

CHAPTER 7: PHARMACOLOGICAL TREATMENT OF ADHD

Principles for Medical Treatment

Seventeen Considerations in Medication Selection in the Treatment of ADHD²⁰⁹

1. Age and individual variation
2. Duration of effect
3. Speed of action of the medication
4. ADHD clinical presentations
5. Comorbid symptom profile
6. Comorbid psychiatric disorder
7. History of family medication use
8. Attitudes towards medication use
9. Affordability
10. Medical problems and other medications
11. Associated features similar to medication side effects
12. Combining stimulants with other medications
13. Potential for misuse/diversion
14. Physician attitude towards ADHD medications
15. A first-line treatment represents a balance of efficacy, tolerability and clinical support and is approved by Health Canada
16. Second-line treatments are medications approved by Health Canada but have lower efficacy rates
17. Third-line treatments are reserved for situations where first-line and second-line treatments have not worked and are usually off-label medications.

1. Age and individual variation

All ADHD medications can be used for all age groups, although not all medications have received the “official” approval for various ages through the process required by the Therapeutic Products Directorate (TPD) of the Canadian government. Treatment before the age of six, if necessary, should only be done under the direction of a specialist²⁶² or in consultation with a specialist. There is no maximum age to treat ADHD if the general health of the patient permits use of those treatments. Women of childbearing age taking ADHD medications should be advised to talk with their physicians if they plan a pregnancy, as effects of ADHD medications on the foetus, and on the baby while breastfeeding, are unknown. Individual variation may exist (e.g. effective dosage is not closely correlated with age, weight or symptom severity), accounting for differences in treatment response and wide variation in dosage requirements. Medications don't work equally well for all patients – for some, results are huge; for others, substantial, but not huge; for others, much more modest; and for a few, currently available medications don't work very effectively at all, even when different classes of drugs are tried. **Caution: clinicians should not oversell the effectiveness of medications.** Some patients may experience difficulty swallowing pills. Although this can be improved by training, it should also be noted that some medication can be sprinkled on soft food or diluted in water.

2. Duration of effect

Exposure to tasks that require mental effort changes over the years. Medication use can be titrated to meet increased demands or to cover longer periods of daytime impairment. When considering duration of medication, it is important to remember that ADHD impacts all aspects of the child, adolescent and adult's life on a daily basis, not just the classroom or workplace. Learning also takes place outside of school and work. The severity and complexity will vary from individual to individual and developmental stages and ages.

However, as mentioned in previous chapters, areas often significantly affected causing impairment include: social functioning (interpersonal relationships, marriage and family life); emotional functioning (self-esteem, anxiety mood); recreational activities (sports, hobbies, etc.); physical exercise; sleep patterns; eating habits; participation in risky, impulsive behaviours (unprotected sex, unplanned pregnancies, HIV, driving and other accidents, SUD, etc.); physical health (poor adherence to medication and follow-up for other medical conditions); and other areas. Therefore it is important not only to optimize treatment for core symptoms and to minimize side effects but, in order to improve the overall quality of life for most individuals of all ages, the duration of medication should extend beyond the classroom/work settings into the p.m. and also include weekend and holidays. Similarly, a patient may need to have individualized treatment based on day-to-day variation. This may be critical for tasks such as driving, where the maximal risk period for young drivers is during the evenings and at weekends. Duration of effect can vary from patient to patient. **Clinical experience indicates that, for some patients, duration of effect is shorter or longer than what is indicated in the product monograph.**

3. The speed of action of the medication

When patients require urgent treatment, psychostimulants are the treatments of choice. However, ADHD is a chronic disorder where long-term management approaches are critical. For ADHD patients in general, ADHD is often perceived as an emergency once it is identified, and faster is seen to be better. However, given the extraordinary rates of low adherence over a year, long-term benefits are more likely if the ultimate goal – once emergencies such as abuse or expulsion from school are dealt with – is not just to obtain reduction of symptoms and better quality of life but also to support long-term adherence by taking into account patient side effects and comfort.

4. ADHD presentations

The core symptoms within ADHD (that also determine the presentations) include inattentiveness, impulsivity and motor hyperactivity. All three of these symptoms are associated with impairment of different sorts. For example, attention problems remain stable and impairing throughout the lifespan and affect academic and organizational functioning. Hyperactivity may diminish in adolescence but is transformed into restlessness, driven behaviour, stimulus-seeking behaviour, and discomfort from always being on the go. This may continue well into adulthood. While adults may present with impairing inattentive symptoms, their childhood progression into adulthood may reveal that some came from an only inattentive background, while others came from a transformation of the combined presentation. It is important to understand the transformation of the clinical symptoms because it may have relevance both in terms of dosing effect as well as emergence of anxiety and other side effects. All of the ADHD medications improve inattention, but not to the same extent.

5. Comorbid symptom profile

The CAP-Guidelines Committee has used a symptom-based inventory to help the clinician determine the possible treatments for each symptom. When comorbid disorders exist, prioritizing the key symptom

makes the choice of medication simpler and widens the medication options. For example, aggression and irritability may be a part of many of the comorbid disorders the patient has, but focusing on this symptom addresses the major area of impairment.

6. Comorbid psychiatric disorders

When there is a comorbid disorder along with ADHD, it is generally advised that the treatment may be determined by the more severe disorder first ^{CB}. A variety of strategies have been used to determine sequence of treatment including diagnostic certainty, patient preference, the primary disorder and the disorder with greatest impairment, or the disorder most likely to respond to treatment ^{CB}. However, major mood disorders like depression, bipolar disorders and substance use disorder should be identified and treated prior to ADHD ^{CB}. Residual symptoms may require additional treatments. It is important to review drug-to-drug interactions to ensure that there is no risk to the patient. It is not unusual for patients to be on more than one medication to deal with “complex ADHD”.

7. Family history of medical treatment

A family history of prior positive medical treatment should also be considered as well as negative experience with a specific medication. Although there is no good research data on these aspects, it is understandable that a positive response to a specific treatment in a family member could increase positive expectations for this treatment while the contrary can occur for a negative outcome.

8. Attitudes towards medication use

All patients and their families need to be educated. The choice of medication should follow the principles of informed consent. Information on informed consent is available in chapter one of the Canadian ADHD Practice Guidelines. Emotional biases against the use of ADHD medications are often due to misinformation regarding side effects and guilt about having ‘caused’ the problem through ‘bad’ parenting. Alternatively, excessive expectation of medication improvement may be present and lead to disappointment. It is important for families to access reliable and valid sources and to rely on parent support groups. Medical treatments are there to facilitate treatment of the patient’s full range of concerns. Also, parents that are at risk for diversion (e.g. substance abusers) should not be given short-acting stimulants for themselves or for their children. Patients should be educated about the risks of diversion of medication to friends.

9. Affordability

All patients should have access to optimum treatment. Unfortunately, some medications are beyond the financial reach of a significant number of patients without extended health insurance. Some medications can be supported through special access programs, but access is often limited by the extensive paperwork required and the constricted time for which medication is supplied. Most medications are covered by third party insurers. However, sometimes patients may have to rely on generic medications that may not be as effective. CADDRA continues to advocate for a resolution of this problem at the government level. Clinicians need to be informed about the cost of medications and the patient's coverage or ability to afford them before deciding what to prescribe.

10. Medical problems and other medications

It is important for the clinician to do a thorough medical assessment including physical examination before prescribing medications. The Canadian ADHD Practice Guidelines provide templates that can guide the clinician. Many conditions look like ADHD (e.g. thyroid, hearing deficits, vision problems, etc.). It is important for clinicians to be aware of any medical risk the patient may have that affects suitability for a medication (e.g. blood pressure problems, interactions with other medications, cardiovascular risk, etc.). When in doubt, a specialist referral is indicated.

11. Associated features similar to medication side effects

All medications may cause side effects. Most side effects settle after two or three weeks of continuous use. One of the most common reasons for non-adherence is related to a lack of physician awareness or understanding of side effects, or patients' reluctance to explain their discomfort. Some pre-existing conditions like tics, sleep problems, very low weight, headaches, GI problems or dysphoria may be aggravated by ADHD medications (although some of these very symptoms might actually be improved by the ADHD medications as well). Patients should be told up front about how to tell if they are getting too much medication, e.g. feeling too "wired", too irritable or too serious during the time medication should be active. In those cases, there is a strong chance that the dose is too high or that the specific medication may not be a good fit for that patient. However, if any symptoms from this triad of too "wired", too irritable or too serious is experienced later in the day, or they are dysthymic at the time when medications would be expected to be wearing off, it is likely that those symptoms are not from an excessively high dose but from rebound, where the medication is wearing off too fast and the patient is "crashing". An understanding of the side effect profile of each medication may afford a better 'fit'.

12. Combining stimulants with other medications

When a clinician feels that a second medication is needed, it is suggested to begin with an ADHD medication that is known to combine safely with the second medication. For example, in the selection of an ADHD medication for a patient with severe anxiety disorder, a psychostimulant could be combined with an antidepressant (note: there are some limitations with atomoxetine). Younger children should be referred if this is being contemplated.

13. Potential for misuse/diversion

It is important to be aware of the issue of diversion and misuse associated with psychostimulants. Non-medical use of prescription stimulants is a growing concern. There are particular groups in society that have misinformation and, in fact, pass on myths that non-medical use of stimulants increase academic performance. As well, other groups use prescription stimulants in hopes to experience euphoria and enhance their experience of partying. The short-acting stimulants have a much higher risk of misuse/diversion than the longer-acting stimulants. All professionals involved in treating ADHD patients should be alert to the signs of diversion and misuse and consider these behaviours as significant and not benign. (For more information about the signs of diversion and misuse, please see Health Canada 2006, Abuse and Diversion of Controlled Substances: A Guide For Health Professionals).

14. Physician attitude towards ADHD medications

Information on ADHD is rapidly evolving (i.e. understanding of comorbidity, adult ADHD, medical treatments, biological underpinnings, etc). It is imperative that physicians seek out reliable sources of information and continue to upgrade their clinical skills. The CADDRA Guidelines, website, conference, continuing medical education courses and other updates are designed to expose clinicians to the latest advances in assessment and treatment for ADHD across the lifespan. Patients today are often as educated about their health conditions as their doctors, and physicians need to be comfortable working with the knowledgeable patient and/or family. Such comfort can be achieved through an open attitude, experience and quality continuing education.

