

Drugs Used in the Management of Attention-Deficit/Hyperactivity Disorder in Adults

Ontario Drug Policy Research Network

The Ontario Drug Policy Research Network (ODPRN) is funded to conduct drug class reviews as part of an initiative to modernize the public drug formulary in Ontario. As such, the ODPRN works closely with the Ontario Public Drug Programs (OPDP), Ministry of Health and Long-Term Care to select key priority areas and topics for formulary modernization, then conducts independent drug class reviews and disseminates the results of each of these reviews directly to the OPDP to facilitate informed decision making on public drug funding policies. The 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.

Conflict of Interest Statement

Muhammad Mamdani was a member of an advisory board for Hoffman La Roche, Pfizer, Novartis, GlaxoSmithKline and Eli Lilly Canada.

Paul Oh was a member of an advisory board for Amgen, Astra Zeneca, Janssen, Novartis, Pfizer, Roche and Sanofi.

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No other 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 drug class review for treatment of attention deficit hyperactivity disorder (ADHD) in adults.

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Note

Some details are censored in this report so as not to preclude publication. Publications (when available) and/or final unpublished reports will be available on the ODPRN website (www.odprn.ca).

List of abbreviations	
AB	Alberta
ADHD	Attention deficit hyperactivity disorder
ATX	Atomoxetine
BC	British Columbia
BIA	Budget impact analysis
CADTH	Canadian Agency for Drugs and Technologies in Health
CDR	Common Drug Review
CIHI	Canadian Institute for Health Information
CNS	Central nervous system
DEX	Dextroamphetamine
DSM	Diagnostic and Statistical Manual
EAP	Exceptional Access Program
HD	High dose
ICES	Institute for Clinical Evaluative Sciences
LAS	Long-acting stimulants
LIS-DEX	Lisdexamfetamine
MAS	Mixed amphetamine salts
MB	Manitoba
MOHLTC	Ministry of Health and Long-Term Care
MPH	Methylphenidate
MR	Multilayer release
NB	New Brunswick
NIHB	Non-insured Health Benefits
NL	Newfoundland
NS	Nova Scotia
NU	Nunavut
NW	Northwest Territories
ODB	Ontario Drug Benefit
ODPRN	Ontario Drug Policy Research Network
ON	Ontario
OPDP	Ontario Public Drug Programs
OROS	Osmotic-release oral system
PEI	Prince Edward Island
Q4	Fourth quarter
QC	Quebec
SAS	Short-acting stimulants
SD	Standard dose
SK	Saskatchewan
SR	Sustained release
SMH	St. Michael's Hospital
YK	Yukon Territories

Executive Summary

In Canada, stimulant and non-stimulant medications 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 lis-dexamfetamine). Atomoxetine is the only non-stimulant medication approved for the treatment of ADHD in adults; guanfacine is a non-stimulant that is approved in Canada only for treatment of children and adolescents with ADHD. In Ontario, all stimulant medications (including long- and short-acting formulations) are funded as General Benefit (with Therapeutic Notes) on the Ontario Drug Benefit (ODB) formulary. Atomoxetine is available in Ontario through the Exceptional Access Program (EAP). Guanfacine is not reimbursed in Ontario by public payers.

ADHD is often thought as a common pediatric mental health disorder, but over the past two decades, greater recognition of ADHD in adults has led to growing utilization of medications in this age group. As part of the formulary modernization review, an evaluation of drugs used in the management of ADHD in adults was undertaken in order to provide policy recommendations for these products in this age group in Ontario. This review is not intended as a clinical practice guideline for the use of medications for the treatment of adult ADHD.

Key Considerations for Reimbursement Options

Efficacy

- Overall, stimulants and atomoxetine were associated with a significant improvement in patient-reported clinical response relative to placebo. As well, most stimulants and atomoxetine were associated with improved observer-reported clinical response relative to placebo. High-dose mixed amphetamine salts was better than other pharmacotherapies at improving observer-reported clinical response.
- The proportion of participants who achieved clinical response varied depending on whether a patient-reported or observer-reported scale was used. In general, standard-dose atomoxetine was better than other pharmacotherapies (stimulants) in the patient-reported assessment of clinical response. In the observer-reported assessment, several pharmacotherapies were associated with better response compared with placebo.
- 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 improvements in quality of life with other stimulants compared to placebo.

Safety

- Our review found that compared with placebo, standard doses of mixed amphetamine salt, atomoxetine and osmotic-release oral system methylphenidate were associated with higher rates of withdrawal due to an adverse event than other therapies; note that these medications were the most frequently studied drugs as well. However, when compared to each other, there were no significant differences among the pharmacotherapies.

- Several Health Canada warnings have been issued regarding stimulant and non-stimulant medication use including risk of priapism (specifically with methylphenidate), psychiatric adverse events (including increased risk of suicidal thoughts and behaviours) and cardiovascular adverse events (e.g., increased risk of sudden death).
- Other studies have shown that long-term stimulant treatment is associated with increases in blood pressure and heart rate; however, our network meta-analysis did not find an association between stimulant or atomoxetine use and increased risk of serious cardiovascular events. Note that this evidence is based on clinical trials that had a mean age between 30 and 40 years of age, and so there is no evidence on these risks in older adults (65+).
- 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.

Accessibility

- The transition from child to adult can be a challenge when accessing mental health services for patients with ADHD; utilization trends in Ontario suggest the existence of breaks in coverage for medication through the ODB among children during this transition (i.e. 17 to 18 years old).
- No other accessibility issues were identified for adult patients with ADHD.

Pharmacoeconomics

- *Cost effectiveness literature review*: No published economic evaluations were identified that examined the comparative cost-effectiveness of adult ADHD medications. A literature review was conducted to outline the societal impact of adult ADHD on employment and criminality. Findings from these studies, albeit of poor quality, indicate an association between adult ADHD and increased unemployment and poorer work performance. In addition, pharmacological treatment of ADHD symptoms is associated with improved work performance and reduced likelihood of criminal behavior.
- *Budget impact analysis (BIA)*: In Ontario in 2014 for the provincially funded drug program, there were 17,482 adult users (≥ 18 years) and 13,529 users under 18 years of age of stimulants/non-stimulants. Spending on ADHD medications in adults was \$14.6 million in 2014 and is projected to increase to \$23.2 million by 2017.
- Listing atomoxetine as Limited Use would increase accessibility for this medication (e.g., for patients who have failed stimulant therapy or for those considered at risk for abuse). Based on opinion from clinical experts, we have estimated that the utilization would increase approximately 12 fold (from 150 patients per year to 1800) with a resultant decrease in use of stimulants. The budget impact of this reimbursement option would result in a decrease in expenditures of approximately \$1 million ($\downarrow 5\%$). In the BIA, it is assumed that atomoxetine would be used as monotherapy; however, our analysis indicates that approximately 30% of Ontario's provincially-funded atomoxetine users may concurrently use stimulants. Note: Even though there are numerous generic companies that manufacture atomoxetine, the 25% generic pricing rule (i.e., cost of generic product is 25% of brand-name cost) cannot be enforced under the Exceptional Access Program

(EAP). This budget impact analysis assumes that generic pricing rules for atomoxetine (i.e., 25% of brand name) would apply.

Findings from the ODPRN Citizens' Panel

Citizens' Panel members rated each of the policy options on factors related to acceptability, accessibility and affordability, and ranked options from most to least preferable from a societal viewpoint. The final rankings were as follows (from most acceptable to least preferable):

1. List atomoxetine as Limited Use (for adults)
2. No age restriction should be applied to stimulants or atomoxetine.
3. All stimulant products on General Benefit and atomoxetine on EAP.

In addition, panel members were in favour of including recommendations regarding cardiovascular safety of stimulants and atomoxetine in older adults, and the potential for misuse/abuse/diversion of stimulant medications.

Recommendations

1. No age restriction should be applied to stimulants or atomoxetine.
 - There is no evidence to suggest that age affects response to ADHD treatment in adult patients.
 - In our review, of the 64 trials that reported the mean age of participants, there were only 4 trials that specifically evaluated treatment in younger adults (mean age <30 years). As well, the mean age across all of the studies included in the systematic review was between 30 and 40 years.
2. List atomoxetine as Limited Use (for adults)
 - Our findings suggest that atomoxetine was more efficacious than placebo and at least as efficacious as other pharmacotherapies for the outcomes studied, except for executive function. In fact, no significant difference was noted in executive function between any of the pharmacotherapies and placebo or among the pharmacotherapies.
 - Currently, atomoxetine is covered under EAP. The 25% generic pricing rule (i.e., cost of generic product is 25% of brand-name cost) and generic interchangeability cannot be enforced for medications covered under EAP. However, if atomoxetine is listed as Limited Use, the cost of generic atomoxetine would significantly decrease.
 - Limited Use is recommended (versus General Benefit listing) to provide guidance for clinicians on the use of atomoxetine as second-line therapy and to help prevent off-label use (e.g., for mood disorders, eating disorders, treatment of addictions).
 - Listing atomoxetine as Limited Use for adults would increase accessibility for this medication and decrease expenditures for ADHD medications in adults overall.

