

**Stakeholder Comments and Responses for
Comprehensive Research Plan:
Treatment of ADHD in Adults**

Consolidated Report

April 29th, 2015

OVERALL

COMMENT

The children and adolescent population is of high relevance to the jurisdictions as highlighted in the past OUWG meetings as well as this meeting. It was reiterated that the larger issue for most jurisdictions is around the child and adolescent population. CADTH will continue to develop a project on ADHD in children and explore how best to address the research needs on the younger population. It was clarified that ODPRN will not be able to expand their scope to the adult population due to time limitations.

***Response:** Due to the timeline of this review, the focus will be on treatment of ADHD in adults. This is the population where Ontario has seen the greatest increase in use over the last nine years.*

COMMENT

Another issue of interest is the transition from adolescent to adulthood and, how many of these patients (adults) took medication as a child versus how many (adults) were treatment naive.

***Response:** The Pharmacoepidemiology team will investigate the transition from adolescent to adulthood. However, we cannot accurately determine the number of adults who were treatment naive, due to fluctuations in ODB eligibility that are unmeasurable in our data and would make this approach difficult to do in a rigorous way.*

COMMENT

Long term safety and efficacy outcomes continue to be of interest to the jurisdictions, although it may be difficult to draw an association in all the cases. However, it would be valuable to look at long term outcomes rather than only the symptom scores (i.e. ADHD rating scale scores). It would be important to assess if the ADHD medications (and the entire drug class) do result in positive long term outcomes (e.g. reduce substance abuse later in life). Another example is the recommendation that these drugs should be started as early as possible (as pediatrics) so that they do not fall behind in school or before the condition becomes chronic. It would be important to see that such advice is actually valid, and that an early start of the medication does result in positive outcomes (e.g. improved performance in school). One approach suggested to assess the long term outcome was a pharmaco- epidemiology type of study.

***Response:** The systematic review team will be investigating long-term safety and efficacy outcomes. As well, the pharmacoepidemiology team will review relevant epidemiologic studies pertaining to the long-term safety and efficacy of these medications, in particular in adult patients.*

COMMENT

It would be important to define suboptimal response i.e. what criteria would determine that the current drug therapy is suboptimal for a patient so that they can be prescribed another drug (i.e. change therapy from first line to second line, and/or augmentation).

Response: The systematic review team will consider a subgroup analysis based on treatment experience if time and data permit. We may be limited in the analyses we can perform within the timelines of this review, however, we will be able to compare any results of treatment experience to existing guidelines as they relate to lines of therapy.

COMMENT

Prescription drugs for ADHD and mental health should not be paid for out of pocket. The cost for medication (as well as therapy) is prohibitive, inconvenient, and makes seeking, obtaining, and RECEIVING help more difficult.

Response: Thank you for your response. We will be evaluating various reimbursement options for coverage of drugs for treatment of ADHD in adults as part of our final recommendations.

Qualitative Team

COMMENT

No mention of impairments caused by ADHD impacting medication compliance. I hope that experts and adults with ADHD are asked if they find that the common ADHD symptom of forgetting routines impacts the consistency that multiple daily doses of medications would actually be taken. Forgetting doses leaving patients untreated for a large part of the day, impacting their ability to function and remain productive in the school and workplace environment.

What is the experience of patients, teachers and caregivers in using short-acting stimulants vs. long-acting stimulants in the specific circumstances of ADHD and associated symptoms?

What is the experience of possible misuse of treatments for ADHD among adult patients in Ontario?

Consider ethnicity, availability of psychiatric care (ie. # of psychiatrists/patient population). A lot of psychiatrists limit to their practices to patients without dual diagnosis (i.e concurrent substance abuse and mental illness)

Response: Thank you for your feedback. We have included questions about the following topics in our interview guides:

- Factors that influence patient compliance
- Perceptions of shorting acting versus long acting stimulants
- Experience of possible misuse of treatments for ADHD among adults
- Please note that since the focus of this review is on adult patients, we will not be interviewing teachers or parents/caregivers about their experiences
- In qualitative research we do not typically stratify samples according to factors such as ethnicity because our samples tend to be small (ex. 6-8 per stakeholder group)
- We will probe psychiatrist interviewees to determine if they limit their practice to patients without dual diagnosis
- We will probe patient interviewees to determine if they have had barriers to treatment because of a dual diagnosis

Environmental Scan

COMMENT

Adherence to medications: impact of disease (e.g., forgetting routines) on taking multiple daily doses

Response: This has been identified as a topic for a rapid review.

