ADHD in children and youth: Part 2—Treatment

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Abstract

Attention-deficit hyperactivity disorder (ADHD) is a chronic neurodevelopmental disorder. Three position statements have been developed by the Canadian Paediatric Society, following systematic literature reviews. Statement objectives are to:

1) Summarize the current clinical evidence regarding ADHD,
2) Establish a standard for ADHD care, and
3) Assist Canadian clinicians in making well-informed, evidence-based decisions to enhance care of children and youth with this condition.

Specific topics reviewed in Part 2, which focuses on treatment, include: evidence and context for a range of clinical approaches, combining behavioural and pharmacological interventions to address impairment more effectively, the role of parent and teacher (or other caregiver) training, the use of stimulant and nonstimulant medications, with effects and risks, and dosing and monitoring protocols. Treatment recommendations are based on current guidelines, evidence from the literature, and expert consensus.

Keywords: ADHD; Adverse effects; Combined interventions; Medication management

NONPHARMACOLOGICAL INTERVENTIONS FOR ADHD

Current ADHD guidelines recommend including nonpharmacological interventions as part of treatment planning for children and adolescents with ADHD (1–3). Some evidence-based interventions, such as organizational skills training, have specific indications, while others, such as physical exercise, have a wide range of benefits. Recommendations for nonpharmacological intervention should be individualized, based on specified treatment goals, follow a thorough evaluation of comorbid conditions and be appropriate for the child’s or youth’s age and stage, as well as being both acceptable to and feasible for the patient, family, and schoolteachers. Table 1 summarizes nonpharmacological interventions for ADHD.

INITIATING TREATMENT

For children with ADHD younger than 6 years of age, evidence is robust that first-line intervention should be parent behaviour training (4). Overall evidence for the effectiveness of psychostimulants is weak, and Health Canada has not approved their use in this age group.

Medication works primarily on core ADHD symptoms and should be considered for children aged 6 years and older (5–7).
### Table 1. Nonpharmacological interventions for ADHD

