Pharmacotherapy for ADHD Management

ADHD pharmacotherapy should be considered for individuals with moderate to severe symptoms that significantly impair daily functioning and quality of life, particularly when non-pharmacological interventions, such as behavioural or psychological therapies are ineffective, insufficient or declined.

Medication is an integral part of a multimodal treatment approach and is especially appropriate in cases where symptoms persist despite other interventions or when the impact on academic, occupational or social functioning is substantial. Treatment should always be tailored to the individual's specific needs, carefully considering the risks, benefits and overall treatment goals.[3,4,11]

Stimulants (Methylphenidate- and Amphetamine-based medications)

Side Effects (most common):

CNS: headache, nervousness, irritability, anxiety, insomnia, dizziness, tics
GI: nausea, vomiting, diarrhea, loss of appetite, weight loss
CV: ↑ HR and BP at initiation, tachycardia, palpitations, hypertension
Anticholinergic: Dry mouth, blurred vision, diplopia, mydriasis

Contraindications:

- Untreated hyperthyroidism
- Advanced arteriosclerosis
- Symptomatic cardiovascular disease
- Moderate to severe hypertension
- Glaucoma
- Agitated states (e.g., history of mania or psychosis)
- Pheochromocytoma
- Use of MAOIs during treatment or ≤ 14 days after discontinuation
- Known hypersensitivity to sympathomimetic amines
- History of substance abuse/misuse (precaution)
- Tic disorders (precaution)

Interactions:

- MAOIs → Hypertensive crisis could occur
- Serotonergic drugs → Risk of serotonin syndrome
- Antihypertensives → May ↓ efficacy of antihypertensives
- Vasopressors → ↑ HR and BP
- Drugs affecting DA/NE pathways → ↑ Extrapyramidal symptom risk
- May reduce, delay or enhance the action of anticoagulants, anticonvulsants, and antidepressants
- Alcohol → Enhanced adverse effects
- Cannabis → Reduced efficacy of stimulants[26,27]
- Acidifying or alkalizing agents → ↓ or ↑ amphetamine blood levels respectively
- PPIs → ↓ absorption time of amphetamine (Tmax), except Vyvanse®

Warnings:

- Potential for abuse, misuse and dependence
- Cardiovascular risks, including sudden death, stroke, myocardial infarction, and hypertension
- Psychiatric risks, such as psychosis, aggression, anxiety, and mania
- Raynaud's phenomenon, monitor for signs of digit changes
- Risk of lowering the seizure threshold
- Risk of serotonin syndrome when used with serotonergic drugs
- Risk of priapism
- Potential for gastrointestinal obstruction in patients with pre-existing gastrointestinal narrowing (Concerta®)