COMMENT

Background information: Inclusion of incidence/prevalence of ADHD, long-term impact of untreated ADHD, burden of illness, comorbidities/comorbid mood disorders, alternative treatments for ADHD (including psychosocial treatments)

Response: Background information on ADHD in adults, including incidence/prevalence, burden of illness, alternative treatments for ADHD will be summarized in the report.

COMMENT

Safety: Driving and ADHD (rapid review)

Response: This has been identified as a topic for a rapid review.

COMMENT

Prevalence by area, # of psychiatrists to see if patients are actually getting diagnosed

Response: Utilization data in Ontario will capture the number of patients dispensed drugs for treatment of ADHD; however, we will not be able to assess the number of patients diagnosed with adult ADHD.

COMMENT

Objective 2 - consider functionality at work, days of productivity at work.

Response: These have been added as potential outcomes.

Pharmacoepidemiology Team

COMMENT

Similar to summary of observational studies on effectiveness and safety of ADHD drugs, a summary of

observational studies for misuse and abuse would be of value to the jurisdictions.

Review of misuse/abuse (including long-acting psychostimulants vs. short-acting psychostimulants, and stimulants vs. non-stimulant medications). [Also, an important issue is the rate of abuse of short-acting formulations versus long-acting formulations, as a goal in the development of long-acting formulations was to reduce misuse of stimulants. We suggest you include a stratification of your data by short-acting and long-acting formulations in your analysis.]

- For misuse - identified risk factors for stimulant misuse and diversion for children. Are you going to consider risk factors for misuse in adults?
 - In a study conducted in 2 Canadian provinces, 8.5% of the grade 7 to 12 students had used non-prescribed stimulants in the past year
 - 15% had given their medication to others
 - 7% sold their medication to other students
 - Lifetime rates of diversion ranged from 16 to 29% of students asked to give, sell or trade their stimulant medications.
 - Risk factors for stimulant misuse and diversion
 - Conduct disorder, substance abuse disorder, male gender, Caucasian, member of fraternity, use of immediate release products

Response: Thank you for your comment and suggestions. We will incorporate the stratification of short-acting and long-acting formulations in our analysis. We are exploring the possible misuse of ADHD treatments among adults in Ontario in Objective 5 of our analysis using drug claims data. Additionally, we have updated our literature review of observational studies to include the issue of misuse/abuse.

COMMENT

Another issue of interest is the transition from adolescent to adulthood and, how many of these patients (adults) took medication as a child versus how many (adults) were treatment naïve.

Response: Thank you for your comment. We agree and to address this, we will be looking at the number of ODB eligible children and adolescents who persist on ADHD therapy after turning 18 (see Objective 4). We cannot accurately determine the number of adults who were treatment naïve, due to fluctuations in ODB eligibility that are unmeasurable in our data and would make this approach difficult to do in a rigorous way.

COMMENT

Use of high doses of stimulants is of concern to some jurisdictions. Evidence on safety and efficacy of high dose stimulants would be of interest to the jurisdictions

Response: This is an important issue but highly complex when using drug claims. We agree future work should look at this issue, and this may be an area that could be explored by the Systematic Review team if sufficient literature exists.

COMMENT

How many of the patients in the studies were diagnosed as adult versus those who had continued to take medication since childhood/adolescence?

- This information could be available from data sources such as CIHI/NPDUIS which has information from public drug plans. However, ODPRN has previously stated that they are unable to look into individual patient data, and follow them over time. Hence, we understand that it may not be feasible to address this question.

Response: *We are able to look at individual patient data in Ontario using ICES databases, as well as some patient-level analyses using CIHI/NPDUIS. To address these issues, we will be looking at the number of children and adolescents who persist on therapy after turning 18 in Ontario (see Objective 4). We will also define the prevalence of an ADHD diagnosis among the cohort of users in Ontario aged 18 and older. Unfortunately, since we only have prescribing data for drugs reimbursed through the provincial drug plan, and because people often gain/lose eligibility over their lifetime, we are unable to determine whether individuals who take ADHD medications as adults also took these medications as children.*

COMMENT

All costs and utilization trends should be examined in relation to the prevalence of ADHD among adults in Canada.

Response: *Thank you for your comment and suggestion. We won't be able to get this information among public drug plan beneficiaries in provinces other than Ontario due to unavailability of data and the challenge of identifying diagnostic codes across Canada.*

COMMENT

The research questions of possible underdiagnosis and undertreatment of ADHD among adults should also be considered, as well as their causes.