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Evidence</th>
<th>Context for use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychoeducation</td>
<td>An RCT comparing a structured psychoeducational intervention with a support group for parents of children and youth with ADHD showed improvements in parent-reported symptoms, with additional benefits in prosocial behaviour after 1 year (9).</td>
<td>When initiating treatment, providing accurate education and information to patients and families are essential for successful management planning and implementation. Misperceptions are common. Many patients and families rely on both online and physician-recommended resources for information (10).</td>
</tr>
<tr>
<td>Shared decision-making</td>
<td>A 6-month longitudinal cohort showed that parents who focused on academic improvements were more likely to initiate medication, while those more concerned with behaviour were likelier to begin behavioural therapy (12).</td>
<td>In shared decision-making, all participants (parents, youth/child, and physician) share information regarding diagnosis and treatment before the latter is implemented. Treatment planning is enhanced by identifying goals for improvement (1): academic performance (2), behavioural compliance (3), interpersonal relationships (11).</td>
</tr>
<tr>
<td>PBT</td>
<td>Meta-analytic examination of RCTs of PBT using observations and teacher ratings showed improved parenting skills for conduct problems. Parent ratings showed effectiveness for ADHD symptoms, social skills and academic performance (95).</td>
<td>For preschool age children, PBT should be the intervention of first choice (4). For disruptive behaviours comorbid with ADHD, initiating PBT before medication proved more effective than medication followed by PBT (96).</td>
</tr>
<tr>
<td>Classroom management</td>
<td>Classroom behaviour management strategies have been considered a well-established treatment for ADHD for over a decade (97).</td>
<td>Teachers help children with special needs by setting classroom rules and expectations, providing students with individual attention and praise, and offering both direct and indirect messages of acceptance.</td>
</tr>
<tr>
<td>Daily report card</td>
<td>An RCT of daily report cards and psychological consultation showed improved compliance with classroom rules, academic productivity and classroom behaviours (98).</td>
<td>Behaviour management strategies that include parent and teacher cooperation have been shown to improve homework completion (98).</td>
</tr>
<tr>
<td>Behavioural peer interventions</td>
<td>RCTs of two such programs (different researchers) observed improved peer skills in classroom settings; therefore, the intervention is considered well established (99).</td>
<td>Adults use behaviour modification techniques to help children improve peer skills in recreational settings, such as summer camps (99).</td>
</tr>
<tr>
<td>Social skills training</td>
<td>No clear evidence of efficacy for improved classroom behaviour or peer interaction skills (5).</td>
<td></td>
</tr>
<tr>
<td>Organizational skills training</td>
<td>RCTs of two such programs (different researchers) showed improvements in organization, time management and planning; therefore, the intervention is considered well established (100).</td>
<td>These programs address specific executive functioning difficulties common in children with ADHD. They are added to other interventions (100).</td>
</tr>
<tr>
<td>Cognitive training</td>
<td>Meta-analysis showed benefit for working memory skills targeted by computerized interventions. Parents, but not teachers, reported improved inattention symptoms (101).</td>
<td>Computerized interventions for specific neuropsychological deficits (e.g., working memory) require additional development before they can be considered clinically useful (102).</td>
</tr>
<tr>
<td>EEG neurofeedback</td>
<td>Systematic reviews showed benefit reported by parents; benefit from blinded outcomes was less clear (103).</td>
<td>Such interventions require additional development before they can be considered clinically useful (104).</td>
</tr>
<tr>
<td>Diet</td>
<td>Small effects on ADHD symptoms were shown for free fatty acid supplementation and restricted elimination diets (e.g., removing artificial food dyes) (6,105).</td>
<td>Children with a suspected dietary deficiency, insufficiency or food allergy should be evaluated (106).</td>
</tr>
<tr>
<td>Exercise</td>
<td>Meta-analysis of exercise interventions (e.g., short-term aerobic exercise and yoga) showed improvement in core ADHD symptoms and in related anxiety and cognitive functions (107).</td>
<td>Exercise provides additional benefits to health and well-being (108).</td>
</tr>
</tbody>
</table>

**ADHD** Attention-deficit hyperactivity disorder; **EEG** Electro-encephalograph; **PBT** Parent behaviour training; **RCT** Randomized control trial.
However, more than one-half of children with ADHD have psychiatric and developmental comorbidities (8). For this reason, nonpharmacological interventions (Table 1) should be considered routinely as part of comprehensive ADHD care, with specific goal-setting to improve compliance, academic performance, and quality of life. Psychoeducation around optimal supportive care should be available for all patients and families of children and youth with ADHD (9,10).

Generally, parents’ preferences for either medication or behavioural interventions for younger children are guided by beliefs and values, which interventions are easily accessible, and concerns about adverse effects (AEs) and stigma (11). Parents who are focused on improving academic skills are more likely to initiate medication, while those more concerned about behaviour are likelier to choose behavioural therapy (12).

Prescribing stimulants for non-ADHD-related learning or behaviour disorders and polypharmacy for ADHD treatment are growing concerns. Prescription rates for ADHD in the UK have risen over the last 20 years from 0.4% to 4% of children (13). One study found that more than 10% of children in some districts of the USA were being treated with stimulants (14). Canadian prescription rates are also reported to be on the rise, and may be approaching US levels (15).

**Recommendation 1:** Treatment approaches for children and youth with ADHD and comorbidities must be multimodal and part of an individualized, comprehensive care plan. A psychoeducational plan of interventions should be initiated first, combined with other nonpharmacological interventions and medication when indicated, always keeping specific functional or behavioural goals in mind.

**Recommendation 2:** Medication use should be reserved for children and youth diagnosed with ADHD (see the companion statement on etiology, diagnosis, and comorbidity in this issue) whose learning or academic performance are impaired by attention difficulties or whose behaviours and social interactions are impaired by lack of impulse control and hyperactivity.