15. First-line treatments

First-line pharmacological treatments for ADHD are medications that have the best risk-benefit profile; longer duration (diminishes need for multiple dosages and therefore augments compliance, coverage and

recovery, diminishes diversion, diminishes rebound); effectiveness as measured by effect size; and are Health-Canada approved treatments.

16. Second-line treatments

Second-line pharmacological treatments for ADHD are medications that have demonstrated efficacy and are approved for ADHD. They can be used for patients who do not tolerate or respond to first-line treatment, or do not have access to first-line medications. They can also be used as a potential augmentation for first-line treatment responders.

17. Third-line treatments

Third-line pharmacological treatments are medications whose use is off-label. They have a higher side-effect profile and are less efficacious.

ADHD Medication Chart

The Canadian ADHD Medication Chart contained in the sleeve of the CAP-G binder provides information on the dosage and appearance of ADHD medications and is a useful tool when discussing medication options with patients and their families. It is available in a Canada-wide and Quebec version on the CADDRA website. The charts were originally developed by the Continuing Medical Education Team at Laval University in Quebec City in collaboration with the organizational committee for the Conference on the Pharmacological Treatment of ADHD in April 2007. This team continues to collaborate with CADDRA to update the medication charts when new medications, changes in indication or in coverage occur. The most recent update is always available at www.caddra.ca

Specific Medication Selection Guidelines and Monitoring

STEP 1

Feedback and Expectations (refer to Chapter 1, Visit 4 for more details)

Use principles of informed consent to ensure the patient is adequately educated when addressing medication questions, particularly regarding degree of efficacy and side effects.

STEP 2

Specific Medication Selection: Considerations

One central philosophy within CADDRA is to treat each patient as a unique being and to use the clinical advice within the “Seventeen Considerations for Medication Selection” as the guide.

Practice Point: There are some practical questions that begin the selection process:

a) Is medication indicated in your age group? Generally speaking, the first choice should be a medication that has an approved indication by Health Canada for ADHD within the specified age group. Even though some ADHD medications are not officially approved by Health Canada for a specific age group, doctors may decide to use them based on scientific evidence and expert consensus.

b) What impairment do you have and at what time of the day? Is it mainly during work hours, meetings, exam times, leisure times, driving periods, morning routines, etc.? Ensure the patient is medicated when it is necessary and that you understand and are responding to his/her individual needs.

c) What medication do you prefer? Have you ever taken any medications before or heard of something you might want to try? Patients respond better to the medications they most strongly believe in. This also addresses the belief that patients must be educated and they should have a partnership in the treatment agenda.

d) Is a family member on medication for ADHD? If yes, then consider trying the same medication first. (Note: there is no evidence at this time about a possible role for such a pharmacogenetics-based approach.)

e) Do you have third party coverage or do you plan to pay for the medication? Many of the current medications are expensive so there should be an open discussion related to government plans, third party insurance coverage, direct payment, co-payment plans and limited benefit plans.

f) Do you have trouble swallowing a pill? If yes, then that will limit certain medications choices, though one should make an attempt to train the individual to swallow a capsule.

g) Do you require urgent treatment? If yes, then a stimulant is likely your first choice due to its speed of onset of effect. However, the treatment of ADHD is a long-term plan so while there may be urgent issues, the patient should be cautioned about rapid fixes.

h) Does the patient have comorbid disorders that require more complex interventions? If yes, the current agenda is to decide which problem to treat first. If it is ADHD, then initiate the ADHD medication and see what residual symptoms are left over that require further management. Anticipate drug-drug interaction issues.

If the patient is expressing suicidal or homicidal thoughts these need to be addressed as a priority.

STEP 3

Monitoring

- Establish a schedule for visits and contact with the patient and parents
- It is useful to establish an objective measure within the patient's domain. For example, the teacher may want to observe a five minute on-task behaviour. An adolescent may target their ability to sustain attention in their most difficult tasks. An adult may use a specific target that needs to change, like hourly work production. Formal observational rating scales help to quantify specific medication changes, particularly at school and home. The CADDRA Clinician ADHD Baseline/Follow-up Form and the ADHD Checklist can be used to evaluate change
- During the titration phase, weekly contact with the patient reporting in either by phone, email, fax or visit is recommended. Ideally, the patient should be seen every two to three weeks where possible for a review of medication doses during the titration period and to check physical health, vital signs, review side effects, family functioning, patient and family well being, coping strategy management, behavioural treatment and other therapies when indicated.

STEP 4

Titration

- Recommended starting dose and schedule for dose increases is a guide only
- Start low and go slow but continue to increase the dose until the desired goals of treatment have been reached or side effects preclude dose increases. Optimal treatment means that the symptoms

have decreased and that there is improvement in general functioning. Optimal dose is also that dose above which there is no further improvement. Sometimes side effects limit the dose titration (refer to unsatisfactory response to treatment section of this chapter and Side Effect Management, Supporting Document 7C). The threshold maximum suggestions in this document are consistent with the off-label standards established by the American Academy of Child and Adolescent Psychiatry.

- It is useful to alert the patient in advance that a peak effect may occur in the first week and a plateau effect may occur over the subsequent three weeks. Sometimes patients interpret this as a tolerance to the medication and request a higher dose. In fact, if the patient improves in their functioning at the plateau dose, they are likely dose-optimized.
- **If there is an unsatisfactory response to one psychostimulant class, then there should be a switch to the other psychostimulant class.**

STEP 5

Managing Side Effects

1. In educating patients about medication it is important to provide the realistic view that individuals have different risk/benefit profiles on medication, ranging from those who cannot tolerate or benefit from medication at all, to those who have full remission with no side effects.
2. While our evidence base on medication allows us to provide patients with a great deal of information on medication options, it is also important to remind patients and parents that all individuals are unique and may require doses that are smaller or larger than are usually recommended. It is important to point out that agreeing to a “trial” of medication is not a decision to use it forever. A trial is an experiment that carries minimal if any risks that would extend beyond a very brief period of time, and can be discontinued at any point.
3. Patients who are good stimulant responders, but whose medication is limited by side effects, should be managed by the techniques described below or switched to a different medication regimen that minimizes that particular problem.
4. Patients who are not responding to medication and obtaining little benefit, but do not have major side effects, may require non-medication strategies.
5. If the patient does not respond to any of the first line medications, augmentation strategies or use of second line medications such as guanfacine XR, third line options like bupropion, clonidine, modafinil or imipramine may be helpful, but a specialist referral should be made. In the rapidly changing field of ADHD, treatment with new medications with different side effect profiles and possibly differential effectiveness in particular patients is becoming possible.
6. If a change in medication is thought necessary, switch medication during long vacations or during the summer to avoid possible side effects that may impair school performance in the short-term. However, sometimes switching medications requires a more immediate intervention due to the urgency of the situation.
7. If a period off medication or on a reduced dose to minimize side effect is required, it should be done during long vacations, the summer, or on long weekends to minimize impact on school performance. Clinically, it is observed that interrupting medication every weekend may in fact increase side effects. Taking the medication each day will help develop a tolerance toward side effects. Some medications (e.g. atomoxetine, guanfacine XR, bupropion, imipramine) need to be taken continuously to maintain clinical effect. These medications should be tapered due to the risk of significant side effects or dangers (e.g. a hypertensive crisis for guanfacine XR and clonidine).

Unsatisfactory Response to Treatment?

If there is no response to treatment, it is important to review the diagnosis, including comorbidities, and the treatment plan in order to ensure compliance to treatment as well as to check if there are new external factors that could complicate the clinical picture. Patients' responses to medication cannot be predicted based solely on the clinical symptoms displayed. Some patients may respond preferentially to one versus the other class of medications, so if response or side effects to one class of medication are not optimal, another class of ADHD medication should be tried. Specifically, if a patient does not have an adequate response to one class of stimulant, then it would be prudent to switch to the other class of stimulant. Sustained-release medications are preferred as they are taken once daily, thus improving adherence, and are less likely to be abused, misused or diverted than immediate-release products. Also sustained-release preparations maintain privacy, dignity and respect for patients and families in the context of the school setting.

There are several reasons why one ADHD medication may be substituted for another:

- Peak and trough effects: change the immediate-release mechanism for a more sustained one.
- End-of-dose rebound effects: change the immediate-release mechanism for a more sustained one or take an additional, perhaps lesser, dose of same psychostimulant in an immediate-release form to be taken just before the rebound is expected to occur.
- Partial effects despite optimization of dosage: change the release mechanism or change the molecule. The combination of a psychostimulant with a non-stimulant like guanfacine XR or atomoxetine (off-label) is also an option sometimes used but there is no official indication, or long-term studies, on the safety of this approach. Closely monitor adverse effects if this option is selected.
- Adverse effects don't allow dosage to be optimized: change the release mechanism or change the molecule.
- Presence of a comorbidity that requires a switch of medication
- Drug-to-drug interaction

Switching from One Type of Medication to Another: Points to consider

Generally, it is best to only be medicating with one medication at a time. Thus, it is often best to gradually decrease on the first medication and stop it before starting on the second. Trying to use two medications at the same time often results in side effects from each medication and prevents the clinician from reaching optimal clinical dosages because of side effects.

Situation A: Switching from a psychostimulant to another psychostimulant

- Choose an opportune time for transition, such as during holidays or at the weekend.
- Consider if there is an equivalent dose or if the new medication needs to be initiated at the starting dose.

Presently on:	Changing to:	Comments:										
MPH-based medication	MPH-based medication	Stop the first and start the second at the calculated equivalent dose while taking into account the release mechanism <table border="1" style="margin-left: 20px;"> <thead> <tr> <th>MPH-Based Medication</th> <th>% Immediate/Delayed Release</th> </tr> </thead> <tbody> <tr> <td>Ritalin</td> <td>100/0</td> </tr> <tr> <td>Biphentin</td> <td>40/60</td> </tr> <tr> <td>Concerta</td> <td>22/78</td> </tr> <tr> <td>Generics</td> <td>Unknown (not disclosed by manufacturer)</td> </tr> </tbody> </table>	MPH-Based Medication	% Immediate/Delayed Release	Ritalin	100/0	Biphentin	40/60	Concerta	22/78	Generics	Unknown (not disclosed by manufacturer)
MPH-Based Medication	% Immediate/Delayed Release											
Ritalin	100/0											
Biphentin	40/60											
Concerta	22/78											
Generics	Unknown (not disclosed by manufacturer)											
MPH-based medication	AMP-based medication	No direct equivalent dose. Stop the first and begin the second at the starting dose. <p style="text-align: right;"><i>Note: Methylphenidate: MPH; Amphetamine: AMP</i></p>										
AMP-based medication	MPH-based medication											
AMP-based medication	AMP-based medication											

Situation B: Switching from a psychostimulant to atomoxetine or guanfacine XR

Since non-stimulants will take time to show clinical response, it is important to decide if the psychostimulant needs to be stopped before or if you combine both as you start atomoxetine or guanfacine XR.

