Medications for Attention Deficit Hyperactivity Disorder (ADHD): Focus on Drug Information

B.C. Provincial Academic Detailing (PAD) Service **January 2024 *updated***

Participants in this PAD session will have the opportunity to:

1. Discuss how the efficacy of medications for ADHD is measured in clinical trials.
2. Review clinical considerations which support treatment decisions, including: basic pharmacology, onset of effect, adverse events, dosing, cost and drug interactions.
3. Consider the clinical relevance of pharmacokinetic differences between available methylphenidate and amphetamine formulations.

This education session will focus on ADHD drug information relevant to people aged 6 years and older. The diagnosis of ADHD (including over-diagnosis, under-diagnosis) and the management of stimulant use disorder are beyond the scope of this session.

Brand Name	Generic Name
Ritalin®	methylphenidate immediate release
Ritalin SR® Concerta®	methylphenidate extended release
Biphentin® Foquest®	methylphenidate controlled release
Dexedrine®	dextroamphetamine immediate release
Dexedrine Spansule®	dextroamphetamine sustained release
Adderall XR®	amphetamine mixed salts extended release
Vyvanse®	lisdexamfetamine
Strattera®	atomoxetine
Intuniv XR®	guanfacine extended release

ADHD Medications: Basic pharmacology & clinical considerations

	Basic pharmacology	Clinical considerations				
methylphenidate Ritalin, Concerta, Biphentin, Foquest **amphetamines** Dexedrine, Adderall XR, Vyvanse	sympathomimetics: inhibit norepinephrine reuptake & inhibit dopamine reuptake or increase dopamine release	↑ blood pressure ↑ heart rate	insomnia	psychosis mania anxiety	↓ appetite ↓ growth	non-medical use dependence
atomoxetine Strattera	sympathomimetic: inhibits norepinephrine reuptake first developed as an antidepressant but marketing shifted to ADHD	↑ blood pressure ↑ heart rate	pediatrics: somnolence >> insomnia adults: insomnia >> somnolence	suicidal ideation psychosis mania	↓ appetite ↓ growth	urinary retention sexual dysfunction CYP2D6: drug interactions genetic metabolic variability
guanfacine Intuniv XR	alpha$_{2A}$-adrenergic receptor agonist also approved as an antihypertensive in other countries	↓ blood pressure ↓ heart rate	somnolence sedation	irritability affective lability nightmares	upon discontinuation: ↑ blood pressure ↑ heart rate	CYP3A4: drug interactions

sympathomimetics: mimic or stimulate the sympathetic nervous system (e.g., increase peripheral vascular resistance, blood pressure, heart rate); epinephrine is considered prototypical
alpha$_{2A}$-adrenergic receptor agonist: opposes sympathetic nervous system activity (e.g., decreases peripheral vascular resistance, blood pressure, heart rate); similar to clonidine
non-medical use: use of a prescription stimulant without a prescription or in a way other than prescribed

ADHD Medications: Evidence for practice

Pre-specify treatment goals. It is reasonable to assess within 12 weeks (or earlier).

- Most ADHD medication clinical trials are ≤ 12 weeks in length and are designed to measure a statistical change in core ADHD symptoms (inattention, hyperactivity, impulsivity).[1-4]
- Measured in this way, methylphenidate and amphetamines have an onset of effect within hours, atomoxetine within 1-4 weeks and guanfacine within 1-2 weeks.[2-4]
- Guidelines and narrative reviews often report on a selection of observational studies indicating potential longer-term benefits but the literature is lacking a comprehensive and systematic overview of these studies.[5]

Adverse events can be anticipated from similarities and differences in basic pharmacology.

- Methylphenidate, amphetamines and atomoxetine stimulate the sympathetic nervous system leading to shared adverse events: increase in heart rate and blood pressure, insomnia and appetite suppression.[2-4]
- Guanfacine has an opposing effect on the sympathetic nervous system leading to: reductions in heart rate and blood pressure, syncope and somnolence.[2-4]
- Non-medical use and dependence is attributed to methylphenidate and amphetamines, which inhibit dopamine reuptake or increase dopamine release.[2,4]

Consider patient and caregiver preferences, onset and duration of medication effect, and cost when choosing a formulation.

