Attention-Deficit Hyperactivity Disorder (ADHD) Drug Therapy
Evidence, Clinical Issues & Comparisons

August 2008

Recent Guidelines:
- 2007-2008 Canadian ADHD Practice Guidelines
  www.caddra.ca
- AACAP 2007 Practice Parameters Children & Adolescents with ADHD
  www.aacap.org/guidelines/PracticeParametersChildrenAdoLebsADHD_2007.pdf
- Oregon 2007
  www.ohsu.edu/drugeffectiveness/reports/documents/ADHD%20Final%20Report%20Update%201.pdf
- NICE 2006

Systematic Reviews:
- Review Article:
  Rappley MD. NEJM 2005;352:165-173
- Screening tools:
  www.caddra.ca/ADHD.net/
- Parents Resources:
  www.caddra.ca/ADHDmenus/html/teachADHD.ca/

ADHD – Overview

- Attention-deficit hyperactivity disorder (ADHD) is the most common neuropsychiatric disorder in school aged children. There are 3 subtypes: inattentive ADHD (10-20%), hyperactive-impulsive ADHD (5-10%) and combined ADHD (70-80%).
- Common co-morbidities associated with ADHD are: learning disabilities (40-70%), oppositional defiant disorder (50%), conduct disorder (10-15%), anxiety disorder (25-30%), depression (15-20%), tics/Tourette’s syndrome (1-2%), depression and substance misuse (1-7).
- The debate over the “overuse” or “underuse” of psychostimulants continues. Studies indicate that patients with ADHD are undertreated, while there is an overuse of these drugs among those who do not meet the diagnostic criteria for ADHD. 1,4,9,10
- There are concerns regarding misuse and diversion associated with the use of these drugs.
- Short-term studies show that psychostimulants and non-stimulant atomoxetine are effective and safe in the management of ADHD symptoms. However, there are few controlled studies evaluating the effects of long-term use of these drugs on outcomes.11

Pharmacotherapy Considerations
(See also Table 3: ADHD & Co-morbidities)

- Factors to consider: patient’s and family history of past medication use and response, comorbidities, adverse effects profile, the potential for drug diversion/misuse, patient specific issues regarding compliance, patient’s preference, cost and coverage.4
- Stimulants such as methylphenidate (MPH) have been the backbone of therapy for 60 years and are a first-line therapy option.1,2
  - About 75% of patients will respond to the therapy initially. However, the use of this drug may be considered as a tool to protect patient & MD.
  - Intermediate-acting products (Ritalin SR, Dexedrine Spanules) may last up to 8 hours.
  - Long-acting products (Concerta, Biphentin) provide the convenience of once-daily dosing and less fluctuation in serum concentrations which may improve compliance. These may affect evening appetite and sleep, are more expensive and often not covered by drug plans. In some individuals, a combination of shorter and longer-acting stimulants may be a useful management strategy (e.g. symptoms of late afternoon “rebound”, homework needs).
- Non-stimulant: Atomoxetine (Strattera) has been shown to be superior to placebo in reducing ADHD symptoms, and is an alternative to stimulants if diversion and/or misuse, comorbid tics or anxiety, or non-response / contraindication to stimulants are concerns. Core symptoms are reduced by at least 25% in 60-70% of individuals after 6-12 weeks of treatment. However, atomoxetine is associated with a smaller effect size (0.62) than stimulants (0.91-0.95).15
  - In addition, it has a slower onset of action than stimulants (2-4 days versus 1 hour with an effective stimulant dose). Its maximum effect may not be reached for 2 months.

What are the cardiovascular risks?
- Data from spontaneous adverse reaction reports show that between Jan 1992 and Feb 2005, there were 45 deaths (31 in children, 14 in adults) related to stimulants or atomoxetine. However, the rate of sudden death in kids and adults taking psychostimulants or atomoxetine did not exceed the background rate.15
- Although there is inadequate evidence to establish a casual relationship, patients with known cardiac structural abnormalities and/or signs and symptoms suggestive of cardiac diseases should not be prescribed these drugs.16
- AHA2008 cardiovascular guidelines suggest assessing the following prior to initiation of therapy:17
  - i) patient and family cardiovascular history
  - ii) physical examination
  - iii) ECG (e.g. HCM, LQTS, & WPW)

[ECG Considerations: There is difficulty in interpreting pediatric ECGs and controversy as to whether necessary in all children. ECGs increase the likelihood of identifying significant cardiac conditions, especially if there are suspicions of high-risk conditions; ECGs should be read by a physician with expertise in reading pediatric ECGs. Pediatric cardiology should be consulted if there are significant findings.18 [Faxing ECG an option?]}