- If the first medication shows no clinical effect despite optimal dosing, stop it and start the non-stimulant as monotherapy, following usual titration strategies.
- Only if it is not possible to stop the first medication and if the first medication shows important clinical effect and needs to be continued until the non-stimulant shows its effects, then keep the first medication and add atomoxetine slowly, following usual titration strategies.
- ✓ If side effects occur, decide between reducing the psychostimulant versus atomoxetine or guanfacine XR dosage.*

Situation C: Switching from atomoxetine or guanfacine XR to a psychostimulant

Decide if the non-stimulant needs to be stopped before, or if you combine both, as you start the psychostimulant.

- If atomoxetine or guanfacine XR shows no clinical effect despite optimal dosing, stop it first and start the psychostimulant as monotherapy, following usual titration strategies.
- Even if atomoxetine or guanfacine XR has a partial effect it can be stopped since stimulant effects are usually seen quite rapidly and this approach allows the patient and clinician to only have to deal with one set of side effects.
- If atomoxetine or guanfacine XR shows important clinical effect and needs to be continued until the psychostimulant shows its effects, then add the psychostimulant to the non-stimulant. Start slowly,

following usual titration strategies.

✓If side effects occur, decide between reducing the psychostimulant versus the non-stimulant dosage.*

***Note:** Guanfacine XR is the only medication with a specific indication as an adjunctive therapy to psychostimulants for the treatment of ADHD in children aged 6-12 years with a sub-optimal response to psychostimulant. Long-term combination (off-label) of a psychostimulant with guanfacine XR in adults or with atomoxetine has not been studied. If the patient gets better with a combination of both a non-stimulant and a psychostimulant, closely monitor adverse effects and try to eventually reduce either the psychostimulant or the non-stimulant.

SUPPORTING DOCUMENT 7A: CANADIAN MEDICATION TABLES PER AGE GROUP

Children's Medical Treatment Options (6-12 years)

Table 1. MEDICAL TREATMENT FOR ADHD UNCOMPLICATED – CHILDREN						
Alphabetically Listed – Refer to product monographs for complete prescribing information.						
Brand Name (active chemical)	Dosage Form	Starting Dose*	Titration Schedule Every 7 days		Maximum per day ¹ (up to 40 kg child)	
			Per product Monograph	Per CADDRA Board	Per Product Monograph	Per CADDRA Board*
FIRST LINE AGENTS – long-acting preparations						
Adderall XR® (amphetamine mixed salts)	5, 10, 15, 20, 25, 30 mg cap	5-10 mg q.d. a.m.*	↑ 5-10 mg	↑ 5 mg	30 mg	30 mg
Biphentin® (methylphenidate HCl)	10, 15, 20, 30, 40 50, 60, 80 mg cap	10-20 mg q.d. a.m.	↑ 10 mg	↑ 5-10 mg	60 mg	60 mg
Concerta® (methylphenidate HCl)	18, 27, 36, 54 mg tab	18 mg q.d. a.m.	↑ 18 mg	↑ 9-18 mg	54 mg	72 mg
Vyvanse® (lisdexamfetamine dimesylate)	20, 30, 40, 50, 60 mg cap	20-30 mg q.d. a.m.	By clinical discretion	↑ 10 mg	60 mg	60 mg
<p>CB Doses per CADDRA Board that are over or under product monograph maximum or minimum doses should be considered off-label use. *CADDRA recommends generally starting at the lowest dose available. Young children should be started at the lower end of the recommended CADDRA dose and titrated slowly, e.g. Concerta: 18, 27, 36 and Biphentin 10, 15, 20 mg. A consensus decision has been made based on clinical use and research data.</p>						
SECOND LINE/ADJUNCTIVE AGENTS – long-acting preparations						
Non psychostimulant - selective norepinephrine reuptake inhibitor						
CB Indications for use: Monotherapy for the treatment of ADHD in children aged 6-12 years (off-label: prescribed as an adjunctive therapy).						
Strattera® (atomoxetine)	10, 18, 25, 40, 60, 80, 100 mg cap	0.5 mg/kg/day	Maintain dose for a min. of 7-14 days before adjusting to 0.8 mg/kg/day then 1.2 mg/kg/day	Maintain dose for a min. of 7-14 days before adjusting to 0.8 mg/kg/day then 1.2 mg/kg/day	lesser of 1.4 mg/kg/day or 60 mg/day	lesser of 1.4 mg/kg/day or 60 mg/day
SECOND LINE/ADJUNCTIVE AGENTS – long-acting preparations						
Non psychostimulant - selective Alpha _{2A} -adrenergic receptor agonist						
CB Indications for use: Monotherapy and as an adjunctive therapy to psychostimulants for the treatment of ADHD in children aged 6-12 years with a sub-optimal response to psychostimulant.						
Intuniv XR® (guanfacine XR)	1, 2, 3, 4 mg tab	1 mg	Maintain dose for a min. of 7-14 days before increasing by no more than 1 mg per week up to a max. 4 mg daily dose	Maintain dose for a min. of 7-14 days before increasing by no more than 1 mg per week up to a max. 4 mg daily dose	4 mg	4 mg

TABLE 1. MEDICAL TREATMENT FOR ADHD UNCOMPLICATED – CHILDREN (CONTINUED)

*Alphabetically Listed – Refer to product monographs for complete prescribing information**

Brand Name (active chemical)	Dosage Form	Starting Dose*	Titration Schedule Every 7 days		Maximum per day ^{1, 2} (>40 kg)	
			Per Product Monograph	Per CADDRA Board	Per Product Monograph	Per CADDRA Board*
SECOND LINE/ADJUNCTIVE AGENTS – short-acting and intermediate-acting preparations						
<p>Ⓢ Indications for use: a) p.r.n. for particular activities; b) to augment long-acting formulations early or late in the day, or early in the evening and c) when LA agents are cost prohibitive. To augment Adderall XR[®] or Vyvanse[®], short-acting and intermediate-acting dextro-amphetamine products can be used. To augment Biphentin[®] or Concerta[®] short-acting MPH products can be used. b.i.d. refers to qam and qnoon and t.i.d. refers to qam, qnoon and q4pm.</p>						
Dexdrine[®] (dextro-amphetamine sulphate)	5 mg tab	2.5-5 mg b.i.d.	⬆ 2.5-5 mg	⬆ 2.5-5 mg	40 mg	20 mg
Dexdrine[®] Spansule² (dextro-amphetamine sulphate)	10, 15 mg cap	10 mg q.d. a.m.	⬆ 5 mg	⬆ 2.5-5 mg	40 mg	30 mg
Ritalin[®] (methylphenidate)	10, 20 mg tab	5 mg b.i.d. to t.i.d.	⬆ 5-10 mg	⬆ 5 mg	60 mg	60 mg
Ritalin[®] SR³ (methylphenidate HCl)	20 mg tab	20 mg q.d. a.m.	⬆ 20 mg	⬆ 20 mg	60 mg	60 mg
<p>¹ The maximum daily dose can be split into once daily (q.d.), twice daily (b.i.d.) or three times daily (t.i.d.) doses except for once a day formulations. Refer to the adolescent table for children over 40kg. ² Dexdrine[®] Spansule may last 6-8 hours ³ Ritalin[®] SR may help cover the noon period but clinical experience suggests an effect similar to short-acting preparations. An increased dose could be spread out to include q2pm dose with a daily maximum of 60 mg. * CADDRA recommends generally starting at the lowest starting dose available.</p>						
GENERIC MEDICATIONS						
PMS[®] or Ratio[®]-methylphenidate	5, 10, 20, mg tab	5 mg q.d. a.m. and noon	⬆ 5 mg	⬆ 5 mg	60 mg	60 mg
			(add q4pm dose)			
Novo-MPH ER-C[®] (methylphenidate)	18, 27, 36, 54 mg tab	18 mg q.d. a.m.	⬆ 18 mg	⬆ 9-18 mg	54 mg	72 mg
THIRD LINE AGENTS						
These medications (except for clonidine) should only be initially or first prescribed by a specialist.						

