

FINAL

**Consolidated Comprehensive Research Plan:
Pharmacologic Treatment of Attention Deficit
Hyperactivity Disorder in Adults**

April 29th, 2015

A. Introduction

Treatments for adults with attention deficit hyperactivity disorder (ADHD) can include psychosocial, pharmacologic therapies, or a combination of both. When pharmacological treatment is indicated, two broad categories of medications are considered – stimulants and non-stimulants. There are several stimulants available on the Canadian market (i.e., amphetamine mixture, dextroamphetamine, lis-dexamfetamine, methylphenidate) and two non-stimulants (i.e., atoxoxetine, guanfacine).

The objective of the drug class review on drugs for treatment of ADHD in adults is to provide evidence-informed recommendations for the use of these agents 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

- Adult patients (age ≥ 18 years) with diagnosis of attention deficit disorders (i.e., attention deficit disorder, attention deficit hyperactivity disorder)
- Subgroup analysis: where possible, the review may consider age, gender, socioeconomic status and geographic location (e.g. urban/rural), co-morbid conditions, different formulations

Drugs of interest

- Stimulants: Amphetamine mixture (Adderall XR), dextroamphetamine (Dexedrine, Dexedrine Spansule), lis-dexamfetamine dimesylate (Vyvanse), methylphenidate (Concerta, Ritalin, Ritalin SR, Biphentin, and generics)
- Non-stimulants: atomoxetine (Strattera and generics), guanfacine (Intuniv SR)
- Off-label indications: bupropion, clonidine, modafinil (these will be only included in Systematic Review team's analysis)

Comparator(s)

- Placebo-controlled trials
- All drugs of interest (as listed above)

Proposal	Research unit	Research question(s)
Patient and Healthcare Professional Perspectives	Qualitative Research Program	<p>What is the perceived effectiveness of drugs used for treatment of ADHD in adults?</p> <p>What is the impact of stimulants/non-stimulants on perceived quality of life?</p> <p>What is the experience of patients using stimulants/non-stimulants regarding access of these drugs?</p> <p>What is the experience of prescribing these drugs?</p> <p>To what extent are the policy recommendations feasible and acceptable?</p>
Systematic Reviews and Network Meta-Analyses	Systematic Review Unit	<p>What is the comparative safety and efficacy of pharmacologic treatments (stimulants and non-stimulants) for adults with ADHD?</p> <p>What is the comparative safety and efficacy of pharmacologic treatments for ADHD in subgroups of patients with ADHD and a psychiatric or mood disorder, or substance abuse?</p>
Environmental Scan and Barriers to Implementation; Local and Historical Context	Formulary Modernization Unit	<p>How are stimulants/non-stimulants currently being funded in public programs in Canada as well as internationally?</p> <p>What mechanisms are in place to maximize access while minimizing costs? How successful are these mechanisms in achieving a cost-access balance?</p>
Costs and Utilization Trends	Pharmacoepidemiology Unit	<p>To examine national and provincial trends in use of treatments for Attention Deficit Hyperactivity Disorder (ADHD) among adults in Canada</p> <p>To perform cross provincial comparisons of the trends in utilization of treatments for ADHD among adults in public drug programs</p> <p>To describe characteristics of adult patients prescribed publically-funded treatment for ADHD in Ontario</p> <p>To investigate the patterns of use of treatments for ADHD among newly initiated adult patients in Ontario</p> <p>To investigate possible misuse of treatments for ADHD among adult patients in Ontario</p> <p>To summarize observational studies evaluating the comparative effectiveness and safety of ADHD treatments in adults</p>
Health Equity	All units	<p>Does sex/gender, age, geographical location (e.g., rural vs. urban) or socioeconomic status play an important role in any of the analyses described?</p>
Reimbursement-based Economics	Pharmacoeconomics Program	<p>What is the current evidence for the comparative cost-effectiveness of pharmacological treatments for attention deficit hyperactivity disorder (ADHD)?</p> <p>What is the budget impact of alternative policies for reimbursing pharmacotherapies in the treatment of ADHD?</p>

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 can be found on our website: www.odprn.ca

1. Qualitative Review Unit

Objectives:

- To explore factors related to the experience of prescription and use of medications for Attention Deficit Hyperactivity Disorder (ADHD) in adults 18 years of age and older
- To determine the social acceptability of reimbursement policy recommendations for ADHD medications