Response: *Although we agree this is an important question, it is unfortunately outside of the scope of this project and would be difficult to accomplish using administrative databases available to us.*

COMMENT

There is an existing scientific literature on misuse, abuse, and diversion of stimulant medications that should be incorporated into the Pharmacoepidemiology Team's report on the possible misuse of ADHD treatments (Objective 5). While the analysis of ODBand IPDB data in Pharmacoepidemiology Objective 5 for a two-year period can be an important contribution to our understanding of this topic, it is a limited geographical and temporal snapshot. We have included relevant citations with data from a larger population and longer time-frame in the Submission Package under the heading "Misuse of ADHD Treatments.

Response: *Thank you for your suggestion; we are exploring the possible misuse of ADHD treatments*

among adults in Ontario in Objective 5 of our analysis using drug claims data. Additionally, we have updated our literature review of observational studies to include the issue of misuse/abuse.

COMMENT

Pg 5 - new users older and younger than 65. Is there a way to sort out use of stimulants for indications other than ADHD. For example methylphenidate use for excessive sedation for palliative care off label. http://palliativecareswo.ca/apps/pocket_reference_guide.html

Response: For Objective 3 to Objective 5, we will exclude patients who are prescribed an ADHD medication while receiving palliative care.

COMMENT

Can you determine any links to prenatal smoking for those individuals diagnoses with ADHD?

ECG prescreening? AHA recommends this before prescribing but several pediatric organizations do not.

Response: Unfortunately, administrative databases available to us do not capture smoking status, and so we will not be exploring these links.

COMMENT

Breaking this down based on ethnicity could be revealing. Also there is a strong genetic component to this illness.

Response: While this could be interesting to understand, we do not anticipate any policy recommendations being based on ethnicity, and so will not be incorporating any analyses specific to patient ethnic background in this study.

Pharmacoeconomics

COMMENT

The jurisdictions were more interested to develop a de-novo economic model to assess the cost-effectiveness of the drug rather than conducting a systematic review of the available studies. Although, development of a de-novo economic model could mean that one would have to extrapolate the data from the scores on ADHD rating scales, which in turn may reduce the quality of the pharmaco-economic analysis. However, jurisdictions noted that it would still be of more value than the systematic review of available studies due to the following two concerns:

- ODPN's pharmacoeconomic CRP states that due to paucity of data, a de novo cost effectiveness model will not be developed. Given the situation, there were concerns about the systematic review of such studies (with limited data). Since we already suspect that that no conclusions can be drawn due to low-quality evidence, there were

- concerns about the systematic review.
- Another concern was that most of the available studies are conducted by the industry which could be potentially biased. Another option would be to explore if an independent (non-industry) researcher has developed economic model. However, knowing that outcome data is limited, this again may be of low value to decision makers.

Response: *We are cognisant of the need for a full independent economic evaluation of the cost effectiveness of therapy for adult ADHD patients. However, we are aware of the paucity of data linking response to outcomes of interest such as school performance and professional capabilities/crime. Any de novo model would be highly speculative and likely open to a high degree of criticism which would likely undermine the perceived legitimacy of the whole class review. We can instead focus on an additional review of any data linking ADHD, ADHD treatment or response to ADHD treatment to broader societal impacts.*

COMMENT

The budget impact should also be evaluated from broad societal perspective, taking into account the economic impact of ADHD in other sectors than health and therefore avoiding a silo approach to budget impact analysis.

Response: *Given the focus of the analysis, we do not feel extending the BIA to cover broader societal costs would be pertinent and given the paucity of data relating to such costs such modelling would be purely speculative. As stated above, we will conduct reviews of any data linking ADHD, ADHD treatment or response to ADHD treatment to broader societal impacts.*

Systematic Review Team

Thank you for taking the time to review our draft research protocol. We have updated the text in the draft protocol for clarity and to reflect some of the input received through stakeholder feedback. See below for response to individual comments.

COMMENT

Inclusion of comorbidities in subgroup analysis (e.g., anxiety disorders, mood disorders, substance abuse disorders)

- Pg 3. I think that it is a must to consider study populations based on comorbidities to aid in future funding for patients with mental illness overall. These illnesses often do not exist independently. ADHD diagnosis linked with conduct oppositional disorder, anxiety disorders, depression and other mood disorders, Tourettes/tics, learning disorders, substance abuse

Response: *Comorbidities (mood, psychiatric, substance abuse) have always been a priority subgroup. The protocol text pertaining to subgroups has been updated for clarity.*

COMMENT

Use of high doses of stimulants is of concern to some jurisdictions. Evidence on safety and efficacy of high dose stimulants would be of interest to the jurisdictions

Could the systematic review also assess the safety and efficacy of high dose stimulants vs the recommended doses of the same drug?