Medication for Adolescents with ADHD

TABLE 2. MEDICAL TREATMENT FOR ADHD UNCOMPLICATED – ADOLESCENTS						
Alphabetically Listed – Refer to product monographs for complete prescribing information.						
Brand Name (active chemical)	Dosage Form	Starting Dose*	Titration Schedule Every 7 days		Maximum per day ^{1, 2} (>40 kg)	
			Per Product Monograph	Per CADDRA Board	Per Product Monograph	Per CADDRA Board*
FIRST LINE AGENTS – long-acting preparations						
Adderall XR® (amphetamine mixed salts)	5, 10, 15, 20, 25, 30 mg cap	5-10 mg q.d. am	↑ 5-10 mg	↑ 5 mg	20-30 mg	50 mg
Biphentin® (methylphenidate HCl)	10, 15, 20, 30, 40 50, 60, 80 mg cap	10-20 mg q.d. am	↑ 10 mg	↑ 5-10 mg	60 mg	80 mg ³
Concerta® (methylphenidate HCl)	18, 27, 36, 54 mg tab	18 mg q.d. am	↑ 18 mg	↑ 9-18 mg	54 mg	90 mg (54 + 36 mg)
Vyvanse® (lisdexamfetamine dimesylate)	20, 30, 40, 50, 60, mg cap	20-30 mg q.d. am	By clinical discretion	↑ 10 mg	60 mg	70 mg
<p>CB * Doses per CADDRA Board that are over or under product monograph maximum or minimum doses should be considered off-label use. Note: CADDRA recommends generally starting at the lowest starting dose available. A consensus decision has been made based on clinical use and research data.</p>						
SECOND LINE/ADJUNCTIVE AGENTS – long-acting preparations						
Non psychostimulant - selective norepinephrine reuptake inhibitor						
CB Indications for use: a) Monotherapy for the treatment of ADHD (off-label: prescribed as an adjunctive therapy).						
Strattera® (atomoxetine)	10, 18, 25, 40, 60, 80 100 mg cap	0.5 mg/kg/day	Maintain dose for a min. of 7-14 days before adjusting 0.8 mg/kg/day then 1.2 mg/kg/day for patients <70kg ⁴	Maintain dose for a min. of 7-14 days before adjusting 0.8 mg/kg/day then 1.2 mg/kg/day for patients <70kg ⁴	lesser of 1.4 mg/kg/day or 100 mg/day	lesser of 1.4 mg/kg/day or 100 mg/day
SECOND LINE/ADJUNCTIVE AGENTS – short-acting and intermediate-acting preparations						
CB Indications for use: a) p.r.n. for particular activities; b) to augment long-acting formulations early or late in the day, or early in the evening and c) when LA agents are cost prohibitive. To augment Adderall XR® or Vyvanse®, short-acting and intermediate-acting dextro-amphetamine products can be used. To augment Biphentin® or Concerta® short-acting MPH products can be used. b.i.d. refers to qam and qnoon and t.i.d. refers to qam, qnoon and q4pm.						
Dexedrine® (dextro-amphetamine sulphate)	5 mg tab	2.5-5 mg b.i.d.	↑ 5 mg	↑ 2.5-5 mg	40 mg	30 mg
Dexedrine® Spansule⁵ (dextro-amphetamine sulphate)	10, 15 mg cap	10 mg q.d. a.m.	↑ 5 mg	↑ 2.5-5 mg	40 mg	30 mg
Ritalin® (methylphenidate HCl)	10, 20 mg tab	5 mg b.i.d. to t.i.d.	↑ 5-10 mg	↑ 5 mg	60 mg	60 mg
Ritalin® SR⁶ (methylphenidate HCl)	20 mg tab	20 mg q.d. am	↑ 20 mg (add q2pm dose)	↑ 20 mg (add q2pm dose)	60 mg	80 mg
<p>¹ Maximum off label doses have been published in the AACAP Practice Parameters¹⁴ but the off label maximums are either the same or lower in the CAP-G based on CB</p> <p>² The maximum daily dose can be split into once daily (q.d.), twice daily (b.i.d.) or three times daily (t.i.d.) doses except for once a day formulations</p> <p>³ While the theoretical maximum off label dose for Biphentin® could be 100 mg, clinical practice currently suggests that 80 mg is the maximum that is used</p> <p>⁴ For adolescents greater than 70 kg, use the adult dose titration schedule</p> <p>⁵ Dexedrine Spansule® may last 6-8 hours</p> <p>⁶ Ritalin SR® may help cover the noon period but clinical experience suggests an effect similar to short-acting preparations.</p>						

Table 2. MEDICAL TREATMENT FOR ADHD UNCOMPLICATED – ADOLESCENTS (continued)
Alphabetically Listed – Refer to product monographs for complete prescribing information.

Brand Name (active chemical)	Dosage Form	Starting Dose*	Titration Schedule Every 7 days		Maximum per day*	
			Per product Monograph	Per CADDRA Board	Per Product Monograph	Per CADDRA Board
GENERIC MEDICATIONS						
PMS® or Ratio®- methylphenidate	5, 10, 20, mg tab	5 mg q.d. a.m. and noon	↑ 5 mg	↑ 5 mg	60 mg	60 mg
			(add q4pm dose)			
Novo-MPH ER-C® (methylphenidate)	18, 27, 36, 54 mg tab	18 mg q.d. a.m.	↑ 18 mg	↑ 9-18 mg	54 mg	90 mg
THIRD LINE AGENTS						
These medications (except clonidine) should only be initiated or first prescribed by a specialist.						

Medication for Adults with ADHD

TABLE 3. MEDICAL TREATMENT FOR ADHD UNCOMPLICATED – ADULTS <i>Alphabetically Listed – Refer to product monographs for complete prescribing information.</i>						
Brand Name (active chemical)	Dosage Form	Starting Dose*	Titration Schedule Every 7 days		Maximum per day ^{1, 2}	
			Per Product Monograph	Per CADDRA Board	Per Product Monograph	Per CADDRA Board*
FIRST LINE AGENTS – long-acting preparations						
Adderall XR® (amphetamine mixed salts)	5, 10, 15, 20, 25, 30 mg cap	10 mg q.d. a.m.	↑ 10 mg	↑ 5 mg	20-30 mg	50 mg
Biphentin® (methylphenidate HCl)	10, 15, 20, 30, 40 50, 60, 80 mg cap	10-20 mg q.d. a.m.	↑ 10 mg	↑ 5-10 mg	80 mg	80 mg ³
Concerta® (methylphenidate HCl)	18, 27, 36, 54 mg tab	18 mg q.d. a.m.	↑ 18 mg	↑ 9-18 mg	72 mg	108 mg
Vyvanse® (lisdexamfetamine dimesylate)	20, 30, 40, 50, 60 mg cap	20-30 mg q.d. a.m.	By clinical discretion	↑ 10 mg	60 mg	70 mg
CB * Doses per CADDRA Board that are over or under product monograph maximum or minimum doses should be considered off-label use. Note: CADDRA recommends generally starting at the lowest dose. A consensus decision has been made based on clinical use and research data.						
SECOND LINE/ADJUNCTIVE AGENTS – long-acting preparations						
Non psychostimulant - selective norepinephrine reuptake inhibitor						
CB Indications for use: Monotherapy for the treatment of ADHD (off-label: prescribed as an adjunctive therapy).						
Strattera® (atomoxetine)	10, 18, 25, 40, 60, 80, 100 mg cap	40 mg ⁴ q.d. for 7-14 days	Maintain dose for a min. of 7-14 days before adjusting to 60 then 80 mg/day max dose/day 1.4 mg/kg/day or 100 mg ⁵	Maintain dose for a min. of 7-14 days before adjusting to 60 then 80 mg/day max dose/day 1.4 mg/kg/day or 100 mg ⁵	Lesser of 1.4 mg/kg/day or 100 mg/day	Lesser of 1.4 mg/kg/day or 100 mg/day
SECOND LINE/ADJUNCTIVE AGENTS – short-acting and intermediate-acting preparations						
CB Indications for use: a) p.r.n. for particular activities; b) to augment long-acting formulations early or late in the day, or early in the evening and c) when LA agents are cost prohibitive. To augment Adderall XR® or Vyvanse®, short-acting and intermediate-acting dextro-amphetamine products can be used. To augment Biphentin® or Concerta® short-acting MPH products can be used. b.i.d. refers to qam and qnoon and t.i.d. refers to qam, qnoon and q4pm points.						
Dexedrine® (dextro-amphetamine sulphate)	5 mg tab	2.5-5 mg b.i.d.	↑ 5 mg	↑ 2.5-5 mg	40 mg	50 mg
Dexedrine® Spansule⁵ (dextro-amphetamine sulphate)	10, 15 mg cap	10 mg q.d. a.m.	↑ 5 mg	↑ 2.5-5 mg	40 mg	50 mg
Ritalin® (methylphenidate HCl)	10, 20 mg tab	5 mg b.i.d. to t.i.d., consider q.i.d.	↑ 5-10 mg	↑ 5 mg	60 mg	100 mg
Ritalin® SR⁶ (methylphenidate HCl)	20 mg tab	20 mg q.d. a.m.	↑ 20 mg (add q2pm dose)	↑ 20 mg (add q2pm dose)	60 mg	100 mg
¹ Maximum off label doses have been published in the AACAP Practice Parameters ¹⁴ but the off label maximums are either the same or lower in the CAP-G based on CB ² The maximum daily dose can be split into once daily (q.d.), twice daily (b.i.d.) or three times daily (t.i.d.) doses except for once a day formulations ³ While the theoretical maximum off label dose for Biphentin® could be 100 mg, clinical practice currently suggests that 80 mg is the maximum that is used since no published study has researched doses higher than 80mg ⁴ Some adults may better tolerate a lower starting dose of 25 mg ⁵ Strattera titration schedule applies to children and adolescents over 70 kg body weight and adults. ⁶ Dexedrine Spansule® may last 6-8 hours ⁷ Ritalin SR® may help cover the noon period but clinical experience suggests an effect similar to short-acting preparations.						

Table 3. MEDICAL TREATMENT FOR ADHD UNCOMPLICATED – ADULTS (continued)
Alphabetically Listed – Refer to product monographs for complete prescribing information.

Brand Name <i>(active chemical)</i>	Dosage Form	Starting Dose*	Titration Schedule Every 7 days		Maximum per day	
			Per product Monograph	Per CADDRA Board	Per Product Monograph	Per CADDRA Board
GENERIC MEDICATIONS						
PMS® or Ratio®- methylphenidate	5, 10, 20, mg tab	10 mg q.d. a.m. and noon CADDRA: 5 mg b.i.d. to t.i.d., consider q.i.d.	↑ 10 mg	↑ 5 mg	60 mg	100 mg
			(add q4pm dose)			
Novo-MPH ER-C® <i>(methylphenidate)</i>	18, 27, 36, 54 mg tab	18 mg q.d. a.m.	↑ 18 mg/wk	↑ 9-18 mg/wk	54 mg	108 mg
THIRD LINE AGENTS						
These medications (except clonidine) should only be initially or first prescribed by a specialist.						

SUPPORTING DOCUMENT 7B: SPECIFIC INFORMATION ON MEDICATIONS


Provincial drug plan coverage may be different from one Canadian province to another and is subject to change (www.drugcoverage.ca). The CADDRA CAP-Guidelines Committee recommends that all medication approved for ADHD treatment should be accessible and covered by provincial drug plans.


