Comment: We support the recommendation to recategorize atomoxetine as Limited Use in adults. We believe this would allow patients to benefit from an important therapeutic option which, as the review noted, is safe and effective. This would be a very positive and progressive change. While we are pleased that ODPRN recommend atomoxetine as Limited Use, it would be our recommendation that atomoxetine be allowed as General Benefit. The data of the ODPRN review itself would appear to argue for this in terms of atomoxetine’s efficacy and it remains unclear why this would not be the case.

Given that the finding suggests that Atomoxetine is equally or more efficacious than placebo for many of the outcomes studied, why didn’t ODPRN recommend that atomoxetine be reimbursed as a full benefit like other ADHD drugs under ODB? What is the rationale e.g. is it to prevent other off-label uses?

Response: Atomoxetine has the potential to be used for off-label indications including mood disorders, eating disorders and treatment of addictions. Limited Use listing of atomoxetine may help to prevent use of atomoxetine for these off-label indications. A statement has been added to further explain this rationale:

- Atomoxetine is indicated for the treatment of ADHD but has also been used for off-label indications including mood disorders, eating disorders and treatment of addictions. The proposed clinical criteria for atomoxetine for Limited Use are specific for treatment of ADHD and do not include off-label use of this drug.
- As well current guidelines for the treatment of adult ADHD recommend stimulants as first-line treatment for adult ADHD; atomoxetine is usually considered a second-line therapy. Clinical criteria for atomoxetine for Limited Use would provide guidance on the appropriate use of this drug.

Comment: Could ODPRN comment on what the clinical criteria should be for limited use of atomoxetine?

Response: Based on review of the evidence and feedback from clinicians, clinical criteria for atomoxetine have been proposed and are included in the final consolidated report (Appendix C).

Comment: We have noticed inconsistencies in how Biphentin is identified in the various draft reports. In some instances, it states “Methylphenidate: Biphentin,” in which case, it could be easily confused with a short acting methylphenidate formulation. In other instances, Biphentin is identified as a controlled-release (CR) formulation, or simply methylphenidate multilayer-release (MR). In order to provide
consistency and ease for the reader, we request that when using the generic nomenclature, Biphentin is identified as methylphenidate multilayer-release throughout all of the final reports.

Response: In order to provide consistency in the nomenclature used throughout the reports, Biphentin will be identified as “methylphenidate multilayer-release”.

Comment: The Canadian ADHD Resource Alliance (CADDRA) practice guidelines list atomoxetine as a second-line therapy for the treatment of uncomplicated ADHD in adults. In the event that a patient has a suboptimal or no response to stimulant treatment, CADDRA recommends that the physician ensure that the dose has been optimized before considering adjunctive or alternative treatments. Upon careful examination of the atomoxetine studies included in ODPRN’s Systematic Review, we found that only one (Ni et al. 2013) was truly a head-to-head study. In this open label study, patients were randomized to receive either immediate-release (IR) methylphenidate or atomoxetine for 8 to 10 weeks. Similar levels of executive functioning were found in both treatment groups. It is worthwhile noting that CADDRA’s practice guidelines list IR methylphenidate as a second-line therapy for the treatment of ADHD, similar to atomoxetine.

We are confused as to why the ODPRN has recommended atomoxetine as a Limited Use benefit when highly esteemed Canadian clinical practice guidelines recommend it as a second line therapy (i.e., after failure on an optimally dosed stimulant).

Response: ODPRN’s drug class reviews may lead to recommendations such as expansion of access to drugs on the formulary, revision or restriction of access to drugs, no change to current listing status and/or education of clinicians regarding appropriate prescribing. The ODPRN’s recommendations are not intended to be guidelines for the use of these drugs in the treatment of adult ADHD. Our recommendation to list atomoxetine as Limited Use on the ODB formulary is based on efficacy and safety data, increased accessibility and potentially decreased overall cost of medications for ADHD. There is no suggestion that atomoxetine should be used as first-line therapy.

