“Be kind, for everyone you meet is fighting a hard battle.”

Plato, philosopher (427-347 BC)
Stimulants

Learning Objectives
1. Describe the MTA study and explain its implications for selecting an ADHD management strategy
2. Summarize the evidence regarding short- and long-term benefits of stimulants for ADHD
3. Identify adverse effects, risks, and necessary precautions associated with stimulant use
4. Explain how to initiate, titrate, adjust, and monitor stimulants

Outline
• MTA study
• Suggested pharmacological algorithm for ADHD
• Stimulants:
  – Indications & clinical use
  – Pharmacodynamics & pharmacokinetics
  – Efficacy
  – Adverse effects
  – Serious risks & controversies
  – Contraindications & drug interactions
  – Choosing, dosing & monitoring
  – Pitfalls & troubleshooting

MTA Study (1999)
• Multimodal Treatment Study of Children with ADHD (MTA Group, 1999):
  – Federally funded, multisite RCT of medication and behavioural treatment for ADHD (initiated in 1994)
  – 579 children, age 7 to 9.9 years
  – All subjects had ADHD, combined type
  – Subjects also had a wide range of comorbid conditions (only 31% had ADHD alone)
  – Subjects were relatively diverse geographically, ethnically, and in SES
  – Duration of treatment: 14 months

Medication vs. Behavioural Treatment for ADHD

MTA: Randomization
1. Systematic medication treatment (MED):
  • Immediate-release MPH dosed TID, 7 days per week
  • If response to MPH was inadequate, then DEX, pemoline, imipramine, and others were tried (in this order)
  • Monthly 30-minute clinic visits
2. Intensive behavioural treatment (BEH):
  • 27-session group parent training, 8 individual parent sessions, 8-week summer treatment program, 12 weeks of classroom administered behaviour therapy with a half-time aide, and 10 teacher consultation sessions
3. Combined treatment (COMB):
  • Combination of 1 and 2
4. Community care (CC):
  • Could include pharmacological treatment

©Daniel Gorman, Amy Cheung, Elia Abi-Jaoude 2017
MTA: Outcomes

- Core ADHD symptoms
- 5 non-ADHD domains:
  a) Oppositional/aggressive symptoms
  b) Social skills
  c) Internalizing symptoms
  d) Parent-child relations
  e) Academic achievement

MTA Results 1

- All 4 groups improved overall
- For core ADHD symptoms:
  - COMB = MED > BEH = CC
  - Effect size = 0.6 ("medium")
- But… Parent satisfaction ratings:
  - COMB = BEH > MED

MTA Results 2: Other Areas of Functioning

- Few differences in the 5 non-ADHD domains were found between the 3 MTA treatments (MED, BEH, and COMB)
- MED > CC and BEH > CC for only 1 non-ADHD domain each
- COMB > CC for all 5 non-ADHD domains

MTA Results 3: Adverse Effects

- Medication was generally well tolerated:
  - Side effects: 36% none, 50% mild, 11% moderate, 3% severe
  - Only 1.4% did not complete titration because of side effects
  - 73% were successfully maintained on immediate-release MPH (the first medication in the algorithm)

MTA Results 4: Medication Doses

- Mean total daily dose of MPH in the COMB group (31.2 mg) was significantly lower than in the MED group (37.7 mg)
- In the CC group, 67% received medication; however, they took it for about half as long as those treated with medication through the study (5.5 vs. 10 months)
- For those in the CC group treated with MPH:
  - Mean number of daily doses was 2.3
  - Mean total daily dose was 22.6 mg
MTA Results 5: Influence of Comorbidity (Jensen et al., 2001)

- For children with ADHD+anxiety, BEH was significantly superior to CC and was not significantly different from treatments that included medication (MED and COMB)
- Children with ADHD+ODD/CD responded best to treatments that included medication (MED and COMB)
- Children with ADHD+anxiety/depression+ODD/CD responded best to COMB

Lessons from the MTA

1. Medication, with or without behavioural treatment, is the most effective short-term treatment for core ADHD symptoms
2. Parents prefer behavioural treatment, with or without medication, to medication treatment alone

MTA Long-Term Outcomes

- After the initial 14-month randomized treatment phase, children in the MTA were followed naturally, and outcomes were assessed after the following number of years from study entry: 2, 3, 6, 8, 10, 12, 14, 16
- At 2 years, COMB & MED retained superiority over BEH & CC for core ADHD symptoms, but the size of this effect was half of that found immediately post-treatment (MTA Group, 2004)

