

# TREATMENT OF ATTENTION- DEFICIT/HYPERACTIVITY DISORDER IN ADULTS

## FINAL ENVIRONMENTAL SCAN REPORT

**December 2015**

## **Conflict of Interest Statement**

No study members report any affiliations or financial involvement (e.g., employment, consultancies, honoraria, stock options, expert testimony, grants or patents received or pending, or royalties) that may present a potential conflict of interest in the treatment of ADHD in adults Drug Class Review.

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## **Study Team**

Environmental Scan: Sandra Knowles

## Executive Summary

### Part A: Pharmacy Benefit Programs in Ontario, across Canada and internationally

In Canada, there are stimulant and non-stimulant medications that have been approved for the treatment of attention deficit hyperactivity disorder (ADHD) in adults. Stimulants are available as short-acting formulations (i.e., methylphenidate, dextroamphetamine) and long-acting formulations (i.e., dextroamphetamine, methylphenidate, amphetamine mixture and lisdexamfetamine). Atomoxetine is the only non-stimulant medication approved for the treatment of ADHD in adults. Generic formulations are available for methylphenidate short-acting and long-acting (specifically Ritalin SR and Concerta), short-acting dextroamphetamine as well as for atomoxetine.

In Ontario, all stimulant medications (including long- and short-acting formulations) are funded as general benefit on the Ontario Drug Benefit (ODB) formulary. Atomoxetine is available in Ontario through the Exceptional Access Program (EAP). Across Canada, short-acting stimulants are available as general benefit in all jurisdictions (except for Yukon), whereas long-acting stimulants are available only with special authorization in many jurisdictions. As well, five provinces have age restrictions (coverage from 6-18 or from 6-25 years) on long-acting stimulant products. Long-acting methylphenidate products and atomoxetine are available in Australia only for children/adolescents up to age 18. In New Zealand, there are no age restrictions for methylphenidate extended release or atomoxetine.

### Part B: Guidelines for the treatment of adults with ADHD

Four guidelines and consensus statements on diagnosis and treatment of adults with ADHD were reviewed. All guidelines emphasize the need for a multi-pronged approach to treatment which includes education, psychotherapy and pharmacotherapy. Stimulants are considered first-line treatment for most patients. Atomoxetine is a second-line treatment, except for patients with substance abuse disorders, where it is considered first-line.

### Part C: Impact of different drug reimbursement schemes for treatment of adults with ADHD

There is limited information regarding the use of various reimbursement schemes for stimulants and non-stimulants for the treatment of ADHD, in particular in adults. One study assessed the effect of copayment increases associated with a 3-tier formulary system in children and found that copayment resulted in lower total ADHD medication spending, sizeable increases in out-of-pocket expenditures for families, and a significant decrease in the probability of using these medications.

### Part D: Rapid review of selected topics

- *Bioequivalence of methylphenidate extended release products:* Current determination of bioequivalence in Canada has determined that Concerta and generic methylphenidate extended release products are bioequivalent. However, there have been isolated case reports, a retrospective study and a prospective clinical trial that

- have suggested that patients who switch from Concerta to the generic methylphenidate extended-release may have a loss in efficacy.
- *Cardiovascular safety of drugs used in the treatment of adult ADHD:* Stimulants and non-stimulants have been shown to increase blood pressure and heart rate; long-term impact in adults, especially those with concomitant diseases, is unknown. Data from two large population-based studies in adults did not demonstrate an increased risk for sudden death or ventricular arrhythmia. One study found an increased risk in sudden death or ventricular arrhythmias with methylphenidate, although lack of dose-response suggests that this is not a causal relationship. Overall, there is lack of data in adults 50 years and older for long-term cardiovascular safety of these medications.
  - *Suicidality and treatment of ADHD in adults:* Limited data suggest that there is no causal association between ADHD drug treatments and suicidality in adults.
  - *Combination therapy with atomoxetine and stimulants in adults:* There is no evidence supporting the use of atomoxetine and stimulants in adults with ADHD.

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## Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a commonly diagnosed psychiatric disorder that is well-recognized in childhood, and often persists into adulthood. It has been estimated that almost 30% of children will continue to have a diagnosis of ADHD as adults.<sup>1</sup> The prevalence rate of ADHD in children and adolescents is 5.3% worldwide,<sup>2</sup> and approximately 3-4% of adults affected.<sup>3</sup> ADHD is characterized by inattention, hyperactivity and impulsivity, which may result in social and functional impairments in adults.<sup>4</sup> According to the Diagnostic and Statistical Manual (DSM) V, for diagnosis, older adolescents and adults (over age 17 years) must present with five symptoms from either (or both) the inattention group of criteria and the hyperactivity and impulsivity criteria.<sup>5</sup>

Although stimulants are all approved in Canada for treatment of ADHD, these agents are used for other indications. Dextroamphetamine regular and sustained release and methylphenidate regular and sustained release are also approved for the management of patients with narcolepsy.<sup>6</sup> Other off-label indications for stimulants include treatment of depression in patients with terminal illness, management of fatigue in adult cancer survivors, and use in bipolar depression, although the evidence for efficacy in some of these conditions is limited.<sup>7-11</sup> Additionally, methylphenidate has been used to improve cognition in patients with brain tumours, for HIV-associated cognitive dysfunction or fatigue, and for fatigue in neurodegenerative disorders (e.g., Parkinson disease).<sup>12</sup>

ADHD in adults is associated with various comorbid conditions including depression, substance abuse, personality disorders, anxiety disorders and learning disabilities.<sup>13</sup> Comorbidity with ADHD may affect treatment compliance as well as treatment response. Treatment of adults with ADHD is important as untreated ADHD may result in higher rates of unemployment and sick leave.<sup>14;15</sup> In addition, a diagnosis of ADHD has been associated with illicit drug use and alcohol addiction, lack of academic achievement and higher rates of poor social adjustment and family or marital conflict.<sup>15</sup> For example, using Swedish population-based data, the crime rate was reduced by 32% in men receiving treatment for ADHD and 41% for women.<sup>16</sup>

Pharmacologic management of adults with ADHD is considered first-line therapy in adults.<sup>17</sup> Stimulant medications are often indicated as initial treatment.<sup>15;18</sup> Non-stimulant medications, in particular atomoxetine, are often used as a second line agent.<sup>18</sup> In general, medications should be started at a low dose and titrated upwards until clinical effect is observed or adverse effects develop.<sup>3</sup>

The objectives of this report are:

- **Part A:** To summarize coverage of stimulant and non-stimulant medications through public drug programs in Ontario and across Canada, as well as in select international jurisdictions
- **Part B:** To summarize the guidelines for pharmacologic treatment of ADHD in adults
- **Part C:** To review the evidence relating to the impact of different drug reimbursement schemes for stimulant and non-stimulant medications (in adults) on patient access and/or utilization and costs
- **Part D:** To provide summary information on selected topics, as needed

## Part A: Pharmacy Benefit Programs in Ontario, across Canada and internationally

### Availability of Stimulant and Non-stimulant Medications in Canada

In Canada, there are stimulant medications and non-stimulant medications available for the treatment of ADHD. Stimulant medications include: dextroamphetamine, methylphenidate, lis-dexamfetamine dimesylate, and amphetamine mixture. Atomoxetine and guanfacine are the available non-stimulant medications.

Stimulant medications are available in either short-acting dosage forms (e.g., dextroamphetamine, methylphenidate) or long-acting preparations (e.g., amphetamine mixture, dextroamphetamine, lis-dexamfetamine, methylphenidate). Generic formulations are available for methylphenidate short-acting and long-acting (specifically for Ritalin SR and Concerta) as well as for atomoxetine. Dextroamphetamine short-acting is also available generically.

#### Summary

- There are stimulant and non-stimulant medications available for the treatment of ADHD in adults.
- Stimulant medications include dextroamphetamine, methylphenidate, lis-dexamfetamine dimesylate and amphetamine mixture. Short-acting formulations include methylphenidate and dextroamphetamine; long-acting formulations include dextroamphetamine, methylphenidate (various), amphetamine mixture and lis-dexamfetamine.
- Atomoxetine is the only non-stimulant medication approved for the treatment of ADHD in adults.
- Generic formulations are available for methylphenidate short-acting and long-acting (specifically Ritalin SR and Concerta), dextroamphetamine short-acting as well as for atomoxetine.

