ODPRN ONTARIO DRUG POLICY RESEARCH NETWORK

FINAL Comprehensive Research Plan:

Treatments for Attention Deficit Hyperactivity Disorder in Adults

Pharmacoepidemiology Unit

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ODPRN Drug Class Review Proposal Pharmacoepidemiology Unit

Study Title: Epidemiologic Analyses of Treatments for Adult Attention Deficit Hyperactivity Disorder

Objectives:

1. To examine national and provincial trends in use of treatments for Attention Deficit Hyperactivity Disorder (ADHD) among adults in Canada
2. To perform cross provincial comparisons of the trends in utilization of treatments for ADHD among adults in public drug programs
3. To describe characteristics of adult patients prescribed publically-funded treatment for ADHD in Ontario
4. To investigate the patterns of use of treatments for ADHD among newly initiated adult patients in Ontario
5. To investigate possible misuse of treatments for ADHD among adult patients in Ontario
6. To summarize observational studies evaluating the comparative effectiveness and safety of ADHD treatments in adults

Objective 1: National and Provincial Trends in use of treatments for adult ADHD

Study Design:

Design: Time series analysis with quarterly time intervals

Study period:

- *National and provincial trends (IMS Compuscript):* January 2009 to December 2014

Population: All provinces in Canada

Data Sources:

- *IMS Compuscript:* aggregated data for all prescriptions dispensed at retail pharmacies across Canada

Study Population:

Inclusion Criteria:

- All privately and publically-funded ADHD treatments dispensed among adults aged 19 and older, in Canada
- ADHD drugs include:
  - Stimulants
    - Dextroamphetamine
    - Lisdexamfetamine
    - Methylphenidate
    - Mixed-Salt Amphetamine
  - Non-Stimulants
    - Atomoxetine
    - Guanfacine

Outcome(s) of Interest:	**Measured over entire study period (quarterly):**
	• Number and rate of prescriptions dispensed
	• Total cost of prescriptions
	Stratify by:
	• Province
	• Payer
	  o Provincially funded (Private, Cash, NIHB)
	  o Non-Provincially funded (Private, Cash, NIHB)
	
	Measured over last year of study period (2014)
	• Number and rate of prescriptions dispensed
	• Total cost of prescriptions
	Stratify by:
	• Province
	• Payer (Public, Private, Cash, NIHB)
	• Age Group (19-29, 30-64, 65+)
	• ADHD Drug
	• Type of ADHD drug
	  o Long-acting stimulants
	  o Short-acting stimulants
	  o Non-stimulant

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 trends in Utilization of Treatments for Adult ADHD in Public Drug Programs

Study Design:	Design: Time series analysis with annual 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 ADHD treatment prescriptions dispensed in Alberta, Saskatchewan, Manitoba, Ontario, New Brunswick, Nova Scotia, PEI and BC
- Adult Patients (18 years of age and older)
- ADHD drugs include:
    - Stimulants
        - Dextroamphetamine
        - Lisdexamfetamine
        - Methylphenidate
        - Mixed-Salt Amphetamine
    - Non-Stimulants
        - Atomoxetine
        - Guanfacine

Outcome(s) of Interest:

Measured over entire study period (annually):

- Number and rate of users

Present overall and stratified by:

- Province
- Type of ADHD drug:
    - Long-acting stimulants
    - Short-acting stimulants
    - Non-stimulant

Measured over last year of study period (2013):

- Number and rate of users
- Total costs of treatments
- Average cost of treatments per user

Present overall and stratified by:

- Province
- Age Group (18-25, 26-35, 36-64 65+)
- ADHD Drug
- Type of ADHD drug
    - Long-acting stimulants
    - Short-acting stimulants
    - Non-stimulant

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 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.
- Only Saskatchewan and Ontario fund non-stimulant ADHD drugs, and therefore limited cross-provincial comparisons for these products are feasible.

Objective 3: Characteristics of Adult Patients Prescribed ADHD Treatments in Ontario

Study Design:

Design: Cross-sectional analysis
Study period: January 2013 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)

Study Population:

Inclusion Criteria: All publically-funded beneficiaries over the age of 18 in Ontario who are prescribed an ADHD treatment

- ADHD drugs include:
  - Stimulants:
    - Dextroamphetamine
    - Lisdexamfetamine
    - Methylphenidate
    - Mixed-Salt Amphetamine
  - Non-Stimulants
    - Atomoxetine

Exclusion Criteria: Individuals with evidence of Palliative Care in past 6 months prior to cohort entry

Cohort Entry Date: defined as date of first prescription for an ADHD treatment following 18th birthday, over the study period.

Index Drug: Defined as the ADHD medication that was prescribed on cohort entry date. Note: For those being treated with dual therapy (two drugs on cohort entry) they will included and defined separately.

Variables of Interest:

For the established cohort, measure:

- Number of patients
- Number of new users
  - New users aged 66 and older defined as having no prescription for a ADHD treatment in the past 365 days
  - New users aged 18 to 65 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 ADHD treatment in the past 180 days
- Age at cohort entry date (mean, SD, and by category (18-25, 26-35, 36-64 65+)
- Proportion of patients who were male
- Proportion of urban residents at cohort entry
- People living in LTC at cohort entry
- Socioeconomic status (measured using income quintiles at cohort entry)
- Number with an ADHD diagnosis
  - Based on outpatient diagnostic codes in the past 10 years
- Concomitant Psychotropic use at cohort entry date:
    - Antipsychotics
    - Antidepressants (SSRI, TCA, MAOI, other)
    - Benzodiazepines
    - Mood stabilizers
- Prescriber of initial prescription:
  - General Practitioner
  - Specialist
      - Psychiatrists
      - Neurologists
      - Other
- Specialist visit in past 3 months prior to cohort entry date (yes/no):
  - Psychiatrists
  - Neurologists
- Number of physician office visits within the last 1 year (median, IQR)
- Comorbidities
  - Charlson comorbidity score (based on last 3 years of hospitalization data)
      - No hospitalization, 0, 1, 2+
  - Number of unique medications used in past 1 year (median, IQR)

Stratify all analyses by:

- ADHD Drug

Limitations:

- No information on medication use when hospitalized.