- Pharmacokinetics (time to maximum concentration, duration of effect) are estimated from small sample sizes and can show substantial variability between patients.[2,6]
- Systematic reviews do not firmly identify differences in efficacy or common and serious adverse events between the various formulations of methylphenidate and amphetamines but few direct comparisons exist.[1,7,8]

[1]CORTESE CIPRIANI Lancet Psychiatry 2018:5:727-38; [2]Health Canada Drug Product Database; [3]Health Canada Drug Health Product Register; [4]US FDA Approved Drugs; [5]WONG Lancet Psychiatry 2019:6:528-37; [6]COGHILL BMC Psychiatry 2013:13:237; [7]Cochrane Database Systematic Reviews CD007813, CD009996, CD012857, CD013011; [8]CATALA-LOPEZ PLoS One 2017:e0180355

ADHD Medications: Translating efficacy from clinical trials

Factors to consider when translating efficacy from ADHD medication clinical trials to clinical practice:[1-6]

- The objective of drug-approval trials submitted to Health Canada & the US Food and Drug Administration (FDA) is to show a statistically-significant reduction in core ADHD symptoms versus placebo (inattention, hyperactivity, impulsivity).
- Most trials are short-term (i.e., ≤ 12 weeks); there is insufficient data to assess outcomes at 26 & 52 weeks.
- The symptom scales used in these trials can vary; this makes meta-analyses difficult to translate clinically (e.g., the statistical difference is reported but not the absolute benefit).
- There is no consensus definition for a clinically-important difference or of 'responder' which could inform the calculation of a number-needed-to-treat (NNT).
- In a 2018 network meta-analysis with 101 comparisons (drug versus placebo & drug versus drug), the certainty of evidence was assessed as high quality for one comparison, moderate for 12, low for 38, and very low for 50.

Systematic Review & Network Meta-Analysis (Lancet Psychiatry 2018)[6,7]

133 trials; 14,346 children & adolescent participants; 10,296 adult participants

Outcomes: efficacy & acceptability at 12 weeks	Medications* statistically-significantly better than placebo			
	Children & Adolescents		Adults	
ADHD core symptoms: reduction in symptoms rated by clinicians	methylphenidate amphetamines atomoxetine guanfacine		methylphenidate amphetamines atomoxetine	
Acceptability: discontinuation for any reason, encompasses efficacy & tolerability	methylphenidate		amphetamines	
Clinician impression of improvement: proportion of participants much or very much improved from baseline**	placebo: 25%	methylphenidate: 65% amphetamines: 72% atomoxetine: 43% guanfacine: 55%	placebo: 25%	methylphenidate: 51% amphetamines: 62%

* Medications approved by Health Canada for ADHD

**Clinical Global Impression-Improvement (CGI-I) 7-point scale: very much improved, much improved, minimally improved, no change, minimally worse, much worse or very much worse relative to baseline state; does not indicate the degree of participants' clinical severity at the end of the trial; proportion of participants 'much or very much improved' was estimated by converting the reported odds ratio to a risk ratio which was then applied to the placebo response rate (25%)

[1]Health Canada Drug Product Database; [2]Health Canada Drug Health Product Register; [3]US FDA Approved Drugs; [4]WONG Lancet Psychiatry 2019:6:528-37; [5]Cochrane Database Systematic Reviews CD007813, CD009885, CD009996, CD012857, CD013011; [6]CORTESE CIPRIANI Lancet Psychiatry 2018:5:727-38 & 871-73; [7]FARAONE CORTESE Molecular Psychiatry 2022:27:212-19

ADHD Medications: Comparing formulations

- The US Food and Drug Administration (FDA) indicates that for methylphenidate and amphetamines, drug blood concentration relates to efficacy and adverse events; modification to a drug's pharmacokinetics may impact the onset and duration of these effects.[1]
- There are differences in the pharmacokinetics between formulations but they are measured in small sample sizes and can show substantial variability between patients, making comparisons between formulations difficult.[2] *This table provides our best estimates.*
- Formulations that combine immediate and sustained-release features (e.g., extended/delayed/controlled release) are principally designed to minimize the need for a dose at school or work.[2,3,4]