Comment: a. In 2014, a review found that the abuse/misuse of short-acting stimulant medication is more prevalent than long-acting medications, and that amphetamine-based stimulant abuse/misuse exceeds that of methylphenidate-based stimulants. Since its launch in 2006, there have been no publically available data which suggest that Biphentin is abused/misused more frequently than other long-acting methylphenidate formulations. For this very reason, the College of Physicians and Surgeons of Alberta decided to remove Biphentin was recently removed from its Triplicate Prescription Program (TPP). At the present time, Novo-MPH ER-C and short-acting methylphenidate formulations remain on the TPP. We request that these findings and reference (attached) be included in the
components of the report with the body of knowledge on the abuse/misuse of stimulants.

b. An important issue that was not addressed is differences in rate of misuse, abuse, and diversion between short-acting and long-acting stimulants. There is an existing scientific literature on misuse, abuse, and diversion of stimulant medications that should be incorporated into the report. Why were differences between short-acting and long-acting stimulants not examined in the report?


Response: a. The Environmental Scan report has been updated to reflect the change in the Triplicate Prescription Program in Alberta.

b. We agree that differences in the rate of misuse, abuse and diversion between short-acting and long-acting stimulants would be an important finding and we plan for future research to help fill in this gap, specifically in the adult population. Both of the papers cited were located by our review but were not include as they did not meet our a priori inclusion criteria for adult studies (>19 years of age). Since both suggested studies included those younger than 19, the studies were excluded.

Comment: Therapeutic note for long-acting stimulants currently refers to DSM-IV diagnostic criteria.

Response: The Therapeutic Notes currently accessible on the ODB Formulary website state: “Patients >6 years of age diagnosed with ADHD according to DSM-IV criteria”. As part of the drug class review process to modernize the ODB formulary, it will be recommended that the Therapeutic Notes be updated to reflect the new clinical diagnosis criteria in the DSM-V.

Comment: Regarding the clinical criteria for Limited Use listing for atomoxetine, “Dual therapy with atomoxetine + stimulant will not be reimbursed.” We understand that this measure has been proposed from a cost-control perspective. However, from a clinical perspective, there is a subset of treatment-resistant patients that respond well to this combination. CADDRA proposes that this combination be permitted under circumstances where it is documented that monotherapy has failed. While this related to a small number of individuals, for these patients access to this option can be critical.
**Response:** The environmental scan team reviewed the literature on efficacy and safety of combined therapy of atomoxetine and stimulants in adults. Based on the literature review, there is no evidence supporting the use of combined atomoxetine and stimulants in the adult population. However, the ODPRN recognizes that there may be patients for whom combination therapy may be beneficial in exceptional circumstances. The criteria has been amended to: Combination therapy with atomoxetine plus stimulants is not supported by clinical evidence for efficacy or safety.

**Comment:** Regarding the Therapeutic Notes for long-acting stimulants, “Has tried methylphenidate (long or short-acting) or dextroamphetamine (long or short-acting) and has experienced unsatisfactory results due to poor symptom control or side effects”, we have grave concerns in regards to this requirement. CADDRA’s guidelines do not recognize short-acting medications as first line treatment for ADHD. Our reasons are well documented in our guidelines; they include efficacy, compliance, abuse potential, privacy, convenience, and side effects. CADDRA requests the opportunity to discuss the advantages of long-acting preparations with the ODPRN. We believe this requirement adversely affects patient health in Ontario, especially in the more disadvantaged population that would be affected by these changes.

**Response:** As per the CADDRA guidelines, there are several factors that need to be considered including efficacy, safety, abuse potential, compliance, convenience and cost.
- **Efficacy:** Our review of treatment of adult ADHD indicated that overall, stimulants and atomoxetine were associated with a significant improvement in patient-related clinical response related to placebo.
- **Safety:** There were few significant differences among the pharmacotherapies.
- **Abuse potential:** Short-acting stimulant medications may be more likely to be abused than some long-acting stimulants.
- **Convenience/compliance:** Long-acting stimulants are taken once daily compared to short-acting stimulants which may be taken 2-3 times daily. Once-daily administration may help to improve compliance.
- **Cost:** Long-acting stimulants are more costly (based on wholesale costs) than short-acting stimulant. Note that cost-effectiveness of long-acting stimulants in adult ADHD was not evaluated in our review.