STIMULANTS

Dextro-amphetamine (DEX) based products – long-acting medications

Adderall XR® (mixed amphetamine salts)

Amphetamines (AMP) work by the blockade of the reuptake of dopamine. They also increase the release of dopamine and noradrenaline from the vesicles accounting for their increased potency over MPH (i.e. a lesser mg dose may be sufficient). AMP is indicated in ADHD patients. Adderall XR® is a controlled drug, made up of a combination of different AMP salts, predominantly dextro-amphetamine (DEX). Adderall XR® comes in an extended release capsule available in six doses (5, 10, 15, 20, 25 and 30 mg). The major strengths of Adderall XR® are that:


- a) the medication can give symptom control that lasts for 10–12 hours covering the major times when impairment occurs (e.g., school, homework, work day periods)
- b) the medication is indicated in all age groups by Health Canada
- c) the capsules may be opened and the beads inside the capsule can be sprinkled (e.g. on apple sauce) with no loss in efficacy (particularly important to improve adherence in young children who can't swallow pills)
- d) a 50/50 delivery system means that fifty percent of the dose is immediately available leading to a fast morning response and 50% is released later during the day, without a need for augmentation
- e) patients can be switched from immediate release AMP very easily
- f) a focused review of sudden unexplained deaths was carried out by Health Canada in 2006 and the medication's safety has been assured
- g) the abuse potential is significantly reduced in comparison to short-acting medication due to the product formulation according to anecdotal reports from Canadian regional addiction centres,  and
- h) the active ingredient DEX has been available for more than 50 years and has a well-known safety and efficacy profile.

Occasionally it may be necessary to "top up" the medication in the late afternoon to extend the clinical effect. 

Vyvanse® (lisdexamfetamine dimesylate)

DEX works by the blockade of the reuptake of dopamine. It also increases the release of dopamine and noradrenaline from the vesicles accounting for its increased potency over MPH. Vyvanse® is a controlled substance made up of a pro-drug, lisdexamfetamine (inactive drug), that needs a biological enzymatic transformation to release DEX (active drug). DEX has effects on noradrenaline and dopamine similar to Adderall XR® and other DEX products but the delivery mechanism is different for all those products. In Canada, Vyvanse® comes in capsules available in five doses (20, 30, 40, 50 and 60 mg). In the United States, since the FDA has approved dosages of Vyvanse from 20 mg to 70 mg, a 70 mg capsule is also available.

The major strengths of Vyvanse® are that:

- a) the medication can give symptom control that lasts for 13 hours in children and up to 14 hours in adults, covering the major times when impairment occurs, including part of the evening
- b) the medication has been indicated in all ages by Health Canada
- c) the capsules may be opened and diluted in water with no loss in efficacy (particularly important to improve adherence in young children who can't swallow pills)
- d) patients can be switched from Dexedrine® or Adderall XR® quite easily
- e) this kind of delivery system is not influenced by gastric PH or transit time
- f) clinical effects have been described as more stable over time for each individual and more constant from one person to the other
- g) because of its pro-drug design, its delivery curve is not changed by mode of administration (oral, inhalation or injection), reducing its possible abuse potential  and
- h) the active ingredient, DEX, has been available for more than 50 years and has a well known safety and efficacy profile.

Dextro-amphetamine (DEX) based products – short-acting and intermediary-acting medications

Dexedrine® and Dexedrine® Spansules

DEX works by the blockade of the reuptake of dopamine. It also increases the release of dopamine and noradrenaline from the vesicles accounting for its increased potency over MPH. DEX is indicated in ADHD patients. It is a controlled substance. Dexedrine® and Dexedrine® Spansules are placed by the CADDRA Guidelines Committee in the second line group as their duration is shorter than that of long-acting versions and they are therefore prone to having peak/valley effects that may be uncomfortable. Their efficacy and safety, however, are well established. The major strengths of DEX are that:

- a) the active ingredient has been available and actively studied for many decades
- b) it may be useful in situations where a top-up of the once-daily medication is required or when the patient desires more flexibility in the dosing schedule
- c) a consensus of the CAP Committee suggests that DEX may be indicated in some adult ADHD patients who want the medication for situational versus continuous use
- d) Dexedrine® Spansules may be covered by some government special access programs, they are relatively inexpensive, and
- e) Dexedrine® Spansules last about six to eight hours while the pill formation last about three to five hours.


Methylphenidate (MPH)-based products – long-acting medications

Biphentin®

MPH, the active ingredient, is a controlled substance which works by the blockade of the re-uptake of dopamine and is indicated in ADHD. Biphentin® is a controlled-release methylphenidate (MPH) product and comes in eight strengths (10, 15, 20, 30, 40, 50, 60 and 80 mg). Biphentin® uses a multi-layer release (MLRTM) delivery system. The major strengths of Biphentin® include the following:


- a) There are long term studies, of over twenty years in duration, which show MPH is safe and the active ingredient is MPH which has a well-known safety and efficacy profile
- b) its delivery is a 40% immediate and 60% gradual effect putting it in the middle of the other medications


- c) the delivery technology has shown an effect that is sustained for 8-10 hours, covering the major times that impairment occurs (e.g. school, homework periods and during the work day)
- d) it is available in eight doses making it easier to titrate the medication even from a much lower dose
- e) the medication has been indicated in all age groups by Health Canada
- f) the medication is actually available only in Canada and is relatively cheaper than the other long acting MPH products (at the lower doses)
- g) the capsules can be opened and sprinkled making it useful for children who can not swallow pills and, since the beads within each capsule are all the same, there is no concern when it is poured, and
- h) patients can be switched from MPH easily and, if necessary, can be augmented with immediate release MPH at the end of the day.

Occasionally it may be necessary to "top up" the medication in the late afternoon to extend the clinical effect. 

Concerta®

MPH, the active ingredient, is a controlled substance which works by the blockade of the reuptake of dopamine and is indicated in ADHD. Concerta® is an extended release MPH that uses the OROS technology and comes in four dosing options (18, 27, 36 and 54 mg capsules). The major strengths of Concerta® are that:

- a) there are long-term studies, of over twenty years in duration, which show MPH is safe
- b) it controls ADHD symptoms for approximately 10–12 hours, covering the major times that impairment occurs (e.g. school, homework periods and during the work day)
- c) it is a 22% immediate release and 78% long acting release combination suggesting a long duration of effect
- d) the non-deformable shell makes it very difficult to break, cut or crush, which reduces its abuse risk (according to anecdotal report from Canadian regional addiction centres) 
- e) patients can easily be converted from immediate release MPH to Concerta® and
- f) the medication has an indication in all age groups by Health Canada. While multiple doses can be used to create a closer titration (18 mg + 27 mg= 45 mg; 27 mg + 36 mg = 63 mg, etc), the higher cost of the combination of two dosages may be prohibitive.

Occasionally it may be necessary to "top up" the medication in the morning to extend the clinical effect. 

Ritalin LA® and Daytrana®

Ritalin® LA, a once-a-day extended-release MPH formulation, and the MPH patch, Daytrana®, are currently not available in Canada.

FocalinXR® and Focalin®

The isomer dextro-methylphenidate is available in the USA in a long-acting (FocalinXR®) and short-acting (Focalin®) formulation. Those products are not available in Canada.

Other long-acting methylphenidate products (delivery mechanism not published)

Novo-Methylphenidate ER-C is a generic methylphenidate-based product with a progressive delivery system that was approved by Health Canada in 2010 as a generic for Concerta®. There are long term studies, of over twenty years in duration, which show MPH is safe. The actual delivery mechanism of Novo-Methylphenidate ER-C has not been described. This medication is not delivered via the OROS pump system, which is utilized for Concerta®. It comes in four dosing options (18, 27, 36 and 54 mg capsules). The major strengths of this generic formulation are cost-related and its active ingredient is MPH. However, the clinical profile of this new delivery system formulation has not been field tested. As with all generics, only bioequivalence needs to be demonstrated.

The CADDRA CAP-Guidelines Committee strongly believes that bioequivalence does not always mean clinical equivalence and that we need clinical data to better comment on this new medication. Side effects and duration of action are still unknown. Monograph information is derived from the Concerta® Monograph; only the bioequivalence data has been researched.

The tablets look like Concerta® but can be more easily crushed; this could affect its abuse potential as the time to maximum concentration (Tmax) is earlier with the generic medication. We don't know if that will influence the side effects profile, onset and duration of action of Novo-Methylphenidate ER-C compared to Concerta™. At present, we don't have enough data to comment on its clinical efficacy. We will need to wait for clinical experience to offer clarity.

CADDRA and Health Canada have received information from families and physicians reporting cases of drastic behavioural changes when a patient's Concerta prescription was switched to the generic formulation. The CADDRA CAP-Guidelines Committee believes these changes can be attributed to the medication formulation change. Meanwhile, the decision to switch to a generic formulation is an individual-based decision and we strongly advocate that the patient/family be advised of the switch, told to check for clinical changes in efficacy or tolerability and report any changes to their pharmacist and doctor.

Methylphenidate (MPH) based products: Short-acting and intermediary-acting medications

PMS®-Methylphenidate, Ratio®-Methylphenidate, Ritalin®, Ritalin® SR

The efficacy and safety of MPH is well established with significant reduction in the core ADHD symptoms. MPH short- and medium-acting products are placed by CADDRA CAP-Guidelines Committee in the second line group as their duration is shorter than that of long-acting versions and they are therefore prone to having peak/valley effects that may be uncomfortable. The major advantages of MPH are that:

- a) there are long-term studies of over twenty years in duration that show MPH is safe
- b) they may be useful in situations where a top-up of the once-daily medication is required or if the patient desires more flexibility over the dosing schedule
- c) a consensus of the CADDRA CAP-Guidelines Committee suggests that MPH may be indicated in some adult ADHD patients who want the medication for situational versus continuous use, and
- d) they are relatively inexpensive.

Ritalin® SR

Ritalin SR lasts longer (5-6 hours) than Ritalin. However, the compound has a wax matrix which at times results in inconsistent release of medication and thus inconsistent effects.


NON-STIMULANTS

Strattera®

Atomoxetine hydrochloride (ATX) is a specific noradrenaline reuptake inhibitor and comes in seven doses (10, 18, 25, 40, 60, 80 and 100 mg). ATX is not classed amongst the psychostimulants and it is not a controlled substance. The major strengths of ATX are that:

- a) it provides continuous coverage including the late evening and early morning periods
- b) it is indicated by Health Canada in all ADHD patients across the lifespan
- c) it may be particularly useful for ADHD patients who have tic spectrum disorders or comorbid anxiety, resistance and/or side effects to stimulant medications, including problems with worsening of sleep
- d) there appears to be no substance abuse or diversion potential and
- e) may be useful in patients with ADHD and comorbid enuresis^{58, 59}.