Formulation		Tmax1	Tmax2	Duration of effect
Methylphenidate	**Drug release features**			
Ritalin tablets[2,3]	immediate release (IR) only	2 hours	not expected	not reported (drug half-life 2-3 hours)
Ritalin SR tablets[2,3]	sustained release (SR) only	4 hours	not expected	8 hours
Concerta tablets[2,3]	biphasic: 22% IR, 78% SR	1 hour	6-10 hours	12 hours
Biphentin capsules[2,4,5]	biphasic: 40% IR, 60% SR	1-3 hours	6-7 hours	12 hours
Foquest capsules[2]	biphasic: 20% IR, 80% SR	1-2.5 hours	8.5-16 hours	16 hours
Amphetamines				
Dexedrine tablets[2,6,7]	immediate release (IR) only	3 hours	not expected	not reported (drug half-life 8-12 hours)
Dexedrine Spansule capsules[2,6,8]	biphasic: 40% IR, 60% SR	8 hours	not reported	10-12 hours
Adderall XR capsules[2,3]	biphasic: 50% IR, 50% SR	5-8 hours		12 hours
Vyvanse capsules[2,6]	prodrug of dextroamphetamine	3.5-4.5 hours	not expected	12-14 hours

Principal source of information: regulatory reviews and prescribing information from Health Canada and the US FDA
Tmax1: time to first maximum concentration (peak); **Tmax2:** time to second maximum concentration (peak); **duration of effect:** time period for which a change in ADHD symptoms was statistically different from placebo; **prodrug:** Vyvanse (lisdexamfetamine) is the parent drug which is converted to dextroamphetamine *in vivo*

[1]US FDA 2019 Attention Deficit Hyperactivity Disorder Guidance; [2]Health Canada Drug Product Database; [3]US FDA Clinical Pharmacology Biopharmaceutics Reviews; [4]COGHILL BMC Psychiatry 2013:13:237; [5]CORTESE CNS Drugs 2017:31:149-60; [6]US FDA Approved Drugs; [7]DOLDER Front Pharmacol 2017:8:617; [8]Paladin Correspondence

ADHD Medications: Comparing cost

Formulation	Generic: cost/30 days[1]	Brand: cost/30 days[1]	BC PharmaCare Coverage[2]
Methylphenidate			
Ritalin, Ritalin SR	$10 - $70		Regular Benefit
Concerta*	$35 - $90	$100 - $255	Limited Coverage
Biphentin		$35 - $185	Non-Benefit
Foquest		$95 - $165	Non-Benefit
Amphetamines			
Dexedrine*	$10 - $135	$15 - $205	Regular Benefit
Dexedrine Spansule*	$30 - $115	$40 - $150	Regular Benefit
Adderall XR†	$20 - $30	$75 - $125	Limited Coverage
Vyvanse**		$70 - $160	Limited Coverage
Atomoxetine			
Strattera	$20 - $45		Limited Coverage
Guanfacine			
Intuniv XR	$85 - $260	$100 - $310	Non-Benefit

Cost per 30 days: does not include mark-up or professional fee; provided as a range which includes approximate cost for initial to maximum doses
* Concerta and Dexedrine brand formulations reimbursed up to the cost of generic formulations
** Vyvanse capsules are Limited Coverage, chewable tablets are a Non-Benefit
† Adderall XR brand formulation is a Non-Benefit

[1]Calculated from McKesson Canada January 18, 2024; [2]BC PharmaCare Formulary

ADHD Medications: BC PharmaCare coverage

Regular Benefit Drug
minimum 1 week trial at adequate dose

methylphenidate
immediate or sustained release
Ritalin IR generics§, Ritalin SR generics§

dextroamphetamine
immediate or sustained release
Dexedrine*, Dexedrine Spansules*, generics

If unsatisfactory trial or intolerance to EITHER class above and patient requires 12 hours of continuous medication coverage, can apply for Special Authority for a long-acting stimulant

methylphenidate
extended release
Concerta*, generics

amphetamine mixed salts
extended release
Adderall XR generics†

lisdexamfetamine
Vyvanse**

Unsatisfactory trial or intolerance defined as no demonstrated effectiveness for symptoms of ADHD or functional impairment secondary to ADHD after a minimum 1 week trial at adequate dose(s)