Study Questions:

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

Phase 1: Exploration of factors affecting the dispensing and utilization of drugs for treatment of ADHD in adults

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 ADHD review include 1) adult ADHD patients (18 years and older); 2) primary care physicians (PCPs); 3) psychiatrists; 4) 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 ADHD medications
- Experiences accessing ADHD medications
- Experiences treating adult patients with and dispensing ADHD medications
- Perceived safety and effectiveness of ADHD medications
- Perceived barriers to access and health equity issues
- Any unanticipated issues related to ADHD medications

Phase 2: Assessment of the social acceptability of recommended policy actions related to the drugs for treatment of ADHD

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 comparative safety and efficacy of pharmacologic treatments (stimulants and non-stimulants) for adults with ADHD?
- What is the comparative safety and efficacy of pharmacologic treatments for ADHD in subgroups of patients with ADHD and a psychiatric or mood disorder, or substance abuse?

PICO (Population, interventions, comparator, outcomes)

Population	Adults (age ≥ 18 years) outpatients with attention deficit disorders. Time permitting, a sub-group comparison of the included study population based on co-morbid psychiatric or mood disorders will be done.
Interventions	Stimulants: amphetamine mixture, lisdexamfetamine, dextroamphetamine, methylphenidate Non-stimulants: atomoxetine, guanfacine Others: bupropion, clonidine, modafinil Time and data-permitting, a sub-group comparison of: <ul style="list-style-type: none"> • Immediate, sustained or extended and modified-release formulations • Generic and innovator (branded) products

Comparator	Comparators: placebo, interventions (as listed above) Combinations of stimulants and non-stimulants will be included if they are identified during the literature search update. Combinations of stimulants and non-stimulants will be included if they are compared to placebo, no treatment or an active comparator of interest.
Outcomes: Efficacy	Potential efficacy outcomes: <ul style="list-style-type: none"> • Clinical response (dichotomous outcome) as the proportion of participants who respond to the intervention based on improvements in the standardized ratings scale. • Disease-specific quality of life (continuous outcome) • Functional (occupational) capacity (continuous outcome) • Executive function (continuous outcome) • Driving Behavior
Outcomes: Safety	Potential safety outcomes include: <ul style="list-style-type: none"> • Treatment discontinuations • Withdrawals due to adverse effects • Serious adverse effects - total • Cardiovascular events, including outpatient myocardial infarction, stroke, unexpected cardiac death* • Hospitalization • Emergency Room Visits <p>* If data permits we will look at both the composite of cardiovascular events and the individual outcomes reported within</p>
Included Study Designs	Randomized controlled trials

Note: Efficacy and safety outcome lists may be truncated if we identify many studies for inclusion, as this is a rapid review. We will work with all stakeholders to select the most important efficacy and safety outcomes with sufficient data to conduct network meta-analysis.

Time and data permitting, and based on prioritization by the research team in consultation with clinical experts, we will consider the following sub-group comparisons:

- Co-morbid psychiatric or mood disorders;
- Standard/recommended and high doses;
- Medium (1-2 yr) or long-term (>2 yrs) efficacy and safety;
- Treatment experience;
- Immediate, sustained or extended and modified-release formulations;
- Generic and innovator (branded) products;

Analysis of subgroups may be limited to select efficacy and safety outcomes.

Methods

The strategy for building and analyzing the evidence base for the efficacy and safety of pharmacotherapies for adults with ADHD consists of two fundamental steps*:

Update of an existing, high-quality systematic review

In order to meet the rigorous timelines of the review process, we will update a comprehensive, well-conducted, recent (within 5 years) evidence synthesis that meets the PICO requirements and contain intervention studies that meet our inclusion criteria [McDonagh MS, Peterson K, Thakurta S, Low A. *Drug Class Review: Pharmacologic Treatments for Attention Deficit Hyperactivity Disorder: Final Update 4 Report. Drug Class Review: Pharmacologic Treatments for Attention Deficit Hyperactivity Disorder: Final Update 4 Report [serial on the Internet]. 2011.*]. 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 (week 4, June 2011) to present, with retrospective overlap of 12 months.