3. Cardiovascular safety of stimulants and atomoxetine should continue to be monitored, especially with the potential increased use of stimulants and atomoxetine in older patients with concomitant medical conditions
 - Long-term stimulant treatment is associated with increases in blood pressure and heart rate. There is little data on the long-term safety of stimulants in older adults with concomitant medical conditions.
 - Although our results did not identify an association between stimulant use and increased risk of serious cardiovascular events in adults, the majority of patients included in the studied were less than 49 years of age.

4. Health care practitioners should remain vigilant about the potential for misuse/abuse/diversion of stimulant medications.
 - Although our report did not show any evidence of large-scale misuse/abuse/diversion with stimulant medications in Canada, a review of the published literature indicates that misuse/abuse/diversion of prescription stimulants occurs and should be considered by clinicians who are considering prescribing these medications.
 - Strategies and programs to prevent diversion could potentially reduce overall misuse of these medications.

5. No changes to the listing status of the available stimulants are recommended.
 - All stimulants commercially available in Canada are available as General Benefit in Ontario for all ages.
 - Based on the efficacy and safety data, no changes to the listing status are recommended.

Table of Contents

Ontario Drug Policy Research Network	2
Conflict of Interest Statement	2
Acknowledgments	2
Study Team	3
Note	3
List of abbreviations	4
Executive Summary	5
List of Exhibits	10
Rationale for Review	11
Background Information	11
Objective	16
Components of the Drug Class Review	16
Overview of Findings	16
Qualitative Research Team: Perspectives of Patients, Primary Care Physicians, Pharmacists and Psychiatrists	16
Pharmacoepidemiology Team	18
Current Utilization across Canada	18
Patterns of ADHD Medication Use in Ontario	19
Characteristics of provincially-funded ADHD medication users in Ontario	21
Patterns of ADHD Medication Use and Discontinuation	21
Patterns of ADHD Medication Use among Youth in Ontario	21
Possible Misuse of Treatments for ADHD across Canada	22
Systematic Review Team	22
Efficacy	22
Safety	23
Pharmacoeconomics Team	28
Cost-Effectiveness Literature Review	28
Budget Impact Analyses	28
Health Equity Issues	30
Recommendations for Consideration	30
Key Considerations	30
Stakeholder Review	32
Findings from the ODPRN Citizens' Panel	32
Final Policy Recommendations	33
Reference List	35
Appendix A: Health Equity Considerations for ADHD Medications (in adults)	39

Appendix B: Assessment of Criteria for Coverage and Therapeutic Notes	41
Appendix C: Clinical Criteria and Therapeutic Notes (proposed)	43

List of Exhibits

Exhibit 1: Public plan listings in Canada for stimulants and non-stimulants for treatment of ADHD	15
Exhibit 2: Total number of prescriptions and cost for ADHD medications dispensed to adults aged 19 and older in Canada, by drug and quarter	18
Exhibit 3: Total utilization and cost of provincially-funded ADHD medications in Ontario, by drug and fiscal year	20
Exhibit 4: Total number of provincially-funded long-acting methylphenidate users aged 18 years and older, by brand name vs. generic formulation and year	20
Exhibit 5: Summary table for efficacy outcomes for ADHD pharmacotherapies approved for ADHD treatment in Canada	25
Exhibit 6: Summary table for safety outcomes for ADHD pharmacotherapies approved for ADHD treatment in Canada	26
Exhibit 7: Forecasted total costs (2017) under alternative reimbursement strategy for patients 18 years and older	29
Exhibit 8: Overall post-meeting option ranking	33

Rationale for Review

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; guanfacine is a non-stimulant that is approved in Canada only for treatment of children and adolescents. Other medications such as bupropion and modafinil have been used off-label for adult patients with ADHD. Generic formulations are available for methylphenidate short-acting and long-acting (specifically Ritalin SR and Concerta), short-acting dextroamphetamine, mixed amphetamine salt as well as for atomoxetine. In Ontario, all stimulant medications (including long- and short-acting formulations) are funded as General Benefit (with Therapeutic Notes) on the Ontario Drug Benefit (ODB) formulary. Atomoxetine is available in Ontario through the Exceptional Access Program (EAP). Guanfacine is not reimbursed in Ontario. Additionally, in Ontario, all stimulant medications are monitored through the Narcotics Monitoring System, as part of Ontario's Narcotics Strategy.¹

ADHD is one of the most commonly diagnosed mental health disorders in children; over the past few decades, greater recognition of adult ADHD has led to a subsequent increase in utilization of stimulants and non-stimulants in adults in Ontario. As part of the formulary modernization review, an evaluation of drugs used in the management of ADHD in adults was undertaken, in order to provide policy recommendations for these products in this age group in Ontario. This review is not intended as a clinical practice guideline for the use of specific medications for the treatment of adult ADHD.

This report outlines the key findings for each of the components of the review. More detailed information for each of the reviews can be found on the ODPRN website: <http://www.odprn.ca>

Background Information

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 30 to 50% of children will continue to have a diagnosis of ADHD as adults.^{2,3} The prevalence rate of ADHD in children and adolescents is 5.3% worldwide,⁴ and approximately 3-4% of adults affected.⁵ ADHD is characterized by inattention, hyperactivity and impulsivity, which may result in social and functional impairments in adults.⁶ In patients diagnosed during childhood, difficulties with organization as well as initiating, maintaining and completing tasks become more prominent and hyperactivity tends to lessen. Adult impulsivity may manifest itself as edginess, shopping sprees, quitting jobs and risky behaviours.⁷ According to the Diagnostic and Statistical Manual (DSM) V, 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 for diagnosis.⁸

ADHD in adults is associated with various comorbid conditions including depression, bipolar

disorder, substance abuse, personality disorders, anxiety disorders and learning disabilities.^{3;9;10} 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.^{11;12} There is limited evidence that adolescents and adults with ADHD have adverse driving outcomes, including increased number of accidents and speeding violations, compared to individuals without ADHD.^{13;14} In addition, a diagnosis of ADHD has been associated with illicit drug use and alcohol addiction, lack of academic achievement, increased criminality and higher rates of poor social adjustment and family or marital conflict.^{12;15} For example, a 10-fold increase in prevalence of ADHD (26.2%) in adult prison populations has been noted.¹⁶ Pharmacological treatment of ADHD may improve driving performance as well as reduce criminal behavior, although there appears to be no significant long-term reduction in crime rate after discontinuation of medication.^{13;17;18} Occupational outcome has been less well studied in adults than education and school-performance in children; nonetheless, limited cross-sectional/retrospective studies have reported a positive correlation between employment status and treatment with stimulants.¹⁹

Pharmacologic management of adults with ADHD is considered first-line therapy in adults.²⁰ Stimulant medications are often indicated as initial treatment.^{12;21} The choice of stimulant is influenced by several factors including duration of action; long-acting medications allow for once or twice-daily dosing which may improve adherence to the medication.²² Non-stimulant medications, in particular atomoxetine, are often used as a second line agent.²¹ In general, medications should be started at a low dose and titrated upwards until clinical effect is observed or adverse effects develop.⁵ Available guidelines suggest that children and adults who respond to pharmacotherapy should continue treatment for as long as it remains effective.²⁰

Public plan reimbursement of drugs used in treatment of ADHD in adults

Canada

Across Canada, short-acting stimulants (methylphenidate, dextroamphetamine) and selected long-acting stimulants (namely dextroamphetamine, methylphenidate sustained release) are available as general benefit in all jurisdictions (except for Yukon Territory) (see Exhibit 1). Other 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. Funding for atomoxetine is only provided in Saskatchewan, Ontario, Quebec and Yukon Territory.

The Common Drug Review (CDR), established in 2003, is a single process for reviewing new drugs and providing listing recommendations to participating provincially funded federal, provincial and territorial drug benefit plans in Canada. Four medications that were marketed after 2003 for the treatment of ADHD have been reviewed by the CDR (Adderall XR-reviewed in 2008, Vyvanse-2009, Strattera-2005, Intuniv XR-2014); the recommendation for all four medications was not to list based on lack of therapeutic advantage over less expensive agents such as methylphenidate (short-acting and intermediate acting) and dextroamphetamine.

Ontario

Stimulants

In Ontario, all stimulant products are listed on the Ontario Drug Benefit (ODB) formulary as a General Benefit (with no age restrictions).