### Exhibit 1: Commercially available stimulant and non-stimulant medications in Canada

Drug Name	Brand name	Manufacturer	Availability	Dosage form	Adult dosage initial/usual	Generic available	30-day cost*	Date available**
<b>Stimulants</b>								
Amphetamine mixture	Adderall XR	Shire	5, 10, 15, 20, 25, 30mg	Extended-release capsule	20mg once daily/ 20-60 mg once daily	Yes	90.86	Jan 2004
	Generic	Actavis					68.15 <sup>†</sup>	Aug 2015
Dextro-amphetamine	Dexedrine	Paladin	5 mg	Tablet	Not specified (10mg bid)	Yes	81.30	Dec 1992
	Dexedrine Spansule	Paladin	10, 15 mg	Sustained-release capsule	Not specified (20mg qam)	No	60.97 <sup>†</sup>	Aug 2015
Methyl-phenidate	Concerta	Janssen	18, 27, 36, 54 mg	Extended release tablet	18mg once daily/ 36-72 mg once daily	Yes	101.75	Jul 2003
	Generic	Various					49.44	Jan 2010
	Ritalin	Novartis	10, 20 mg	Tablet	10 mg two to three times daily/ 20 mg three times daily	Yes	72.88	Dec 1956
	Generic	Various	5, 10, 20 mg				14.69	Oct 1997
	Ritalin SR	Novartis	20mg	Extended release tablet	10-20mg once daily/ 60 mg once daily	Yes	63.93	Dec 1984
	Generic	Various					25.38	Apr 2005
	Biphentin	Purdue	10, 15, 20, 30, 40, 50, 60, 80mg	Controlled release capsule	10-20mg once daily/ 60-80mg once daily	No	96.24	Aug 2006
Lisdex-amfetamine dimesylate	Vyvanse	Shire	10, 20, 30, 40, 50, 60 mg	Capsules	Initial: 30 mg daily, may increase to 50 mg daily after 1 week	No	95.57	Aug 2009
Atomoxetine	Strattera	Eli Lilly	10, 18, 25, 40, 60, 80, 100mg	Capsule	40 mg once daily/ 60-80mg once daily	Yes	132.80 <sup>†</sup>	Mar 2005
	Generic	Various					111.07 <sup>†</sup>	July 2011
Guanfacine	Intuniv XR	Shire	1, 2, 3, 4mg	Extended release capsule	Not indicated in adults	No	NA	Aug 2013

\*Cost for the lowest initial dose based on prices obtained from the Ontario Drug Benefit Formulary (Accessed: August 10, 2015)

\*\*Date obtained from Health Canada Database

<sup>†</sup>Wholesale acquisition cost for the lowest initial dose based on prices obtained from McKesson (Accessed: September 18, 2015)

Current as of October 8, 2015

## Common Drug Review

The Common Drug Review (CDR) is a single process for reviewing new drugs and providing listing recommendations to participating publicly funded federal, provincial and territorial drug benefit plans in Canada; it was established in September 2003. Four medications for the treatment of ADHD were reviewed by the CDR (see Exhibit 2 and Appendix A).

### Exhibit 2: Summary of Common Drug Review recommendations for medications used for treatment of ADHD

Product	Recommendation
Amphetamine mixture (Adderall XR)	<i>Do not list</i>
Lisdexamfetamine (Vyvanse)	<i>Do not list</i>
Atomoxetine (Strattera)	<i>Do not list</i>
Guanfacine (Intuniv XR)	<i>Do not list</i>

## Product listing in Ontario

### Stimulant medications

All available products are listed on the Ontario Drug Benefit formulary as a general benefit.

- Methylphenidate (short-acting): generics, Ritalin
- Methylphenidate (long-acting): generics, Ritalin SR
- Methylphenidate (sustained release): generics, Concerta
- Methylphenidate: Biphentin
- Lisdexamfetamine: Vyvanse
- Amphetamine mixture (Adderall XR)

A therapeutic note is associated with all CNS stimulants.

- Stimulant medication should only be used when diagnostic criteria for narcolepsy or attention deficit disorder have been met and when stimulant medication has been demonstrated to produce clinical benefits. The use of conventional-release medication should almost always precede the use of extended-release preparations.

In addition, long-acting products (i.e., Concerta + generics, Biphentin, Vyvanse, Adderall XR) include the following therapeutic note:

- NOTE: Patients >6 years of age diagnosed with ADHD according to DSM-IV criteria and where symptoms are not due to other medical conditions which affect concentration, and who require 12-hour continuous coverage due to academic and/or psychosocial needs and who meet the following:
  1. Patients who demonstrate significant and problematic disruptive behaviour or who have problems with inattention that interfere with learning

AND

2. Prescribed by or in consultation with a specialist in pediatric psychiatry, pediatrics or a general practitioner with expertise in ADHD

AND

3. Have been tried on methylphenidate immediate release (IR) or methylphenidate slow release (SR) or Dexedrine IR or Dexedrine SR (Spansules), and have experienced unsatisfactory results due to poor symptom control, side effects, administrative barriers or societal barriers.

*Administrative barriers include:*

- a. inability of a school to dose the child at lunch*
- b. the school lunch hour does not coincide with the dosing schedule*
- c. poor compliance with noon or afternoon doses*
- d. the patient is unable to swallow tablets.*

*Societal barriers include:*

- a. the patient or patient's caregiver(s) has (have) a history of substance abuse or diversion of listed immediate-release alternatives*
- b. the patient or patient's caregiver(s) is/are at risk of substance abuse or diversion of listed immediate-release alternatives*

#### Non-stimulant medications

Atomoxetine is available in Ontario's public drug plan through the Exceptional Access Program (EAP) according to the following clinical criteria:

- Patients  $\geq$  six years of age diagnosed with ADHD according to Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria and where symptoms are not due to other medical conditions which affect concentration, and who require 12-hour continuous coverage due to academic and/or psychosocial needs, and who meet all of the following:
  - 1) The patient demonstrates significant and problematic disruptive behaviour or has problems with inattention that interfere with learning; AND
  - 2) The medication is prescribed by or in consultation with a specialist in pediatric psychiatry, pediatrics or a general practitioner with expertise in ADHD; AND
  - 3) The patient has been tried on methylphenidate immediate-release or methylphenidate slow-release or Dexedrine IR or Dexedrine Spansules, and has experienced unsatisfactory results due to poor symptom control or side effects; AND
  - 4) Evidence of benefit from a one month trial with Strattera.

#### Committee to Evaluate Drugs:

The Committee to Evaluate Drugs (CED) is the Ministry of Health and Long-term care's independent expert advisory committee on drug-related issues. In 2011, the CED re-evaluated the funding of long-acting medications for the management of ADHD. Key findings of the report include<sup>19</sup>:

- ◆ Randomized controlled studies on long-acting ADHD medications have shown that they are effective at improving measures of behaviour, attention and performance, but suggest that they are similar to short-acting agents in terms of efficacy and safety.
- ◆ There is a lack of good quality, direct comparison studies to assess the relative efficacy and safety of long-acting ADHD medications compared with short-acting agents. Although

long-acting agents are dosed once daily, there is no evidence that this added convenience translates into improved treatment adherence or other important clinical outcomes.

◆ Long-acting ADHD medications cost two to three time more than short-acting agents. Because long-acting products have not been shown to be therapeutically superior, they are funded only in patients who cannot be adequately managed with short-acting treatments. These include patients who do not receive sufficient symptom control or experience side effects from short-acting agents.

◆ Long-acting treatments can also be considered in situations where there are administrative or societal barriers associated with short-acting products, such as the inability of a child to receive ADHD medications at school or where there is a risk of abuse of short-acting products.

◆ To ensure that long-acting agents are used in the clinical settings where they are most likely to be cost-effective and to obtain better value for money, the Ontario Public Drug Programs pursued listing agreements with the manufacturers of long-acting ADHD medications.

◆ Based on listing agreements that address appropriate utilization and cost, Adderall XR (extended release mixed amphetamine salts), Concerta (extended-release methylphenidate), and Biphentin (extended-release methylphenidate) are now listed on the Ontario Drug Benefit Formulary with therapeutic notes.

◆ As a listing agreement has not been reached, Strattera (atomoxetine) will continue to be funded through the Exceptional Access Program according to the previous criteria.

### Summary

- In Ontario, all stimulant medications (including long and short-acting formulations) are funded as general benefit on the ODB formulary.
- Atomoxetine, a non-stimulant medication, is available on the Ontario public drug plan through the Exceptional Access Program (EAP).

## Public Plan Listings in Canada

### Part 1: Listing Status

In order to determine the listing of medications for the treatment of ADHD across Canada, the relevant webpages of the provincial drug formularies were searched (See Appendix B). In Canada, at least one medication is available on public plans, as a general benefit or through a special authorization process. A summary of the various listings is found in Exhibit 3.

### Restriction Criteria

In order for patients to be eligible for publically funded stimulant or non-stimulant medications, several provinces use a special authorization process that includes the use of clinical criteria. For a list of clinical criteria, see Appendix C.