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Medication	Features	Dosing (Adults)	Cost and coverage (1-month supply)
First-Line: *Long-acting psychostimulants are first-line treatments for ADHD due to their strong evidence base, favourable risk-benefit profile, and extended duration of effect, which enhance privacy, compliance, and symptom coverage. They reduce the need for multiple daily doses, lower risks of diversion and rebound, and are generally better tolerated than immediate-release formulations. While both methylphenidate and amphetamine-based medications have similar efficacy at the population level, individual responses may vary Thus, a trial of both classes of long-acting stimulants should be considered before second-line treatments.*[11]			
Amphetamine-based medications (ages ≥ 6 years) *Amphetamines act as substrates for dopamine and norepinephrine transporters, facilitating their release into the synaptic cleft. They also inhibit monoamine oxidase and reverse the DA and NE transporters, further increasing synaptic levels of dopamine and norepinephrine. This leads to enhanced neurotransmission and improves cognitive control.*			
Mixed salts amphetamine extended-release Adderall XR 5, 10, 15, 20, 25, 30mg ER capsules 3:1 dextroamphetamine to levoamphetamine	**Release Ratio (IR%/ER%):** 50/50 **Onset:** 0.5-1h **TmaxIR:** 5-8h Food can delay Tmax by 2.5h; no effect on extent of absorption) **TmaxER:** not reported **Duration of Action:** 12h **Delivery Mechanism:** Immediate and delayed-release beads allow for biphasic release. **Formulation:** Can be sprinkled onto applesauce and consumed immediately; do not crush or chew.	**Initial:** 5-10mg daily in the morning **Titration:** ↑ by 5-10mg at weekly intervals **Max:** 20-30mg Inadequate evidence of additional efficacy at doses > 20mg/day in adolescents and adults. **Administration:** With or without food (maintain consistency) **Renal**: Severe impairment: ↓ if eGFR < 30mL/min to max of 20mg/day with further reductions if on dialysis **Hepatic**: Impairment may alter elimination resulting in prolonged exposure.	**Brand:** $91-145 **Generic:** $31-43 **ODB:** ✓ **NIHB:** x
Lisdexamfetamine (Vyvanse®) 10, 20, 30, 40, 50, 60, 70mg capsules 10, 20, 30, 40, 50, 60mg chewable tablets Also indicated for binge-eating disorder (BED)	**Release Ratio (IR%/ER%):** N/A, prodrug **Onset:** 1-2h **Tmax:** 3.5-4.5h (with food: 4.5-5.5h) (Food can delay Tmax by 1h) **Duration of Action:** 13-14h **Delivery Mechanism:** Inactive when ingested and converted to dextroamphetamine in the body via enzymes in the small intestine and bloodstream that slowly cleave off the lysine amino acid, ensuring gradual release and tamper resistance. **Formulation:** Capsules can be opened and diluted in water, orange juice or yogurt and consumed immediately. Do not split chewable tablets; chew thoroughly before swallowing.	**Initial:** 20-30mg daily in the morning **Titration:** ↑ by 10-20mg/day at weekly intervals **Max:** 70mg **Administration:** With or without food (maintain consistency) **Switch:** Start with Vyvanse® 20 to 30mg **Renal**: Severe impairment: ↓ if eGFR < 30mL/min to max of 50mg/day ESRD: max of 30mg/day **Hepatic**: No studies have been conducted.	**Brand:** Cap: $88-205 Tab: $88-254 **Generic:** Cap: $51-168 Tab: $54-146 **ODB:** ✓ (except 70mg cap) **NIHB:** ✓ (except 70mg cap)

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Medication	Features	Dosing (Adults)	Cost and coverage (1-month supply)
Methylphenidate-Based Medications (ages ≥ 6 years unless noted otherwise) *Methylphenidate blocks the reuptake of dopamine and norepinephrine into the presynaptic neuron by inhibiting their respective transporters. This increases the extracellular concentration of these neurotransmitters in the prefrontal cortex, enhancing attention and reducing impulsivity. It has minimal direct effects on serotonin.*			
Methylphenidate controlled-release (Biphentin®) 10, 15, 20, 30, 40, 50, 60, 80mg CR capsules	**Release Ratio (IR%/ER%):** 40/60 **Onset**: 1h **Tmax$_{IR}$**: 1-3h **Tmax$_{ER}$**: 6-7h **Duration of Action**: 10-12h **Delivery Mechanism**: Multi-layer delivery system allows for a controlled biphasic release of methylphenidate from beads with an immediate-release layer followed by a controlled-release layer (mimics delivery of three separate IR doses). **Formulation**: Granules can be sprinkled onto applesauce or yogurt. Do not sprinkle into liquids or crush/chew.	**Initial:** 10-20mg daily in the morning **Titration:** ↑ by 10mg weekly **Max:** 80 mg **Administration:** With or without food **Switch:** The starting dose of Biphentin® should be the next lower available strength relative to the patient's total daily methylphenidate dose. **Renal**: No dose adjustment **Hepatic**: No studies have been conducted.	**Brand:** $45-208 **Generic:** $30-115 **ODB:** ✓ **NIHB:** ✓
Methylphenidate extended-release (Concerta®) 18, 27, 36, 54 mg ER tablets	**Release Ratio (IR%/ER%):** 22/78 **Onset:** 1h **TmaxIR:** 1h **TmaxER:** 6-10h **Duration of Action:** 12h **Delivery Mechanism:** Osmotic Controlled-Release Oral Delivery System (OROS®) The OROS® delivery system combines an immediate release of methylphenidate from its outer coating upon ingestion with a controlled, delayed release of the remaining through an osmotic pressure-driven mechanism leading to a biphasic release (mimics delivery of three separate IR doses). **Formulation:** Tablets should be swallowed whole.	**Initial:** 18mg daily in the morning **Titration:** ↑ by 18mg weekly **Max:** 72mg **Administration:** With or without food **Switch:** Previous daily total methylphenidate dose: 10-15mg IR or 20mg SR = 18mg Concerta® 20-30mg IR or 40mg SR = 36mg Concerta® 30-45mg IR or 60mg SR = 54mg Concerta® 40-60mg IR = 72mg Concerta ® **Renal**: No dose adjustment **Hepatic**: No studies have been conducted.	**Brand:** $119-185 **Generic:** $48-69 **ODB:** ✓ **NIHB:** ✓

