ODPRN ONTARIO DRUG POLICY RESEARCH NETWORK

Comprehensive Research Plan:

Cognitive enhancers for the treatment of Alzheimer's disease

Pharmacoepidemiology Unit

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ODPRN Drug Class Review Proposal: Pharmacoepidemiology Unit

Study Title: Epidemiologic Analyses of Cognitive Enhancers

Objectives:

1. To examine national and provincial trends in use of cognitive enhancers across Canada
2. To perform cross provincial comparisons of the trends in cognitive enhancer utilization
3. To describe characteristics of elderly patients prescribed publically-funded cognitive enhancers in Ontario
4. To investigate the patterns of use of cognitive enhancers among elderly patients in Ontario
5. To summarize any observational studies evaluating the comparative safety and effectiveness of cognitive enhancers

Objective 1: National and Provincial Trends in Cognitive Enhancers Drug Use

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

Study Population:

Inclusion Criteria:

- All privately and publically-funded cognitive enhancer prescriptions dispensed in Canada:
  - Donepezil
  - Galantamine
  - Rivastigmine
  - Memantine

Outcome(s) of Interest:

Measured over entire study period (quarterly):

- Number and rate of prescriptions dispensed
- Total cost of prescriptions
- Total number of units dispensed

Stratify all analyses by:

- Province
- Payer (Public, Private, Cash)
- Cognitive Enhancer Drug (Donepezil, Galantamine, Rivastigmine, Memantine)

Limitations:	• The IMS data is only available at the prescription and unit level. Therefore, national and provincial trends in prescribing cannot differentiate by indication.

Objective 2: Cross-Provincial Changes in Prescribing of Cognitive Enhancers in Public Drug Programs

Study Design:	Design: Time series analysis with quarterly time intervals Study period: January 2000 to December 2013 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 cognitive enhancer prescriptions dispensed in Alberta, Saskatchewan, Manitoba, Ontario, New Brunswick, Nova Scotia, PEI and BC ○ Elderly Patients (65 years of age and older)
Outcome(s) of Interest:	Measured over entire study period (annually) • Number and rate of users • Number of prescriptions dispensed • Total costs of cognitive enhancers • Average cost of cognitive enhancers per user Stratify all analyses by: • Province • 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 cognitive enhancers 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.

Objective 3: Characteristics of Elderly Patients Prescribed Cognitive Enhancers in Ontario	
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)
Study Population:	**Inclusion Criteria:** ○ All publically-funded beneficiaries over the age of 65 in Ontario who are prescribed a cognitive enhancer ○ **Cohort Entry Date**: defined as date of first prescription for a cognitive enhancer drug following 65th birthday, over the study period. ○ **Index Drug**: Defined as the cognitive enhancer drug that was prescribed on cohort entry date

Variables of Interest:	For the established cohort, measure:
	• Number of patients
	• Number of <u>new</u> users
	  ○ New users aged 66 and older defined as having no prescription for a cognitive enhancer in the past 365 days
	  ○ New users <66 years of age defined as having a prescription for any drug in the past 181-365 days and who did not have a prescription for a cognitive enhancer 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 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 cognitive enhancer prescriptions <u>per person</u>
	• 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
	• Concomitant Psychotropic use at index:
	  ▪ Antipsychotics
	  ▪ 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 hospitalization or ED visit within the last 1 year (median, IQR)
	• Number of physician office visits within the last 1 year (median, IQR)
	• Comorbidities
	  ○ Charlson comorbidity score (based on last 3 years of hospitalization data)
	  ▪ Individual Components
	  ○ Number of medications used in past 1 year

	Stratify analyses by: • Cognitive Enhancer drug (Donepezil, Galantamine, Rivastigmine, Memantine)
Limitations:	• No information on medication use when hospitalized.

Objective 4: **Investigate the Adherence and Patterns of Use for Newly initiated Cognitive Enhancer Medications among Elderly Patients in Ontario**	
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)
Study Population:	**Inclusion Criteria:** ○ All publically-funded beneficiaries over the age of 66 in Ontario who newly initiate a cognitive enhancer over the study period (defined as no prescription for a cognitive enhancer in the past 365 days) **Cohort Entry Date**: defined as date of first prescription for a cognitive enhancer drug following 66th birthday, over the study period. **Index Drug**: Defined as the cognitive enhancer drug that was prescribed on cohort entry date

Outcomes of interest:

Duration of Cognitive Enhancer Therapy (defined in 2 ways):

- Relaxed Definition Of Continued Cognitive Enhancer Use
  - Define ongoing use of cognitive enhancer therapy according to receipt of a subsequent prescription within 180 days of the prior prescription. If no subsequent prescription, then person discontinued use.
  - Date of discontinuation: date of last prescription + days supply of final prescription
- Strict Clinical Definition of Continued Cognitive Enhancer Use
  - Define ongoing use of cognitive enhancer therapy according to receipt of a subsequent prescription within 1.5 times the days supply of the prior prescription. If no subsequent prescription, then person discontinued use.
  - Date of discontinuation: date of last prescription + days supply of final prescription.

For each definition report the following:

- Total number of new users
- Number of cognitive enhancer users with only 1 prescription before discontinuing
- Among patients with more than 1 prescription for a cognitive enhancer drug dispensed over period of continuous use report the following:
  - Age at cohort entry date (mean, SD, and by category (66-69, 70-75, 75-80, 80+))
  - Proportion of patients who were male
  - Proportion of patients residing in LTC at cohort entry
  - Among patients residing in the community at cohort entry, report the proportion who enter into LTC within 1 year
  - Proportion of urban residents at cohort entry
  - Socioeconomic status (measured using income quintiles at cohort entry)
  - Comorbidities
    i. Charlson comorbidity score (based on last 3 years of hospitalization data)
       - Individual Components
    ii. Number of medications used in past year based on the drug name on prescription
  - Prescriber of initial prescription:
    i. Specialist
       1. Psychiatrists
       2. Geriatricians
       3. Neurologists
    ii. General Practitioner
  - Specialist visit in past 3 months prior to cohort entry (yes/no):
    i. Psychiatrists
    ii. Geriatricians
    iii. Neurologists
  - Proportion with a diagnosis of dementia in last 3 years
  - Number of hospitalization or ED visits within the last 1 year (median, IQR)

	• Number of physician office visits within the last 1 year (media, IQR)

Outcomes of interest (continued):	• <u>Over period of ongoing use:</u>
	  ○ Number of different cognitive enhancer drugs prescribed over follow-up (Median (IQR), 1, 2, 3+)
	  ○ Proportion of users who are prescribed a different cognitive enhancer drug within 6 months and 12 months of cohort entry
	  ○ Average cost of cognitive enhancer prescriptions <u>per person</u>
	  ○ Concomitant psychotropic medications prescribed:
	  ▪ Antipsychotics
	  ▪ Antidepressants (SSRI, TCA, MAOI, other)
	  ▪ Benzodiazepines
	  ▪ Stimulants
	  ▪ Mood stabilizers
	  ○ Median duration of cognitive enhancer therapy
	  ○ Percent adherent to therapy at 1 year after cohort entry
	  ○ Analysis:
	  ▪ Kaplan Meier curves constructed and log-rank test used to test for differences
	  • Stratified by LTC residence, age group and sex
	  ▪ Adjusted Cox Proportional Hazards Model
	
	Stratify above analysis by:
	• Cognitive Enhancer drug (Donepezil, Galantamine, Rivastigmine, Memantine)

Limitations	• Information is not available for medication use when hospitalized. • 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.