**EFFECTS OF STIMULANT MEDICATION**

Outcomes from well-designed, long-term trials to evaluate the effectiveness of stimulants for ADHD are under-researched (16) and, due to publication bias (17), may also be under-reported. Stimulants appear to improve parent-reported quality of life in children being treated for ADHD (18–21) and are associated with improved academic achievement and lower rates of comorbid anxiety and depression in young adulthood (22). However, lasting impact on the core symptoms of ADHD has not been confirmed (23).

Short-term randomized control trials of stimulant use for ADHD have shown that these medications can improve function in multiple domains, including decision-making (21), handwriting (24), and school work productivity (25). Among adolescents and young adults with ADHD, longer-acting preparations of extended-release (ER) stimulants have demonstrated improved evening driving performance (26). Population-based observational studies have indicated that stimulant treatment is also associated with better math and reading scores (27), fewer injuries leading to emergency room visits (28,29) and reduced morbidity and mortality related to motor vehicle injuries (30).

Long-term cohort studies following children who were diagnosed in childhood with ADHD into adulthood, compared with children living without ADHD, have documented that individuals with ADHD who continue to experience higher rates of inattention, impulsiveness and hyperactivity than their typical peers will also have greater difficulties with educational and occupational adjustments, risky sexual behaviours, and psychiatric disorders than those for whom core ADHD symptoms diminished over time (31,32).

These studies suggest that when ADHD symptoms persist into young adulthood, there is reason to continue stimulant treatment to address them. Indeed population studies show that stimulant use is associated with better employment outcomes (31,32), and reduced morbidity and mortality related to motor vehicle injuries (30).

**INITIATING AND MONITORING STIMULANT MEDICATIONS**

Initial titration and monitoring to evaluate the benefits and AEs of ADHD medication should include using standardized questionnaires (33–35) and checklists (33,34) (www.cps.ca/en/tools-outils/mental-health-screening-tools-and-rating-scales). Parents and older children can provide baseline observations regarding symptom severity and potential AEs. Baseline and follow-up teacher observations are also essential for monitoring treatment response (36).

**Recommendation 3:** When initiating treatment with ADHD medication, set goals or target outcomes focused on symptom reduction and improved functioning (e.g., improving family or peer relationships, reducing disruptive behaviours, enhancing independence in self-care or homework) to guide the treatment plan.

**Recommendation 4:** Use standardized checklists to monitor treatment response. Information must be obtained from two or more settings and include direct input from school.

The differences in efficacy and AE profiles between methylphenidate (MPH) and dextroamphetamine (DEX) stimulant preparations are minimal. Both MPH and DEX are available in short-, medium- and ER formulations. To start, the choice of one stimulant over another depends on duration of effect, cost and ease of administration. Differences in effectiveness or AE profiles among stimulant brands, as experienced by individuals, appear to be idiosyncratic. Switching from one stimulant formulation to another is recommended over switching from a stimulant...
medication to a nonstimulant. The child’s or youth’s family and physician, with input from teachers and caregivers, can usually determine whether a specific psychostimulant and dose is effective and well-tolerated within 2 to 4 weeks of initiation.

**Recommendation 5:** Initiate treatment with a stimulant formulation from either the MPH or DEX subclass. Switching to another formulation within the same subclass or within the other subclass should be tried before concluding that a child or youth does not respond to or cannot tolerate stimulants.

**Choosing initially between ER versus immediate-release (IR) stimulant preparations**

Medication adherence correlates better with once-daily ER prescriptions than with short-acting prescriptions (37–43). AEs are a common reason for discontinuing stimulant medications (44). Finding the optimal dose within a relatively short time improves adherence because poor adherence is correlated with dosing that is too low for too long (45) or with high dosing that causes unacceptable side effects (44,46). Lower medication adherence is also associated with older age and with having a learning, mood or behavioural comorbidity (40–43). Unfortunately, ER preparations are prohibitively expensive for many families (46).