A Bayesian network meta-analysis of randomized evidence

When data were available, sufficiently similar, and of sufficient quality, Bayesian network meta-analyses (NMA) will be considered for each of the efficacy and safety outcomes specified a priori. Choice of outcomes for NMA will be based on their importance and the sufficiency of the data available to derive robust and consistent network models. 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.

Information sources and literature search

The literature search (or update of the literature search) will be conducted by a professional Information Scientist (IS). Databases and grey literature will be searched from 12 months prior to the date of the last literature search to present.

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 update.

Studies identified from the existing SR will be subjected de novo to the standard SR methods following title and abstract screening, namely: eligibility assessment and 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 literature search update, 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 data tables for analysis.

Synthesis of included studies

We will first describe our results, reporting study characteristics, patient characteristics, risk of bias results, and efficacy and safety results. Subsequently, we will conduct meta-analysis, and Bayesian network meta-analysis, if deemed appropriate.

3. Pharmacoepidemiology Unit

Analysis 1 – National and provincial trends in use of treatments for adult ADHD

Study question: To examine national and provincial trends in use of treatments for adult (19 years of age and older) ADHD over the last 5 years

Short description of analysis: We will examine trends in treatments for adult ADHD (stimulants and non-stimulants) between January 2009 and December 2014.

Analysis 2 – Cross-provincial trends in utilization of treatments for adult ADHD in Public Drug Programs

Study question: to examine cross-provincial comparisons of the trends in utilization of treatments for ADHD among adults in public drug programs

Short description of analysis: We will examine changes in ADHD treatment prescriptions dispensed in Alberta, Saskatchewan, Manitoba, Ontario, New Brunswick, Nova Scotia, PEI and British Columbia between January 2000 and December 2013.

Analysis 3 – Characteristics of adult patients prescribed ADHD treatments in Ontario

Study question: To characterize adult patients prescribed ADHD treatments in Ontario

Short description of analysis: We will look at descriptive characteristics (January 2013-December 2013), including age, gender, socioeconomic status, concomitant psychotropic use, prescriber of initial prescription, number of physician office visits within the last 1 year, comorbidities.

Analysis 4 – Investigate the adherence and patterns of use for newly initiated ADHD treatments among adult patients in Ontario

Study questions: To describe patterns of use for adult patients with ADHD newly initiated on treatment

Short description of analysis: We will look at all publically-funded beneficiaries of Ontario who initiate treatment for ADHD over the study period (adult cohort: 18 years and older; pediatric cohort: <18 years).

Analysis 5 – Investigate possible misuse of ADHD treatments among adult patients in Ontario

Study questions: To describe patterns of possible misuse of ADHD treatments among adult patients

Short description of analysis: We will include all publically-funded ADHD treatment prescriptions dispensed to adult patients in Ontario, and measure the number and rate of possibly inappropriate prescriptions.

Analysis 6 – Summarize any observational studies evaluating the comparative effectiveness and safety of ADHD treatments in adults

Study questions: To review population-based studies investigating comparative effectiveness and/or comparative safety of ADHD treatments in adults

Short description of analysis: We will summarize all observational studies that evaluate comparative effectiveness or comparative safety in adult patients using ADHD treatments.

4. Pharmacoeconomic Unit

Research Questions

- What is the current evidence for the comparative cost-effectiveness of pharmacological treatments for attention deficit hyperactivity disorder (ADHD) in adults?
- What is the budget impact of alternative policies for reimbursing pharmacotherapies in the treatment of ADHD?

Methods

RQ1 Systematic Review of Published Economic Evaluations

We will conduct a review of the available literature on the comparative cost-effectiveness of pharmacotherapies for treating ADHD in adults. Selected comparators will include stimulants in comparison with each other, with non-stimulants, and with combination therapy (i.e. stimulants + non-stimulants).

RQ2 Reimbursement Based Economic Assessment

We will develop a model which will identify the budget impact of alternative policies for the pharmacologic treatment of ADHD. 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 drugs for treatment of ADHD (stimulants and non-stimulants) 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:

- Stimulants (amphetamine mixture, dextroamphetamine, lis-dexamfetamine, methylphenidate)
 - Non-stimulants (atomoxetine, guanfacine)
2. To determine the impact of different drug reimbursement schemes for drugs for treatment of ADHD (stimulants and non-stimulants) 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 adult patients with ADHD

Method: Literature review

Intervention: Guidelines/recommendations for the use pharmacologic treatments in adult patients with ADHD