MTA Outcomes at 3 Years

- At 3 years, all groups were improved substantially across all outcome areas, and in fact only about half continued to meet full criteria for ADHD (Jensen et al., 2007)
- The groups did not differ significantly on any measure, but note the percentage of children taking medication >50% of the time in the first 14 months vs. the final year:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>0-14 months</th>
<th>24-36 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>MED+COMB</td>
<td>91%</td>
<td>71%</td>
</tr>
<tr>
<td>BEH</td>
<td>14%*</td>
<td>45%</td>
</tr>
<tr>
<td>CC</td>
<td>60%</td>
<td>62%</td>
</tr>
</tbody>
</table>

*Overall, 23% of the BEH group started a stimulant (on their own) during the 14-month study period! (Poulton, 2006)

©Daniel Gorman, Amy Cheung, Elia Abi-Jaoude 2017
MTA Outcomes at 3 Years (cont.)

- In the overall sample (all treatment groups), 3 “latent classes” of children with differing ADHD symptom trajectories from pretreatment to 3 years were identified:
  - “Class 1” (34%): linearly decreasing symptom trend over time
  - “Class 2” (52%): large initial symptom decrease that was maintained over time
  - “Class 3” (14%): initial decrease in symptoms followed by a return to baseline

MTA Outcomes at 3 Years (cont.)

- Baseline variables were similar in classes 1 and 3, but class 2 had higher birth weight, higher IQ, and better ratings of ADHD symptoms, social skills, and psychopathology
- Initial assignment to MED or COMB significantly increased the chance of being in Class 2 (COMB=62%, MED=55%, BEH=46%, CC=45%)
- Symptom ratings for all 3 classes were still well above those for the local normative control group (LNCG) (classmates of the ADHD subjects)

MTA Outcomes at 8 Years (Molina et al., 2009)

- Of the 406 subjects with complete medication data, 1/3 were medicated >50% of days in the past year, and group differences in medication use based on original randomization were not significant
- No significant effects of original randomized treatment on any of the 24 outcome variables tested

MTA Outcomes at 8 Years (cont.)

- ADHD symptom trajectory in childhood was a strong predictor of outcome, with children in class 2 faring better than children in classes 1 and 3
- Despite maintenance of improvement in functioning relative to pretreatment baseline, the MTA group as a whole was functioning much more poorly than the non-ADHD classmate sample (LNCG)

©Daniel Gorman, Amy Cheung, Elia Abi-Jaoude 2017
MTA Outcomes In Adulthood
(Swanson et al., 2017)

• Observations at 12-16 years were available for 82% (476/579) of the original sample.
• At 12-16 years, only 7.1% of subjects were using medication more than minimally.
• 3 patterns of medication use from childhood through adolescence were identified:
  – “Negligible” (23.5%)
  – “Inconsistent” (69.1%)
  – “Consistent” (7.4%)

MTA Outcomes In Adulthood (cont.)

• Compared to the LNCG, ADHD symptoms in the MTA group were significantly higher, with a large effect size (d=1.11, p<0.001).
• No significant differences in ADHD symptoms in the following group comparisons:
  – Consistent + Inconsistent vs. Negligible
  – Consistent vs. Inconsistent
• No significant differences in ADHD symptoms between the original randomized treatment groups.

Suggested Pharmacological Algorithm

1. Stimulants* (try methylphenidate and at least one amphetamine before moving on)
   2a. Atomoxetine*
   2b. α-2 agonists (guanfacine*, clonidine**)
   3a. Bupropion
   3b. Tricyclic antidepressants
   4. Modafinil
   5. Other medications and medication combinations

*Only stimulants, atomoxetine, and guanfacine extended-release are approved by Health Canada for the treatment of ADHD.
**Clonidine extended-release is approved by the FDA for the treatment of ADHD, but it is not available in Canada.