Should we be concerned about growth?
- Results from studies have been inconsistent perhaps reflecting that ADHD itself could affect growth. A recent review concluded that stimulants may be associated with a reduction in expected height gain, at least in the first 1 to 3 years of therapy.19
- Follow-up studies of the MTA trial n=485 3yr data showed reduced growth rates after 2 years of stimulant treatment compared to those who received no medication and these deficits persisted at 36 months (average growth of 2cm and 2.7 kg less than the not-medicated subgroup).20,21,22
- It would appear that most children achieve a satisfactory adult height but there may be a subgroup whose growth is permanently attenuated.23
- Patients receiving stimulant therapy should have their height, weight and BMI monitored at baseline and then 1 to 2 times a year during treatment. If a patient has a change in height, weight or BMI that is two percentile lines lower, consider drug holidays (during summers, school breaks, etc.) or a switch to a non-stimulant.2

Highlights:
1) Most patients respond to stimulant therapy; alternatives include atomoxetine and off-label non-stimulants.
2) Rating scales such as the SNAP-IV, Connors’, and CGI are important in screening and monitoring in ADHD. Reassess need for therapy every 2 years.
3) Short vs Long Acting
4) Short and intermediate acting stimulants are effective, low cost and covered by drug plans.
5) Long-acting stimulants offer convenience, compliance & less abuse potential. Cost & lack of coverage have limited use. (Concerta & Strattera recently added to SK Formulary with hopes of less abuse.)
6) Stimulant Abuse & Diversion
7) Advise regarding the potential for misuse and diversion, noting strategies to minimize risk.
8) Use of a treatment agreement may be considered as a tool to protect patient & MD.
9) Non-stimulants & long-acting agents preferred.

RxFiles ADHD Chart: Link
For www.RxFiles.ca subscribers.
**What are the psychiatric risks?**

- **Suicidal thinking:** In controlled trials, the average risk of suicidal thinking was 4/1,000 in the atomoxetine-treated group versus none in those receiving placebo. Although the risk is small, it should be discussed with patients and family, and children should be monitored for the onset of suicidal thinking, particularly in the first few months.2

- **Aggression/emotional lability:** Controlled trials of stimulants do not support the widespread belief that stimulants or atomoxetine induce aggression.2,24 Clinicians should distinguish between aggression/emotional lability that is present when the stimulant is active, and increased hyperactivity/impulsivity in the evening when the drug is no longer effective.2 The latter may be remedied by a switch to longer acting agent or adding a small dose of short-acting stimulant in the late afternoon.3 Of note, oppositional-defiant symptoms usually decrease with therapy in true ADHD.

**How should patients be monitored?** (See also chart)

- Regular documentation of the progress of symptoms and impairment should be made through the appropriate use of rating scales, such as SNAP-IV, Swanson, Nolan and Pelham Questionnaire, CGI Clinical Global Impression Scale, and Conners’ rating scale, and academic performance. Request teachers to fax rating scales every 3 months and report cards each term.

- The patients should be monitored for adverse effects from drug therapy, especially during dose initiation and titration. Some of the adverse effects are transient or may be managed by simple strategies.

- In some patients, a drug holiday may be considered during summer holidays to assess the level of ADHD symptoms while off therapy and the clinical need for medications. Decisions regarding drug holidays must be made on a case by case basis. The patient, parents and physician should review the goals of therapy every 2 years.

**What is the risk of developing substance use disorders in patients treated with stimulant therapy?**

- There are conflicting data in this area. Overall, stimulant treatment does not appear to increase the risk for developing substance use disorders. The more recent studies,25,26 however, could not confirm the earlier claim27 that adequate stimulant treatment lowered the risk for developing substance use disorders.

**What about diversion & misuse?**

- In a study conducted in two Canadian provinces, 8.5% of the grades 7-12 students had used non-prescribed stimulants in the past year, 15% who received prescribed stimulants had given their medication to others, while 7% had sold their medication to other students.28

- In a systematic review, the rates of past year non-prescribed stimulant use ranged from 5% to 9% in grade school- and high school-age children and 5% to 35% in college-age individuals. **Lifetime rates of diversion ranged from 16% to 29% of students asked to give, sell, or trade** their stimulant medications.29

- **Risk factors** for stimulant misuse and diversion include: conduct disorder, substance use disorder, male gender, Caucasian race, member of fraternity or sorority, and use of immediate-release stimulant (extended-release formulations may be less frequently abused due to difficulties in extracting drug from delivery system).30

**A few notes on Adult ADHD**

- About 60% of children with ADHD continue to have significant symptoms into adulthood.1 Inattentive presentation predominates.