If unsatisfactory trial or intolerance to BOTH a methylphenidate AND an amphetamine above (at least one extended release or long acting), can apply for Special Authority for atomoxetine

→ **atomoxetine**
Strattera generics

§Ritalin brand name no longer marketed in Canada
*Concerta and Dexedrine brand formulations reimbursed up to the cost of generic formulations
**Vyvanse capsules are Limited Coverage, chewable tablets are a Non-Benefit
†Adderall XR brand formulation is a Non-Benefit

Methylphenidate, Amphetamines: Clinical considerations

Select adverse events - not intended to reproduce a product monograph; see separate reference list

Cardiovascular 1-27	▪ Medical history: recommended to assess for cardiovascular symptoms & family history before treatment with ADHD medications ▪ ECG: not recommended if no specific indication from personal or family history or physical exam (Canadian Paediatric, Cardiovascular, Psychiatry joint position statement & Canadian ADHD Guideline) ▪ Health Canada contraindications: symptomatic cardiovascular disorders, moderate to severe hypertension ▪ caution where increases in heart rate & blood pressure may compromise cardiovascular status ▪ rare serious cardiovascular events have been reported during ADHD medication use ▪ large cohort studies have not confirmed increased cardiovascular risk in general pediatric or adult populations ▪ Blood pressure & heart rate: monitor after each dose change & every 6 months (UK NICE) ▪ mean increases: BP 2-4 mmHg, HR 3-6 bpm ▪ Congenital Long QT: avoid use → CredibleMeds® ▪ Peripheral vasculopathy including Raynaud's disease: reduce dose or discontinue ▪ Priapism (children, adolescents, adults): rare cases associated with methylphenidate, atomoxetine ▪ case reports with amphetamines when in combination with other priapism-causing medications ▪ seek medical attention if painful or long lasting
Neuropsychiatric 2,4-19,28-34	▪ Insomnia: reported by up to 25% of trial participants ▪ review non-pharmacologic strategies, reduce dose, change formulation or timing ▪ Agitation-type adverse events: if agitation, psychosis, mania, aggressive behaviour emerge or are accompanied by suicidal thoughts, consider possible causal role of medication (Health Canada) ▪ Anxiety, depression: address most impairing disorder first (Canadian ADHD Guideline) ▪ Bipolar: ensure mood stabilized prior to initiating ADHD medication ▪ increase vigilance for manic episodes (Canadian ADHD Guideline) ▪ Tics (motor, verbal): may be improved or exacerbated ▪ meta-analyses do not show an increase in new onset or worsening of tic disorders in most patients ▪ monitor at each visit & after dose changes (Health Canada)
Appetite, Growth 3-19,35-41	▪ Appetite (decrease or loss): dose related ▪ reported by up to 1/3 of trial participants ▪ strategies: take medication with or after meals, time meals or snacks for when stimulant effects are reduced ▪ review for possible dose reduction ▪ Height (pediatrics): suppression by 1-4 cm with early childhood medication exposure or persistent use through adolescence, dependent on cumulative drug exposure ▪ limiting lifetime exposure associated with greater adult height ▪ Monitoring (pediatrics): measure weight every 3 months, measure height every 6 months (UK NICE Guideline) ▪ Planned medication breaks: consider if height or weight concerns ▪ optimal duration of break unknown
Non-Medical Use 5-19,42-44	▪ All formulations have Health Canada & US FDA warnings for the potential for non-medical use (NMU) & dependence ▪ Available evidence does not associate pediatric medical use of methylphenidate or amphetamines for ADHD with later development of substance use disorders ▪ evidence does not consistently suggest a protective effect ▪ Data on NMU is limited to self reports, surveys & emergency centre reporting, with highly variable estimates & definitions ▪ oral is the most frequently self-reported NMU route by post-secondary students ▪ other routes are associated with increased risk of serious adverse outcomes ▪ British Columbia Centre on Substance Use provides a 2022 Practice Update for the management of Illicit Stimulant Use Disorder

Atomoxetine (Strattera): Clinical considerations

Select adverse events - not intended to reproduce a product monograph; see separate reference list