**Exhibit 3: Public drug plan benefit listings**

Drug	Brand name	BC	AB	SK	MB	ON	QC	NB	NS	PEI	NL	YK	NIHB / NU / NW
Amphetamine mixture (Mixed amphetamine salts)	Adderall XR	No	No	No	No	FB*	Res	No	No	No	No	No	No
Atomoxetine	Generic	No	No	Res	No	Res	Res	No	No	No	No	Res	No
Dextro-amphetamine	Dexedrine	FB	FB	FB	FB	FB*	FB	FB	FB	FB	FB	Res	FB
	Dexedrine Spansule	FB	FB	FB	FB	FB*	FB	FB	FB	FB	FB	Res	FB
Lis-dexamfetamine dimesylate	Vyvanse	No	Res	Res	FB	FB*	Res	No	No	No	No	No	FB
Methylphenidate	Generic (Concerta)	Res	No	FB	FB	FB*	Res	Res	Res	No	Res	Res	FB
	Generic (Ritalin)	FB	FB	FB	FB	FB*	FB	FB	FB	FB	FB	Res	FB
	Generic (Ritalin SR)	FB	FB	FB	FB	FB*	FB	FB	FB	FB	FB	Res	FB
	Biphentin	No	Res	Res	FB	FB*	Res	Res	Res	Res	Res	Res	No
Guanfacine	Intuniv	No	No	No	No	No	Res	No	No	No	No	No	No

\*Therapeutic note

NO=not listed

RES=restricted listing

FB=unrestricted listing

## Part 2: Telephone Interview with Public Drug Program Representatives

A representative from each public drug program invited to participate in a 30 minute telephone interview (see Appendix D) to gather further information about formulary listing of drugs used in the treatment of ADHD. Exhibit 4 summarizes the information obtained in the interviews.

### **Exhibit 4: Summary of interviews with representative from public drug program**

Province	Listing	Information on listing
British Columbia	Full benefits Restricted (Concerta+ generics)	Dextroamphetamine and methylphenidate (long-acting, short-acting) are available as full benefits for all age groups Coverage for methylphenidate ER is for patients aged 6-18 years of age; benefits of extended-release preparations in adults is unknown
Saskatchewan	Full benefits Restricted (atomoxetine, Vyvanse)	Dextroamphetamine and methylphenidate (long-acting, short-acting) are available as full benefits for all age groups Coverage for atomoxetine and Vyvanse is available as a special authorization product with no restrictions for age
Manitoba	Full benefits for all available products	Dextroamphetamine and methylphenidate (long-acting, short-acting) are available as full benefits for all age groups In addition, Vyvanse, Concerta + generics, Biphentin available as full benefits (no age restrictions)
Ontario	Full benefits Restricted (atomoxetine)	All medications (except for Intuniv and atomoxetine) are available as full benefits. Atomoxetine is available through the EAP program.
Nova Scotia, New Brunswick	Full benefits Restricted (Biphentin, Concerta+ generics)	Dextroamphetamine and methylphenidate (long-acting, short-acting) are available as full benefits for all age groups Coverage for Biphentin and methylphenidate ER is for patients aged 6-25 years of age; this is to allow for use of these products in young adults who are "college-age", although no data to support this
Prince Edward Island	Full benefits Restricted (Biphentin, Concerta+ generics)	Dextroamphetamine and methylphenidate (long-acting, short-acting) are available as full benefits for all age groups Coverage for Biphentin and methylphenidate ER is for patients aged 6-18 years of age; benefits of extended-release preparations in young adults is unknown
NIHB	Full benefits	Dextroamphetamine and methylphenidate (long-acting, short-acting) are available as full benefits for all age groups In addition, Vyvanse, Concerta + generics are available as full benefits No listing for Adderall XR as concerns were raised regarding abuse potential
Yukon	Restricted	All covered medications are only available through a restricted basis; concern regarding misuse/abuse of these medications as well as use of these medications for weight-loss resulted in a restricted listing

**Summary.**

- Dextroamphetamine (short and long-acting) and methylphenidate (short and long-acting) are listed in all jurisdictions as a general benefit, except for Yukon, which lists these products as a restricted benefit.
- Other long acting stimulant products (i.e., Adderall XR, Vyvanse, Concerta, Biphentin) are listed in various jurisdictions as medications requiring special authorization, except for Ontario, where they are available as a general benefit.
- Age restrictions on long-acting stimulant products are enforced in British Columbia (6-18 years), Prince Edward Island (6-18 years), Nova Scotia (6-25 years), Newfoundland (6-25 years) and New Brunswick (6-25 years).
- Funding for atomoxetine is only provided in Saskatchewan, Ontario, Quebec and Yukon.

## Selected International Jurisdictions

### United States

As a measure to control ever-increasing costs associated with healthcare, the use of a preferred drug list (“formulary”) has been implemented in some jurisdictions. For example a preferred drug list is a list of medications that the provider will cover the cost for without the need to request a prior authorization. The preferred drugs are usually medications that are available generically or are the result of price negotiations between the pharmaceutical company and the provider.

A tiered co-payment system is a combination of cost-sharing and a preferred drug list.<sup>20</sup> Three-tier structures commonly assign generic medications the lowest copay, formulary brand medications a somewhat higher copay, and non-formulary brand medications the highest copay. Three-tier copays provide consumers with more choice than in a closed formulary (where tier three drugs would not be covered at all) and attempt to reduce the number of prior authorizations that are needed for drug approval.<sup>21</sup> In a five-tier system, tier 1 includes preferred generic drugs, tier 2 non-preferred generic drugs, tier 3 preferred brand drugs, tier 4 non-preferred brand drugs and tier 5 specialty drugs (e.g., injectables) (see Appendix E for examples of copayments with tiered formulary systems). (Exhibit 5) 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.

### Exhibit 5: Listing of drugs for treatment of ADHD for select plans in the United States

Drug Plan	Adderall XR	Concerta/ generic	Methylphenidate (short acting)	Vyvanse
AETNA Preferred List ( <a href="http://www.aetna.com">www.aetna.com</a> )	Tier 3	Tier 3/ Tier 1	Tier 1	Tier 2
Amerigroup Medication Formulary (Medicaid markets in Florida, Louisiana, Maryland, Nevada, New Jersey and Washington) ( <a href="http://www.Providers.amerigroup.com">www.Providers.amerigroup.com</a> )	Non-preferred	Non-preferred/ preferred	Preferred	Non-preferred
Blue Cross Blue Shield of South Carolina Preferred Drug List ( <a href="http://www.southcarolinablues.com">www.southcarolinablues.com</a> )	Non-preferred	Non-preferred/ preferred	Preferred	Preferred
Blue Cross Blue Shield of Texas Standard Preferred Drug List (July 2015) ( <a href="http://www.bcbstx.com">www.bcbstx.com</a> )	Non-preferred	Tier 4/ Tier 2	Tier 1	Tier 3
Connecticut Medicaid Preferred Drug List ( <a href="http://www.ctdssmap.com">www.ctdssmap.com</a> )	Preferred	Non-preferred/ preferred	Preferred	Preferred
Idaho Medicaid Preferred Drug List ( <a href="http://www.healthandwelfare.idaho.gov">www.healthandwelfare.idaho.gov</a> )	Preferred	Non-preferred/ preferred	Preferred	Preferred
Illinois Medicaid Preferred Drug List* <a href="http://www2.illinois.gov/hfs/sitecollectiondocuments/pdl.pdf">http://www2.illinois.gov/hfs/sitecollectiondocuments/pdl.pdf</a>	Preferred	Non-preferred/ preferred	Preferred	Non-preferred
Kaiser Permanente 2015 Medicare Part D Comprehensive Formulary (5-tier system) ( <a href="http://www.healthy.kaiserpermanente.org">www.healthy.kaiserpermanente.org</a> )	Tier 3	Tier 4/ Tier 2	Tier 2	Tier 3
Kentucky Preferred Drug List 2015 ( <a href="http://www.16subsidiz.magellanmedicaid.com">www.16subsidiz.magellanmedicaid.com</a> )	Preferred	Non-preferred/ preferred	Preferred	Preferred
Texas Medicaid Preferred Drug List ( <a href="http://www.txvendordrug.com/pdl/">http://www.txvendordrug.com/pdl/</a> )	Preferred	Non-preferred/ preferred	Preferred	Preferred
WellCare Comprehensive Formulary (Medicare Advantage Plans) (covers New York, Connecticut, Florida, Georgia, Hawaii and others) (5-tier system) ( <a href="https://www.wellcare.com/medicare_formulary/new_york">https://www.wellcare.com/medicare_formulary/new_york</a> )	Tier 3	Tier 2 (generic)	Tier 2	Not listed
Wellmark Prior authorization/Step therapy ( <a href="http://www.wellmark.com/HealthAndWellness/DrugInformation/PharmacyHome.aspx">http://www.wellmark.com/HealthAndWellness/DrugInformation/PharmacyHome.aspx</a> )	Preferred	Non-preferred/ preferred	Preferred	Preferred

### Other Countries

*Australia:* In Australia, the Pharmaceutical Benefits Scheme (PBS)<sup>22</sup> provides coverage for regular release methylphenidate and dextroamphetamine for the adult population.