**Recommendation 6:** In combination with nonpharmacological interventions, ER stimulants are recommended as first-line therapy for most children and youth with ADHD.

The occasional use of IR formulations may be indicated for children who cannot yet tolerate ER stimulants (e.g., because they are preschool-age) or for individuals with short-term attention and behavioural targets.

Longer-acting ER formulations are especially appropriate for older children whose homework demands protracted attention or for individuals experiencing impulsive or at-risk behaviours or difficulties with peer and family relationships outside of school hours. Continuing ER medication use over weekends and holidays may benefit children or youth with ADHD who are at high risk for poor outcomes, engaged in risk-taking behaviours or struggling with peer interactions. In these circumstances, ‘drug holidays’ should not be recommended routinely, unless there are specific concerns about a medication’s AEs. Dosing and duration become particularly important medication features for adolescents, who may drive during evening hours or at night (26). An additional benefit of ER medications is that they are less likely to be diverted for recreational use (47,48) than IR-stimulants because ER capsules are difficult to crush, effectively prohibiting intranasal or intravenous administration. Also, the controlled rate of release minimizes rapid absorption and delivery to the brain (49–51).

The duration of action of ER stimulants can range between 6 and 13 hours (Table 2). A single dose of any ER stimulant is usually given at breakfast time. Administered more than 30 minutes before breakfast, an ER stimulant can diminish appetite for breakfast. Appetite suppression is the most commonly reported AE with stimulant use. Although appetite suppression may be acceptable at lunchtime, it should no longer be present by dinnertime. Titration should aim for medication to ‘wear off’ to avoid dinnertime appetite suppression and sleep problems.

Dosing should be individualized based on response to careful titration to the lowest effective dose, not on severity of presentation or (solely) on the child or youth’s age or size. Close monitoring is essential until medication effectiveness and tolerability have been optimized. When the initial dose is tolerated but not effective, small increments at weekly, biweekly or monthly intervals may be helpful, until symptoms are improved or AEs appear.

Dosing requirements may need to be increased initially because of ‘up-regulation’ of the liver enzymes that catabolize stimulants, which causes tachyphylaxis (47). When dosage response has been optimized, monitoring every few months helps ensure the dose remains appropriate and can be adjusted as necessary.

Dose adjustments must be closely tied to reports of benefits or AEs from families and teachers. Clinicians must remember that preconceived notions concerning stimulants persist in the popular mind and sometimes colour perceptions of treatment effectiveness (52–54). Moreover, the different natures of home and school settings and the duration of medication action can sometimes cause or enhance true differences in functioning between school and home. For example, when teachers report improvements not observed by parents, the duration of medication action may be limiting observable benefits to school hours. When caregivers report benefits that are not seen by teachers, be sure to consider a comorbid learning difficulty, bullying or the placebo effect. When parents and teachers both report inadequate response to a medication, despite counselling, trials of more than one medication and careful dose titration, revisit the original diagnosis.

If medication requirements appear to exceed maximum recommended doses (Table 2), consulting with an expert in ADHD management is essential.

**Monitoring the AEs of stimulant medications**

There is significant variability among individual dosing requirements and dose-related AEs. Before initiating any medication, it is important to determine baseline symptom rates, specifically for low appetite, sleep difficulties, moodiness, irritability, and tics, as these are among the most common AEs of stimulant medications but are also common symptoms in untreated children and youth with ADHD.
### Table 2. Stimulant and nonstimulant medications for ADHD