- Diagnosis and treatment of adult ADHD is similar to those for children and adolescents. Consider screening for substance abuse.

- Cognitive-behavioral therapy may be particularly useful for adults. The structured nature of the sessions allows the patient and therapist to follow a specific agenda relevant to the patient’s goals.31

- All stimulants are useful in adult ADHD; however, only long-acting stimulants and atomoxetine are officially indicated.

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### Table 1: Strategies To Adress Diversion & Misuse

- Educate patient & parents regarding diversion risk, and safeguard of the medications (i.e. handle the medication like your wallet)
- Instruct parents, children, teachers to refrain from informing others about stimulant therapy; remove vial labels when discarding.
- When concern heightened, avoid short-acting stimulants; consider long-acting stimulants e.g. Concerta or non-stimulants e.g. Strattera.
- Consider generic methylphenidate (as opposed to Ritalin brand which is preferred by abusers due to the lowest amount of insoluble incipient constituents).
- Consider use of a treatment agreement (see sample at [www.RtFiles.ca](http://www.RtFiles.ca)).
- Institute random pill counts (A pill count is performed by notifying the patient a day before or on the day of the patient's appointment that they are requested to bring any unused pills to the appointment.)
- Random urine screening to confirm compliance
- Alternative dispensing (e.g. weekly from pharmacy)
- Drug administration through suitable school program (implement with parental consent as part of the agreement)
- In collaboration with other physicians in a clinic setting → no replacement prescriptions from other ‘covering’ physicians.
- Consider inquiry into substance abuse in immediate & extended family with collaboration through the referring physician/school

### Table 2: Side Effect Management Strategies

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Management Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>Use acetaminophen; usually ↓ after meds used for 1-3 wks</td>
</tr>
<tr>
<td>Appetite</td>
<td>↓ give med with meals; give high-calorie meals when stimulant effects are low (breakfast, bedtime)</td>
</tr>
<tr>
<td>Appetite</td>
<td>↓ supplemental Boost, Ensure</td>
</tr>
<tr>
<td>Appetite</td>
<td>↓ engage child in meal prep &amp; shopping for favourite foods</td>
</tr>
<tr>
<td>Appetite</td>
<td>↓ manage drug-induced dry mouth, e.g. ↑ fluid intake</td>
</tr>
<tr>
<td>Insomnia</td>
<td>↓ optimal sleep hygiene: give doses earlier in the day avoid stimulant after 2 pm if possible, change to shorter-acting meds</td>
</tr>
<tr>
<td>Tics</td>
<td>↓ noon or afternoon stimulant dose</td>
</tr>
<tr>
<td>Tics</td>
<td>↓ consider clonidine, trazodone, an antidepressant, or melatonin 3-6 mg 1/2-1 hr pre-HS; (others: benzos, TCAs, atypical antipsychotics)</td>
</tr>
<tr>
<td>Irritability</td>
<td>↓ dose; adjust longer-acting meds</td>
</tr>
<tr>
<td>Irritability</td>
<td>↓ add clonidine or an atypical antipsychotic</td>
</tr>
<tr>
<td>Rebound</td>
<td>↓ Hyperactivity</td>
</tr>
<tr>
<td>Rebound</td>
<td>↓ Overlap stimulant dosing pattern, switch to longer-acting stimulant, combine IR with SR forms, or add other meds; switch to a non-stimulant</td>
</tr>
</tbody>
</table>