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Medication	Features	Dosing (Adults)	Cost and coverage (1-month supply)
Methylphenidate-Based Medications (ages ≥ 6 years unless noted otherwise) *Methylphenidate blocks the reuptake of dopamine and norepinephrine into the presynaptic neuron by inhibiting their respective transporters. This increases the extracellular concentration of these neurotransmitters in the prefrontal cortex, enhancing attention and reducing impulsivity. It has minimal direct effects on serotonin.*			
Methylphenidate controlled-release (Foquest®) 25, 35, 45, 55, 70, 85, 100mg CR capsules	**Release Ratio (IR%/ER%):** 20/80 **Onset:** 1h **TmaxIR:** 1-2.5h **TmaxER:** 8.5-16h **Duration of Action:** 13-16h **Delivery Mechanism:** Multi-layer delivery system allows for a controlled biphasic release of methylphenidate from beads with an immediate-release layer followed by a controlled-release layer (mimics delivery of three separate IR doses). **Formulation:** Granules can be sprinkled onto applesauce or yogurt. Do not sprinkle into liquids or crush/chew.	**Initial:** 25mg daily in the morning **Titration:** ↑ by 10-15mg after at least 5-day intervals **Max: Adult =** 100mg **Administration:** With or without food **Switch:** Starting dose of Foquest® is the next lower strength based on the total methylphenidate daily dose. **Renal**: No dose adjustment **Hepatic**: No studies have been conducted.	**Brand:** $109-179 **Generic:** N/A **ODB:** ✓ **NIHB:** ✓
Methylphenidate extended-release (Quillivant® ER) 20, 30, 40mg ER chewable tablets Powder for oral suspension: 300, 500, 750, 900mg/bottle (5mg/mL oral suspension) **Indication: ages 6-12y** ER chew tablets and ER oral suspension ARE NOT INTERCHANGEABLE	**Release Ratio (IR%/ER%):** Chew: 30/70 Susp: 20/80 **Onset:** 0.75h – 1hr **TmaxTab:** 5h **TmaxSusp:** 5h (high-fat meal: 4h) **Duration of Action:** Chew = 8-12h Susp = 12h **Delivery Mechanism:** A biphasic release mechanism, where an immediate-release dose is delivered upon chewing (chewable tablet) or ingestion (suspension), followed by a controlled extended-release through a matrix (chewable) or coated particles (suspension) for sustained effect. **Formulation:** 20mg and 30mg tablets are scored and can be split; chew thoroughly before swallowing. Reconstituted suspension should be shaken for 10 seconds before withdrawing the dose for administration.	**Initial:** Chew/Susp: 20mg daily in the morning **Titration:** ↑ or ↓ by 10, 15, or 20mg at weekly intervals **Max:** 60mg **Administration:** With or without food **Renal**: No dose adjustment **Hepatic**: No studies have been conducted.	**Brand:** Tab: $107-215 Suspension: $83-431 **Generic:** N/A **ODB:** x **NIHB:** x