<table>
<thead>
<tr>
<th>Medication</th>
<th>Duration of action (hours)</th>
<th>Mechanism of sustained action</th>
<th>Palatability considerations</th>
<th>Starting dose</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER methylphenidate formulation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concerta (OROS-MPH)</td>
<td>8–12 h</td>
<td>Osmotic release in multiple stages</td>
<td>Capsule must be swallowed whole</td>
<td>0.5 mg/kg</td>
<td>0.8 mg/kg to 1.5 mg/kg</td>
</tr>
<tr>
<td>Biphentin (MPH-HCl, controlled-release capsules)</td>
<td>6–10 h</td>
<td>Enteric coating of minute ‘beads’ within capsule</td>
<td>Beads can be sprinkled on a spoon of soft food (must not be chewed)</td>
<td>0.5 mg/kg</td>
<td>0.8 mg/kg to 1.5 mg/kg</td>
</tr>
<tr>
<td>ER methylphenidate formulation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generic MPH ER</td>
<td>4–5 h (varies widely)</td>
<td>Compressed powder</td>
<td>Intended to be swallowed whole</td>
<td>0.5 mg/kg</td>
<td>0.8 to 1.5 mg/kg</td>
</tr>
<tr>
<td>Ritalin SR</td>
<td>4–5 h (varies widely)</td>
<td>Compressed powder</td>
<td>Intended to be swallowed whole</td>
<td>0.5 mg/kg</td>
<td>0.8 to 1.5 mg/kg</td>
</tr>
<tr>
<td>Amphetamine/Dextroamphetamine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vyvanse</td>
<td>8 to 13 h</td>
<td>‘Pro-drug’ only bioavailable after slow enzymatic cleavage of lysine from dexamphetamine</td>
<td>Capsule contains powder and may be mixed with food or drink</td>
<td>0.5 mg/kg</td>
<td>0.8 mg/kg to 1.5 mg/kg</td>
</tr>
<tr>
<td>Lisdexamphetamine dimesylate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adderall XR</td>
<td>6–8 h</td>
<td>Enteric coating of minute ‘beads’ within capsule</td>
<td>Beads can be sprinkled on a spoon of soft food (must not be chewed)</td>
<td>0.25 mg/kg</td>
<td>0.4 mg/kg to 0.7 mg/kg</td>
</tr>
<tr>
<td>Mixed amphetamine salts</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexedrine spansule</td>
<td>4–6 h</td>
<td>Spansule with sustained-release capsule</td>
<td>Spansule to be swallowed whole (must not be crushed or chewed)</td>
<td>10 mg taken daily</td>
<td>range 20 mg to 30 mg per day</td>
</tr>
</tbody>
</table>
### Table 2. continued

<table>
<thead>
<tr>
<th>Nonstimulant formulation</th>
<th>Duration of action (hours*, varies widely)</th>
<th>Mechanism of sustained action</th>
<th>Palatability considerations</th>
<th>Starting dose</th>
<th>Range</th>
<th>Maximum</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strattera (Atomoxetine HCl)</td>
<td>24 h</td>
<td>Selective norepinephrine reuptake inhibitor</td>
<td>Capsule should be swallowed whole and not opened</td>
<td>0.5 mg/kg/d</td>
<td>40 mg per day</td>
<td>0.5 mg/kg/d to 1.2 mg/kg/d</td>
<td>Increase by 0.3 mg/kg intervals every 1–2 weeks</td>
</tr>
<tr>
<td>Intuniv XR (Guanfacine XR)</td>
<td>24 h</td>
<td>Selective alpha 2a-adrenergic receptor agonist</td>
<td>Matrix tablet to be swallowed whole once daily</td>
<td>1 mg/d</td>
<td>0.05 mg/kg/d to 0.12 mg/kg/d, in AM or PM</td>
<td>At 6–17 years old: 4 mg/day</td>
<td>MAXIMUM, in combination with stimulants At 6–12 years old: 4 mg/day MAXIMUM monotherapy At 13–17 years old: 7 mg/day MAXIMUM monotherapy</td>
</tr>
</tbody>
</table>

Data adapted from ref. (109)*.

