

## Comprehensive Research Plan:

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

Pharmacoepidemiology Unit

October 1<sup>st</sup>, 2014

## ODPRN Drug Class Review Proposal Pharmacoepidemiology Unit

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### **Study Title: Epidemiologic Analyses of Antipsychotic use in the Elderly**

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- Objectives:**
1. To examine national and provincial trends in use of antipsychotics in the elderly across Canada
  2. To perform cross provincial comparisons of the trends in antipsychotic use in the elderly
  3. To describe characteristics of elderly patients prescribed publically-funded antipsychotics in Ontario
  4. To investigate the patterns of use of antipsychotics medications among elderly patients with dementia in Ontario
  5. To summarize any observational studies evaluating the safety and effectiveness of antipsychotics in elderly patients

### **Objective 1: National and Provincial Trends in Antipsychotic Drug Use**

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- Study Design:**
- Design: Time series analysis with quarterly time intervals
- Study period:
- *National and provincial trends (IMS Compuscript):* January 2009 to September 2014
- Population: All provinces
- Data Sources:
- *IMS Compuscript:* aggregated data for all prescriptions dispensed at retail pharmacies across Canada
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<b>Study Population:</b>	<b>Inclusion Criteria:</b>
	<ul style="list-style-type: none"><li>○ All privately and publically-funded antipsychotic prescriptions dispensed in Canada;<ul style="list-style-type: none"><li>○ Atypicals<ul style="list-style-type: none"><li>▪ Aripiprazole</li><li>▪ Asenapine</li><li>▪ Clozapine</li><li>▪ Olanzapine</li><li>▪ Lurasidone</li><li>▪ Paliperidone</li><li>▪ Quetiapine</li><li>▪ Risperidone</li><li>▪ ziprasidone</li></ul></li><li>○ Typicals<ul style="list-style-type: none"><li>▪ Chlorpromazine</li><li>▪ Flupentixol</li><li>▪ Fluphenazine</li><li>▪ Haloperidol</li><li>▪ Loxapine</li><li>▪ Methotrimeprazine</li><li>▪ Molindone</li><li>▪ Periciazine</li><li>▪ Perphenazine</li><li>▪ Pimozide</li><li>▪ Pipotiazine</li><li>▪ Prochlorperazine</li><li>▪ Thioridazine</li><li>▪ Thiothixene</li><li>▪ Trifluperazine</li><li>▪ Zuclopenthixol</li></ul></li></ul></li></ul>

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<b>Outcome(s) of Interest:</b>	Measured over entire study period (quarterly): <ul style="list-style-type: none"><li>• Number and rate of prescriptions dispensed</li><li>• Total cost of prescriptions</li><li>• Total number of units dispensed</li></ul> Report: <ul style="list-style-type: none"><li>• Overall rates of use by province</li><li>• National rates of use by typical or atypical</li><li>• Distribution of prescriptions by age (&lt;65, &gt;65)</li></ul> Stratify all analyses by: <ul style="list-style-type: none"><li>• Antipsychotic Class (typical, atypical)</li><li>• Age (&lt;65, &gt;65)</li></ul>
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<b>Limitations:</b>	<ul style="list-style-type: none"><li>• The IMS data is only available at the prescription and unit level. Therefore, national and provincial trends in prescribing cannot differentiate by indication.</li></ul>
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## Objective 2: Cross-Provincial Changes in Prescribing of Antipsychotics in Public Drug Programs

### Study Design:

Design: Time series analysis with quarterly time intervals

Study period: January 2000 to December 2012

Data Source:

- *National Prescription Drug Utilization Information System Database (NPDUIS)*: aggregated data for all publically funded prescriptions dispensed in Alberta, Saskatchewan, Manitoba, New Brunswick, Nova Scotia, PEI and BC
- *Ontario Drug Benefit Database (ODB)*: individual level data for all publically funded prescriptions dispensed in Ontario. This dataset contains additional variables (long-term care residence, public drug plan coverage) that is not available through NPDUIS

### Study Population:

#### Inclusion Criteria:

- All publically-funded antipsychotic prescriptions dispensed in Alberta, Saskatchewan, Manitoba, Ontario, New Brunswick, Nova Scotia, PEI and BC
  - Atypicals
  - Typicals
- Elderly Patients (65 years of age and older)

### Outcome(s) of Interest:

Measured over entire study period (annually)

- Number and rate of antipsychotic users
- Number of antipsychotic prescriptions dispensed
- Total costs of antipsychotics
- Average cost of antipsychotics per user

Stratify all analyses by:

- Province
- Antipsychotic (typical, atypical)
- Age groups (65-69, 70-75, 75-80, 80+)

### Limitations:

- Publically-funded, patient-level prescription data is only available as of 2005 for PEI and 2006 for BC. We are therefore unable to determine antipsychotic use prior to that date.
- There is no patient-level data available for publically paid prescriptions in Quebec, Newfoundland & Labrador or the Territories. Therefore, we will be unable to make comparisons between Ontario rates and rates of use in these provinces.