### Table 3: Co-morbidities & Drug Selection

<table>
<thead>
<tr>
<th>Co-morbidities</th>
<th>Drug Selection</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADHD + aggression</td>
<td>↓ atomoxetine unlikely beneficial; consider behavioural therapy; consider atypical antipsychotics, clonidine</td>
</tr>
<tr>
<td>ADHD + anxiety</td>
<td>↓ slow titration of stimulants is recommended; consider atomoxetine (ADHD effect only), the use of SSRIs (↓ anxiety) or TCAs (for both ADHD &amp; anxiety)</td>
</tr>
<tr>
<td>ADHD + bipolar disorder</td>
<td>Uncommon → refer to specialist</td>
</tr>
<tr>
<td>ADHD + tics disorders</td>
<td>(Biphetid, Concerta, Deserpid, MPH products are contraindicated in tics or family hx of tics disorders)</td>
</tr>
<tr>
<td>ADHD + depression</td>
<td>↓ consider buproprion or TCAs</td>
</tr>
<tr>
<td>ADHD + enuresis</td>
<td>↑ watch for DI with paroxetine or fluoxetine → may ↑ atomoxetine serum concentration</td>
</tr>
<tr>
<td>ADHD + sleep problems</td>
<td>↑ Ref: options. TCAs, atomoxetine, desmopressin</td>
</tr>
<tr>
<td>ADHD + substance abuse</td>
<td>↑ consider TCAs, atomoxetine or clonidine</td>
</tr>
<tr>
<td>ADHD + swallowing problems</td>
<td>↑ Adderall XR, Biphentin, Dexeridne Spasules</td>
</tr>
<tr>
<td>ADHD + nicotine dependence</td>
<td>↑ Consider buproprion or non-nicotine</td>
</tr>
</tbody>
</table>

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*Canadian Guidelines. Psychostimulants are used with precaution in tic spectrum disorders but the guidelines agree that use can be indicated if ADHD symptoms warrant treatment. In these cases, medication for ADHD is often combined with other drugs for tics (e.g. atypical antipsychotics or clonidine).*
References – RxFiles Newsletter

ADHD Drug Therapy: Evidence, Clinical Issues and Comparisons


17. Voller VL et al. Cardiovascular Monitoring of Children and Adolescents with Heart Disease Receiving Stimulant Drugs. A Scientific Statement from the American Heart Association Council on Cardiovascular disease in the Young Congenital Cardiac Defects Committee and the Council on Cardiovascular Nursing. Circulation. Published online April 21, 2008. DOI: 10.1161/CIRCULATIONAHA.107.189473

18. Voller VL et al. Cardiovascular Monitoring of Children and Adolescents with heart Disease Receiving Stimulant Drugs. A Scientific Statement from the American Heart Association Council on Cardiovascular disease in the Young Congenital Cardiac Defects Committee and the Council on Cardiovascular Nursing. Circulation. Published online April 21, 2008. DOI: 10.1161/CIRCULATIONAHA.107.189473


22. Swanson J, Greenhill L, Wigal T, et al. Stimulant-related reductions of growth rates in the PATS. J Am Acad Child Adolesc Psychiatry. 2006 Nov;45(11):1304-13. For 95 children who remained on medication, annual growth rates were 20.3% less than expected for height (5.41 cm/yr-6.79 cm/yr=-1.38 cm/yr) and 55.2% for weight (1.07 kg/yr-2.39 kg/yr=-1.32 kg/yr).


29. Poulton A. Medical and nonmedial stimulant use among adolescents: from sanctioned to unsanctioned use. CMAJ 2001;165:1039-1044.


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Sample Patient Agreement for Psychostimulant Therapy

This agreement template has been developed in the interest of promoting optimal drug therapy while minimizing risks to the patient, health care provider and society. Consider routine use of such agreement to help in providing essential patient education and best practice.

1. I, _______________________________ agree that Dr. ____________________________ will be the only physician prescribing _____________________________ (also known as STIMULANT), a medication for managing ADHD and that I will obtain all of my prescriptions for this medication at one pharmacy. The exception would be an emergency situation or in the unlikely event that I run out of medication. Should such occasions occur, I will inform my physician as soon as possible.

2. I understand the importance of taking the medication at the dose and frequency prescribed by my physician. I agree not to increase the dose of the medication without first discussing it with my physician. I understand that expected prescription refill dates will be used to promote optimal use of this medication.

3. My physician may require random urine testing as a matter of routine monitoring.

4. I will attend all reasonable appointments, treatments and consultations as requested by my physician. I will pursue other ADHD consultations/management strategies as necessary.

5. I understand that I should check with my physician or pharmacist before taking other medications including over-the-counter and herbal products.

6. I agree to be responsible for the secure storage of my medication at all times. I understand the importance of not informing others about my stimulant therapy. I agree not to give or sell my prescribed medication to any other person. I acknowledge that my physician is not obligated to replace any medication shortfall.

7. I consent to open communication between my doctor and any other health care professionals involved in my ADHD management, such as pharmacists, other doctors, emergency departments, etc.

8. I understand that if I break this agreement, my physician reserves the right to stop prescribing stimulant medications for me.

Date: ___________________________

________________________________         ______________________________
(Signature - Patient)     (Signature Physician)

See www.RxFiles.ca for customizable form for your office.