Methylphenidate long-acting and extended-release formulations and atomoxetine are only covered for children age 6-18 years (inclusive).

Product	Dosage form	Criteria (Authority required)
Methylphenidate	Ritalin LA	ADHD in patient between ages 6-18 yrs, who has demonstrated a response to immediate release methylphenidate with no emergence of serious adverse events, and who requires continuous coverage over 8 hours
Methylphenidate	Concerta	ADHD in patient between ages 6-18 yrs, who has demonstrated a response to immediate release methylphenidate with no emergence of serious adverse events, and who requires continuous coverage over 12 hours
Methylphenidate	Regular release	Use in ADHD, in accordance with State/Territory law
Dextroamphetamine	Regular release	Use in ADHD, in accordance with State/Territory law Narcolepsy
Atomoxetine	Strattera	Authority Required Streamlined ADHD must be or have been diagnosed by a paediatrician or psychiatrist according to the DSM-5 criteria and patient must have a contraindication to dexamphetamine or methylphenidate, OR patient must have a comorbid mood disorder that has worsened as a result of dexamphetamine or methylphenidate treatment and is of a severity necessitating treatment withdrawal or patient must be at an unacceptable medical risk of a severity necessitating permanent stimulant treatment withdrawal if given a stimulant treatment with another agent or patient must have experienced adverse reactions of a severity necessitating permanent treatment withdrawal following treatment with dexamphetamine and treatment with methylphenidate AGE: 6-18 years (inclusive)

*New Zealand*<sup>23</sup>: In New Zealand, methylphenidate regular release and dextroamphetamine regular release are fully subsidized. Methylphenidate extended release (Concerta) and modified release (Ritalin LA) are available by special authority. Criteria for coverage for these agents:

- Patient is taking a currently subsidized formulation of methylphenidate (immediate release or sustained release) which has not been effective due to significant administration and/or compliance difficulties OR
- There is significant concern regarding the risk of diversion or abuse of immediate-release methylphenidate hydrochloride.

Atomoxetine is also available under special authority with the following clinical criteria:

- The patient will not be receiving treatment with atomoxetine in combination with a subsidised formulation of a stimulant, except for the purposes of transitioning from subsidised stimulant therapy to atomoxetine AND
- Treatment with a subsidised formulation of a stimulant has resulted in the development or worsening of serious adverse reactions or where the combination of subsidised stimulant treatment with another agent would pose an unacceptable medical risk OR
- Treatment with a subsidized formulation of a stimulant has resulted in worsening of a co-morbid substance abuse or there is significant risk of diversion with subsidised stimulant therapy OR
- An effective dose of a subsidised formulation of a stimulant has been trialed and has been discontinued because of inadequate clinical response OR
- Treatment with a subsidised formulation of a stimulant is considered inappropriate because the patient has a history of psychoses or has a first-degree relative with schizophrenia

*Scotland*<sup>24</sup>: Lisdexamfetamine (Elvanse or Vyvanse in Canada) was reviewed by the Scottish Medicines Consortium and accepted for use within NHS Scotland in children aged 6 years of age and over when response to previous methylphenidate treatment is considered clinically inadequate. As well, treatment must be under the supervision of a specialist in childhood and/or adolescent behavioural disorders.

### Summary

- In the United States, all drug plans reviewed provide coverage for methylphenidate regular release as well as methylphenidate extended release (generic). For other long-acting preparations such as Vyvanse or Adderall XR, these products are available as “preferred” medications on some drug plans.
- Australia and New Zealand provide coverage through the public plan programs for methylphenidate regular release and dextroamphetamine regular release. Long-acting methylphenidate products and atomoxetine are available in Australia only for children/adolescents up to age 18. In New Zealand, there are no age restrictions for methylphenidate extended release or atomoxetine.

## Part B: Guidelines for the use of pharmacotherapy in treatment of ADHD in adults

Several working groups and professional organizations have developed practice guidelines for assessment and treatment of adults with ADHD. These include the Canadian ADHD Resource Alliance (CADDRA)<sup>18</sup>, the National Institutes of Health<sup>17</sup>, the British Association for Psychopharmacology and the European Network Adult ADHD.<sup>25</sup>

### Canadian ADHD Practice Guidelines(2011 with update in 2014)<sup>18</sup>

The guidelines were developed to help Canadian physicians diagnose and treat ADHD across the lifespan. The guideline committee reviewed other ADHD guidelines and consensus statements in current use. Note that there were no details of searching, selection or synthesis of evidence to support the recommendations, as concluded by CADTH Rapid Response Service.<sup>26</sup>

- There are five tiers of holistic-based care for the patient with ADHD including: adequate education of patients and their families, behavioural and/or occupational interventions, psychological treatment, educational accommodations and medication management.
- CADDRA identified seventeen considerations in medication selection in the treatment of ADHD including:
  - Age and individual variation
  - Duration of effect
  - Speed of action of the medication
  - ADHD clinic presentations
  - Comorbid symptom profile
  - Comorbid psychiatric disorder
  - History of family medication use
  - Attitudes towards medication use
  - Affordability
  - Medical problems and other medications
  - Associated features similar to medication side effects
  - Combining stimulants with other medications
  - Potential for misuse/diversion
  - Physician attitude towards ADHD medications
  - First-line treatment represents a balance of efficacy, tolerability and clinical support and is approved by Health Canada
  - Second line treatments are medications approved by Health Canada but have lower efficacy rates
  - Third-line treatments are reserved for situations where first-line and second-line treatments have not worked and are usually off-label medications
- First line agents are long-acting preparations including Adderall XR, Biphentin, Concerta and Vyvanse. Second line agents are atomoxetine, dextro-

amphetamine (short and long acting) and methylphenidate (short and long-acting).

British Association for Psychopharmacology (2014)<sup>15</sup>

These guidelines were developed for healthcare practitioners who diagnosis and treat children, adolescents and adults with ADHD. The guidelines encompass a comprehensive assessment of current literature on ADHD.

- Stimulants are first-line treatment for adults with ADHD.
- Atomoxetine is considered first-line treatment in patients with substance use disorders
- Drug treatment should be continued as long as clinically useful and reviewed at least annually
- Careful titration and monitoring of side effects is required, particularly when using stimulants
- Drug holidays may be useful to ascertain the need of continuation of treatment
- Co-administration of drugs (e.g., stimulants and atomoxetine) is relatively common in clinical practice for resistant cases but there is a lack of studies investigating its efficacy.

National Institutes of Health (2013)<sup>17</sup>

Recommendations for the diagnosis and management of ADHD in children, young people and adults were developed in 2008 and updated in 2013. Treatment recommendations specific for adults are:

- Drug treatment for adults with ADHD should always form part of a comprehensive treatment programme that addresses psychological, behavioural and educational or occupational needs.
- Following a decision to start drug treatment in adults with ADHD, methylphenidate should normally be tried first.
- Atomoxetine or dexamfetamine should be considered in adults unresponsive or intolerant to an adequate trial of methylphenidate (this should usually be about 6 weeks).
- Where there may be concern about the potential for drug misuse and diversion (for example in prison services), atomoxetine may be considered as the first-line drug treatment for ADHD in adults.
- Modified release methyl phenidate preparations may be preferred to increase adherence and in circumstances where there are concerns about substance misuse or diversion.
- Following an adequate response, drug treatment for ADHD in adults should be continued for as long as it is clinically effective.

European Network Adult ADHD (2010)<sup>25</sup>

The European Network Adult ADHD was founded in 2003 and includes professionals from 18 countries across Europe. The recommendations were based on consensus

statements based on reviews and randomized controlled trials identified from Medline, Embase and Cochrane database.

- A multi-modal approach to treatment of adults with ADHD and associated co-morbid disorders is needed. This includes psychoeducation, pharmacotherapy, coaching, cognitive behavior psychotherapy and family therapy.
- For pharmacotherapy, stimulants (methylphenidate and dexamphetamine) are first-choice medication treatments for ADHD. Atomoxetine is usually considered the second-line treatment, followed by other non-stimulants such as bupropion, guanfacine, modafinil and tricyclic antidepressants.

#### Summary

- There have been four guidelines and consensus statement that have published by various organizations for diagnosis and treatment of adults with ADHD.
- Guidelines emphasize the need for a multi-pronged approach to treatment which includes education, psychotherapy and pharmacotherapy.
- Stimulants are considered first-line treatment. Atomoxetine is usually considered second-line treatment, except for patients with substance abuse disorders, where it is considered first-line.