Based on the results of our review, consideration of published guidelines and feedback from stakeholders, our proposed “Therapeutic Notes for Long-acting Stimulants” does **not** include the stipulation that patients need to be tried on short-acting stimulants prior to using long-acting formulations.

**Comment:** Could ODPRN also comment on the place of therapy for stimulants in general or if there specific stimulants that should be used as first line, second line therapy etc.?
Response: ODPRN’s drug class reviews may lead to recommendations such as expansion of access to drugs on the formulary, revision or restriction of access to drugs, no change to current listing status and/or education of clinicians regarding appropriate prescribing. The ODPRN’s recommendations are not intended to be guidelines for the use of these drugs in the treatment of adult ADHD. Currently in Ontario, the all of the stimulants are available as General Benefit. No changes in listing for these medications are recommended based on the results of our review; a further recommendation has been added to the final report to reflect this.

Comment: Could the Key Considerations in the consolidated report also note about the efficacy of high-dose mixed amphetamines salts, and other stimulants, as appropriate?

Response: Additional statements have been added to the “Key Consideration” section in the Executive Summary namely:
When compared to placebo, high-dose mixed amphetamine salt was better than most other pharmacotherapies at improving observer-reported clinical response. Standard-dose atomoxetine and high-dose mixed amphetamine salts were associated with significant improvements in quality of life relative to placebo. However, there were no significant differences among the pharmacotherapies.

Comment: Given that the pharmacotherapies have similar efficacy and safety profile; can ODPRN also comment on what other criteria (e.g. cost-effectiveness or misuse/abuse potential) be the basis for reimbursement decisions? Could ODPRN include a comment (in the key consideration) on the “…..a limited use listing for brand name only long-acting stimulants with enforced step therapy” i.e. as per the conclusion of the budget impact analysis?

Response: With regards to the abuse/misuse potential of these agents, a separate bullet point has been added in the “Key Consideration” section in the safety section:
Our data analysis indicated that there was minimal misuse/abuse occurring at the prescription level. However, in our review of studies summarizing observational literature, the misuse of prescription stimulants occurs especially in college-age adults. In addition, according to our data analysis, there may be a higher rate of abuse/misuse occurring with short-acting stimulants compared to long-acting stimulants. Although the pharmacoeconomic team explored several different reimbursement options as part of their BIA, these were not included in our final recommendation for several reasons including lack of evidence to suggest that short-acting stimulants should be used as first-line therapy, lack of cost-effectiveness data for the treatment of adult ADHD and possible greater abuse potential or short-acting products compared to long-acting.
medications. A statement has been added to the pharmacoeconomic section of the “Key Consideration” to reflect this.

**Pharmacoepidemiology Report**

**Comment:** For Exhibit 16–Is Biphentin included with Concerta (i.e., as a brand product)? Biphentin is reimbursed for adults on the ODBF and should be included as a line on the graph.

**Response:** Biphentin was not included with Concerta in the draft report. However, we have revised the exhibit to include all long-acting methylphenidate products with Biphentin separate from other products. Please see Figure 16 of our updated report.

**Comment:** 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. Why was there no examination of Preferential Response in the review?

**Response:** This is a good question that we are unfortunately unable to address with our data because there is no available data for clinical response. All we are able to determine using administrative data is the rates of prescribing for certain medications and continued use of specific medications. We are not able to explore causality related to treatment outcomes associated with taking medications based on the data we have available. Future work exploring real-world effectiveness of these medications would be of great importance.

**Comment:** What is the utilization of Biphentin in Ontario?

**Response:** Please see exhibit 16 in our updated report.

**Comment:** What proportion of patients in the analysis were using atomoxetine in conjunction with a stimulant?

**Response:** This is a great question. Based on your feedback and feedback of other stakeholders we have updated our analysis to explore the level of concurrent use of stimulants and atomoxetine. Please see exhibit 23.

**Comment:** Did this analysis examine diagnoses other than ADHD?

**Response:** No we only examined ADHD and did not include other indications. Other
indications, such as narcolepsy, may be difficult to identify using OHIP codes.