The onset of action is slower than stimulants as it acts differently on neurotransmitters and the maximum treatment effect may not be reached for six to eight weeks. The clinical changes are gradual. It would not be suitable in cases where there is an urgency to obtain a rapid onset of action. The dose is calibrated to the weight of the patient (see relevant tables for initiation, titration and maximum doses in Supporting Document 7A). There appears to be no increased benefit past 1.4 mg/kg/day though there may be some improvement of oppositional defiant disorder after 1.8 mg/kg/day²¹¹. The American Academy of Child and Adolescent Psychiatry has stated that the doses could go as high as 2.2 mg/kg/day but this is much higher than the Canadian standard³.

If higher doses are contemplated, a referral to an ADHD specialist should be made. If the doses exceed one pill a day, the cost of the medication increases. The medication's safety profile has been established, including risk factors related to cardiovascular conduction irregularity similar to those of stimulant drugs. Rare cases of reversible alteration in hepatic enzyme are noted. No special monitoring protocol is required (i.e. blood tests) but patients should be advised of the clinical symptoms of hepatic dysfunction. Poor metabolizers (i.e., 7% Caucasians and 2% African-Americans) are unlikely to have toxic effects given the slow titration schedule. Measurements of blood levels are not required. There have been rare reports of increase in suicidal ideation; one suicide attempt (overdose) was identified; no completed suicides occurred^{212, 213}. Clinicians need to carefully monitor suicidal ideation, especially in the early phases of treatment, not unlike with many antidepressant medications. The clinical efficacy was the same as stimulants in patients who were treatment naive²¹⁴. ATX can also be combined with stimulants to augment the effect if the clinician feels the patient has not achieved an adequate response , but in these circumstances, a referral to an ADHD specialist may be indicated. Strattera® can be given as a morning and evening split dose which is sometimes optimal to reduce side effects (but this strategy increases costs). Strattera can cause significant nausea and stomach upset in some patients. Strattera capsules should not be opened because the contents are an ocular irritant. If the contents get in the eye, there should be immediate eye-flushing and seek medical attention if needed.

Intuniv XR

Guanfacine hydrochloride extended-release (GXR) is a selective alpha 2A-adrenergic receptor agonist and comes in four doses (1, 2, 3 and 4mg). GXR is not classed among the psychostimulants and it is not a controlled substance. It is indicated by Health Canada for the treatment of ADHD in children aged 6-12 with sub-optimal response to psychostimulants either as an adjunctive therapy to psychostimulants or as a monotherapy. The major strengths of GXR are that:

- a) it provides continuous coverage including the late evening and early morning periods.
- b) it may be particularly useful for ADHD patients who have tic spectrum disorders or significant comorbid

anxiety, oppositional behaviours, aggression, or in cases of resistance and/or side effects to stimulant medications, including problems with worsening of sleep or pulse/blood pressure elevation.

The onset of action is slower than stimulants as it acts differently on neurotransmitters and the maximum treatment effect may not be reached for several weeks. The clinical changes are gradual. It would not be suitable in cases where there is an urgency to obtain a rapid onset of action. The side effects profile is very unique and necessitates close follow-up. There may be a dose-response related to weight. Dose is calibrated slowly (see relevant tables for initiation, titration and maximum doses in Supporting Document 7A).

Considering that GXR has a lower response rate than psychostimulants and requires close follow-up due to its side effects profile, the CADDRA Guidelines Committee recommends it as a second-line therapy. But in specific circumstances where psychostimulants are not recommended, GXR could be a first choice. In such cases, referral to an ADHD specialist may be made. The tablets should not be crushed, chewed or broken down before swallowing as this will alter the rate of guanfacine release. The medication's safety profile has been established. The risk factors related to cardiovascular side effects differ from those associated with stimulant drugs and atomoxetine. Somnolence, sedation and a lowering of pulse and blood pressure may occur, particularly at the initiation, after dose adjustments and following discontinuation. GXR should not be stopped abruptly since this may significantly increase pulse and blood pressure. Use caution when administered to patients taking medications like CYP3A4/5 inhibitors (e.g. ketoconazole), CYP3A4 inducers, valproic acid, heart rate-lowering and QT prolonging drugs. GXR should not be administered with high fat meals. It is recommended not to use grapefruit products.

Intuniv XR does not require any blood tests before starting treatment. As well, no ECG is required (if using as monotherapy) as long as there is NOT a positive cardiac history (which should be asked before initiating any medication for ADHD). To help maintain adequate blood pressure, patients should be advised to avoid dehydration. GXR is the only medication indicated in Canada as an adjunctive therapy to psychostimulants for the treatment of ADHD in children, aged 6-12 years, with sub-optimal response to psychostimulants, but in these circumstances, a referral to an ADHD specialist may be indicated. Intuniv XR™ can be given as a morning or an evening dose. Intuniv XR has been studied in adolescents with ADHD but no literature is available for adult ADHD, therefore all prescriptions for patients over 12 years old are off-label use and should be supervised by an ADHD specialist.

OFF-LABEL MEDICATIONS

Treatment by these medications should be initiated by specialists only or in consultation with a specialist in ADHD.

SUPPORTING DOCUMENT 7C: SIDE EFFECTS MANAGEMENT

Sleep Problems in ADHD

Problems with sleep are a common complaint from parents of ADHD children and patients of all ages²¹⁴. Children with ADHD are at increased risk of sleep disorders²¹⁵, and ADHD is overrepresented in sleep disorder clinics^{216, 217}. In addition, stimulant medication may increase the difficulty of falling asleep^{218, 219}. The most common sleep problem comorbid with ADHD is delayed sleep phase syndrome (DSPS), which is a disorder in which patients go to bed late and then want to sleep longer in the morning^{217, 220}. Patients often complain that "they cannot turn their thoughts off" and resist going to bed since they do not feel sleepy. DSPS is one of several circadian rhythm sleep disorders (CRSD)^{220, 221}.

Patients with ADHD are also at increased risk of other sleep disorders including obstructive sleep apnea^{215, 222}. Children with ADHD should always be screened for sleep disorders. The acronym **BEARS** is useful for this purpose: **B**edtime resistance, **E**xcessive daytime sleepiness, **A**wakenings, **R**egularity, **S**norings²²³. Most sleep problems can be diagnosed clinically and treated effectively with significant improvement in quality of life¹¹. Although there is some evidence of cases in which sleep problems were misdiagnosed as ADHD, treatment of sleep problems does not usually cure ADHD itself^{219, 220}.

Stimulants may induce insomnia: Administer medication as early as possible in the morning. Try to assure that the patient is not in rebound at the time that they are trying to fall back asleep by either lowering the dose late in the day or shaping a slow offset of action.

Strategies to Improve Sleep

Sleep Hygiene

Optimize sleep hygiene: maintain a quiet and comfortable sleep environment. Maintain a consistent time of going to bed and waking in the morning. If the patient is allowed to sleep late in the day this will phase delay the circadian rhythm. Exposure to passive stimulation activities such as watching television, playing computer games or going on chat lines will disrupt the initiation of sleep, despite beliefs that these activities promote fatigue. It is better that the individual do active stimulation such as reading as a means to make themselves mentally fatigued. It is helpful if the individual is physically active through the day (though not within two hours of bedtime) to aid in physical exhaustion. Limit the use of the bed to sleep and sex only as this will create a positive association. The bed is not for watching TV, eating or doing homework. As patients often have a difficult time getting up in the morning, it is best to ask the individual what would be the best way for them to be approached. Strategies such as giving a sugar-free carbonated drink first thing in the morning (which causes the eyes to water and wakes a child up) or warming up the room (otherwise the room feels cold and the bed feels warm) have also been anecdotally tried.

Validated Treatments for Sleep Disturbance

The only over the counter preparation that has been tested in randomized, double blind trials for insomnia in children with ADHD is melatonin. Two trials demonstrated efficacy, one in combination with sleep hygiene²²¹ and one without sleep hygiene^{225, 263}. The CADDRA Guidelines Committee feels that this data demonstrating efficacy, safety and very low cost make this a first line intervention when initiation of sleep is a problem, either off or on medication. Melatonin 3-6 mg should be administered at least 30 minutes (up to 2-3 hours) before the desired bedtime and is a safe and effective way of treating initial insomnia associated with ADHD. We have no available information on the safety and efficacy of melatonin use longterm.

Non-validated Treatments for Sleep Disturbance

None of the following suggestions have been investigated proving their efficacy. More research is required. At all times, the patient should consult his/her doctor regarding these choices.

Dietary snacks that maybe sedating: Dietary interventions are often foods that are high in tryptophan, a common amino acid found in many foods including turkey, beans, rice, hummus, lentils, hazelnuts, peanuts, sesame seeds, sunflower seeds, tuna, soy milk, cow's milk and other dairy products. An example of an ideal bedtime snack is a peanut butter sandwich with ground sesame seeds and a glass of warm whole milk, consumed one hour before sleep.

Naturopathic remedies Valerian root (450-900 mg extract) has not been clinically investigated but is felt to be relatively safe and anecdotal reports suggest efficacy.

Problems With Appetite and Their Management

Many parents of ADHD complain that their children are "picky eaters". In addition, stimulant medication can further suppress appetite and often shifts the timing of food intake to periods of the day in which stimulant blood levels are waning. There is a long history of research on ADHD and nutrition. Early studies of the relationship between special diets, sugar, red food dye, food allergies and ADHD did not confirm that diet is a significant contributor to the etiology of ADHD²²⁶.

More recently there has been increasing interest in whether ADHD is associated with either delay in growth or poor nutrition^{13, 227-231}. Many parents are concerned that their children with ADHD are thin or small and, as a group, children with ADHD are slightly smaller than age-matched controls²³². Children who receive continuous stimulant medication are found to show growth deceleration as compared to children who do not receive medication for up to three years. Most recent evidence from the Multisite Multimodal Treatment study of children with ADHD suggests a 2 cm suppression in adult height with continuous medication treatment for 12 years.