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### Objective 3: Characteristics of Elderly Patients Prescribed Antipsychotics in Ontario

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**Study Design:**

Design: Cross-sectional analysis

Study period: January 2012 to December 2013

Data Sources:

- Ontario Drug Benefit Database (ODB)
  - Canadian Institute for Health Information-Discharge Abstract Database (CIHI-DAD)
  - National Ambulatory Care Reporting System Database (NACRS)
  - Ontario Health Insurance Plan Claims Database (OHIP)
  - ICES Physician Database (IPDB)
  - Continuing Care Reporting Systems (for Chronic Care) (CCRS)
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**Study Population:****Inclusion Criteria:**

- All publically-funded beneficiaries over the age of 65 in Ontario who are prescribed an antipsychotic
  - **Cohort Entry Date:** defined as date of first prescription of an antipsychotic product following 65<sup>th</sup> birthday, over the study period.
  - **Index Drug:** Defined as the antipsychotic product that was prescribed on cohort entry date
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**Variables of Interest:**

For the established cohort, measure:

- Number of patients
  - Number and rate of new antipsychotic users
    - New users aged 66 and older defined as having no past antipsychotic use in prior 365 days
    - New users <66 years of age defined as having a prescription for any drug in the past 181-365 days and who didn't have a prescription for an antipsychotic in the past 180 days
  - Age at cohort entry date (mean, SD, and by category (65-69, 70-75, 75-80, 80+))
  - Proportion of patients who were male
  - Proportion by county (new and prevalent use)
  - Proportion of patients residing in LTC at cohort entry
  - Proportion of urban residents at cohort entry
  - Socioeconomic status (measured using income quintiles at cohort entry)
  - Average cost of antipsychotic prescriptions per person
  - Proportion of patients with diagnosed dementia within 5 years of index
    - Defined by: 5-year look back for physician OHIP diagnosis codes or CIHI-DAD admission codes related to dementia or use of cognitive enhancers in year prior
  - Number of doses dispensed, per user
    - Calculated based on days supply and quantity
  - Equivalent daily dosing of antipsychotic used (low, medium, high)
    - Defined by chlorpromazine equivalents
  - Number of patients treated with multiple antipsychotics concurrently
  - Concomitant Psychotropic use at index:
    - Antidepressants (SSRI, TCA, MAOI, other)
    - Benzodiazepines
    - Mood stabilizers
    - Stimulants
  - Prescriber of initial prescription:
    - Specialist
      - Psychiatrists
      - Geriatricians
      - Neurologists
    - General Practitioner
  - Specialist visit in past 3 months prior to index (yes/no):
    - Psychiatrists
    - Geriatricians
    - Neurologists
  - Number of past hospitalization or ED visit (past 1 year)
  - Number of physician office visits within the last 1 year
  - Comorbidities
    - Charlson comorbidity score (based on last 3 years of hospitalization data)
    - Number of medications used in past year
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Stratify analyses by:

- LTC/Community
- Antipsychotic (atypical, typical)
- Age groups (65-69,70-75,75-80, 80+)

**Limitations:**

- No information on medication use when hospitalized. Also for some medications that may be given as needed for sleep it is unknown the level of utilization.

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**Objective 4: Investigate the Patterns of Use for Newly initiated Antipsychotic Medications among Elderly Patients with Dementia in Ontario**

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**Study Design:**

Design: Cohort Study

Study period: January 2009-December 2013

- Accrual period: January 2009-December 2012
- Maximum follow-up date: December 2013 (*1 year minimum follow-up*)

Data Sources:

- Ontario Drug Benefit Database (ODB)
  - Canadian Institute for Health Information-Discharge Abstract Database (CIHI-DAD)
  - National Ambulatory Care Reporting System Database (NACRS)
  - Ontario Health Insurance Plan Claims Database (OHIP)
  - ICES Physician Database (IPDB)
  - Continuing Care Reporting Systems (for Chronic Care) (CCRS)
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**Study Population:**

**Inclusion Criteria:**

- All publically-funded beneficiaries of Ontario with dementia who initiate an antipsychotic over the study period (defined as no prescription for an antipsychotic in the past 365 days)
- Past diagnosis of dementia (within 5 years to cohort entry date)

**Cohort Entry Date:** defined as date of first prescription of an antipsychotic product following 66<sup>th</sup> birthday, over the study period.