ER Extended-release; Rx Prescription; SR Sustained-release

Duration of action is highly variable and may be shorter or longer than indicated for certain individuals.
Another concern commonly expressed by families is that a child or youth seems ‘too quiet’ or over-focused when their medication dose is too high. Some adolescents also describe personality changes or feeling constricted. Preschool children experience higher rates of side effects, especially irritability and moodiness, and, typically, better tolerate smaller doses of stimulant medications (55). At typical doses, the overall risk for developing or exacerbating a tic disorder is not increased in children with ADHD who are treated with stimulants, compared with untreated children (56–59). Transient fluctuations in tic severity are common, particularly with stress. Tics should be monitored and may require dose adjustments without discontinuing the medication. A comorbid tic disorder is not a contraindication for ADHD treatment.

Psychostimulants and nonstimulants are associated with a variety of peripheral vasculopathic symptoms, including Raynaud’s phenomenon (60). Symptoms are often triggered months or years after starting these medications, by a change of dose or drug (61,62).

Only rarely has psychosis been noted as an AE of stimulants (63). Priapism has been reported, again rarely, in individuals with ADHD who are taking stimulants (64), but is also observed in unmedicated individuals with ADHD (65). Until more evidence is available, families should be counselled about possible risks and management.

Cardiovascular changes with stimulants include slight increases in heart rate and blood pressure. However, the presence of abnormal blood pressure (i.e., in the hypertensive or prehypertensive range) does not appear to differ significantly in youth with ADHD who are taking a stimulant compared with those who are not (66). Although there is no clear consensus among experts, the product monographs for stimulants recommend monitoring blood pressure at appropriate intervals, especially in individuals with hypertension. In children or youth with ADHD being treated with stimulants, risk for developing a dysrhythmia is not significantly increased (67). Routine pretreatment ECG screening is not recommended. A careful history and physical examination to assess risk factors (68) should be completed before initiating treatment with a stimulant medication.

**Recommendation 7:** Only children and youth at risk for stimulant-induced cardiovascular AEs (based on family history or a personal history/cardiac examination) should undergo ECG testing or a paediatric cardiology consultation before treatment with stimulants is initiated (68).

**Special considerations regarding appetite, growth, and stimulant medication**

One recent study has suggested that a diminution in growth of approximately 2.5 cm is associated with consistent use of stimulant medication over years, compared with negligible use of medication. The final height decrement appears to be associated with cumulative dose of stimulant medications (23). However, final adult height in most children or youth is likely to remain minimally affected by stimulant treatment for ADHD (69,70).

Stimulant-treated children or youth with ADHD may experience a slight overall reduction in BMI (71), particularly if they are overweight when treatment begins (72). This weight loss may help explain why stimulants sometimes delay pubertal growth-spurt timing slightly, compared with peers with ADHD who are not being treated with a stimulant (72).

**Recommendation 8:** Monitor growth parameters for all children and youth being treated with stimulants for ADHD.

**NONSTIMULANT MEDICATIONS**

Two long-acting nonstimulants, atomoxetine and guanfacine, chlorohydrate XR, are approved by Health Canada for treating ADHD in children and youth 6 to 17 years old (Table 2) (73–75).

Clonidine, a short-acting nonstamint, is a nonselective alpha adrenergic agonist. Although controlled trials using clonidine have shown slow but gradual improvement in ADHD symptoms and tics (76), paediatric use of clonidine is not approved by Health Canada at the present time.

Nonstimulants are considered to be second-line medications for managing ADHD symptoms, due to lower treatment response rates (77–81) and effect size (82) compared with stimulants. Although atomoxetine is often used in combination with stimulants for young persons experiencing only a partial response to a stimulant (77), one recent systematic review concluded that there is little evidence to support administering a stimulant and atomoxetine adjunctively (83).

**Recommendation 9:** Nonstimulant medications are second-line interventions for ADHD treatment. They are typically used when stimulants are contraindicated, ineffective or not tolerated.

Because nonstimulants lack both a mechanism of action linked to abuse potential (such as increased norepinephrine and dopamine release) and immediacy of effect (such as speed of action and feeling stimulated), their potential for abuse or diversion is low compared with stimulant medications (84). Atomoxetine may also have a lower risk for weight loss and for exacerbating tics and has been reported to improve anxiety (85). Studies supporting these benefits are limited, however.