Cardiovascular [1-11]	▪ Medical history: recommended to assess for cardiovascular symptoms & family history before treatment with ADHD medications ▪ ECG: not recommended if no specific indication from personal or family history or physical exam (Canadian ADHD & American Academy of Paediatrics Guidelines) ▪ Health Canada contraindications: symptomatic cardiovascular disorders, moderate to severe hypertension, conditions where heart rate & blood pressure increases may compromise cardiovascular status ▪ rare serious cardiovascular events have been reported during ADHD medication use ▪ large cohort studies have not confirmed increased cardiovascular risk in general pediatric or adult populations ▪ Blood pressure & heart rate: monitor after each dose change & every 6 months (UK NICE Guideline) ▪ 5-10% of participants experienced increases in HR (≥ 20 bpm) or BP (≥ 15-20 mmHg) in ADHD trials (all ages) ▪ orthostatic hypotension, syncope ▪ QTc prolongation: Congenital Long QT: avoid use → CredibleMeds® ▪ caution with CYP2D6 inhibitors, genetic phenotype poor metabolizers ▪ Peripheral vasculopathy including Raynaud's disease: reduce dose or discontinue
Neuropsychiatric [2,5,6]	▪ Pediatric trials: somnolence (~10% of trial participants), more common than insomnia ▪ lower incidence of somnolence & fatigue with dose divided twice daily (but ↑ cost) compared to once a day dosing ▪ rapid dose escalations associated with increased rates of somnolence ▪ Adult trials: insomnia (~15% of trial participants), more common than somnolence ▪ Agitation-type adverse events: suicidal ideation reported in pediatric trials, post-marketing reports in all ages ▪ monitor for emergence & behaviour changes (e.g., agitation, aggression, anxiety, panic attacks, hostility, mania, psychosis) on initiation & dose changes (Health Canada) ▪ Bipolar: ensure mood stabilized prior to initiating ADHD medication & increase vigilance for manic episodes (Canadian ADHD Guideline)
Appetite, Growth [3,5,6,12]	▪ Appetite (decrease or loss): reported by 10-25% trial participants ▪ children, adolescent trials: lower incidence of decreased appetite & nausea with twice daily (but ↑ cost) compared to once a day dosing ▪ rapid dose escalations associated with increased rates of digestive complaints ▪ Growth: associated with a lag in height & weight over initial 9-12 months of treatment, normalizing at 3 years on average ▪ Monitoring (pediatrics): measure weight every 3 months, measure height every 6 months (UK NICE Guideline) ▪ Planned medication breaks or dose reduction: consider if height or weight concerns ▪ optimal duration of break unknown
Genitourinary [5,6,14-16]	▪ Priapism (children, adolescents, adults): rare cases associated with methylphenidate, atomoxetine ▪ case reports with amphetamines when combined with other priapism-causing medications ▪ seek medical attention if painful or long lasting ▪ Sexual dysfunction (female & male): decreased libido, abnormal orgasm, erectile dysfunction, impotence, dysmenorrhea ▪ Urinary hesitancy, retention, dysuria: up to 8% in adult trials, post-marketing reports in children
CYP2D6 metabolic variability [2,5,6,13]	▪ CYP2D6 inhibitor medications (see drug interaction table on page 11) & genetic phenotype poor metabolizers (populations affected: White 7%, Black 2%, Asian <1%): up to 5 fold higher peak concentration & 10 fold higher exposure to atomoxetine ▪ Pharmacogenetic testing: routine testing not recommended (Canadian ADHD Guideline) ▪ Use lowest effective dose, titrate slowly, only increase dose if ADHD symptoms are not improved & if previous dose well tolerated

Guanfacine (Intuniv XR): Clinical considerations

Select adverse events - not intended to reproduce a product monograph; see separate reference list