Objective 4: **Investigate the Adherence and Patterns of Use for Newly Initiated ADHD Treatments among Adult Patients in Ontario**

Study Design:

Design: Cohort Study

Study period: January 2002-December 2013

- Accrual period: January 2002-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)

Study Population:	**Inclusion Criteria:** • All publically-funded beneficiaries Ontario who newly initiate a ADHD treatment over the study period (defined as no prescription for a ADHD treatment in the past 365 days) o New users aged 66 and older defined as having no prescription for a ADHD treatment in the past 365 days o New users <=65 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 ADHD treatment in the past 180 days • ADHD drugs include: o Stimulants: ▪ Dextroamphetamine ▪ Lisdexamfetamine ▪ Methylphenidate ▪ Mixed-Salt Amphetamine o Non-Stimulants ▪ Atomoxetine **Exclusion Criteria:** Individuals with evidence of Palliative Care in past 6 months prior to cohort entry **Cohort Entry Date**: defined as date of first prescription for an ADHD over the study period. Adult Cohort (Cohort 1): Defined as those aged 18 and older, who newly initiated an ADHD treatment. Pediatric Cohort (Cohort 2): Defined as those younger than 18, who newly initiated an ADHD treatment. **Index Drug**: Defined as the ADHD treatment that was prescribed on cohort entry date.
Baseline Characteristics of Interest:	Report the following for both new-user cohorts: • Total number of new users • Number of users with only 1 prescription before discontinuing

Outcomes of interest: Duration of ADHD treatment defined as:

- Define ongoing use of ADHD treatment according to receipt of a subsequent prescription within 180 days of the prior prescription. If no subsequent prescription, then person discontinued use.
    i. Date of discontinuation: date of last prescription + days supply of final prescription
- Follow individuals forward until first of:
    i. Drug discontinuation
    ii. Death
    iii. End of study period (December 31, 2013)
    iv. COHORT 1 ONLY: 2 years maximum follow-up

Outcomes of interest (continued):	**For Cohort 1:**
	Over period of ongoing use, report:
	• Number of different ADHD treatments prescribed over follow-up (Median (IQR), 1, 2, 3+)
	• Proportion of users who are prescribed a different ADHD treatment within 6 months and 12 months of cohort entry
	• Percent adherent to therapy at 1 year after cohort entry
	• Analysis:
	  o Kaplan Meier curves constructed and log-rank test used to test for differences
	  ▪ Median time to discontinuation of ADHD treatment
	
	Report above overall and stratified by:
	• ADHD Drug
	• Type of Drug
	  o Long-acting stimulants
	  o Short-acting stimulants
	  o Non-stimulant
	
	Methodological Note: Rates of mortality will be calculated to assess the need for a competing risks analysis.
	
	For Cohort 2:
	Over period of ongoing use (No maximum follow-up):
	
	• Percent who persist on therapy past age of 18
	  o N(%) of individuals in pediatric cohort who persist on therapy after turning 18 (e.g. number with at least 1 prescription after 18th birthday)
	• Analysis:
	  o Kaplan Meier curves constructed and log-rank test used to test for differences
	  ▪ Among those who continue therapy past 18th birthday, measure median time of therapy as adult as:
	  • [Overall median time to discontinuation of ADHD treatment] – [number of days between start date and 18th birthday]

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

Objective 5: **Investigate Potentially Inappropriate Prescribing of ADHD Stimulants among Adult Patients in Ontario**

Study Design:	Design: Cross-sectional analysis Study period: January 2013 to December 2014 Data Sources: • Ontario Drug Benefit Database (ODB) • ICES Physician Database (IPDB)
Study Population:	**Inclusion Criteria:** • All publically-funded ADHD treatment stimulant prescriptions dispensed in Ontario among adults (18 years of age and older) • Drugs of interest: o Dextroamphetamine o Lisdexamfetamine o Methylphenidate o Mixed-Salt Amphetamine **Exclusion Criteria:** Individuals with evidence of Palliative Care in past 6 months prior to cohort entry
Outcomes of interest:	Possible Misuse: • Define possible misuse of ADHD treatments as prescriptions for stimulant ADHD treatments where at least 30 units were dispensed. Then identify all prescriptions for stimulant ADHD treatments that were dispensed in the 7 days following the initial prescription. The prescription is deemed inappropriate if it was issued by a different physician and dispensed at a different pharmacy from the initial prescription. Measured over entire study period: • Number and % of all prescriptions that are potentially inappropriate Stratify by Age Group (18-25, 26-35, 36-64 65+)
Limitations	• Information is not available for medication use when hospitalized.

Objective 6: To Summarize any Observational Studies Evaluating the Misuse and Abuse of ADHD Treatments in Adults	
Objective:	Review of population-based studies investigating misuse and abuse of ADHD treatments in adults
Study Population	Adults patients using ADHD treatments
Study Design:	Observational studies • Misuse and Abuse studies
Study Inclusion Criteria	1. English Language 2. Published in last 10 years
Interventions	ADHD treatments
Comparators	ADHD Treatments
Outcomes	Any reported outcomes
Limitations	If time permits, we will also explore comparative effectiveness and safety studies in adults