursing atypical antipsychotics in the management of behavioural and psychological symptoms of dementia in the elderly. Analysis will identify the change in the forecasted drug budget for the next three years associated with different reimbursement policies and will be discussed in conjunction with any impact on clinical effectiveness.

5. Environmental Scan

Research Questions

1. To summarize the pharmacy benefit programs for atypical antipsychotics in Ontario, across Canada and in select international jurisdictions

Method: summary of available information available through the Internet; interviews with individuals at the government agencies responsible for the public drug plan

Interventions: Atypical antipsychotics
   - aripiprazole, asenapine, clozapine, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone

2. To determine the impact of different drug reimbursement schemes for antipsychotics (e.g., restricted access) on patient access, quality of life and/or utilization and costs

Method: Literature review

Intervention: various drug reimbursement schemes, including general benefits, step therapy, special authorization

3. To summarize the guidelines for management of antipsychotic use in the elderly, with a particular emphasis on dementia and related behaviours

Method: Literature review

Intervention: Guidelines/recommendations for the management of behavioural disorders in the elderly patient with dementia