Several studies of the nutritional status of children with ADHD show deficits in zinc^{233, 234}, serum ferretin²³⁵, and general omega 3 fatty acids²³⁶, but the clinical implications of this are unclear. Parents who are concerned about their child not eating, eating too much junk food, or refusing to eat a particular food group may be helped if the physician takes the time to review dietary intake and gives strategies to encourage good nutrition. In particular, people with ADHD may not sit for long meals, may need to snack when medication wears off, and benefit from access to healthy snacks. Reliable randomized control trials demonstrating the impact of improved diet on ADHD are not available. There is some research suggesting the benefit of omega 3 fatty acids but the methodology is poor^{237, 238}. Common sense dictates that while improved sleep hygiene and sound nutrition are not likely to cure ADHD, sound sleep and nutrition would improve overall health and well being, and thus indirectly benefit behaviour and attention²³⁹⁻²⁴¹. More information is located in the section on Psychosocial Interventions (Chapter 6).

Strategies to Improve Caloric Intake

1. Offer parents a weight and height chart so they can monitor from a baseline any changes in these critical areas. Reassure parents that although the child may lose weight, this will stabilize, but the child's height percentiles will not change, though it is important to monitor them. This information helps to reduce parents' anxiety.
2. Supplemental strategies are often indicated, such as nutritional supplements or meal replacements (e.g., Boost®, Breakfast Anytime®, Ensure®, PediaSure®, PediaSure Complete®). Because dry mouth can be a

side effect of medication, the patient will have significant thirst. Allowing them to have frequent fluids throughout the day and high protein/high calorie drinks for lunch exclusively is usually sufficient to maintain their caloric needs.

3. Children should be encouraged to eat when they are hungry, especially early in the morning and in the evening. In the evenings, when there may be rebound appetite, supper can be spread out into two or three sessions to prevent gorging and stomach distress.
4. A significant snack equivalent to lunch can be instituted before bedtime.
5. Encourage the consumption of energy dense foods, especially at breakfast, prior to taking medication, to take advantage of the child's hunger, even if this means letting them choose less typical breakfast foods (such as a peanut butter and jelly sandwich, leftover supper, etc.).
6. Switch to whole dairy products (including milk, yogurt and cheese).
7. Ensure availability of nutritious snack foods.
8. Engage the child in meal preparation and in shopping for their favourite foods.
9. Structure and routine is important even at mealtimes. Encourage patients and their families to try to eat as a family in a calm environment.
10. Referral to a registered dietician may be necessary to optimize nutritional intake in cases of growth faltering.
11. If there is familial short stature, the CAP-G Committee has suggested drug holidays.

Problems With Headaches and Their Management

Headache is a common side effect occurring in greater than 3% of patients who use medications for ADHD. Headache may or may not be accompanied by nausea or gastric irritation. Headache is most common within the first two to three hours of taking the medication and tends to be a tension-type headache, characterized by a constant ache as opposed to a vascular headache that has a throbbing sensation. Vascular headache can also occur but is more of a suggestion of activating pre-morbid migraine propensities.

Strategies to Improve Headaches

Treatments include mild analgesics such as acetaminophen or ASA. Headaches usually dissipate after the ADHD medication has been used at a set dose for one to three weeks. It is important to remember that headaches are quite often associated with hunger and this issue needs to be addressed.

SUPPORTING DOCUMENT 7D: POTENTIAL CARDIOVASCULAR RISKS OF ADHD MEDICATIONS

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Regulatory History

In May, 2006, Health Canada issued important safety information on ADHD medications which included the following warning:

ADHD drugs should be started at the lowest possible dose, and increased slowly, as individual patient response to these drugs is known to vary widely.

- ADHD drugs should not be used if a patient has: symptomatic cardiac disease; moderate to severe hypertension; advanced arteriosclerosis; or hyperthyroidism
- ADHD drugs should generally not be used in patients with known structural cardiac abnormalities
- Before prescribing an ADHD drug, it is important to be aware of whether the patient: has a family history of sudden death or death related to cardiac problems; participates in strenuous exercise; or takes other sympathomimetic drugs; as these are thought to be additional risk factors. In patients with relevant risk factors, and based on the physician's judgement, further evaluation of the cardiovascular system may be considered before starting on the drug
- Patients who are considered to need long-term treatment with ADHD drugs should undergo periodic evaluation of their cardiovascular status, based on the physician's judgement
- Patients taking drugs for the management of ADHD are being advised not to discontinue their medication without consultation with their physician
- Similar information will appear in the Information for the Patient materials for these drugs.

The complete article is available on the www.caddra.ca website and should be read by any clinician who is contemplating treatment in a patient they deem as being at risk. The CAP-G Committee enlisted the help of two prominent Canadian cardiology consultants to prepare some guidance in at-risk patients who have a combination of some prior history of cardiac problems and ADHD. The opinions are those of the consultants and were not peer-reviewed, but were written to provide guidance to physicians who need direction in complicated cases.

Clinical Recommendations

American Heart Association Recommendations for Monitoring

In the American Heart Association Scientific Statement: Cardiovascular Monitoring of Children and Adolescents Receiving Psychotropic Drugs (A Statement for Healthcare Professionals)^{242, 243}, the Committee on Congenital Cardiac Defects, Council on Cardiovascular Disease in the Young states that:

1. "Reports of sudden deaths of children and adolescents treated with psychotropic medications have

raised concerns regarding the appropriateness of this therapy, as well as the advisability of baseline and periodic electrocardiographic (ECG) monitoring of such patients."

2. "Stimulants such as the amphetamines and methylphenidate (Ritalin®) cause slight but clinically insignificant increases in heart rate and blood pressure."
3. "Clonidine, a widely used antihypertensive medication, has been associated with two deaths in patients who also received methylphenidate, but the mechanism for these deaths is unknown and may have been sudden cessation of treatment."

The American Heart Association Recommends:

1. Before therapy with psychotherapeutic agents is initiated, a careful history should be obtained with special attention to symptoms such as palpitations, syncope, or near syncope. Medication use (prescribed and over-the-counter) should be determined. The family history should be reviewed with reference to the long QT syndrome or other causes of sudden, unexplained death. Detection of these symptoms or risk factors warrants a cardiovascular evaluation by a pediatric cardiologist before initiation of therapy.
2. At follow-up visits, patients receiving psychotropic drug therapy should be questioned about the addition of any drugs and the occurrence of any of the above symptoms. The physical examination should include determination of heart rate and blood pressure.

Conclusions

1. Sudden death in the young is fortunately very rare (1.2 - 1.3/100,000 population). **Sudden death in the ADHD population occurs in similar proportion to the general population**, even if only 50% of cases have been reported. However, higher rates of under-reporting could be concealing an ADHD effect on sudden death, and rare deaths have occurred on the first day of administration.
2. **There are similar associated conditions** in patients with sudden death on ADHD medications to those with sudden death in the general population (structural heart disease, history of syncope, family history of sudden death, exercise triggering sudden death), and some of these clues can help to suspect a higher risk sudden death, whether in the untreated or treated population.
3. ECG abnormalities can identify some individuals in the general population at risk for sudden death, and has been recommended and implemented as a cost-effective screening tool in some at risk populations, such as competitive athletes. Cost-efficacy in the general school-age population is less clear and the usefulness of ECG screening in patients being treated with or considered for ADHD medications is unknown. There is no consensus here, and American Heart Association recommendations for ECG screening relate specifically to tricyclic antidepressant therapy or phenothiazine therapy. There is **no indication for ECG's** for the treatment of ADHD using stimulant medications (except in at-risk populations).
4. The small (but unproven) potential contribution of ADHD drugs to the rare incidence of sudden death in children and adolescents **must be weighed against the clinical benefit of the medication**. Risk/benefit should be discussed with the parent/patient as appropriate.
5. **Cardiac consultation should be considered in at-risk patients** with cardiac conditions. ADHD medications should only be considered after a thorough discussion of the risks and potential benefits with the patient, family and consultants.

Practice Point

Practical questions and answers: Management of patients with combined cardiovascular risk and concurrent ADHD.

Q: Is there a way to specifically know ahead of time the risk of sudden death in individual patients with ADHD, and the potential increase in risk in such patients following treatment?

A: It is not possible to accurately assess the magnitude of increases in risk with ADHD medications, or even if there is any increase in risk. However it is helpful to consider, for discussion purposes, some possible numbers to place these risks in perspective. If the risk of sudden death in an individual without evident structural heart disease is approximately 1 per 100 000 /year (age under 25), then even a 50% increase in risk would translate into an absolute increase of 0.5/100 000 deaths/year, or a 1/200 000 chance of death.

Q: Are there disorders where structural cardiac defects pose low risk?

A: Patients with cardiac conditions whose sudden death risk is only marginally elevated from the general population are likely at very low risk if taking ADHD medications. Risks/benefits should be discussed with the parent/patient as appropriate. Such conditions might include (but not be limited to) patients with: a) an asymptomatic or well-repaired atrial septal defect; b) a small or well-repaired ventricular septal defect; c) a well-repaired coarctation of the aorta, without hypertension or significant associated aortic valve disease and d) a mild or well-repaired pulmonary valve stenosis.

Q: What reasonable steps should be taken to ensure patients' cardiovascular safety before starting pharmacological therapy for ADHD?


A: As described above, patients and families should be questioned about a family history of sudden death, a history of loss of consciousness particularly with exercise, and a history of marked exercise intolerance. There is no proof that routine 12 lead ECGs are useful in screening in unselected patients, and most consultants do not recommend such screening unless there is a history or symptoms to suggest cardiac disease. During follow up, new onset syncope, severe dizziness, or exercise intolerance should be asked about, particularly in the early months of pharmacological treatment. If any of these symptoms occur, these should prompt a referral to a pediatrician or a cardiologist, and a consideration at least temporarily stopping the medication for ADHD.

If an ADHD pharmacological treatment is contemplated in a patient with previously known structural heart disease, or in a patient who has a personal or a family history of syncope or sudden death respectively, a pediatric or cardiologic consultation prior to ADHD pharmacological treatment is strongly advised.

It must be emphasized that in the average child or adolescent with ADHD, who has no cardiac symptoms, the risk of cardiac adverse events from ADHD medications is extremely low. On the other hand, a cautious and vigilant attitude with respect to the potential risks is highly advisable.