Stimulant Formulations in Canada

1. Methylphenidate (MPH)
   • Ritalin*, Ritalin SR*
   • Concerta*
   • Biphentin*
2. Amphetamines (AMPH)
   a) d-amphetamine
      • Dextedrine*, Dextedrine Spansule*
   b) Mixed salts amphetamine (d- and l-amphetamine salts in a ratio of 3:1)
      • Adderall XR*
   c) Lisdexamfetamine
      • Vyvanse*

©Daniel Gorman, Amy Cheung, Elia Abi-Jaoude 2017
Trade and Generic Names

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Generic Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ritalin</td>
<td>Immediate-release methylphenidate</td>
</tr>
<tr>
<td>Ritalin SR</td>
<td>Sustained-release methylphenidate</td>
</tr>
<tr>
<td>Concerta</td>
<td>Osmotic release oral system (OROS) methylphenidate</td>
</tr>
<tr>
<td>Biphentin</td>
<td>Multi-layer release methylphenidate</td>
</tr>
<tr>
<td>Dexedrine</td>
<td>Immediate-release dextroamphetamine</td>
</tr>
<tr>
<td>Dexedrine Spansule</td>
<td>Sustained-release dextroamphetamine</td>
</tr>
<tr>
<td>Adderall XR</td>
<td>Extended-release mixed salts amphetamine</td>
</tr>
<tr>
<td>Vyvanse</td>
<td>Lisdexamfetamine</td>
</tr>
</tbody>
</table>

Indications

• ADHD:
  – Stimulants are approved by Health Canada and the FDA for use in youth, generally down to age 6
  – The FDA has approved Dexedrine down to age 3, but much more evidence exists regarding the use of MPH for preschool ADHD (Greenhill et al., 2006 [PATS])
  – Except for Dexedrine, all stimulant formulations available in Canada are approved by Health Canada for use in adults as well

Indications (cont.)

• ADHD:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Health Canada</th>
<th>FDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ritalin</td>
<td>youth ≥ 6 yrs, adults</td>
<td>youth ≥ 6 yrs, adults</td>
</tr>
<tr>
<td>Ritalin SR</td>
<td>youth 6-18 yrs, adults ≥ 18 yrs</td>
<td>youth 6-17 yrs, adults 18-65 yrs</td>
</tr>
<tr>
<td>Concerta</td>
<td>youth 6-18 yrs, adults ≥ 18 yrs</td>
<td>youth 6-17 yrs, adults 18-65 yrs</td>
</tr>
<tr>
<td>Biphentin</td>
<td>youth ≥ 6 yrs, adults not available in the U.S.</td>
<td>not available in the U.S.</td>
</tr>
<tr>
<td>Dexedrine</td>
<td>“children” ≥ 6 yrs</td>
<td>youth 3-16 yrs</td>
</tr>
<tr>
<td>Dexedrine Spansule</td>
<td>youth ≥ 6 yrs, adults</td>
<td>youth ≥ 6 yrs, adults</td>
</tr>
<tr>
<td>Adderall XR</td>
<td>youth ≥ 6 yrs, adults</td>
<td>youth ≥ 6 yrs, adults</td>
</tr>
<tr>
<td>Vyvanse</td>
<td>youth ≥ 6 yrs, adults</td>
<td>youth ≥ 6 yrs, adults</td>
</tr>
</tbody>
</table>

Other Indications and Clinical Uses

• Some evidence supports the use of stimulants for ADHD symptoms in children with ASD, but benefits tend to be smaller and adverse effects greater than in children without ASD (RUPP, 2005; Cortese et al., 2012 [review])
• Ritalin and Dexedrine have Health Canada and FDA indications for narcolepsy in children (≥ 6 years) and adults
• In January 2015, the FDA approved Vyvanse for binge-eating disorder in adults; however, this has caused controversy because of concerns about both efficacy and risks
• Stimulants are sometimes used for depression in geriatric patients (Lavretsky et al., 2015) and in medically ill patients with low energy

Pharmacodynamics

• Methylphenidate:
  – Blocks dopamine (DA) and norepinephrine (NE) transporters in the presynaptic neuron, thus inhibiting reuptake and resulting in ↑ synaptic concentrations of these neurotransmitters

• Amphetamines:
  – Stimulate release of DA and, to a lesser extent, NE from presynaptic sites
  – Secondary effects involving inhibition of DA reuptake

Pharmacokinetics

(Patrick et al., 1987; Connor & Melzer, 2006; Frölich et al., 2014; Hutson et al., 2014)

• Rapid absorption, low plasma protein binding
• Up to 80% of...
  – MPH undergoes de-esterification in the plasma
  – AMPH is excreted unchanged in the urine
• Minimal involvement of the CYP450 system
• Nonetheless...
  – MPH undergoes extensive first-pass hepatic metabolism (major enzyme is carboxylesterase CES1A1)
  – AMPH is metabolized partly by the liver

©Daniel Gorman, Amy Cheung, Elia Abi-Jaoude 2017
Short-Term Efficacy

• Benefits of amphetamine for childhood disruptive behaviour were first reported by psychiatrist Charles Bradley in a study of Benzedrine sulfate over 75 years ago (Bradley, 1937; Strohl, 2011).