Pharmacoeconomics Report

Comment: Regarding the following comment: “…we have determined that little is known about the economic impact of adult ADHD.” In 2013, The Centre for ADHD Awareness, Canada authored a report entitled Paying Attention to the Cost of ADHD … The Price Paid by Canadian Families, Government and Society.(5) This article provided a detailed overview of the socioeconomic impact of issues related to ADHD in adults, as well as its associated costs. This article has been attached for your reference.

Response: No published economic evaluations in this area were identified which examined the cost effectiveness of ADHD treatments. We therefore reviewed the published data on the impact of ADHD in adults due to the lack of economic evaluations in this area.

Comment: Will listing of atomoxetine under the Limited Use (LU) criteria result in off-label use for other indications?

Response: It is difficult for the ODPRN to predict how a potential change of listing status of atomoxetine will affect off-label use.

Comment: Do all strengths of atomoxetine fall under the tiered pricing framework, and that generic atomoxetine and all of its strengths will be priced at 25%? In some provinces, the tiered pricing may not apply to all generics and all strengths.

Response: As this main objective of the report was to provide recommendations to Ontario Public Drug Programs (OPDP), the BIA was based solely on Ontario prescribing information and drug policies.

Systematic Review Report

Comment: Effects of medications on Executive Function were analyzed in the Systematic Review. Have you considered adding the study by Alder et al 2013 on executive function, already included in other parts of the Systematic Review, to that analysis? (Reference 39 in the Systematic Review: Adler et al. 2013. Lisdexamfetamine dimesylate in adults with attention-deficit/ hyperactivity disorder who report clinically significant impairment in executive function: results from a randomized, double-blind, placebo-controlled study. Journal of Clinical Psychiatry. 74(7):694-702)

Response: Thank you for your question. For each outcome in the systematic review, we
used an a priori defined list of eligible outcome scales, in consultation with the ODPRN research team and clinical experts. In Alder and colleagues (2013), executive function was evaluated using the BRIEF-A scale, which was not one of our a priori approved scales. As such, data from this study was not eligible for inclusion for the analysis of executive function.

**Comment:** How does ODPRN’s recommendation and key findings from SR compare with that 2011 DERP report, which the ODPRN’s SR builds upon?

**Response:** Thank you for your question. There are differences between our review and the 2011 DERP Review that make direct comparisons of findings difficult.

In the DERP review, the authors felt the included data at that time were insufficient for network meta-analysis and there were other methodological differences between the two reviews that must be considered when comparing findings. The DERP 2011 Review included observational studies, evaluated switching from one drug to another, and compared the included drugs only where direct evidence was available. In addition, there were few outcomes in common between the two reviews. In general, DERP 2011 reported that the evidence from placebo-controlled trials was “insufficient to support conclusions about the comparative effectiveness and harms in drugs for ADHD in adults.” However, the authors did report that, “Compared with placebo, the response rates were significantly greater for atomoxetine, immediate-release dextroamphetamine, dexamphetamine ER, lisdexamfetamine, immediate-release methylphenidate, methylphenidate OROS, methylphenidate ER, immediate-release mixed amphetamine salts, and mixed amphetamine salts XR.” In our review, we found that most pharmacotherapies were associated with improvement relative to placebo, although there were differences in response between patient- and observer-reported responses.

**Comment:** Did any of the studies report hard outcomes (e.g. work performance) as opposed to surrogate outcomes (i.e. scores on ADHD scales)? If yes, would ODRPN consider commenting on those in the report?

**Response:** Thank you for your question. Each outcome in the systematic review was prioritized in consultation with the ODPRN research team and clinical experts. As the current review was completed in a timely manner to inform provincial decision-makers, the systematic review team had to make decisions at the time of protocol development to limit our scope and analyses to those that would be most informative to the research questions being investigated. We cannot currently comment on the availability of outcome data that were not presented in our report findings as it was not comprehensively extracted from the included studies.

**Environmental Scan**

**Comment:** Recently, Biphentin has been approved by the FDA under the trade
name of Aptensio XRTM. Therefore, it would not have been included in this review. Please update the report to indicate this.