SUPPORTING DOCUMENTS 7E: OTHER MEDICATION INFORMATION

Long-Acting Medication Comparison Profiles

	Adderall XR®	Vyvanse®	Biphentin®	Concerta®	Novo-MPH-ER-C®	Strattera®	Intuniv XR®
CLINICAL COMPARISONS							
Active Ingredient	Mixed Amphetamine Salts	DEX	MPH HCL	MPH HCL	MPH HCL	ATX	Guanfacine extended-release
Canadian Indication	All age groups	All age groups	All age groups	All age groups	A generic substitute for Concerta	All age groups	6-12 y.o. children: monotherapy/adjunct therapy to psychostimulants when associated with a suboptimal response
Clinical Efficacy Studies	Yes	Yes	Yes	Yes	No	Yes	Yes
Long-acting Technology Used	Two beads	Pro-drug	Multilayer beads	OROS	Unknown	Blood level based	Polymer matrix
Duration of Effect¹	~12 hours	13-14 hours	10-12 hours	10-12 hours	Unknown	Continuous	Continuous
(%IR/%LA) Delivery	50/50	Continuous	40/60	22/78	Unknown	Continuous	Continuous
Sprinkle Format	Yes	Dissolvable in water	Yes	No	Unknown	No	No
Available Doses	6	5	8	4	4	7	4
Abuse Potential 	Low	Very Low	Low	Very Low	Likely High	None	None
Cost	\$\$	\$\$	\$+ low doses but \$\$ higher doses	\$\$	\$	\$\$\$	\$\$\$
Controlled Substance	Yes	Yes	Yes	Yes	Yes	No	No

¹Clinical experience indicates that, for some patients, duration of effect is shorter or longer than what is indicated in the product monograph.

SIDE EFFECTS (PUBLISHED LITERATURE)

	First Line Agents					Second Line or Adjunctive Agents						
	Adderall XR®	Biphentin®	Concerta®	Vyvanse®	Dexedrine®	Dexedrine Spansules®	MPH Generic®	Ritalin®	Ritalin SR®	Strattera®	Intuniv XR®	
Appetite suppression	X	X	X	X	X	X	X	X	X	X	Reported at lesser incidences	
Decrease in weight	X	X	X	X	X	X	X	X	X	X		
Initial insomnia	X	X	X	X	X	X	X	X	X	X ¹		
Somnolence										X	X	
Headache	X	X	X	X	X	X	X	X	X	X ²	X	
Dry mouth	X	X	X	X	X	X	X	X	X	X	X	
Rebound irritability	X	X	X	X	X	X	X	X	X	X	X	
Nausea/vomiting	X	X	X	X	X	X	X	X	X	X	X	
GI upset	X	X	X	X	X	X	X	X	X	X	Upper abdominal pain was reported	
Dizziness	X	X	X	X	X	X	X	X	X	X	X	
Anxiety	X	X	X	X	X	X	X	X	X	X ²		
Uncovering tics	X	X	X	X	X	X	X	X	X	possible		
BP and HR increase	X	X	X	X	X	X	X	X	X	X	When ceased abruptly	
BP and HR decrease											X	
Constipation/diarrhea	X	X	X	X	X	X	X	X	X	X		
Sexual dysfunction	minor		minor	minor	minor	minor				X		
Dysphoria	X	X	X	X	X	X	X	X	X	X		
Skin reactions	X	X	X	X	X	X	X	X	X	X		

¹ Clinically observed initial insomnia in adults reported by CAP-G Committee

² Clinically reported by CAP-G Committee

PHARMACOKINETICS

First Line Agents				Second Line or Adjunctive Agents							
	Adderall XR®	Biphentin®	Concerta®	Vyvanse®	Strattera®	Dexedrine®	Dexedrine Spansules®	MPH Generic®	Ritalin®	Ritalin SR®	Intuniv XR®
Protein binding	12-15%		8-15%		98%	12-15%	12-15%	8-15%	8-15%	8-15%	70%
Peak plasma levels	7 hours	2 hours, then 6 hours	1 hour, then 6-10 hours	3.5 hours	1-2 hours	6-10 hours	6-10 hours	3.8-4.6 hours	0.3-4 hours	1-8 hours	5 hours
% immediately released	50%	40%	22%	Continuous	Continuous	100%		100%	100%		Continuous
T 1/2	9 hour child 10 hour adult	5 hours	3-5 hours	9.6 hours	5 hours	6-8 hours	6-8 hours	2.5 hours	2.5 hours	3-4 hours	18 hours
Duration of action¹	~12 hours	10-12 hours	10-12 hours	13-14 hours	24 hours	~6-8 hours	~6-8 hours	3-4 hours	3-5 hours	3-8 hours	24 hours
Enzyme inhibited					CYP2D6						
Controlled substance	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No
Neurochemical	DA/NA	DA	DA	DA/NA	NA	DA/NA	DA/NA	DA	DA	DA	Alpha 2A noradrenergic agonist

DA: Dopamine

NA: Noradrenaline

¹Clinical experience indicates that, for some patients, duration of effect is shorter or longer than what is indicated in the product monograph.

DRUG INTERACTIONS*

Second Line or Adjunctive Agents											
First Line Agents											
	Adderall XR®	Biphentin®	Concerta®	Vyvanse®	Strattera®	Dexedrine®	Dexedrine Spansules®	MPH Generic®	Ritalin®	Ritalin SR®	Intuniv XR®
Acidifying Agents e.g. fruit juices	↓ absorption ↑ elimination ↓ plasma level			↓ absorption ↑ elimination ↓ plasma level ¹		↓ absorption ↑ elimination ↓ plasma level					
Alkaline Agents e.g. sodium bicarb	↑ absorption ↓ elimination ↑ half-life			↑ absorption ↓ elimination ↑ half-life ²		↑ absorption ↓ elimination ↑ half-life					
Analgesics e.g. Meperidine	↑ analgesic effect			may ↑ analgesic effect							
Antiarrhythmic e.g. Quinidine					↑ ATX						generally not recommended
Antiasthmatic					↑ HR with nebulizer						
Antibacterial e.g. Linezolid		avoid	avoid					avoid	avoid	avoid	
Anticoagulation e.g. Warfarin		↑ effects of Warfarin	↑ effects of Warfarin						↑ effects of Warfarin		
Anticonvulsants e.g. Carbamazepine											↑ concentrations of valproic acid ↓ effects of GXR
Phenobarbital	may ↑ effects of anti-epileptic	↑ effects of anti-epileptic	↑ effects of anti-epileptic	may ↑ effects of anti-epileptic		synergistic effects			↑ effects of anti-epileptic		
Phenytoin											
Primidone											

¹ GI acidifying agents do not affect Vyvanse but urinary acidifying agents do

² GI alkalinizing agents (e.g. antacids) won't affect Vyvanse but urinary ones could

* Reviewed by the relevant pharmaceutical manufacturer, except for Glaxo Smith Klein, Novartis and Novopharm.

DRUG INTERACTIONS* (continued)

First Line Agents					Second Line or Adjunctive Agents						
	Adderall XR®	Biphenitin®	Concerta®	Vyvanse®	Strattera®	Dexedrine®	Dexedrine Spansules®	MPH Generic®	Ritalin®	Ritalin SR®	Intuniv XR®
Antidepressants - MAOI e.g. Phenelzine	↑ Noradrenaline - may lead to hypertensive crisis - do not combine										
RIMA e.g. Moclobemide	do not combine		↑ BP	do not combine	↑ BP	precaution			there may be an adjunctive quality; may ↑ BP		
SSRI e.g. Fluoxetine	↑ effects of SSRI	↑ effects of SSRI	↑ effects of SSRI	↑ effects of SSRI	↑ ATX plasma concentration	may be additive effects			↑ effects of SSRI		CYP450 3A4 inhibitor ↑ levels of GXR
TCA - Secondary e.g. Desipramine	may lead to ↑ levels of TCA or AMP	↑ effects of TCA	↑ effects of TCA	may lead to ↑ levels of TCA or AMP	should not be used in combination	may lead to ↑ levels of either TCA or amphetamine					
TCA - Tertiary e.g. Amitriptyline											
Antihypertensives Beta Blockers e.g. Propranolol	may ↓ hypotensive effects			may ↓ hypotensive effects							may ↑ hypotensive effects
Alpha 2 Agonists e.g. Clonidine	may ↓ hypotensive effects	precaution	precaution	may ↓ hypotensive effects		may ↓ hypotensive effects			precaution		not recommended
Antipsychotics e.g. Chlorpromazine, Haloperidol											may interact with other medications that prolong QTc
CNS Depressants Antihistamines e.g. Diphenhydramine	may inhibit central stimulant effect of AMP			may inhibit central stimulant effect of AMP				may antagonize sedative effects			may be additive to sedative effect

ATX= ATOMOXETINE

*Reviewed by the relevant pharmaceutical manufacturer, except for Glaxo Smith Klein, Novartis and Novopharm.

CONTRAINDICATIONS(C) OR PRECAUTIONS(P) (PUBLISHED LITERATURE)

	First Line Agents					Second Line or Adjunctive Agents					
	Adderall XR®	Biphentlin®	Concerta®	Vyvanse®	Strattera®	Dexedrine®	Dexedrine Spansules®	MPH Generic®	Ritalin®	Ritalin SR®	Intuniv XR®
Tic Disorders¹	p	c	c	p		p		c	c	c	
Epilepsy	p	p	p	p		p		p	p	p	
Cardiac Disease²	p/c	p/c	p/c	p/c	p/c	p/c		p/c	p/c	p/c	p
Hepatic Disease											p
Eating Disorders											
Psychosis	p	p	p	p	p	c		c	c	c	
Kidney Disease											p
Glaucoma	c	c	c	c	c	c		c	c	c	
Hyperthyroidism	c	c	c	c	c	c		c	c	c	
Adrenal Tumours	p	p	p	p	p	p		p	p	p	
Asthma					p ³						
GI Obstruction			p								

¹ Psychostimulant medications are used with precaution in tic spectrum disorders but the CAP-G Committee agrees that use can be indicated if there is sufficient impairment of the concurrent ADHD. In these cases, the medications for ADHD are often combined with other drugs for tics (e.g., atypical neuroleptics or alpha-2 agonists).

² Refer to Chapter 7, Supporting Document 7D.

³ Strattera may be used in combination with inhaled Beta2 agonists, e.g., salbutamol, but should be used with caution in patients being treated with systemically administered (oral or intravenous) Beta2 agonists, including salbutamol.