Response: *The text pertaining to subgroups was updated to reflect this request. High and standard doses will be considered if time and data permit.*

COMMENT

Could the systematic review also include long term efficacy and safety as one of the outcome measures?

Response: *The text pertaining to subgroups was updated to reflect this request. Randomized controlled trials (> 2 years) will be considered for separate analysis if time and data permit.*

COMMENT

Will the SR/ recommendations also assess/determine lines of therapy (i.e. first line, second line of therapy) and define criteria for suboptimal response (i.e. when the patient needs to be switched to second line of therapy or augmentation)? Will there be a subgroup analysis for patients that are treatment experienced versus treatment naïve? Such information could potentially assist the public drug plans in listing successful (proven) drugs in a tiered manner, if the findings are consistent.

Response: *The research protocol has been updated to state that we will consider a subgroup analysis based on treatment experience if time and data permit. We may be limited in the analyses we can perform within the timelines of this review, however, we will be able to compare any results of treatment experience to existing guidelines as they relate to lines of therapy.*

COMMENT

It should be noted that guanfacine hydrochloride extended-release tablets (INTUNIV XR) is not indicated in adults. It should be therefore included in the “Off-label indications” category of the “Drugs of interest”.

Response: *Guanfacine is mentioned in two places in the protocol: First in the introduction where it is noted that all non-stimulants are not indicated in adults; Second, in the table of pharmacologic therapies of interest inside the PICO statement, where there is no text pertaining to the indication or on/off-label use. The protocol text has not been updated to reflect this comment.*

COMMENT

Preferential Response to Amphetamine or Methylphenidate: Stimulants are highly effective treatments for ADHD, but individual ADHD patients may respond better to one of the two classes of stimulant: amphetamines and methylphenidate. The evidence that many ADHD patients have a preferential response to one class of stimulant, and an inadequate (or suboptimal) response to the other, comes from 1) cross-over studies, 2) examination of sub-populations within clinical trials, and 3) examination of medication use patterns and switches in real-world populations. The availability of both amphetamine and methylphenidate products are required to ensure all ADHD patients have the best medication for them. We have included relevant citations in the submission package under the heading “Preferential Response to Amphetamine or Methylphenidate”.

Response: *The base-case analyses for the indirect treatment comparisons will be carried out on the most granular set of pharmacologic therapies, including individual stimulants and non-stimulants, that form a robust network geometry. Subpopulations will be considered where time and data permit, and the protocol text has been clarified to address comments from interested stakeholders. Crossover studies, as noted in the original draft protocol, will be included. Data will be extracted from crossover studies where first period efficacy results are reported, and for the entire duration of the study for safety. Examination of real world medication use patterns and switches is not possible within the timelines of this review. As stated in the draft protocol, we will consider all evidence received through evidence submission packages and will include any studies that meet our eligibility requirements.*

COMMENT

Reference to DSM - IV diagnostic criteria. The most current document is DSM 5 from May 2013. <http://www.cdc.gov/ncbddd/adhd/guidelines.html>

- To make a diagnosis of ADHD, the primary care clinician should determine that diagnostic criteria have been met based on Diagnostic and Statistical Manual of Mental Disorders – Fifth edition (DSM-5, which replaced the Fourth Edition (DSM-IV) in May 2013).

Response: *Study populations must be adults over age 18 with a diagnosis of ADD or ADHD. As noted in our draft protocol, we plan on carefully exploring the study-level diagnostic criteria used for ADHD and ADD. Limiting participants to a single diagnostic criteria (i.e., DSM5) for inclusion may exclude older studies, and in turn, bias our results against treatments that entered the market when an older, or more non-specific diagnostic criteria was applied. We may consider sensitivity analyses around diagnostic criteria if time permits and if the ODPRN research team and clinical experts decide this analysis is necessary based on the objectives of the review.*

COMMENT

Pg 5. Need subgroup analysis of generic vs brand name products considering the unique formulations of some of these products

Response: *The issue of brand/innovator products compared to generic equivalents is of interest, and this subgroup was noted in the draft protocol posted on the ODPRN website. The protocol text pertaining to subgroups has been updated for clarity, and analysis of this subgroup will be considered if time and*

data permit.