## Part C: Impact of different drug reimbursement schemes for treatment of adults with ADHD

### Methods

A literature search was conducted in Pubmed using the terms: methylphenidate OR dextroamphetamine OR atomoxetine OR central nervous system stimulants) AND (healthcare accessibility OR health policy OR reimbursement incentive OR cost sharing OR deductibles and coinsurance OR insurance coverage OR health benefit plans employee or insurance pharmaceutical service or managed care programs). Bibliographies of identified articles were scanned for additional relevant articles.

### Results

In one study that investigated the characteristics of US ambulatory care visits made by adults with ADHD, psychiatric comorbidity (odds ratio [OR]6.5, 95% CI, 3.5-12.4,  $p < 0.05$ ) and self-pay reimbursement source (OR 2.7, 95% CI, 1.3-5.7,  $p < 0.05$ ) significantly increased the likelihood of behavioural treatment. Insurance reimbursement sources other than private and self-pay significantly decreased the likelihood of an ADHD-specific pharmacotherapy (OR 0.4, 95% CI 0.2-0.7,  $p < 0.05$ ) or any ADHD-treatment (OR 0.2, 95% CI 0.1-0.5,  $p < 0.05$ ) as compared to private insurance.<sup>27</sup> The authors caution that healthcare providers be vigilant and consider the possibility of barriers to ADHD diagnosis and treatment in patients with “other insurance” reimbursement sources.

Only one study was identified that assessed the effect of copayment increases associated with 3-tier formulary adoption on use and spending patterns for ADHD medications for

children.<sup>28</sup> In this observational study, major changes were made to an employer-sponsored plan. The plan moved from a 1-tier to a 3-tier formulary and implemented an across-the-board copayment increase. The 3-tier formulary resulted in a 17% decrease in the monthly probability of using medication ( $p < 0.001$ ), a 20% decrease in expected total medication expenditures and substantial shifting of costs from the plan to families. A 3-tier formulary typically has the lowest copayment for generic drugs in the first tier, a higher copayment for brand-name drugs preferred by the payer in the second tier, and the highest copayment for brand-name drugs not preferred by the payer in the third tier.

### Summary

- There is limited information regarding the use of various reimbursement schemes for stimulants and non-stimulants for the treatment of ADHD, in particular in adults.
- One study assessed the effect of copayment increases associated with a 3-tier formulary system in children and found that copayment resulted in lower total ADHD medication spending, sizeable increases in out-of-pocket expenditures for families, and a significant decrease in the probability of using these medications.

## Part D: Rapid Review of Selected Topics

### Methylphenidate Extended Release Products and Bioequivalence

Methylphenidate is available in many different formulations in Canada, including immediate release, sustained release and extended release products. Biphentin and Concerta are two extended release products that provide controlled, predictable dosing throughout the day, allowing for once daily dosing. Biphentin uses beaded technology with 40% of the total methylphenidate dose as immediate release and 60% for delayed release; Biphentin can also be used by patients with difficulties swallowing (e.g., by opening the capsule and sprinkling on food). Concerta uses the OROS technology (progressive delivery system) to provide both immediate release and long-acting methylphenidate over a 12 hour period.<sup>29</sup> There are generic versions of Concerta available in Canada that have been deemed to be bioequivalent to Concerta. There are currently no generic versions of Biphentin available.

#### Bioequivalence

Due to the complexities of the extended release products, traditional bioequivalence metrics that have been used for generic products may not adequately represent the specific immediate- or sustained response components. One study showed that the in vivo pharmacokinetic profiles of Concerta and Novo-Methylphenidate were distinct and proposed that partial AUC be used as additional criteria to measure therapeutic equivalence.<sup>30;31</sup> However, in 2010, a Health Canada panel concluded that there was insufficient evidence to support the need for additional bioequivalence parameters.<sup>32</sup> 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.<sup>33</sup>

In 2014, the FDA expressed concerns about therapeutic equivalence between two generic versions of Concerta manufactured in the US. They noted that in some individuals, the Mallinckrodt and Kudco products may deliver drug in the body at a slower rate during the 7- to 12-hour range, resulting in some patients not having the desired effect. As a result, the FDA indicated that these two products, albeit still approved, could no longer be recommended as automatically substitutable at the pharmacy. As well, the FDA revised its draft guidance for industry for bioequivalence testing and asked that within 6 months, Mallinckrodt and Kudoc confirm the bioequivalence of their products.<sup>34</sup> The European Medicines Agency (EMA) guidelines require for biphasic products that bioequivalence must be established in both the immediate- and extended-release phases.<sup>35</sup>

#### Clinical efficacy

Concerta and the generic equivalents have not been compared in a randomized clinical trial. A retrospective, observational review was undertaken to determine whether bioequivalence between Concerta and methylphenidate extended release (Novo-Methylphenidate) translated into therapeutic equivalence.<sup>36</sup> Of the total 153 patients prescribed Concerta, 53 patients were switched to Novo-Methylphenidate. Forty-six (87%) patients were considered “destabilized” with the switch from Concerta to the generic brand, compared to 26% patients who remained on Concerta. Destabilization was defined clinically as a change in symptoms and/or function resulting from a change in ADHD medication or dosage. Twenty-one patients (43%) who reported destabilization noted a shorter duration of action. In a randomized, double-blind, cross-over study, 20 adult patients who were stable on Concerta for at least 3 months were randomised to receive generic methylphenidate extended release or Concerta in a two-way cross-over design; each treatment period was 3 weeks in duration. Patient and physician-reported outcomes were assessed at baseline of each period. Nineteen patients were included in the efficacy analysis. Overall, patients were more satisfied with Concerta in terms of efficacy as well as side effects than those receiving an equivalent dose of the generic. All patients elected to return to Concerta at the end of the study.<sup>37</sup> There have also been isolated case reports of patients who have been transferred from Concerta to generic equivalent with resultant loss of efficacy, including return of hyperactivity, destabilization or physical or verbal difficulties.<sup>32, 18</sup>

#### Summary:

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.

#### **Summary**

- 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.

## Cardiovascular safety of drugs used in treatment of adult ADHD

Pharmacotherapy for ADHD is generally well tolerated, although there have been reports of serious cardiovascular events associated with exposure to stimulants and non-stimulants.<sup>38,39</sup> There is evidence that these medications increase blood pressure and heart rate. However, most evidence does not support a causal relationship between stimulants and serious cardiovascular events in adults. This rapid review summarizes the relevant literature regarding cardiovascular safety of stimulants/non-stimulants in the adult population.

### Heart rate and blood pressure

A recent review evaluated the literature relevant to the cardiovascular safety of stimulants for adult ADHD.<sup>40</sup> A total of ten randomized, placebo-controlled trials of CNS stimulants were identified and included in the meta-analysis. The median age of the studies was 36 (range: 22-40), most studies focused on long-acting preparations, and the median study duration was 6 weeks (range: 4-24 weeks). Subjects randomized to CNS stimulant treatment demonstrated a statistically significant increased resting heart rate (+5.7 bpm (3.6, 7.8),  $p < 0.001$ ) and systolic blood pressure findings (+2.0 mmHg (0.8, 3.2),  $p = 0.005$ ) compared with subjects randomized to placebo.

### Serious cardiovascular events

Several large epidemiological studies have been published evaluate serious cardiovascular events in adults taking stimulants.

A retrospective cohort study examined whether current use of medications used to treat ADHD is associated with increased risk of serious cardiovascular events in young and middle-aged adults (age 25-64).<sup>41</sup> Each medication user ( $n = 150,350$ ) was matched to two non-users. During 806,182 person-years of follow-up (median 1.3 years), current use of ADHD medications compared to nonuse was significantly protective against serious CV events (RR 0.83, 95% CI 0.72-0.96). However, the adjusted risk ratio may have been masked by a health user bias, as the cohort had a low rate of cardiovascular risk factors.

Another retrospective cohort study that included 1,200,438 children and young adults between the ages of 2 and 24 years (mean age: 11.1 years) with 373,667 person-years of follow-up did not find any evidence that current use of an ADHD drug was associated with an increased risk of serious cardiovascular events (adjusted HR, 0.75; 95% CI, 0.31-1.85).<sup>42</sup> Since there were no events in the current user group for cohort members of age 18-24 years, hazard ratios were not calculated for this age group.

In a retrospective cohort study examining amphetamine or atomoxetine use and rates of serious cardiovascular events in adults (79.7% between ages 18-47), no increased risk of serious cardiovascular events was observed for amphetamines (HR 1.18; 95% CI, 0.55-2.54) or atomoxetine (HR 0.41; 95% CI, 0.10-1.75).<sup>43</sup> Similarly, no increased rate of sudden death was noted in patients (2-21 years of age) taking medication for ADHD (incident rate ratio 1.63, 95% CI 0.04, 9.71).<sup>44</sup>

In contrast to these studies, a population-based study of ADHD medications in adults 18 years and older, found a significantly increased risk of transient ischemic attack (TIA)

over a mean follow-up of 1.5 years (hazard ratio 3.44; 95% CI, 1.13-10.60).<sup>45</sup> Eighty-four percent of stimulant ADHD medication users were between the ages of 18-49. However, no increased risk for cerebrovascular accident (CVA) was observed (HR, 0.71; 95% CI, 0.34-1.47). Use of atomoxetine was not associated with a greater risk of stroke or TIA, compared to stimulant ADHD medications. Limitations included a low absolute rate of TIA in the study, and likely higher rates of medical comorbidities in the ADHD cohort versus the population sample.