- Methylphenidate (short-acting): generics, Ritalin
- Methylphenidate (long-acting): generics, Ritalin SR
- Methylphenidate (sustained release): generics, Concerta
- Methylphenidate multilayer release: Biphentin
- Lisdexamfetamine: Vyvanse
- Amphetamine mixture: generics, Adderall XR
- Dextroamphetamine: Dexedrine + generic, Dexedrine Spansule

A therapeutic note on the ODB formulary often includes criteria for reimbursement. 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, Dexedrine Spansule) 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-stimulants

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

Patients ≥ 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.

Exhibit 1: Public plan listings in Canada for stimulants and non-stimulants for treatment of ADHD

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	Strattera	No	No	Res	No	Res	Res	No	No	No	No	Res	No
	Generic	No	No	No	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 ER	No	No	No	FB	FB*	Res	Res	Res	Res	Res	Res	No
	Concerta	Res	No	FB	FB	FB*	Res	Res	Res	Res	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=Full Benefit; unrestricted listing
 Current as of August 10, 2015

Objective

The objective of the drug class review for treatment of adult patients with ADHD is to provide evidence-informed policy recommendations for these drugs in Ontario.

Components of the Drug Class Review

The treatment of adult patients with ADHD drug class review is comprised of:

- qualitative analyses of perspectives of patients and prescribers
 - one-on-one semi-structured telephone interviews regarding specific experiences and perceptions relevant to funding policies for drug therapy for adult patients with ADHD
- environmental scans of:
 - national and international drug policies
 - considerations relating to health equity
- analysis of real-world drug utilization using:
 - administrative claims data from Ontario and across Canada (where available)
 - summaries of relevant observational literature
- systematic review of the literature
- reimbursement-based economic analyses

Results from all of the above components were reviewed and consolidated into a set of policy recommendations.

Overview of Findings

Qualitative Research Team: Perspectives of Patients, Primary Care Physicians, Pharmacists and Psychiatrists

Findings of the qualitative study represented common experiences and perceptions described across patient, pharmacist and physician groups.

Diagnosis of adult ADHD

- Patient and physician participants described that the process of diagnosis of adult ADHD includes an extensive battery of tests and consideration of childhood history of symptoms.
 - Physician participants believed that ADHD is a lifelong disease and not something that spontaneously arises in adulthood.
- Patient participants were promoted to ask their doctor about ADHD in different ways, such as watching a documentary or reading a book on ADHD; or having their child diagnosed with ADHD. Physician participants had concerns about the possibility of “symptom mimicry”, which occurs when alternative conditions such as depression or anxiety present with ADHD-like symptoms. They perceived that a key part of

diagnosis should include specific investigation to rule out these conditions.

“Too often a quick diagnosis is made, you know if it looks like a horse, it is a horse, therefore it is a horse, ergo I am going to treat it like a horse, it gets put down as a diagnostic on the patient’s chart and forever on then the patient has adult ADHD. That degree of root cause analysis and asking the question why multiple times, why is the patient presenting this way, why do they have this, why are they experiencing this, etc. etc., is unfortunately not done in a way that I would say is an existing trend in not just Ontario but also Canada.” –Psychiatrist

Management of ADHD

- Physician participants described that they prefer to prescribe long-acting stimulant medications to their adult ADHD patients because they need to be active for more hours in the day, compared with children, and because long acting medications are more difficult to misuse.
- In general, both clinician and patient participants found stimulant medications to be the most effective for ADHD management.
- Some physician participants perceived that the generic version of some ADHD medications (e.g., methylphenidate) may be easier to abuse than the brand name version (e.g. Concerta[®]) and may also be less effective.
- The majority of patient participants described their ADHD medication to be helpful for improving their quality of life and easing symptoms.
- There was overall consensus between clinician and patient participants that non-pharmacological approaches in combination with medications are important for proper management of ADHD.

Access to ADHD medications

- Physicians and patients felt that Ontario Drug Benefit (ODB) coverage of ADHD medications is fair and reasonable. Patient participants who are receiving ODB coverage did not report any access barriers. No patients reported having had experience obtaining medications through the exceptional access program (EAP). Most clinician participants also did not have experience with EAP or awareness of the therapeutic notes.
- Some psychiatrist participants were aware of the EAP criteria and felt that they were not in line with current clinical practice.

“...one of the difficulties with [the criteria] is they require prior treatment with short-acting meds, which really – clinically – is not what people do who treat ADHD. We don’t use short-acting medicines as a starting point, because they’re not as effective as the long-acting and they have a big problem with diversion so this recommendation is not a sensible one, but it’s what’s required by ODB– before they would approve one of the long-acting medicines and it seems to me to be a very outdated recommendation. It’s not... up-to- speed with current clinical practice” –Psychiatrist

- Physicians play an important role in access to ADHD medications because of their pharmacological and non-pharmacological treatment preferences, their willingness to provide drug cards and the length of their referral list.

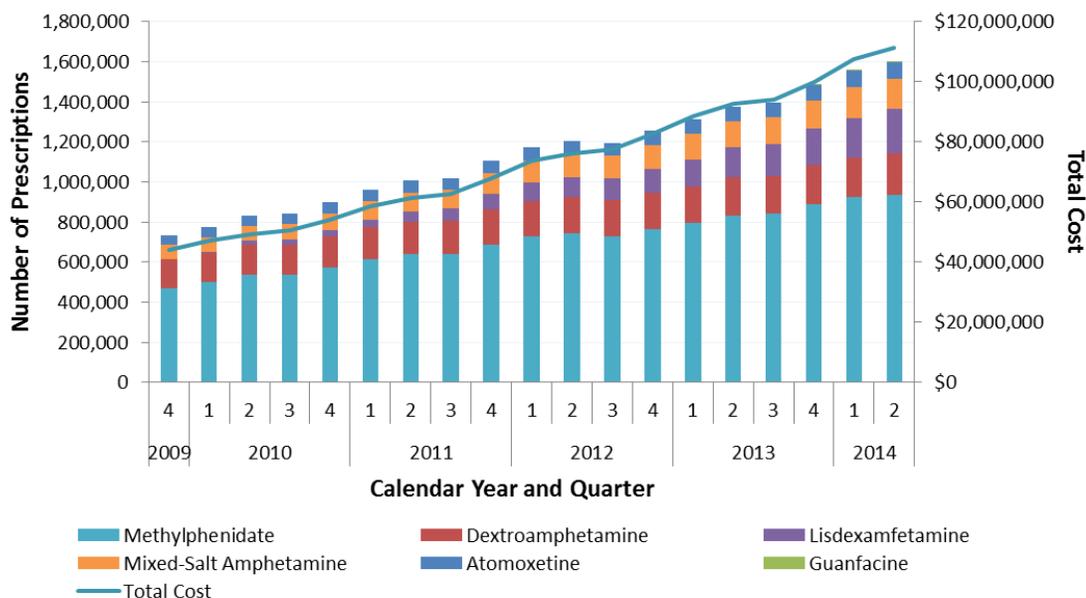
Pharmacoepidemiology Team

Current Utilization across Canada

The number of prescriptions dispensed and the cost of medications used to treat ADHD among all individuals (children, youth and adults) in Canada has increased by 78% and 94% between the fourth quarter (Q4) of 2009 and Q4 of 2014, respectively. In Q4 2014, there were 4,008,735 prescriptions for ADHD medications dispensed nationally costing \$297.4 million. Half of all ADHD medications dispensed were privately funded (50.2%; 2,013,897) and a third (31%; 1,253,693) were paid for by provincially-funded drug coverage programs in Q4 2014.

Among adults aged 19 years and older in Canada, the increase in prescriptions dispensed (119% increase) and cost (153% increase) of ADHD medications was even greater between Q4 2009 and Q2 2014. By Q2 2014, 1,603,896 prescriptions for ADHD medications were dispensed costing \$111.1 million. In Q2 2014, over half of prescriptions dispensed to treat ADHD in adults (58.4%; 937,374 prescriptions) were for methylphenidate, followed by lisdexamfetamine (13.6%; 217,416 prescriptions), dextroamphetamine (12.9%; 273,026 prescriptions), mixed-salt amphetamine (9.6%; 153,616 prescriptions), atomoxetine (5.2%; 84,008 prescriptions), and guanfacine (0.3%; 4,753 prescriptions) (Exhibit 2).

Exhibit 2: Total number of prescriptions and cost for ADHD medications dispensed to adults aged 19 and older in Canada, by drug and quarter



Patterns of ADHD Medication Use in Ontario

Similar to national trends, the number of prescriptions dispensed and costs for ADHD medications among adults aged 19 years and older in Ontario have increased 82% (from 271,684 prescriptions to 493,571 prescriptions) and 112% (from \$17.9 million to \$39.2 million) between Q4 2009 and Q2 2014, respectively. Methylphenidate was the most commonly dispensed ADHD medication (57.4% of prescriptions) in Q2 2014.