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Medication	Features	Dosing (Adults)	Cost and coverage (1-month supply)
Methylphenidate-Based Medications (ages ≥ 6 years unless noted otherwise) *Methylphenidate blocks the reuptake of dopamine and norepinephrine into the presynaptic neuron by inhibiting their respective transporters. This increases the extracellular concentration of these neurotransmitters in the prefrontal cortex, enhancing attention and reducing impulsivity. It has minimal direct effects on serotonin.*			
Methyphenidate delayed-release and extended-release (JORNAY PM®) 20, 40, 60, 80, 100mg ER capsules **Indication: ages 6-12y** ***Approved, but not currently marketed in Canada**	**Release Ratio (IR%/ER%):** 0/100 **Onset:** 8-10h delay before onset **Tmax:** 14h **Duration of Action:** 12 hours **Delivery Mechanism:** Dual-coating system with an outer delayed-release and inner extended release leading to an 8–10-hour delay once administered before onset. **Formulation:** Granules can be sprinkled	**Initial:** 20mg daily in the evening at 8pm (between 6:30pm-9:30pm based on tolerability and efficacy) **Titration:** ↑ by 20mg at weekly intervals **Max:** 100mg **Administration:** With or without food **Renal**: No dose adjustment **Hepatic**: No studies have been conducted.	**Brand:** N/A **ODB:** N/A **NIHB:** N/A
Second line: Atomoxetine, guanfacine XR, and short/intermediate-acting psychostimulants** are second-line ADHD treatments approved by Health Canada. These are used when first-line treatments are ineffective, poorly tolerated, or inaccessible, and are suitable in cases where stimulants are contraindicated due to misuse risks. Non-stimulants can also augment first-line treatments for suboptimal responders [3,11]* ***Amphetamine -Based Medications			
Dextroamphetamine (Dexedrine®) 5mg IR tablet Dextroamphetamine sustained-release (Dexedrine® Spansule®) 10, 15mg SR capsule Also indicated for narcolepsy	**Release Ratio (IR%/ER%):** IR: 100/0 SR: 50/50 **Onset:** IR: 0.5-1h SR: 1h **Tmax:** IR: 3h SR: 8h **Duration of Action:** IR: 4h SR: 6-12h **Formulation:** IR: can be split or crushed SR: Spansule® should not be crushed or chewed; opening the capsule does not compromise SR properties.	**Initial:** IR: 2.5-5mg daily or BID (morning and noon) SR: 10mg in the morning (Spansule® used for once-daily dosing) **Titration:** ↑ by 2.5-5mg/day at weekly intervals **Max: 40mg** ↓ dose if eGFR < 30mL/min or on dialysis ↓ dose and monitor for serotonin toxicity with concomitant use of CYP 2D6 inhibitors **Administration:** With or without food. **Renal**: Use with caution in severe impairment ↓ dose if eGFR < 30mL/min or on dialysis **Hepatic**: Impairment may alter elimination resulting in prolonged exposure.	**Brand:** IR: $27-247 SR: $54-155 **Generic:** IR: $21-147 SR: $40-105 **ODB:** ✓ **NIHB:** ✓

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Medication	Features	Dosing (Adults)	Cost and coverage (1-month supply)
Methylphenidate -Based Medications			
Methylphenidate (RITALIN®) 5, 10, 20mg IR tablet Methylphenidate extended-release (RITALIN® SR) 20mg SR tablet Also indicated for narcolepsy	**Release Ratio (IR%/ER%):** 100/0 **Onset:** IR: 0.5h SR: 1-2h **Tmax:** IR: 2h SR: 4h **Duration of Action:** IR: 3-4h SR: 8h **Formulation:** **IR: scored tablets; can be split or crushed** **SR: wax matrix preparation; swallow whole**	**Initial:** IR: 5-10mg BID or TID SR: 20mg daily in the morning (Used in place of IR when doses align in an 8-hour interval) **Titration:** IR: ↑ by 5-10mg at weekly intervals SR: May add daily 2 PM dose. **Max:** 60mg **Administration:** With or without food **Switch:** Replace 8-hour dosage of methylphenidate IR with Ritalin® SR at the same total dose. **Renal**: No studies have been conducted. **Hepatic**: No studies have been conducted.	**Brand:** D/C **Generic:** IR: $16-48 SR: $35-80 **ODB:** ✓ (10mg IR and 20mg SR only) **NIHB:** ✓

Non-Stimulant Medications

Selective Norepinephrine Reuptake Inhibitors (ages ≥6 years)
Selectively inhibits the norepinephrine transporter, increasing norepinephrine levels in the synaptic cleft, particularly in the prefrontal cortex. This enhances attention and reduces impulsivity and hyperactivity. It has minimal direct action on dopamine or serotonin.