A cohort study investigated the risk of serious cardiovascular events in adults (18 years and older; 67.3% between ages 18-47 years of age) in association with methylphenidate.<sup>46</sup> An increased risk of sudden death or ventricular arrhythmia was observed among new methylphenidate users (n=43,999; median follow-up 60 days) as compared to nonusers (n=175,955) (adjusted HR 1.84; 95% CI, 1.33-2.55). However, no dose-response relationship was found between methylphenidate and sudden death or ventricular arrhythmias.

#### Safety in adults with concomitant medical conditions

There is little data on the long-term safety of stimulants in adults with concomitant medical conditions. No specific guidelines have been developed for adults receiving stimulants; in contrast, the American Heart Association recommends screening in children for cardiovascular risk.<sup>47</sup>

*Summary:* The longer-term impact of minor elevations in blood pressure and heart rate in adult patients, in particular patients with concomitant diseases such as hypertension or heart disease, is unknown. Data from large population-based studies did not demonstrate any increased risk for sudden death or ventricular arrhythmia.<sup>41;42</sup> One study found an increased risk in sudden death or ventricular arrhythmias with methylphenidate, although lack of a dose-response relationship suggested that this was not causal.<sup>46</sup> Since the studies either did not include or had very small numbers of patients 65 years and older, no conclusion about the cardiovascular safety of these medications can be made for the elderly.

#### **Summary**

- Stimulants and non-stimulants have been shown to increase blood pressure and heart rate; long-term impact in adults, especially those with concomitant diseases, is unknown.
- Data from two large population-based studies in adults did not demonstrate an increased risk for sudden death or ventricular arrhythmia.
- One study found an increased risk in sudden death or ventricular arrhythmias with methylphenidate, although lack of dose-response suggests that this is not a causal relationship.

## Suicidality and ADHD drug treatment in adults

Warnings have been issued by various regulatory agencies regarding potential psychiatric events (including reports of agitation and hallucinations in children, increased risk of self-harm) associated with ADHD treatments. However, there are limited studies that have investigated the association between ADHD treatments and suicide in adults.

A register-based longitudinal study investigated the association between drug treatment for ADHD and risk for suicidal behavior among patients with ADHD.<sup>48</sup> Among 37,936 patients with ADHD, there were 7,019 suicide-related events that occurred during 150,721 person-years of follow-up. Interestingly, there was a reduced rate of suicide-related events during stimulant treatment periods (HR 0.81, 95% CI 0.70-0.94). Among non-stimulant/mixed users, no significantly increased within patient rate of suicide-related events during non-stimulant treatment periods was observed (HR 0.96, 95% CI 0.72-1.30).

Clinical trial data reported a greater risk of suicidal ideation in the early treatment of children and adolescents with atomoxetine.<sup>49</sup> A meta-analysis examined suicide-related events during double-blind placebo-controlled atomoxetine trials in pediatric and adult patients with ADHD.<sup>50</sup> A total of 3883 pediatric and 3365 adult patients were included. The frequency of combined suicidal behavior or ideation with atomoxetine treatment was 0.11% in adults (vs. 0.12% with placebo), and the risk compared with placebo (for all age groups) was not statistically significant.

*Summary:* There is limited data to indicate a causal association between ADHD drug treatments and suicidality in adults. Nevertheless, in view of reports of suicide-related behavior in children treated with atomoxetine, it is recommended that adults treated with atomoxetine should be observed for agitation, irritability, suicidal thinking, self-harming behaviour and unusual behaviour, particularly in the first months of treatment, or after a change in dose.<sup>51</sup>

### Summary

- Limited data suggest that there is no causal association between ADHD drug treatments and suicidality in adults.

## Combination therapy with atomoxetine and stimulants in adults

Combination therapy with atomoxetine and stimulants has been suggested in patients who had inadequate response to previous treatment.<sup>18</sup> As well, combination therapy has been used in patients with dose-limiting side effects. One study conducted in Quebec found that 5.5% children and adolescents (aged 6-17 years) who received a stimulant had concurrent use of atomoxetine.<sup>52</sup> A literature review was completed to examine the evidence of efficacy and safety of combination therapy of atomoxetine and stimulants in adults for treatment of ADHD.

*Results:* One systematic review, published in 2013, was identified that evaluated the evidence for efficacy and safety of combination of atomoxetine and stimulants in children and adults. A total of 16 publications were included: 3 prospective studies (4 publications), 7 retrospective studies, 3 narrative reviews/medication algorithms, and 2 prospective studies in healthy volunteers. There was only one prospective randomized controlled trial identified in this

review; this small RCT (N=17 children) found that adding OROS methylphenidate to the treatment regimen after 4 weeks of atomoxetine monotherapy did not enhance the efficacy of atomoxetine at the end of 6 weeks of combination therapy. In addition, only two of the studies included in the systematic review evaluated the combination in adults.<sup>53;54</sup> One retrospective study examined the prevalence of combination therapy in adults (18 years and older) with ADHD.<sup>53</sup> A total of 18,609 patients were identified from claims data from US managed care organizations. Patients received medication combinations 19.7% of months for atomoxetine, and in 8-9% of months, stimulants and atomoxetine and bupropion were found in combination. In the second retrospective chart review, the clinical effects and tolerability of atomoxetine and stimulant therapy were evaluated in 29 adult patients.<sup>54</sup> In this study, all of the patients who tolerated the therapy (22 patients or 76%) elected to receive ongoing treatment with combination therapy.

A retrospective observational chart review study evaluated treatment with atomoxetine monotherapy versus atomoxetine with another ADHD-indicated medication in children and adults.<sup>55</sup> The authors concluded that atomoxetine combination therapy showed no evidence of additional benefit over atomoxetine monotherapy in the treatment of ADHD in a community-based setting.

### Summary

- There is no evidence supporting the use of atomoxetine and stimulants in adults with ADHD.

### Health Canada Warnings

- Health Canada issued a warning regarding risk of priapism associated with methylphenidate products in 2015. The priapism occurred during treatment, after increasing the dose or after discontinuing methylphenidate.<sup>56</sup>
- An important safety information update was issued in 2015 by Health Canada regarding the risk of suicidal thoughts and behaviours in some people treated with ADHD drugs, although benefits of treatment still outweigh the risks in most patients.<sup>57</sup>
- Health Canada issued a safety update in 2006 regarding treatment of ADHD in adults and children and possible increased risk of sudden/cardiac death.<sup>38</sup>
- Health Canada suspended market authorization of Adderall XR in 2005 based on rare reports of sudden deaths.<sup>58</sup> Note that Adderall XR was returned to the market in 2005 after discussions with Health Canada.
- Information regarding the potential for psychiatric adverse events (including reports of agitation and hallucinations in children) associated with drugs used for the management of ADHD was issued by Health Canada in 2006.<sup>59</sup>
- Health Canada issued an advisory regarding increased heart rate and blood pressure associated with atomoxetine.<sup>39</sup>
- Information on Strattera and the potential for behavioural and emotional changes, including risk of self-harm, was issued by Health Canada in 2005.<sup>60</sup>

# Discussion

## Part A: Pharmacy Benefit Programs in Ontario, across Canada and internationally

### Availability in Canada

- There are stimulant and non-stimulant medications available for the treatment of ADHD in adults.
- Stimulant medications include dextroamphetamine, methylphenidate, lis-dexamfetamine dimesylate and amphetamine mixture. Short-acting formulations include methylphenidate and dextroamphetamine; long-acting formulations include dextroamphetamine, methylphenidate (various), amphetamine mixture and lis-dexamfetamine.
- Atomoxetine is the only non-stimulant medication approved for the treatment of ADHD in adults.
- Generic formulations are available for methylphenidate short-acting and long-acting (specifically Ritalin SR and Concerta), short-acting dextroamphetamine as well as for atomoxetine.

### Public Plan Listing in Ontario

- In Ontario, all stimulant medications (including long and short-acting formulations) are funded as general benefit on the ODB formulary.
- Atomoxetine, a non-stimulant medication, is available on the Ontario public drug plan through the Exceptional Access Program (EAP).