• Short-term efficacy of stimulants for ADHD symptoms is supported by hundreds of RCTs (Pliszka et al., 2007).

• Most studies are in school-age children, but evidence in adolescents and adults has grown considerably in recent years.

Methylphenidate vs. Amphetamine

• The response rate for AMPH is about 10% greater than for MPH (Arnold, 2000).

• AMPH has also been found to have a “moderately” greater effect size than MPH (Faraone & Buitelaar, 2009 [meta-analysis]):
  – AMPH effect size=1.0-1.2 (NNT=2.0)
  – MPH effect size=0.7-0.9 (NNT=2.6)

• However, while ~25% of patients respond preferentially to AMPH, ~20% respond preferentially to MPH (Arnold, 2000).

Cochrane Reviews

• Although the evidence supporting the short-term efficacy of stimulants for ADHD in children and adolescents is arguably stronger than for any other treatment in psychiatry, 2 recent Cochrane reviews concluded that the quality of the evidence for both MPH and AMPH is low to very low.

Cochrane Review of MPH

• Storebo et al., 2015:

  – “The quality of the evidence was very low for all outcomes. It was possible for people in the trials to know which treatment the children were taking, the reporting of the results was not complete in many trials and for some outcomes the results varied across trials. These considerations limit our confidence in the overall results of the review.”

Cochrane Review of AMPH

• Punja et al., 2016 (AMPH):

  – The quality of the included studies was low to very low because of problems in their design and large differences between the studies. Well-designed and clearly reported RCTs that are longer in duration are needed, so we may better understand the long-term effects (both positive and negative) of AMPH.”
Long-Term Efficacy

• “The key paradox is that while ADHD clearly responds to medication and behavioral treatment in the short term, evidence for long-term effectiveness remains elusive” (Hinshaw et al., 2015)
• Reasons for limited long-term benefit may include (Poulton, 2006):
  – Natural course and variability of ADHD
  – Influence of social and environmental factors
  – Inadequate long-term monitoring and treatment

Long-Term Academic Outcomes

• Langberg & Becker, 2012 (review):
  – Identified 9 studies reporting on 8 longitudinal samples treated naturalistically with ADHD medication for an average of 8 years
  – ADHD medication use was associated with a small improvement in standardized achievement scores that was significant statistically, but perhaps not educationally
  – Evidence on the benefits of ADHD medication with respect to school grades and grade retention was found to be limited and mixed
• Currie et al., 2014:
  – In Quebec, ↑ stimulant treatment in children was associated with greater probability of grade repetition and lower math scores

Long-Term Efficacy (cont.)

Long-Term Academic Outcomes (cont.)

• In contrast, a review of 176 studies had far more optimistic findings for the effects of ADHD treatment on long-term (≥2 years) academic outcomes (Arnold et al., 2015a):

<table>
<thead>
<tr>
<th>Medication Treatment</th>
<th>Non-medication Treatment</th>
<th>Combined Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of achievement test outcomes that improved</td>
<td>75</td>
<td>75</td>
</tr>
<tr>
<td>% of academic performance outcomes that improved</td>
<td>33</td>
<td>50</td>
</tr>
</tbody>
</table>

Long-Term Psychiatric Outcomes

• Evidence is limited and mixed regarding the long-term effect of stimulant treatment on psychopathology associated with ADHD:
  – Some evidence suggests that stimulant treatment decreases the risk of developing MDD, ODD/CD, anxiety disorders, and bipolar disorder:
    • Davis et al., 2008; Biederman et al., 2009; Chang et al., 2016; Lee et al., 2016; Wang et al., 2016
  – Other evidence suggests that stimulants have no effect on the risk of depression or delinquency, or even increases the risk of depression in girls:
    • Molina et al., 2007; Smith et al., 2012; Curie et al., 2014