Side effects (most common):
Insomnia, decreased appetite, dry mouth, nausea, dizziness, constipation, erectile dysfunction, urinary hesitation, and urinary retention.

Interactions
- Increased risk of serotonin syndrome with serotonergic drugs
- Interaction with CYP2D6 inhibitors (e.g., fluoxetine, paroxetine), leading to increased atomoxetine plasma levels
- Potential interactions with drugs that prolong QT interval or disturb electrolyte balance
- Additive effects on blood pressure with antihypertensive drugs and pressor agents.

Contraindications:
- Hypersensitivity to atomoxetine or any formulation components.
- Use of MAOIs during treatment or ≤ 14 days of discontinuation
- Narrow-angle glaucoma
- Pheochromocytoma or history of pheochromocytoma
- Severe cardiovascular disorders
- Moderate to severe hypertension.

Warnings:
- Potential for severe liver injury, including rare cases of acute liver failure
- Risk of cardiovascular effects, such as increased heart rate and blood pressure
- Potential for orthostatic hypotension and syncope
- Risk of priapism
- Psychiatric risks, including agitation, mood swings, and aggression
- Risk of exacerbating pre-existing psychiatric or cardiovascular conditions - QT interval prolongation and associated risks for torsades de pointes.
- Aggression and hostility monitoring in pediatric patients.
- Suicidal behavior and ideation monitoring during treatment.
- Potential withdrawal hypertension if abruptly discontinued.
- Risk of liver dysfunction in patients with hepatic impairment.

Medication	Features	Dosing (Adults)	Cost and coverage (1-month supply)
Atomoxetine (Strattera®) 10, 18, 25, 40, 60, 80, 100mg capsules	**Release Ratio (IR%/ER%):** N/A **Onset:** 1-2 weeks Full efficacy could take 4-6 weeks. **Tmax:** 1h High-fat meal in adults did not affect the extent of oral absorption but did decrease the rate of absorption, resulting in a 37% lower Cmax and delayed Tmax by 3 hours. **Duration of Action:** Up to 24h **Formulation:** Do not open capsules as it can cause nausea and upset stomach.	**Initial:** Adults 25-40mg once daily for 7 to 14 days **Titration:** ↑ by 20mg/day at 1-2-week intervals **Max:** Lesser of 1.4mg/kg or 100mg **Administration:** With or without food **Renal**: No dose adjustment **Hepatic**: Moderate impairment (Child-Pugh B): ↓ dose to 50% of the usual dose Severe impairment (Child-Pugh C): ↓ dose to 25% of the usual dose	**Brand:** D/C **Generic:** $29-157 **ODB:** ✓ (except 80mg and 100mg) **NIHB:** ✓

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Selective Alpha-2a adrenergic receptor agonist: *selectively stimulates alpha-2a adrenergic receptors in the prefrontal cortex, enhancing postsynaptic receptor function. This action strengthens prefrontal cortical network activity, improving attention, working memory, and impulse control by reducing hyperactivity of the sympathetic nervous system.*

Side effects (most common):
Fatigue, headache, somnolence/sedation, dizziness, decreased appetite, and abdominal pain.

Interactions
- ↑ guanfacine exposure with CYP3A4 inhibitors (e.g., ketoconazole)
- ↓ guanfacine exposure with CYP3A4 inducers (e.g., rifampin)
- Additive effects with CNS depressants (e.g., alcohol, benzodiazepines)
- Potential interactions with antihypertensive drugs, leading to additive hypotension and, if stopped abruptly, may lead to rebound ↑ BP
- Avoidance of concurrent use with QT-prolonging drugs
- Increased valproic acid levels when co-administered