Cardiovascular [1-6]	▪ Medical history: recommended to assess for cardiovascular symptoms & family history before treatment with ADHD medications ▪ ECG: not recommended if no specific indication from personal or family history or physical exam (Canadian ADHD & American Academy of Pediatrics Guidelines) ▪ Caution: history of hypotension, syncope, heart block, bradycardia ▪ avoid dehydration ▪ Blood pressure & heart rate: reductions are dose related ▪ mean decreases: BP 3-8 mmHg, HR 3-9 bpm ▪ orthostatic hypotension or syncope ▪ Monitor blood pressure & heart rate: at baseline, after dose increases or decreases, every 6 months, during taper & after discontinuation (Health Canada) ▪ QTc prolongation: mean increase from baseline of approximately 5 msec ▪ consider if known history of QT prolongation, risk factors for Torsades de Pointes or on concomitant QT prolonging or heart rate lowering medications (Health Canada)
Tapering [2-4]	▪ Rebound hypertension, increased heart rate: possible if guanfacine stopped without tapering or if multiple doses missed (for example, during acute gastrointestinal illness) ▪ Caution: when prescribing other medications that can elevate blood pressure & heart rate immediately following guanfacine discontinuation, including methylphenidate, amphetamines, atomoxetine ▪ Taper: total daily dose by no more than 1 mg every 3 to 7 days & monitor blood pressure & heart rate during taper ▪ Missed doses: if multiple doses are missed (2 or more consecutive), re-titration based on tolerability recommended ▪ Planned medication breaks: require tapering
Somnolence, Sedation [3,4,6,7]	▪ Occurs in up to 54% of participants in monotherapy studies & 18% of participants when combined with a stimulant ▪ Common reason for drug discontinuation ▪ Dose related: more pronounced early in treatment & as dose increases (28% of participants on 2 mg to 51% on 4 mg) ▪ Morning & evening dosing resulted in similar incidence of somnolence ▪ drug elimination half-life is 18 hours
Neuropsychiatric [3]	▪ Most common psychiatric adverse effects in trials: irritability, affective lability, nightmares ▪ Agitation-type adverse events: if agitation, psychosis, mania, aggressive behaviour emerge or are accompanied by suicidal thoughts, consider possible causal role of medication (Health Canada)

ADHD Medications: Drug interaction overview

Not intended as an exhaustive drug interaction list; for complete information, consult a drug interaction resource.

Avoid | Caution / Monitor | Dose modification recommended

Pharmacokinetic interactions	methylphenidate	amphetamines	atomoxetine	guanfacine
Cytochrome 3A4 inhibitors (e.g., clarithromycin, ketoconazole, ritonavir)	-	-	-	begin with a 50% dose reduction of guanfacine
Cytochrome 3A4 inducers (e.g., carbamazepine, phenytoin)	-	-	-	a dose increase of guanfacine may be needed
Cytochrome 2D6 inhibitors (e.g., bupropion, fluoxetine, paroxetine, mirabegron) or Cytochrome 2D6 poor metabolizers (genetic phenotype)	-	low amphetamine doses to start; slow dose titration	slow atomoxetine dose titration	-
Alkalinizing agents (e.g., sodium bicarbonate, acetazolamide)	-	monitor for: increased amphetamine effect	-	-
Valproic acid and derivatives	-	-	-	monitor for: valproic acid toxicity
Pharmacodynamic interactions				
MAOIs (e.g., linezolid, selegiline, moclobemide)	contraindicated within 14 days			-
Serotonergic drugs (e.g., SSRIs, serotonergic antidepressants)	monitor for: serotonin toxicity		-	-
Antihypertensives	caution: opposing effects on blood pressure and heart rate			caution: hypotension
Heart rate lowering drugs (e.g., beta blockers, clonidine, diltiazem, verapamil)				avoid: bradycardia
Sympathomimetics (e.g., pseudoephedrine, caffeine, cocaine, modafinil)	caution: synergistic increases in blood pressure and heart rate			-
Antipsychotics	monitor for: decreased stimulant effect, extrapyramidal symptoms		-	caution: potential additive sedation
CNS depressants (e.g., benzodiazepines, sedative hypnotics)	-	-	-	caution: potential additive sedation

Health Canada Drug Product Database; US FDA Approved Drugs; Lexicomp Interactions; Indiana University Cytochrome P450 Drug Interaction Table

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Pre-specify treatment goals. It is reasonable to assess within 12 weeks (or earlier).

Adverse events can be anticipated from similarities and differences in basic pharmacology.

Consider patient and caregiver preferences, onset and duration of medication effect, and cost when choosing a formulation.

Reference list is available upon request.

Materials are designed to be used in conjunction with an academic detailing session provided by a PAD pharmacist.
For more information, or to schedule an academic detailing session, please contact:

BC Provincial Academic Detailing Service
Email: PAD@gov.bc.ca Web: www.bcpad.ca

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