**Index Drug:** Defined as the antipsychotic product that was prescribed on cohort entry date

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**Outcomes of interest:**
Duration of Antipsychotic Therapy (defined in 2 ways):

- RELAXED DEFINITION OF CONTINUED ANTIPSYCHOTIC USE
- Define ongoing use of antipsychotic therapy according to receipt of a subsequent prescription within 180 days of the prior prescription.
- Date of discontinuation: date of last prescription + days supply of final prescription
- STRICT CLINICAL CONTINUATION OF ANTIPSYCHOTIC USE
  - Subsequent prescription within 1.5 times the days supply of the prior prescription. If no subsequent prescription, then person discontinued use. Set discontinuation date as date of last prescription plus days supply of final prescription.

For each definition report the following:

- Total number of new antipsychotic users
  - Number of antipsychotic users with only 1 prescription before discontinuing
  - Among patients with more than 1 prescription dispensed over period of continuous use report the following:
    - Age at cohort entry date (mean, SD, and by category (65-69, 70-75, 75-80, 80+))
    - Gender
    - Residence in LTC at cohort entry
    - For community – entry into LTC within year
    - Urban vs rural residents
    - Socioeconomic status (measured using income quintiles at cohort entry)
    - Dose equivalence levels (low, medium, high)
      - i. Defined by chlorpromazine equivalents
    - Comorbidities
      - i. Charlson comorbidity score (based on last 3 years of hospitalization data)
      - ii. Number of medications used in past year
    - Prescriber of initial prescription:
      - i. Specialist
      - ii. General Practitioner
    - Specialist visit in past 3 months prior to index (yes/no):
      - i. Psychiatrists
      - ii. Geriatricians
      - iii. Neurologists
    - Change of dose level (6 months and 12 months after index)
    - Change to another antipsychotic (6 months and 12 months after index)
    - Cost of therapy
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<b>Outcomes of interest (continued):</b>	<ul style="list-style-type: none"> <li>○ Past hospitalization or ED visits (past 1 year)</li> <li>○ Over period of ongoing use:</li> <li>○ Number of different antipsychotics prescribed</li> <li>○ Treated with multiple antipsychotics concurrently</li> <li>○ Concomitant psychotropic medications:</li> <li>○ Antidepressants (SSRI, TCA, MAOI, other)</li> <li>○ Benzodiazepines</li> <li>○ Stimulants</li> <li>○ Mood stabilizers</li> <li>○ Median duration of therapy</li> <li>○ Percent adherent after: 1 year</li> <li>○ Analysis: Kaplan Meier curves constructed and log-rank test used to test for differences</li> <li>○ Stratified by LTC, age group, and sex</li> </ul>
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Stratify above analysis by:

- LTC/Community
- Antipsychotic Class (atypical, typical)
- Dose level of antipsychotics at cohort entry (low, medium, and high)

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<b>Limitations</b>	<ul style="list-style-type: none"> <li>● No information on medication use when hospitalized.</li> <li>● The level of utilization for antipsychotics that are given as needed for sleep maybe misestimated.</li> <li>● Due to issues with incomplete data and unavailability of eligibility information, this analysis is restricted to patients aged 66 and older. Therefore, these findings may not be generalizable to the younger population.</li> </ul>
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### Objective 5: To Summarize Observational Studies Evaluating the Comparative Effectiveness and Safety of Antipsychotic Use in the Elderly

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<b>Objective:</b>	Review of population-based studies investigating comparative effectiveness and/or safety of antipsychotics in the elderly
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<b>Study Population</b>	Elderly patients using antipsychotics
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<b>Study Design:</b>	Observational studies <ul style="list-style-type: none"> <li>● Effectiveness studies</li> <li>● Safety studies</li> </ul>
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<b>Study Inclusion Criteria</b>	<ol style="list-style-type: none"> <li>1. English Language</li> <li>2. Published in last 20 years</li> </ol>
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<b>Interventions</b>	Antipsychotics
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<b>Comparators</b>	Comparative or non-users
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<b>Outcomes</b>	Any reported outcomes
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