Among provincially-funded adults aged 18 and older in Ontario, the number of ADHD prescriptions dispensed increased nearly 2-fold from 67,521 prescriptions in Q4 2009 to 132,083 prescriptions in Q4 2014. In Q4 2014, total public drug program expenditure for ADHD products was approximately \$6.5 million. The majority of prescriptions dispensed in Q4 2014 were for methylphenidate (67.6%; 89,265 prescriptions), followed by lisdexamfetamine (16.3%; 21,520 prescriptions), mixed-salt amphetamine (10.1%; 13,308 prescriptions), dextroamphetamine (4.6%; 6,274 prescriptions), and atomoxetine (1.3%; 1,716 prescriptions) (Exhibit 3).

The increase in provincially-funded stimulant users (156.9% between 2008 and 2014) was largely driven by an increase in long-acting brand ADHD products. The number of brand ADHD stimulant medication users surpassed the number of generic stimulant users in 2013. Since being listed in 2009, the number of provincially-funded extended release methylphenidate users has increased, from 2,496 users in 2009 to 7,345 users by 2014. For OROS methylphenidate, there were consistently more brand-name users compared to generic users (except in 2011) over the study period (Exhibit 4), which may reflect the introduction of brand-name drug reimbursement cards.

Exhibit 3: Total utilization and cost of provincially-funded ADHD medications in Ontario, by drug and fiscal year

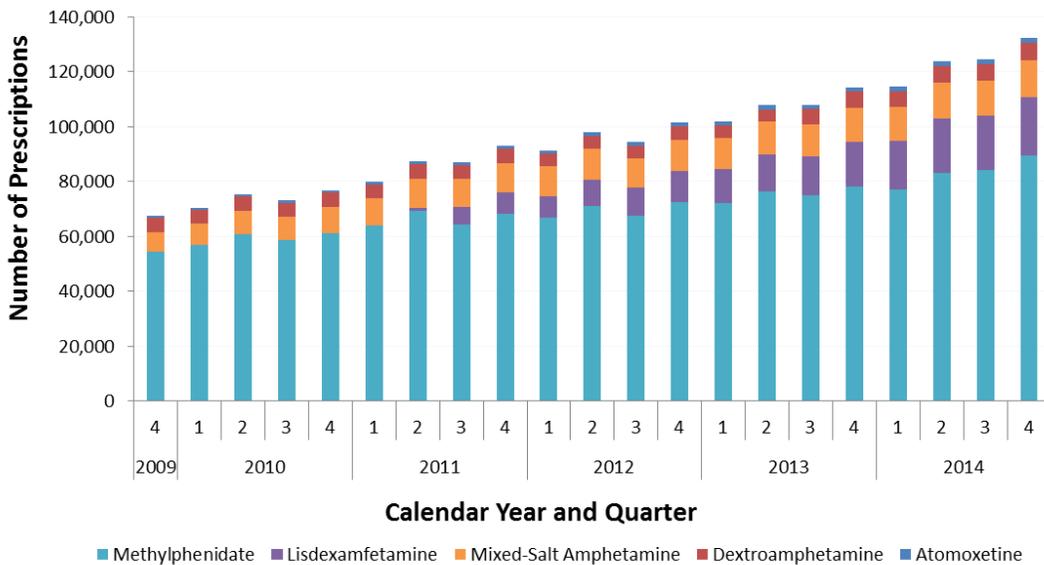
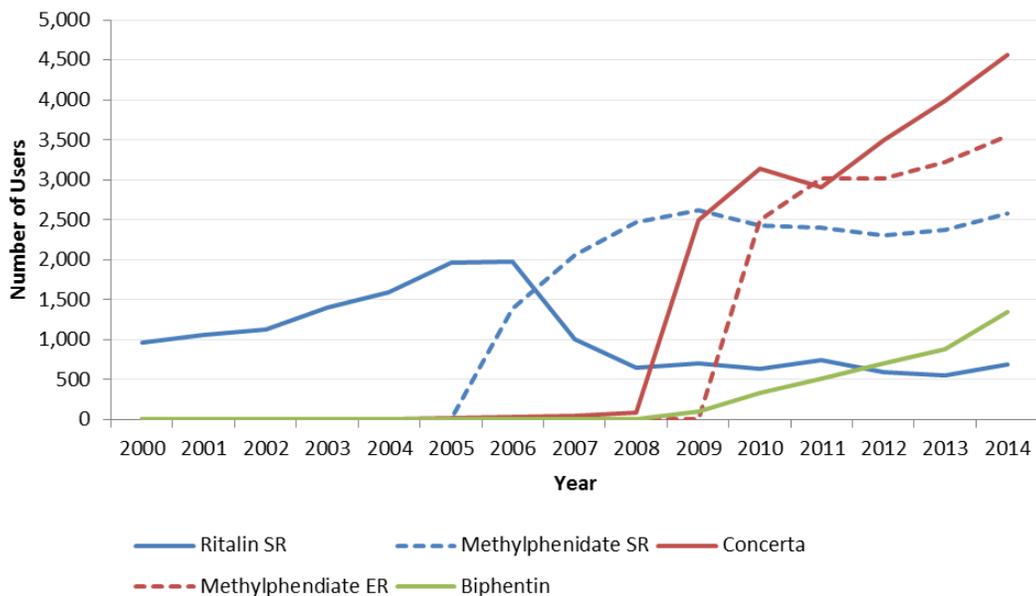


Exhibit 4: Total number of provincially-funded long-acting methylphenidate users aged 18 years and older, by brand name vs. generic formulation and year



Characteristics of provincially-funded ADHD medication users in Ontario

There were 19,615 adults aged 18 and older who were prescribed provincially-funded ADHD medications in Ontario in 2013. The majority of users were dispensed methylphenidate (66.5%; N=13,049), were under 65 years of age (86.3%; N=16,929), more than half were male (54.9%; N=10,778) and the majority lived in urban areas (88.4%; N=17,344). Among those younger than 65, the highest number of users was found among those aged 36-64. Only 26.3% of the users 18 years and older were between the ages of 18 and 25.

Although lisdexamfetamine, mixed-salt amphetamine, and atomoxetine are not indicated for new users of these drugs, lisdexamfetamine was the most commonly newly initiated treatment (36.3%; N=906), and nearly one quarter of mixed-salt amphetamine (22.7%; N=520) and atomoxetine (24.5%; N=35) users had no prior use of ADHD medications dispensed through the public drug program. Among new-users of atomoxetine (N=619) approximately a third (32.8%; N=203) received a stimulant therapy along with their atomoxetine.

Patterns of ADHD Medication Use and Discontinuation

There were approximately 15,500 individuals aged 18 and older who initiated an ADHD medication in Ontario between 2002 and 2012, the majority of whom initiated methylphenidate (80-85%). Patients on lisdexamfetamine and mixed-salt amphetamine were most likely to switch to another drug within 6 months of therapy initiation (12-14%) compared to other users (<10%). The median time to discontinuing ADHD therapy among new users was 328 days. This differed significantly by the drug initiated, ranging from 300-325 days among methylphenidate users to 575-600 days for atomoxetine users. When comparing users who initiated a stimulant ADHD medication (short acting stimulants and long-acting stimulants), the median time to discontinuation for patients on short-acting stimulants (275-300 days) was significantly shorter compared to patients on long-acting stimulants (375-400 days). The median time to ADHD medication discontinuation also differed significantly across age groups, with younger (ages 18 to 25) and older (ages 65 and older) users discontinuing ADHD medication use sooner (250-275 days) compared to users aged 26 to 35 and users aged 36 to 64 (325-425 days).

Patterns of ADHD Medication Use among Youth in Ontario

There were approximately 32,500 youth aged younger than 18 in Ontario who received two or more provincially-funded ADHD medication prescriptions within 180 days between 2002 and 2013, of whom approximately 16-20% continued to use these medications past their 17th birthday. Among those who continued use of an ADHD medication after their 17th birthday, close to half continued their use into adulthood (past 18th birthday). On average, the median time to ADHD medications for these individuals following their 18th birthday was greater than a year. A large number of those who stopped therapy (56-60%) were still ODB eligible meaning other factors may influence the continuation of ADHD therapy at this transition, other factors may also influence the discontinuation of ADHD therapy at this transition including inability to find medical care when no longer in care of a pediatrician.