Response: A note has been added to clarify the status of Biphentin in the US at the time of the review. “Note that Biphentin was approved by the FDA under the trade name of Aptensio XR after this review was initiated, and is therefore not included in Exhibit 5.”

Comment: Regarding the comment: “In Alberta, the Triplicate Prescription Program, which is designed to monitor all drugs with the potential for misuse/abuse, includes all methylphenidate products with the exception of Concerta.” In October, 2015, the College of Physicians and Surgeons of Alberta removed Biphentin was recently removed from its Triplicate Prescription Program (TPP). At the present time, Novo-MPH ER-C and short-acting methylphenidate formulations remain on the TPP.

Response: The text has been updated to reflect this recent change. “In Alberta, the Triplicate Prescription Program, which is designed to monitor all drugs with the potential for misuse/abuse, includes short-acting methylphenidate formulations and generic methylphenidate ER-C, but not long-acting preparations.”

Comment: In the section entitled “Methylphenidate extended-release products and bioequivalence”, it is stated that: “There are no prospective studies that have been published in a peer reviewed journal that have investigated this potential lack of therapeutic equivalence.” Please note that the clinical trial that is referenced has been accepted for publication in a peer-reviewed journal entitled: “Therapeutic advances in psychopharmacology”.

Response: The summary paragraph has been changed to: Current determination of bioequivalence in Canada has concluded that Concerta and generic methylphenidate extended release products are bioequivalent. However, there have been isolated case reports, a retrospective study and a small randomized clinical trial that have suggested that patients who switch from Concerta to the generic methylphenidate extended-release may have a loss in efficacy.

Qualitative Report

Comment: Biphentin is not included in the list of long-acting medications available. This should be added.

Response: Biphentin was now been included in the report as part of the long-acting medications available for ADHD.

Comment: Regarding the comment: “For adults in the working world and
parents and students, like older students I find that “drug XXX” is superior because of the long length of time so you are covering the evening, you’re covering evening meetings, evening driving and it is definitely smoother.” To what is “drug XXX” superior (e.g., IR stimulant, other long-acting products)? If this statement is not substantiated, it should be removed from the report. At present, it feels highly promotional.

Response: Thank you for your comment; the quote has been removed from the report.

Comment: “When discussing non-stimulants, the majority of clinician participants did not perceive Strattera® or any of the other drugs in this class to be especially effective. However, most participants admitted that they did not have much experience prescribing these medications. In the case of Strattera®, some described that it can take a long time before the patient can perceive a difference in ADHD symptoms, if at all. In terms of alternatives, a few physician participants mentioned that they have used bupropion (Wellbutrin®) in some patients and have found these to be effective for patients who have history of substance abuse.” What was the weight assigned to the clinician perspective since it does not seem to correspond with the authors’ final recommendation?

Response: The ODPRN’s recommendations are not intended to be guidelines for the use of these drugs in the treatment of adult ADHD. Our recommendation to list atomoxetine as Limited Use on the ODB formulary is based on efficacy and safety data, increased accessibility and potentially decreased overall cost of medications for ADHD. There is no suggestion that atomoxetine should be used as first-line therapy.

Comment: Regarding comments on non-pharmacological strategies, we believe and promote that treatment should always be multimodal and not just medication. We struggle with access to psychosocial treatments for our stakeholders on a daily basis. In reality we have a two tier health system where ADHD is concerned. One is due to access to these treatments in non-urban settings, but more importantly most psychosocial treatments such as ADHD coaching, CBT, mindfulness and other therapies are out-of-pocket expenses which are out of reach for many suffering with ADHD. This may very well be one of the reasons that physicians do not bring up the topic as much as they should; there are very limited accessible and affordable options for these treatments.

Response: Thank you for your comment. You have raised some good points.

Comment: Were all patient Ontario Drug Benefit (ODB) recipients?

Response: Approximately one third of participants were ODB recipients, one third were receiving private coverage and one third were paying out of pocket. This information has been added to the report under Appendix B – demographics.
Comment: Did patient participants only have a diagnosis of ADHD or did they have other comorbidities?

Response: A majority of the patients interviewed only had a diagnosis of ADHD but there was one individual with a history of substance abuse and two who are living with depression and anxiety.