### Public Plan Listing in Canada

- Dextroamphetamine (short and long-acting) and methylphenidate (short and long-acting) are listed in all jurisdictions as a general benefit, except for Yukon, which lists these products as a restricted benefit.
- Other long acting stimulant products (i.e., Adderall XR, Vyvanse, Concerta, Biphentin) are listed in various jurisdictions as medications requiring special authorization, except for Ontario, where they are available as a general benefit.
- Age restrictions on long-acting stimulant products are enforced in British Columbia (6-18 years), Prince Edward Island (6-18 years), Nova Scotia (6-25 years), Newfoundland (6-25 years) and New Brunswick (6-25 years).
- Funding for atomoxetine is only provided in Saskatchewan, Ontario, Quebec and Yukon.

### Selected International Jurisdictions

- In the United States, all drug plans reviewed provide coverage for methylphenidate regular release as well as methylphenidate extended release (generic). For other long-acting preparations such as Vyvanse or Adderall XR, these products are available as “preferred” medications on some drug plans.
- Australia and New Zealand provide coverage through the public plan programs for methylphenidate regular release and dextroamphetamine regular release. Long-acting

methylphenidate products and atomoxetine are available in Australia only for children/adolescents up to age 18. In New Zealand, there are no age restrictions for methylphenidate extended release or atomoxetine.

## **Part B: Guidelines for the use of pharmacotherapy for treatment of ADHD in adults**

- There have been several guidelines and consensus statement that have published by various organizations for diagnosis and treatment of adults with ADHD.
- Guidelines emphasize the need for a multi-pronged approach to treatment which includes education, psychotherapy and pharmacotherapy.
- Stimulants are considered first-line treatment. Atomoxetine is usually considered second-line treatment, except for patients with substance abuse disorders, where it is considered first-line.

## **Part C: Impact of different drug reimbursement schemes for drugs used in the treatment of ADHD**

- There is limited information regarding the use of various reimbursement schemes for stimulants and non-stimulants for the treatment of ADHD, in particular in adults.
- One study assessed the effect of copayment increases associated with a 3-tier formulary system in children and found that copayment resulted in lower total ADHD medication spending, sizeable increases in out-of-pocket expenditures for families, and a significant decrease in the probability of using these medications.

## **Part D: Rapid Reviews of Selected Topics**

- *Bioequivalence of methylphenidate extended release products:* 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 prospective clinical trial that have suggested that patients who switch from Concerta to the generic methylphenidate extended-release may have a loss in efficacy.
- *Cardiovascular safety of drugs used in the treatment of adult ADHD:* Stimulants and non-stimulants have been shown to increase blood pressure and heart rate; long-term impact in adults, especially those with concomitant diseases, is unknown. Data from two large population-based studies in adults did not demonstrate an increased risk for sudden death or ventricular arrhythmia. One study found an increased risk in sudden death or ventricular arrhythmias with methylphenidate, although lack of dose-response suggests that this is not a causal relationship. Overall, there is lack of data in adults 50 years and older for long-term cardiovascular safety of these medications.
- *Suicidality and treatment of ADHD in adults:* Limited data suggest that there is no causal association between ADHD drug treatments and suicidality in adults.
- *Combination therapy with atomoxetine and stimulants in adults:* There is no evidence supporting the use of atomoxetine and stimulants in adults with ADHD.

## Health Equity

In Ontario, stimulants are available as a general benefit on the ODB formulary. Atomoxetine is available through the Exceptional Access Program, with no age restrictions. No health equity issues were identified for Ontario.

## Conclusion

In Ontario, all stimulant medications (including long- and short-acting formulations) are funded as general benefit on the ODB formulary. Atomoxetine, a non-stimulant medication, is available in Ontario through the Exceptional Access Program. Across Canada, short-acting formulations are generally available as general benefit, compared with long-acting products which require special authorization for coverage. In addition, age restrictions (6-18 or 6-25 years) on long-acting stimulant products are enforced in five provinces. Similarly, in Australia, long-acting methylphenidate products and atomoxetine are only available for children/adolescents up to age 18.

Four guidelines on the treatment of ADHD in adults were reviewed. All guidelines emphasize the need for a multi-pronged approach to treatment which includes education, psychotherapy and pharmacotherapy.

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## Appendix A: Common Drug Review Recommendations

### Mixed amphetamine salts (Adderall XR) (June 2008)

*New indication: use in adolescents and adults*

Recommendation:

The Canadian Expert Drug Advisory Committee (CEDAC) recommends that Adderall XR not be listed.

Reasons for the Recommendation:

- There is insufficient evidence that Adderall XR offers a therapeutic advantage over less expensive formulations of other stimulant agents such as methylphenidate and dexamphetamine.
- While Adderall XR has been shown to improve some clinical rating scales in children, adolescents and adults when compared with placebo in short-term (<4 week) trials, no long-term randomized trials have investigated whether this translates into improvement in clinically important outcomes such as quality of life, academic performance and behavioural outcomes.
- Adderall XR has not been shown to be cost-effective when used as first-line therapy. The Committee considered whether Adderall XR should be listed for patients who had not achieved adequate control of symptoms with a trial of methylphenidate or dexamphetamine. However, there is insufficient evidence from clinical trials that Adderall XR is effective, and therefore cost-effective, in this group of patients.
- Given the prevalence and importance of ADHD, the Committee felt that it would be important, feasible and ethical to conduct a trial in patients who have failed to respond to methylphenidate or dexamphetamine.

### Lisdexamfetamine dimesylate (Vyvanse) (Dec 2009)

Recommendation:

The Canadian Expert Drug Advisory Committee (CEDAC) recommends that lisdexamfetamine not be listed.

Reason for the Recommendation:

There is insufficient evidence that lisdexamfetamine offers a therapeutic advantage compared with less expensive alternatives.

*Of Note:*

The Committee considered whether or not lisdexamfetamine has less abuse potential compared with other agents. Based on evidence from three abuse liability studies comparing lisdexamfetamine with placebo or short acting agents and also considering post-marketing sources that there was insufficient evidence to support that abuse potential is less with lisdexamfetamine compared with other long acting agents.

### **Atomoxetine (Strattera) (September 2005)**

#### Recommendation:

The Canadian Expert Drug Advisory Committee recommends that atomoxetine not be listed.

#### Reasons for the recommendation:

1. In randomized controlled trials (RCTs), atomoxetine has been shown to be more effective than placebo for ADHD symptoms. However, atomoxetine has not proven superior to methylphenidate products. There are no published studies that assess the efficacy of atomoxetine in patients who have not responded to methylphenidate or dexamphetamine.
2. Atomoxetine is the only agent approved in Canada for ADHD in adults. However, there is clinical evidence and experience with the use of less expensive alternatives in adults with ADHD.
3. Atomoxetine is not contraindicated in patients with ADHD who also have motor tics or Tourette's syndrome. Although methylphenidate product monographs list patients with motor tics or with a family history of diagnosis of Tourette's syndrome under "Contraindications", there are studies that show that methylphenidate can be used to treat ADHD in patients with co-morbid tics or Tourette's syndrome.
4. The cost of atomoxetine is higher than the cost of methylphenidate products or dexamphetamine, particularly if taken more than once per day.
5. Although there are no RCTs in patients who are intolerant to methylphenidate or dexamphetamine, atomoxetine may be considered an alternative in patients who have not been able to tolerate an appropriate trial of methylphenidate and dexamphetamine.

#### *Of note:*

1. The adverse effects of atomoxetine are qualitatively similar to methylphenidate and dexamphetamine, and include increases in blood pressure, heart rate, mydriasis, insomnia, urinary disorders and reduced weight gain.
2. Both published and unpublished data were reviewed and taken into consideration in making this recommendation.

### **Guanfacine (Intuniv SR) (September 2014)**

#### Recommendation:

The Canadian Drug Expert Committee (CDEC) recommends that guanfacine hydrochloride extended release (GXR) not be listed.

#### Reasons for the Recommendation:

1. There was insufficient evidence from randomized controlled trials (RCTs) to assess the comparative clinical benefit of GXR as monotherapy relative to other less costly treatments for attention deficit hyperactivity disorder (ADHD).
2. Evidence for the use of GXR as adjunctive therapy in ADHD is limited to one RCT (SPD503-313; N = 461) of only eight weeks duration. Although there is an absence of treatments approved for use as adjunctive therapy in ADHD, the single included study provided insufficient evidence to adequately assess the overall and longer-term clinical benefit of GXR in this patient population.