Possible Misuse of Treatments for ADHD across Canada

The prevalence of potentially inappropriate stimulant ADHD medication prescriptions in 2013 and 2014 was low (<0.3%) across all provinces in Canada. Ontario had the highest prevalence of potentially inappropriate ADHD medications, followed by Alberta and British Columbia, which ranged between 0.2-0.5% in 2013 and 2014. The number of prescriptions that were potentially inappropriate was less than 100 across all provinces, except Ontario and British Columbia which largely exceeded 100. The percent of potentially inappropriate short acting stimulant ADHD medication prescriptions in Ontario was similar to the rate of potentially inappropriate prescriptions for all stimulant ADHD medications.

Systematic Review Team

An existing, high-quality systematic review was updated to summarize the randomized evidence of the efficacy and safety of pharmacotherapies for ADHD in adults. The population of interest was adults with attention deficit disorder or ADHD. The efficacy outcomes of interest were clinical response, quality of life, executive function, driving behavior, safety outcomes were withdrawals due to adverse events, serious adverse events, treatment discontinuations, cardiovascular events, hospitalizations, and emergency room visits. Meta-analysis and Bayesian network meta-analyses were performed to directly and indirectly compare the efficacy and safety of the identified pharmacotherapies.

Seventy-three randomized controlled trials, published between 1985 and 2014, were included in our review. Most used a parallel design ($k = 49$). The number of included patients ranged from 17 to 725, and the duration of therapy ranged from 2 weeks to 1.5 years; however, the majority of studies involved treatment between 4 and 12 weeks. All studies required participants to have a clinical diagnosis of ADHD. Participants were both treatment naïve and experienced; most studies required a washout period if ADHD pharmacotherapy had been used before enrollment (duration of washout period varied by route of administration).

In general, the mean age of most studies was between 30 and 40 years of age (54 studies). Four trials involved participants with a mean age of less than 30 years, and six involved participants with a mean age over 40 years. No study had a mean age above 45 years of age. One study did not report the mean age of participants.

Efficacy

- Most of the pharmacotherapies were associated with a significant improvement in patient-reported clinical response relative to placebo (See Exhibit 5).
- Mixed amphetamine salt, atomoxetine (standard dose), lisdexamfetamine, osmotic-release oral system (OROS) methylphenidate (standard dose), and immediate-release methylphenidate (high dose) were associated with improved observer-reported clinical response relative to placebo. High-dose mixed amphetamine salts was better than other pharmacotherapies at improving observer-reported clinical response.
- The proportion of participants who achieved clinical response varied depending on whether a patient-reported or observer-reported scale was used. In general, standard-dose atomoxetine was better than other pharmacotherapies in the patient-reported assessment of clinical response. In the observer-reported assessment, several

pharmacotherapies were associated with better response compared with placebo (e.g., mixed amphetamine salts ER, atomoxetine, lisdexamfetamine, methylphenidate OROS, methylphenidate immediate release).

- Standard-dose atomoxetine and high-dose mixed amphetamine salts were associated with significant improvements in quality of life relative to placebo. There were no significant differences in quality of life when comparing the various pharmacotherapies.
- There were no significant differences in executive function between any of the pharmacotherapies and placebo or among the pharmacotherapies.

Safety

- Compared with placebo, standard doses of mixed amphetamine salts, atomoxetine, OROS methylphenidate and long-acting methylphenidate were associated with higher odds of withdrawal due to an adverse event. High doses of mixed amphetamine salts, lisdexamfetamine and OROS methylphenidate had higher odds of withdrawal compared with placebo. There were few significant differences among the pharmacotherapies (see Exhibit 6).
- There were no significant differences in serious adverse events between any of the ADHD pharmacotherapies and placebo. Comparison among the pharmacotherapies was not possible for this outcome.
- Compared with placebo, atomoxetine (standard and high doses) and OROS methylphenidate (standard dose) were associated with higher odds of all-cause treatment discontinuation. Mixed amphetamine salts (high dose) and extended-release methylphenidate (standard dose) had lower odds of discontinuation relative to placebo. High-dose mixed amphetamine salts and standard-dose extended release methylphenidate were associated with a lower odds of treatment discontinuation compared with most other pharmacotherapies.
- Stroke and hospitalization were rare events reported during clinical trials; only 4 events were reported in treated patients in 3 studies compared to no events in placebo group. No trial reported myocardial infarction, cardiovascular death, or emergency room visits during the study period.
- Common adverse effects of stimulants include insomnia, dry mouth, decreased appetite, weight loss and headaches.^{23;24} For atomoxetine, the most common adverse events are nausea, dry mouth, decreased appetite, insomnia and fatigue.
- Several Health Canada warnings have been issued regarding stimulant and non-stimulant medication use including risk of priapism (specifically with methylphenidate), psychiatric adverse events (including increased risk of suicidal thoughts and behaviours) and cardiovascular adverse events (e.g., increased risk of sudden death).

Other reviews:

- A rapid review of cardiovascular adverse events possibly associated with ADHD drug treatment concluded that long-term stimulant treatment is associated with increases in blood pressure and heart rate²⁵; however, much of the evidence does not support a causal relationship between stimulant use and increased risk of serious cardiovascular events in adults.²⁶⁻²⁹ A black box warning is included in the product monograph for

Adderall XR that states that the misuse of amphetamines may cause serious cardiovascular adverse events and sudden death.³⁰

- Limited data suggest that there is no causal association between ADHD drug treatments and suicidality in adults.^{31;32}

Exhibit 5: Summary table for efficacy outcomes for ADHD pharmacotherapies approved for ADHD treatment in Canada

Pharmacotherapy*	Dose category	Clinical response assessed using continuous measure		Proportion of patients with clinical response		Quality of life	Executive function
		Patient-reported	Observer-reported	Patient-reported	Observer-reported		
Mixed amphetamine salts, ER	Standard	—	Placebo ATX-STD MPH-OROS-STD	—	NS	—	—
	High	—	Placebo ATX-STD DEX-IR-STD LIS-DEX-STD/HD MPH-OROS-STD/HD MPH-SR-STD MPH-IR-STD	—	Placebo MPH-SR-HD	Placebo	NS
Atomoxetine	Standard	Placebo MPH-SR-HD	Placebo	Placebo ATX-HD MPH-IR-STD MPH-SR-STD/HD	Placebo	Placebo	NS
	High	—	NS	NS	NS	NS	—
Dextroamphetamine, IR	Standard	NS	NS	NS	—	—	—
	High	—	—	—	—	—	—
Dextroamphetamine, SR	Standard	—	—	—	—	—	—
	High	—	—	—	—	—	—
Guanfacine, ER	Standard	—	—	—	—	—	—
	High	—	—	—	—	—	—
Lisdexamfetamine	Standard	—	Placebo	—	Placebo MPH-SR-HD	NS	—
	High	—	Placebo	—	Placebo	—	—
Methylphenidate, osmotic-release oral system	Standard	Placebo MPH-SR-STD	Placebo	Placebo MPH-SR-STD/HD	Placebo	NS	NS
	High	NS	MPH-IR-HD	Placebo MPH-SR-STD/HD	NS	—	—
Methylphenidate, IR	Standard	NS	Placebo	—	NS	—	NS
	High	Placebo MPH-SR-HD	MPH-IR-STD	—	Placebo	—	—
Methylphenidate, multilayer-release	High	—	—	—	—	—	—
	Standard	—	—	—	—	—	—
Methylphenidate, SR	Standard	—	NS	NS	NS	—	—
	High	NS	—	NS	NS	—	—

* Pharmacotherapy in the row header is significantly better than the pharmacotherapies listed under each outcome

Note: MAS-XR = mixed amphetamine salts, ER; ATX = atomoxetine; DEX-IR = dextroamphetamine IR; DEX-SR = dextroamphetamine SR; GUAN-ER = guanfacine, ER; LIS-DEX = lisdexamfetamine; MPH-OROS = methylphenidate osmotic-release oral system; MPH-IR = methylphenidate, IR; MPH-MR = methylphenidate multilayer-release; MPH-SR = methylphenidate SR; ER = extended release, HD = high dose, IR = immediate release, NS = not significantly different compared to other treatments in this table standard = standard dose, SR = sustained release, — indicates pharmacotherapies not included in the network.

NOTE: Does not contain all pharmacotherapies included in the systematic review and network meta-analysis. Only select pharmacotherapies approved for ADHD treatment in Canada are presented in this table. Full details will be available in the short and full reports.