**Recommendation 10:** For individuals with ADHD and a history of substance use disorders (SUDs), treatment with a nonstimulant or ER stimulant medication with lower risk for abuse and diversion should be considered as part of a multimodal intervention plan. More research is needed to provide evidence-based recommendations for atomoxetine’s effectiveness in alleviating anxiety in children and youth.
Guanfacine chlorohydrate XR has shown utility as a monotherapy (86) or when used adjunctively with a stimulant medication (73) for treating both ADHD and comorbid oppositional symptoms (87) in children and adolescents with ADHD.

**Monitoring the AEs of nonstimulant medications**

AEs associated with atomoxetine include gastrointestinal (GI) symptoms (e.g., appetite loss, upper abdominal pain), somnolence, headaches, moodiness, and irritability. Serious risks, such as suicide-related events (88) and hepatic disorders, are rare but should be screened for in all patients. Unless symptomatic, baseline liver function tests are not indicated. Norepinephrine reuptake inhibitors like atomoxetine can raise blood pressure and heart rate but increases do not differ from levels associated with MPH (89) or DEX (81).

Sedation, somnolence, and fatigue are common side effects with guanfacine XR. Orthostatic hypotension, bradycardia and syncopal episodes have also been reported (87,89). Clonidine causes a higher frequency of side effects, like sedation, dizziness, and hypotension, compared with guanfacine. Raynaud’s phenomenon may occur with all nonstimulants (60). Blood pressure monitoring to establish a baseline is recommended before starting treatment, during dose adjustments, at regular intervals during treatment and when treatment is stopped. Studies in children, youth, and adults have shown a dose-dependent prolongation of the QTc interval (90), although little is known about the clinical significance of this effect. One Federal Drug Administration report in the United States concluded that evidence is lacking to support the potential for drug interaction between stimulants and alpha-agonists (91–93), which implies that they can be used adjunctively with stimulants.

**Recommendation 11:** Monitor blood pressure in patients on alpha-adrenergic drugs (e.g., guanfacine XR and clonidine) before initiating treatment, following dose increases and periodically throughout treatment.

Atomoxetine is metabolized in the liver by the CYP2D6 (a cytochrome P450 enzyme) pathway to 4-hydroxyatomoxetine. The elimination half-life for atomoxetine can extend from 5 to 22 hours and its rate of clearance is 10% that of extensive metabolizers in persons who are slow CYP2D6 metabolizers. Longer half-life may be caused by genetic polymorphisms of the cytochrome P450 enzyme system or by drugs that inhibit this system (i.e., bupropion, paroxetine, fluoxetine) (94). In such cases, an atomoxetine dose of 0.5 mg/kg/day (to a maximum 40 mg/day) is continued for 2 to 4 weeks before considering increasing the dose.

Unlike atomoxetine, alpha adrenergic drugs (e.g., guanfacine XR and clonidine) must be tapered slowly to prevent rebound hypertension, tachycardia or, more rarely, hypertensive encephalopathy.

**Recommendation 12:** Patients and their families must be counselled about the dangers of abruptly stopping guanfacine or clonidine.

In summary, children and youth with ADHD benefit from implementation of a multimodal treatment plan with specified goals developed through a shared understanding of the child or youth’s needs. For most families, clinical management includes accurate psychoeducation and inclusion of parent and school interventions, as well as management of general health and well-being, with ongoing conversations about sleep, diet and exercise. Medications are an important option for families to consider because they are safe and effective therapy for the symptoms of inattention, impulsivity and hyperactivity associated with ADHD. Psychostimulant medications are the first-line choice because they are generally safe and effective for use over months to years. When stimulants are not well tolerated or no longer effective, additional medication options, such as atomoxetine or guanfacine XR, are available.

**Acknowledgements**

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