*Of Note:*

CDEC noted that there is an unmet need for patients with ADHD requiring adjunctive therapy; however, the available evidence for GXR is limited to a single, short-term RCT that was insufficient to support a listing recommend

## Appendix B: Webpages for Provincial Drug Formularies

Province	Webpage for Drug Formulary
<b>British Columbia</b>	<a href="http://www.health.gov.bc.ca/pharmacare/benefitslookup/faces/Search.jsp">http://www.health.gov.bc.ca/pharmacare/benefitslookup/faces/Search.jsp</a>
<b>Alberta</b>	<a href="https://idbl.ab.bluecross.ca/">https://idbl.ab.bluecross.ca/</a>
<b>Saskatchewan</b>	<a href="http://formulary.drugplan.health.gov.sk.ca/">http://formulary.drugplan.health.gov.sk.ca/</a>
<b>Manitoba</b>	<a href="http://web6.gov.mb.ca/eFormulary/">http://web6.gov.mb.ca/eFormulary/</a>
<b>Ontario</b>	<a href="https://www.healthinfo.moh.gov.on.ca/formulary/index.jsp">https://www.healthinfo.moh.gov.on.ca/formulary/index.jsp</a>
<b>Quebec</b>	<a href="http://www.ramq.gouv.qc.ca/en/regie/legal-publications/Pages/list-medications.aspx">http://www.ramq.gouv.qc.ca/en/regie/legal-publications/Pages/list-medications.aspx</a>
<b>New Brunswick</b>	<a href="http://www.gnb.ca/0212/nbpdpformulary-e.asp">http://www.gnb.ca/0212/nbpdpformulary-e.asp</a>
<b>Nova Scotia</b>	<a href="http://novascotia.ca/dhw/pharmacare/formulary.asp">http://novascotia.ca/dhw/pharmacare/formulary.asp</a>
<b>Prince Edward Island</b>	<a href="http://healthpei.ca/formulary">http://healthpei.ca/formulary</a>
<b>Newfoundland</b>	<a href="http://www.health.gov.nl.ca/health/nlpdp/fmlsearch.asp">http://www.health.gov.nl.ca/health/nlpdp/fmlsearch.asp</a>
<b>Yukon Territories</b>	<a href="https://apps.gov.yk.ca/pls/apex40p/f?p=161:9000:4324580815029961::::">https://apps.gov.yk.ca/pls/apex40p/f?p=161:9000:4324580815029961::::</a>
<b>NIHB (Non-insured Health Benefits) Program</b>	<a href="http://www.hc-sc.gc.ca/fniah-spnia/nihb-ssna/provide-fourmir/pharma-prod/med-list/index-eng.php">http://www.hc-sc.gc.ca/fniah-spnia/nihb-ssna/provide-fourmir/pharma-prod/med-list/index-eng.php</a>

## Appendix C: Restriction Criteria for Drugs used in the Treatment of ADHD

Jurisdiction	Drug	Criteria
British Columbia	Concerta	<p>For patients 6 to 18 years of age diagnosed with ADHD who require 12 hours of continuous coverage for significant and problematic disruptive behaviour or problems with inattention that interfere with learning AND have been previously tried on one of the following with unsatisfactory results: immediate or sustained-release methylphenidate OR immediate or sustained-release dextroamphetamine.</p> <p>Practitioner exemptions: Pediatricians, child psychiatrists and general practitioners are invited to apply for individual specialist exemption from completing SA forms.</p> <p>Notes: Unsatisfactory results are defined as continuing symptoms of ADHD or functional impairment secondary to ADHD, while on a trial of immediate- or sustained-release ADHD medication of adequate dose and 4-week duration Coverage is not intended for “performance enhancement” in children or youth who do not have symptoms or functional impairment.</p>
Alberta	Vyvanse, Biphentin	For the treatment of ADHD as a restricted benefit for patients 6 years of age and older.
Saskatchewan	Atomoxetine	<p>For the treatment of ADHD in patients who meet all of the following criteria:</p> <ol style="list-style-type: none"> <li>Has failed or is intolerant to treatment with methylphenidate and an amphetamine.</li> <li>Treatment with atomoxetine must be recommended by or in consultation with a specialist in psychiatry, pediatrics or a general practitioner with an expertise in ADHD</li> </ol>
	Lisdexamfetamine (Vyvanse)	<p>For the treatment of ADHD in patients:</p> <ol style="list-style-type: none"> <li>Where the use of methylphenidate (short or long-acting) or the use of dexamphetamine has not properly controlled the symptoms of the disease</li> </ol> <p>OR</p> <ol style="list-style-type: none"> <li>Who cannot swallow tablets/capsules whole and require a liquid form of a long-acting ADHD medication</li> </ol>
	Methylphenidate (Concerta)	<p>For the treatment of ADHD in patients:</p> <ol style="list-style-type: none"> <li>Where the use of an alternative long-acting methylphenidate has not properly controlled the symptoms of the disease</li> </ol> <p>OR</p> <ol style="list-style-type: none"> <li>Who cannot swallow tablets/ capsules whole and require a long-acting ADHD medication</li> </ol>

Jurisdiction	Drug	Criteria
Quebec	Adderall XR, Vyvanse, Biphentin, Concerta	For treatment of persons suffering from attention deficit disorder and in whom the use of short-acting methylphenidate or of dexamphetamine has not properly controlled the symptoms of the disease. Before it can be concluded that these treatments are ineffective, the stimulant must have been titrated optimally, unless there is a proper justification.
	Atomoxetine (Strattera)	For treatment of children and adolescents suffering from attention deficit disorder in whom it has not been possible to properly control the symptoms of the disease with methylphenidate and an amphetamine or for whom these drugs are contraindicated. Before it can be concluded that these drugs are ineffective, they must have been titrated at optimal doses and in addition, a 12-hr controlled release form of methylphenidate or a form of amphetamine mixed salts or lisdexamfetamine must have been tried, unless there is proper justification for not complying with these requirements.
New Brunswick	Biphentin, Concerta	For the treatment of ADHD in children aged 6 to 25 years who demonstrate significant symptoms and who have tried immediate release and slow release methylphenidate with unsatisfactory results. Requests will be considered from specialists in pediatric psychiatry, pediatricians or general practitioners with expertise in ADHD.
Nova Scotia	Biphentin, Concerta	For patients 6-25 years of age diagnosed with ADHD who require 12-hour continuous coverage use to academic and/or psychosocial needs, and who meet the following: 1. patients who demonstrate significant and problematic disruptive behaviour or who have problems with inattention that interfere with learning AND 2. Prescribed by or in consultation with a specialist in pediatric psychiatry, pediatrics, general practitioners or other prescribers with expertise in ADHD AND 3. have been tried on immediate release or slow-release methylphenidate with unsatisfactory results
PEI	Biphentin	For the treatment of children age 6 to 18 years of age diagnosed with ADHD, who require 12 hours of continuous drug coverage due to academic and psychosocial need and who meet the following: 1. demonstrate significant and problematic disruptive behaviour OR 2. have problems with inattention that interferes with learning AND 3. Have been tried on methylphenidate (Ritalin) immediate or sustained-release tablets with unsatisfactory results.

Jurisdiction	Drug	Criteria
NFLD	Concerta	In patients age 6-25 years of age, diagnosed with ADHD who require 12-hour continuous coverage due to academic and/or psychosocial needs, and who meet the following: 1. patients who demonstrate significant and problematic disruptive behaviour or who have problems with inattention that interfere with learning AND 2. prescribed by or in consultation with a specialist in pediatric psychiatry, pediatric or a general practitioner with expertise in ADHD AND 3. have been tried on immediate release or slow release methylphenidate with unsatisfactory results
Yukon	Atomoxetine	For the treatment of ADHD in patients who failed treatment of methylphenidate and an amphetamine, on recommendation of a specialist
	Biphentin, Concerta	Treatment of psychiatric disorder on recommendation of psychiatrist or pediatrician and where the other forms of methylphenidate have been ineffective
	Methylphenidate (Ritalin, Ritalin SR)	Treatment of psychiatric disorder on recommendation of psychiatrist or pediatrician
	Dextroamphetamine (Dexedrine, Dexedrine spansules)	For the treatment of psychiatric disorders on recommendation of a psychiatrist or pediatrician. For the treatment of fatigue on multiple sclerosis

## Appendix D: Interview Questions

How long have you listed stimulants/nonstimulants on your provincial formulary? How are they listed (e.g., restricted, general benefit)?
Why did you decide to list these agents this way?
What was the basis for this listing (e.g., quantity limits, general listing)?
Do you have any studies comparing usage/costs before and after implementation of this listing?
Why are certain stimulants/non-stimulants NOT funded?
Do you restrict prescribing to certain specialties (or are certain specialties exempt from restrictions)?
Do you have any special restrictions regarding the use of stimulants/non-stimulants?

## Appendix E: Tiered cost-sharing options

Prescription Drug Plan	Tier 1 (generic)	Tier 2 (preferred brand)	Tier 3 (non-preferred brand)	Tier 4 (specialty)
Plan A	\$5	\$28	\$55	25%
Plan B	\$2	\$20	\$40	N/A
Plan C	\$10	\$25	50%	25%
Plan D	\$4	\$17	75%	25%

Adapted from:

<http://www.cancer.org/treatment/findingandpayingfortreatment/managinginsuranceissues/medicare/medicarepartd/medicare-part-d-formularies-and-drug-coverage>