Exhibit 6: Summary table for safety outcomes for ADHD pharmacotherapies approved for ADHD treatment in Canada

Pharmacotherapy	Dose category	Withdrawals due to adverse events†	Serious adverse events‡	All-cause treatment discontinuation‡
Placebo	—	MAS-XR-STD/HD ATX-STD LIS-DEX-HD MPH-OROS-STD/HD	NS	ATX-STD/HD MPH-OROS-STD
Mixed amphetamine salts, ER	Standard	NS	§	ATX-HD
	High	NS	NS	ATX-STD/HD MPH-OROS-STD/HD MPH-IR-STD
Atomoxetine	Standard	NS	NS	NS
	High	¶	NS	Placebo DEX-IR-STD LIS-DEX-STD
Dextroamphetamine, IR	Standard	NS	—	ATX-HD
	High	—	—	—
Dextroamphetamine, SR	Standard	—	—	—
	High	—	—	—
Guanfacine, ER	Standard	—	—	—
	High	—	—	—
Lisdexamfetamine	Standard	NS	NS	ATX-STD/HD MPH-OROS-STD
	High	NS	NS	NS
Methylphenidate, osmotic-release oral system	Standard	NS	NS	NS
	High	NS	§	NS
Methylphenidate, IR	Standard	NS	—	NS
	High	¶	—	NS
Methylphenidate, multilayer-release	Standard	—	—	—
	High	—	—	—
Methylphenidate, SR	Standard	NS	—	NS
	High	¶	—	NS

* Pharmacotherapy in the row header is significantly better than the pharmacotherapies listed under each outcome

Note: MAS-XR = mixed amphetamine salts, ER; ATX = atomoxetine; DEX-IR = dextroamphetamine IR; DEX-SR = dextroamphetamine SR; GUAN-ER = guanfacine, ER; LIS-DEX = lisdexamfetamine; MPH-OROS = methylphenidate osmotic-release oral system; MPH-IR = methylphenidate, IR; MPH-MR = methylphenidate multilayer-release; MPH-SR = methylphenidate SR; ER = extended release; HD = high dose; IR = immediate release; NS = not significantly different compared to other treatments in this table; standard = standard dose; SR = sustained release; — indicates pharmacotherapies not included in the network.

*Does not contain all pharmacotherapies included in the systematic review and network meta-analysis. Only select pharmacotherapies approved for ADHD treatment in Canada are presented in this table. Full details will be available in the short and full reports.

†Based on network meta-analysis

‡Based on meta-analysis: comparison is relative to placebo (no comparison between individual treatments).

§Data not estimable owing to zero events in both groups.

¶Estimates were not robust owing to zero event counts for the treatment or placebo arm.

Misuse, abuse and diversion of prescription stimulants

“Diversion” of medication is defined as the transfer of medication from one patient for whom it is prescribed to another patient for whom it is not prescribed. “Misuse” refers to the use of nonprescribed medications or the use of prescribed medications at doses, times or in combinations other than for which they were prescribed.³³ In our analysis of possible misuse of ADHD treatments across provincially funded drug plans in Canada, we found that misuse rarely occurred at the prescription level. Only 0.3% of all prescriptions were considered potentially inappropriate defined as an early refill that was from both a different doctor and different pharmacy than the prior prescription.

In contrast to our findings, in our review of studies summarizing observational literature, the misuse of prescription stimulants appears to be prevalent, especially among college students. Motives for misuse include improvement of concentration, increasing alertness and/or for recreational purposes.^{34:35} The rate of non-prescription stimulant misuse in the general adult population ranged across studies with prevalence between 1.8% to 4.7%. However in college students, prevalence of misuse was found to be higher, with reported prevalence of misuse ranging largely between 4.6% to 48%. The difference in reported misuse between college students compared to the adult population could be due to the perceived cognitive enhancing ability of these medications which is thought to lead to a higher prevalence of misuse, especially among college students. Only one Canadian study was included in this observational literature review highlighting the need for further research in Canada surrounding misuse and diversion of prescription stimulants.³⁶ Prescription holders who divert their medications are a significant source of supply for the general misuser population. In an Internet survey targeted at individuals aged 18-49 years whose private insurance paid for some costs of ADHD medications, 16.6% diverted medications from these prescriptions.³⁷

Among the studies that reviewed specific medication misuse, the majority suggested that dextroamphetamine, amphetamine and amphetamine mixed salts were the most misused stimulants. Short-acting stimulant medications are more likely to be abused, since phasic dopamine increase is more reinforcing than therapeutic dopamine release.^{38:39} In addition, longer-acting stimulant medications are less likely to be abused, as maximum plasma concentration is observed later after dosing compared to an equivalent dose of a short-acting formulation; as well the coating of long-acting preparations may make the active stimulant more difficult to extract and less likely to produce euphoria³³. Anecdotal evidence suggests that the street value of long-acting ADHD medications is considerably less than short-acting preparations.⁴⁰ Common routes for abuse include oral, intranasal or parenteral administration.

CADTH published a report in 2013 on the abuse and misuse potential of drugs used for the treatment of ADHD.⁴¹ After a review of one systematic review, one RCT and 12 observational studies, the report concluded that misuse of methylphenidate and amphetamine-based ADHD drugs was evident in adolescent and young adult populations, especially in undergraduate university students. Due to limited evidence, no conclusion could be made regarding the abuse potential of atomoxetine.

Summary: Although our review did not see an indication of widespread misuse of these medications, the definition that we used in our analysis was stringent. In light of the existing literature identifying misuse/abuse/diversion of stimulants, it is prudent to consider this potential when providing access to these drugs, in particular in college-aged adults.

Pharmacoeconomics Team

Cost-Effectiveness Literature Review

A total of 93 unique citations relating to the cost-effectiveness of treatments for adults with ADHD were identified from our initial searches and were screened for inclusion in this review. All the records that were reviewed for inclusion were deemed irrelevant to our research question and were eliminated from our review. Given the lack of evidence regarding the cost-effectiveness of treatments for ADHD among adults, we conducted a literature review to outline the societal impact of adult ADHD on employment and criminality.

Using a combination of hand-searching and database searching with keywords, we were able to identify some relevant literature regarding the link between adult ADHD and employment/criminality. Findings from these studies were supportive of an association between adult ADHD and increased unemployment and poorer work performance. We also identified a few studies providing evidence that receiving treatment for ADHD helps to improve work performance and reduce criminal behaviour. Again, findings from these studies were generally supportive of the notion that pharmacological treatment of ADHD symptoms is associated with improved work performance and reduced likelihood of criminal behaviour. However, in both instances, the studies we reviewed were generally of poor quality and had several limitations including small numbers of participants and poor generalizability. There was also little mention of the economic implications of adult ADHD from a broader societal perspective. None of the studies that we reviewed were conducted in the Canadian context, further limiting the applicability of this evidence to our study question.

Based on the findings from both our systematic review and our literature review, we have determined that little is known about the economic impact of adult ADHD. There is a clear need for more research in this area to address questions of cost-effectiveness and economic burden on the health care system.

Budget Impact Analyses

- In 2014, there were 17,482 adult users (≥ 18 years) and 13,529 users under 18 years of age of stimulants/non-stimulants. Based on data from OPDP from 2000-2014, spending on adult ADHD medications was \$14.6 million in 2014 and is projected to increase to \$23.2 million by 2017.
- Several reimbursement strategies were considered as part of the budget impact analysis (see Exhibit 7). Because our review is focused on adult ADHD patients, most of the alternative reimbursement strategies do not impact ADHD medication expenditure for children (< 18 years of age).
- Listing atomoxetine as Limited Use for adults with no change in current listing status of stimulants (i.e., remain as General Benefit listing) would result in increased utilization for

atomoxetine (estimated from 150 to 1800 patients annually, based on the assumption that 10% of users of other medications would move to atomoxetine) and resultant decrease in use of stimulants. The budget impact of this reimbursement option would result in a decrease in expenditures of approximately \$1 million (↓5%).

- Even though there are numerous generic companies that manufacture atomoxetine, the 25% generic pricing rule (i.e., cost of generic product is 25% of brand-name cost) cannot be enforced under the Exceptional Access Program (EAP). This budget impact analysis assumes that generic pricing rules for atomoxetine (i.e., 25% of brand name) would apply.⁴²
- In the BIA, it is assumed that atomoxetine would be used as monotherapy; however, our analysis of Ontario’s provincially funded atomoxetine users suggest that approximately 30% of users may concurrently use stimulants. Note that the evidence for efficacy for dual therapy is extremely limited.^{21;43}

Exhibit 7: Forecasted total costs (2017) under alternative reimbursement strategy for patients 18 years and older

AVERAGE COST OF ADHD MEDICATIONS IN 2017						
REIMBURSEMENT STRATEGY	Long-acting stimulants ¹	Short-acting stimulants ²	Non-stimulants ³	TOTAL	NET BUDGET IMPACT	%
Status quo (base case)						
	\$21,040,321.67	\$1,811,070.83	\$365,413.79	\$23,216,806.29	N/A	N/A
Limited Use listing for atomoxetine						
	\$18,936,289.50	\$1,629,963.75	\$1,620,211.44	\$22,186,464.69	-\$1,030,341.60	-5%
Limited Use listing for long-acting stimulants in adults (≥18 years)						
	\$18,936,289.50	\$3,090,722.81	\$365,413.79	\$22,392,426.10	-\$824,380.19	-4%
Limited Use listing for atomoxetine AND long-acting stimulants in adults						
	\$17,042,660.55	\$2,781,650.53	\$1,620,211.44	\$21,444,522.52	-\$1,772,283.76	-8%
General Benefit generic extended release methylphenidate AND Limited Use listing brand name only long-acting stimulants in adults						
	\$18,141,707.87	\$2,962,757.61	\$365,413.79	\$21,469,879.27	-\$1,746,927.02	-8%
General Benefit generic extended release methylphenidate AND Limited Use listing brand name only long-acting stimulants AND atomoxetine Limited Use in adults						
	\$16,327,537.08	\$2,847,588.93	\$1,343,643.19	\$20,518,769.20	-\$2,698,037.09	-13%
¹ LAS = long-acting stimulants, includes amphetamine mixed salts, dextroamphetamine (long-acting), lisdexamfetamine, methylphenidate (long-acting) ² SAS = short-acting stimulants, includes dextroamphetamine (short-acting) & methylphenidate (short-acting) ³ NS = non-stimulants, includes atomoxetine						

Health Equity Issues

No major health equity issues were identified in this review. See **Error! Reference source not found.** for Health Equity Considerations.