Contraindications:
- Hypersensitivity to guanfacine or any formulation component

Warnings:
- Risk of somnolence and sedation, particularly at treatment initiation or dose increases
- Cardiovascular risks, including hypotension, bradycardia, and syncope
- ↑ HR and BP upon discontinuation (rebound hypertension)
- QT interval prolongation and associated risks for torsades de pointes
- Aggression and hostility → Monitor during treatment
- Suicidal behavior and ideation → Monitor during treatment
- Risk of liver dysfunction in patients with hepatic impairment

Medication	Features	**Dosing** (Adults)	**Cost and coverage** (1-month supply)
Guanfacine extended-release (Intuniv® XR) 1, 2, 3, 4mg ER tablets Do not substitute immediate-release formulations in a 1:1 ratio **Indication:** ages 6-17y Safety and efficacy not established in < 25kg	**Release Ratio (IR%/ER%):** N/A **Onset: 1-2 weeks** Full efficacy could take 4 weeks **Tmax:** 5 h **Duration of Action:** Up to 24h **Formulation:** Swallow whole to keep delivery mechanism intact (do not crush, chew or break).	**Initial:** 1mg in the morning or evening with a small amount of liquid **Titration:** ↑ by no more than 1mg/day at weekly intervals Monitor blood pressure and heart rate for sedation. **Max:** *As monotherapy:* Children (6-12y): 4mg Adolescent (12-17y): Target Lesser of 7mg or 0.12 mg/kg/day *As adjunct:* Children/Adolescent (6-17y): 4mg ↓ dose if significant renal and/or hepatic impairment ↓ dose if concomitant use of moderate/strong CYP3A4/3A5 inhibitor (50% dose reduction) ↑ dose if concomitant use of strong CYP3A4 inducer (up to a max of 7mg) **Administration:** With or without food. Do not take with high-fat meal or grapefruit. **Renal**: Severe impairment: Use with caution due to potential for hypotension and bradycardia **Hepatic**: Severe impairment: Use with caution and monitor for exaggerated hypotensive effects.	**Brand:** $114-180 **Generic:** $64-97 **ODB:** ✓ (LU 540) **NIHB:** ✓

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Third-line: *Bupropion, clonidine, imipramine, and modafinil are third-line options for the treatment of ADHD, often used in treatment-resistant cases. These medications are off-label, carry higher risks or side effects, and may require specialized care, including for comorbidities.*

Legend
ADHD = Attention Deficit Hyperactivity Disorder; **BID** = twice a day; **BP** = Blood Pressure; **CNS** = Central Nervous System; **CR** = Controlled-release; **CV** = Cardiovascular; **CVD** = Cardiovascular Disease; **DA** = Dopamine; **D/C** = Discontinued; **ER** = Extended-release; **GI** = Gastrointestinal; **HR** = Heart Rate; **IR**: Instant-release; **MAOI** = Monoamine oxidase inhibitor; **NE** = Norepinephrine; **N/A** = Not Applicable; **PPI** = Proton-pump Inhibitor; **SR** = Sustained-release; **TID** = three times a day

Cost: an approximate range for a 1-month supply using the initial and max dose (includes a markup of 10% and a dispensing fee of $12.99)
Tmax: Time to max blood plasma concentrations
Titration: Dose escalations can be completed at a slower pace than outlined above based on clinician discretion and patient satisfaction.
Dosing: Dosing should be individualized based on response to careful titration to identify the optimal dose, not on the severity of presentation or solely on the person's age or size. Close monitoring is essential until medication effectiveness and tolerability have been optimized.[3]
Switching: Specific to switching from another stimulant (methylphenidate to amphetamine or vice versa). Methylphenidate 1 mg is approximately 0.5 mg Adderall® XR or 0.4 mg of dextroamphetamine. If converting patients, monitor closely for clinical efficacy and adverse effects.
Follow-up: May be more frequent during the titration phase to monitor the efficacy and safety of the chosen treatment. Once a patient is stabilized, follow-up appointments can occur at regular points up to the provider's discretion.[2]
Monitoring: Look for new or worsening mood, anxiety, psychotic, manic, or substance use symptoms. Additionally, consider changes in suicidal ideation or behaviour (e.g., aggressive), as well as sleep, appetite, and mood stability (including irritability and mood swings).[11]

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