Accessibility of Medications for ADHD

Patients under the age of 65 who do not have private insurance will have barriers to access some medications, in particular the long-acting formulations. As well, patients outside of urban centres may find it difficult to access a psychiatrist who specialized in ADHD.

Recommendations for Consideration

Key Considerations

Efficacy

- Overall, stimulants and non-stimulants were associated with a significant improvement in patient-reported clinical response relative to placebo. As well, most stimulants and atomoxetine were associated with improved observer-reported clinical response relative to placebo. High-dose mixed amphetamine salts was better than other pharmacotherapies at improving observer-reported clinical response.
- The proportion of participants who achieved clinical response varied depending on whether a patient-reported or observer-reported scale was used. In general, standard-dose atomoxetine was better than other pharmacotherapies in the patient-reported assessment of clinical response. In the observer-reported assessment, several pharmacotherapies were associated with better response compared with placebo.
- Standard-dose atomoxetine and high-dose mixed amphetamine salt were associated with significant improvements in quality of life relative to placebo. There were no significant differences in quality of life when comparing the various pharmacotherapies.
- There were no significant differences in executive function between any of the pharmacotherapies and placebo or among the pharmacotherapies.

Safety

- Our review found that compared with placebo, standard doses of mixed amphetamine salt, atomoxetine and osmotic-release oral system methylphenidate were associated with higher odds of withdrawal due to an adverse event. However, when compared to each other, there were no significant differences among the pharmacotherapies. As well, there were no significant differences in serious adverse events between any of the ADHD pharmacotherapies and placebo. Comparison among the pharmacotherapies was not possible for this outcome.
- Common adverse effects of stimulants include insomnia, dry mouth, decreased appetite, weight loss and headaches.^{23;24} For atomoxetine, the most common adverse events are nausea, dry mouth, decreased appetite, insomnia and fatigue.
- Several Health Canada warnings have been issued regarding stimulant and non-stimulant medication use including risk of priapism (specifically with methylphenidate), psychiatric

- adverse events (including increased risk of suicidal thoughts and behaviours) and cardiovascular adverse events (e.g., increased risk of sudden death).
- Other studies have shown that long-term stimulant treatment is associated with increases in blood pressure and heart rate; however, much of the evidence does not support a causal relationship between stimulant or atomoxetine use and increased risk of serious cardiovascular events. Note that these studies were not conducted in older adults.
 - Our data analysis indicated that there was minimal misuse/abuse occurring at the prescription level across Canada. However, in our review of studies summarizing observational literature (largely reliant on surveys), there is evidence that misuse of prescription stimulants occurs, especially in college-age adults.

Accessibility

- The transition from child to adult can be a challenge when accessing mental health services for patients with ADHD; utilization trends in Ontario suggest the existence of breaks in coverage for medication through the ODB among children during this transition (i.e. 17 to 18 years old).⁴⁴
- No other accessibility issues were identified for adult patients with ADHD.

Pharmacoeconomics

- *Cost effectiveness literature review:* Given the lack of evidence regarding the cost-effectiveness of treatments for ADHD in adults, a literature review was conducted to outline the societal impact of adult ADHD on employment and criminality. Findings from these studies, albeit of poor quality, indicate an association between adult ADHD and increased unemployment and poorer work performance. In addition, pharmacological treatment of ADHD symptoms is associated with improved work performance and reduced likelihood of criminal behavior. Overall, based on the findings from both our systematic review and our literature review, we have determined that little is known about the economic impact of adult ADHD. There is a clear need for more research in this area to address questions of cost-effectiveness and economic burden on the health care system.
- *Budget impact analysis:* In Ontario in 2014 for the provincially funded drug program, there were 17,482 adult users (≥18 years) and 13,529 users under 18 years of age of stimulants/non-stimulants. Spending on adult ADHD medications was \$14.6 million in 2014 and is projected to increase to \$23.2 million by 2017.
 - Listing atomoxetine as Limited Use with no change in current listing status of stimulants (i.e., remain as General Benefit listing) would increase accessibility for this medication (e.g., for patients who have failed stimulant therapy or for those considered at risk for abuse). Based on opinion from clinical experts, we have estimated that the utilization would increase approximately 12 fold (from 150 patients per year to 1800) with a resultant decrease in use of stimulants. The budget impact of this reimbursement option would result in a decrease in expenditures of approximately \$1 million (↓5%). In the BIA, it is assumed that atomoxetine would be used as monotherapy; however, our analysis indicates that approximately 30% of Ontario's provincially-funded atomoxetine users may concurrently use stimulants. Note: Even though there are numerous generic

companies that manufacture atomoxetine, the 25% generic pricing rule (i.e., cost of generic product is 25% of brand-name cost) cannot be enforced under the Exceptional Access Program (EAP). This budget impact analysis assumes that generic pricing rules for atomoxetine (i.e., 25% of brand name) would apply.

- Although the pharmacoeconomics 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 of short-acting products compared to long-acting medications.

Stakeholder Review

Findings from the stakeholder review contributed to selection of final policy recommendations, and include feedback solicited from an open call for review, comments received during a workshop for stakeholders, as well as results from the ODPRN Citizen's Panel.

Findings from the ODPRN Citizens' Panel

Citizens' Panel (CP) members considered each of the policy options on factors related to acceptability, accessibility and affordability, and ranked options from most to least preferable from a societal viewpoint.

Overall, panel members found draft policy option two to be the most acceptable, which was followed by draft policy option three and one (Exhibit 8).

- Panelists' ranked policy option two as most acceptable because they believed it increased access to individuals who require a non-stimulant medication and the cost could be lowered through generic pricing. There was some debate whether atomoxetine should be listed as general benefit as opposed to limited use. However, many agreed that there should still be some oversight in prescribing because of the limited research available for the broader population.
- Draft policy option three received mixed reviews with some feeling the age restriction should not be removed until more research in older age groups is conducted whereas other felt the restriction should be lifted due to the growing adult population in need of these drugs.
- The panel was in unanimous agreement that the listing should not remain as status quo (the draft policy option 1). One person elaborated:

"Burdensome process for any patients who require atomoxetine. Limits access to non-stimulant option, and does not address the economic benefit that can be obtained from adding this drug to the formulary."

Panel members were in favour of both recommendations for consideration. However, the group had questions as to how these recommendations would be enforced and monitored.

Exhibit 8: Overall post-meeting option ranking

	Mean Ranking (1 = Most Acceptable 3 = Least Acceptable)
	Post-meeting
Option 1: All stimulant products on General Benefit and atomoxetine on EAP (status quo).	2.9 (0.4)
Option 2: List atomoxetine as Limited Use (for adults).	1.1 (0.4)
Option 3: No age restriction should be applied to stimulants or atomoxetine.	2 (0.6)

Final Policy Recommendations

1. No age restriction should be applied to stimulants or atomoxetine.
 - There is no evidence to suggest that age affects response to ADHD treatment in adult patients.
 - In our review, of the 64 trials that reported the mean age of participants, there were only 4 trials that specifically evaluated treatment in younger adults (mean age <30 years). As well, the mean age across all of the studies included in the systematic review was between 30 and 40 years.
 - In our analysis, the majority of users of provincially-funded ADHD medications were between the ages of 36-64 years; only 26% were between 18-25 years of age.
2. List atomoxetine as Limited Use (for adults).
 - Our findings suggest that atomoxetine is more efficacious than placebo and at least as efficacious as other pharmacotherapies for the outcomes studied, except for executive function. In fact, no significant difference was noted in executive function between any of the pharmacotherapies and placebo or among the pharmacotherapies.
 - Currently, atomoxetine is covered under EAP. Even though there are numerous generic companies that manufacture atomoxetine, the 25% generic pricing rule (i.e., cost of generic product is 25% of brand-name cost) cannot be enforced because it is not listed on the formulary. However, if atomoxetine is listed as Limited Use on the formulary, the cost of atomoxetine would significantly decrease, while increasing access.
 - Listing atomoxetine as Limited Use would increase accessibility for this medication (e.g., for patients who have failed stimulant therapy or for those considered at risk for abuse). Based on opinion from clinical experts, we have

estimated that the utilization would increase approximately 12 fold (from 150 patients per year to 1800). The budget impact of this reimbursement option is a decrease in expenditures of approximately \$1 million (↓5%).

- 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.⁴⁵ 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.
 - 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.
3. Cardiovascular safety of stimulants and atomoxetine should continue to be monitored, especially with the potential increased use of stimulants and atomoxetine in older patients with concomitant medical conditions.
 - Long-term stimulant treatment is associated with increases in blood pressure and heart rate. There is little data on the long-term safety of stimulants in older adults with concomitant medical conditions.
 - Although our results did not identify an association between stimulant use and increased risk of serious cardiovascular events in adults, the majority of patients included in the studied were less than 49 years of age.
 4. Health care practitioners should remain vigilant about the potential for misuse/abuse/diversion of stimulant medications.
 - Although our report did not show any evidence of misuse/abuse/diversion with stimulant medications in Canada, a review of the published literature indicates that misuse/abuse/diversion of prescription stimulants occurs and should be considered by clinicians who are considering prescribing these medications.
 - Strategies and programs to prevent diversion could potentially reduce overall misuse of these medications.
 5. No changes to the listing status of the available stimulants are recommended.
 - All stimulants commercially available in Canada are available as General Benefit in Ontario for all ages.
 - Based on the efficacy and safety data, no changes to the listing status are recommended.

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Appendix A: Health Equity Considerations for ADHD Medications (in adults)

Populations Identify which populations may experience significant unintended health impacts (positive or negative) as a result of the planned policy, program or initiative.	Proposed ADHD medication recommendations
Aboriginal peoples (e.g., First Nations, Inuit, Métis, etc.)	No accessibility issues identified. Coverage of medications, including ADHD medications, for Aboriginal peoples is available through Ontario Ministry of Health and Long-term Care.
Age-related groups (e.g., children, youth, seniors, etc.)	Elderly: No restrictions for ADHD medications were identified.
Disability (e.g., physical, D/deaf, deafened or hard of hearing, visual, intellectual/developmental, learning, mental illness, addictions/substance use, etc.)	No accessibility issues identified. Patients with disability and receiving Ontario Disability Support Program Income Support, receive prescription drug coverage through ODB.
Ethno-racial communities (e.g., racial/racialized or cultural minorities, immigrants and refugees, etc.)	No accessibility issues identified.
Francophone (including new immigrant francophones, deaf communities using LSQ/LSF, etc.)	No accessibility issued identified.
Homeless (including marginally or under-housed, etc.)	Not eligible for ODB coverage.
Linguistic communities (e.g., uncomfortable using English or French, literacy affects communication, etc.).	No accessibility issues identified.
Low income (e.g., unemployed, underemployed, etc.)	No accessibility issues identified; low income individuals who receive public drug coverage will have access to ADHD medications through ODB.
Religious/faith communities	No accessibility issues identified.
Rural/remote or inner-urban populations (e.g., geographic or social isolation, under-served areas, etc.)	No accessibility issues identified.
Sex/gender (e.g., male, female, women, men, trans, transsexual, transgendered, two-spirited, etc.)	No accessibility issues identified for sex/gender in the review.

Populations Identify which populations may experience significant unintended health impacts (positive or negative) as a result of the planned policy, program or initiative.	Proposed ADHD medication recommendations
Sexual orientation , (e.g., lesbian, gay, bisexual, etc.)	No accessibility issues identified.
Other: please describe the population here.	None identified.

(based on Health Equity Impact Assessment <http://www.health.gov.on.ca/en/pro/programs/hea/>)

Appendix B: Assessment of Criteria for Coverage and Therapeutic Notes

Criteria	Pros	Cons
Atomoxetine as Limited Use		
Adult patients diagnosed with ADHD according to DSM-V criteria	This review only evaluated the efficacy and safety of atomoxetine in the adult population. Diagnostic and Statistical Manual of Mental Disorders, 5 th edition (DSMV) criteria is used for classification and diagnosis of ADHD.	None
Prescribed by or in consultation with a practitioner with expertise in treatment of adults with ADHD	Adult ADHD patients are often treated by a general practitioner who specializes in treatment of adults with ADHD or a psychiatrist.	None
Has tried a stimulant medication and has experienced unsatisfactory results due to poor symptom control or side effects	Stimulants are recommended as first-line therapy and atomoxetine as second-line therapy by various guidelines including CADDRA ²¹ .	Our network meta-analysis showed that atomoxetine may be as effective as stimulants for some of the outcomes investigated; this suggests that atomoxetine may be considered first-line therapy for some patients.
Patient or member of patient's family has a history of substance abuse, or patient has a history of abuse/diversion of listed stimulants, or is at risk of abuse/diversion of listed stimulants	Atomoxetine has low abuse potential based on neurochemical, preclinical and early clinical studies, as well as analysis of post-marketing events. ⁴⁶	There are limited studies (including survey-based studies) assessing the abuse/misuse potential of atomoxetine. ⁴¹
NOTE: Combination therapy with atomoxetine plus stimulants is not supported by clinical evidence for efficacy or safety.	There is no evidence supporting the use of combination therapy (atomoxetine + stimulants) in the adult population.	There may be patients for whom combination therapy may be beneficial in exceptional circumstances such as patients who are unable to tolerate maximum doses of individual drugs, or patients who require dual therapy during times of transition from atomoxetine to stimulants, or vice versa.
Therapeutic Notes for long-acting stimulants		

Criteria	Pros	Cons
Patient diagnosed with ADHD according to DSM-V criteria	Diagnostic and Statistical Manual of Mental Disorders, 5 th edition (DSM-V) criteria is used for classification and diagnosis of ADHD.	None
Prescribed by or in consultation with a practitioner with expertise in treatment of adults with ADHD	Adult ADHD patients are often treated by a general practitioner who specializes in treatment of adults with ADHD or a psychiatrist.	None
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	Long-acting and short-acting stimulants have similar efficacy and safety profiles. However, short-acting stimulants (methylphenidate, dextroamphetamine) are less expensive than brand-name long-acting preparations.	CADDRA recommends long-acting stimulants as first-line therapy. Although there is limited evidence, long-acting stimulants appear to have a lower risk of abuse/diversion ⁴⁷ and may have a better adherence profile.
Requires 12-hour continuous coverage (e.g., extended work/school hours, driving, parenting)	Long-acting medications require less frequent dosing, which may improve patient adherence with treatment regimens. ⁴⁰	Some adults prefer short-acting preparations to accommodate work or academic schedules.
Patient or member of patient's family has a history of substance abuse or diversion of immediate-release stimulants or patient is at risk of substance abuse or diversion of immediate-release stimulants	Short-acting stimulant medications are more likely to be abused compared to long-acting formulations, due to more rapid rate of absorption and delivery to the brain. As well the coating of some long-acting preparations may make the active stimulant more difficult to extract and less likely to produce euphoria.	None

Appendix C: Clinical Criteria and Therapeutic Notes (proposed)

Atomoxetine (Limited Use criteria for adults)

1. Adult patients diagnosed with ADHD according to DSM-V criteria
AND
2. Prescribed by or in consultation with a practitioner with expertise in treatment of adults with ADHD
AND
- 3a. Has tried a stimulant medication with unsatisfactory results due to poor symptom control (lack of efficacy) or side effects
OR
- 3b. Patient or member of patient's family has a history of substance abuse, or patient has a history of abuse/diversion of listed stimulants, or is at risk of abuse/diversion of listed stimulants

NOTE: *Combination therapy with atomoxetine plus stimulants is not supported by clinical evidence for efficacy or safety.*

Therapeutic Notes for Long-acting Preparations (for adults)

For adults (>18 years of age):

1. Patient diagnosed with ADHD according to DSM-V criteria;
AND
2. Prescribed by or in consultation with a practitioner with expertise in treatment of adults with ADHD
AND
3. Requires 12-hour continuous coverage (e.g., extended work/school hours, driving, parenting)
OR
4. Patient or member of patient's family has a history of substance abuse or diversion of immediate-release stimulants, OR patient is at risk of substance abuse or diversion of immediate-release stimulants