Long-Term Substance Use Outcomes

• Evidence on risk of later substance use is mixed:
  – Some studies found that stimulants are protective:
    • Wilens et al., 2003 (meta-analysis); Wilens et al., 2008; Mannuzza et al., 2008; Groenman et al., 2013; Dalsgaard et al., 2014; Schoenfelder et al., 2014 (meta-analysis for cigarette smoking); Chang et al., 2014; McCabe et al., 2016; Upadhyay et al., 2017
  – 1 study found that stimulants increase the risk:
    • Lambert, 2005
  – Some studies found that stimulants have no effect:
    • Barkley et al., 2003; Biederman et al., 2008; Harty et al., 2011; Winters et al., 2011; Molina et al., 2013 (MTA 8-year follow-up); Humphreys et al., 2013 (meta-analysis)
Long-Term Injury Outcomes

- Several large studies found that treatment with ADHD medication reduced the risk of injury (Dalsgaard et al., 2015; Mikolajczyk et al., 2015; Merrill et al., 2016; Chen et al., 2017)

Benefits of Combined Treatment on Long-term Functional Outcomes

- Arnold et al., 2015b:
  - Systematic review of pharmacological, non-pharmacological, and combined treatment modalities on long-term (≥2 years) functional outcomes in ADHD
  - Included 51 studies with 111 outcomes in 9 domains:
    - Academics, antisocial behaviour, driving, addiction, obesity, occupation, services use, self-esteem, social function
  - Combined treatment was found to have the highest proportion (83%) of improved outcomes and the largest effect sizes
  - The most evidence for treatment benefit was found for self-esteem, social function, academics, and driving

Adverse Effects

- Initial insomnia
- ↓ Appetite, weight loss
- Stomach upset
- Headache
- Thirst
- Social withdrawal
- Mood symptoms, ↑ activity, aggression:
  - However, stimulants often improve pre-existing mood symptoms and aggression (Fernandez de la Cruz et al., 2015 [MTA analysis]; Blader et al., 2016)
- Anxiety:
  - However, stimulants ↓ the risk of anxiety (RR=0.86) on average (Coughlin et al., 2015 [meta-analysis])
  - ↑ HR (mean ≤10 bpm)
  - ↑ BP (mean ≤5 mmHg)
  - Palpitations
  - Tics:
    - However, the risk of tics with stimulants (6%) is the same as with PBO (Cohen et al., 2015 [meta-analysis])

Adverse Effects: MPH vs. Amphetamine

- Adverse effects of MPH and AMPH are generally similar, but some subtle tendencies have been suggested (Arnold, 2000):
  - AMPH is “probably” associated with more insomnia, appetite suppression/weight loss, and tic exacerbation
  - MPH is “possibly” associated with more depression/apathy, stomachaches, and risk of seizure exacerbation

Risk of Psychosis & Mania

- Health Canada Advisory (Sept. 2006):
  - “[T]he prescribing and patient information for all drugs used for the management of ADHD…is being revised to provide information about the potential for psychiatric adverse events, including rare reports of agitation and hallucinations in children.”

- Risk of psychotic symptoms with stimulant use may be increased by a family history of MDD, bipolar disorder, or schizophrenia (MacKenzie et al., 2016)

Risk of Psychosis & Mania (cont.)

- Mosholder et al., 2009:
  - In clinical trial data, rates of psychosis/mania events with stimulants, atomoxetine, and modafinil vs. placebo:
    - 11/5717 (0.2%) vs. 0/3990 (0%)
    - 1.48 per 100 person-years vs. 0 in 420 person-years
  - Postmarketing data:
    - 865 unique case reports describing evidence of psychosis/mania with stimulants and atomoxetine

©Daniel Gorman, Amy Cheung, Elia Abi-Jaoude 2017
Mosholder et al., 2009 (cont.)
- In ~90% of cases of psychosis/mania, there was no previous history of a similar psychiatric condition
- Case reports included strong temporal association, many with positive dechallenge, and some with positive rechallenge
- In ⅔ of cases, the onset of psychotic/manic symptoms occurred within days or weeks of starting the ADHD drug, but in the remaining ⅓, the onset was after months or, in a few cases, years of treatment
- A common theme in young children with hallucinations involved descriptions of visual and/or tactile sensations of insects, snakes, or worms

Conflicting Evidence
- Man et al., 2016:
  - Self-controlled case series study in a clinically referred sample of youth (6-19 yrs) prescribed MPH in Hong Kong from 2001 to 2014
  - Of 20,586 patients prescribed MPH, 103 had a psychotic event
  - Of the 103 psychotic events, 78 occurred off medication and 25 occurred during MPH treatment
  - Overall incidence of psychotic events during the MPH exposure period was 6.14 per 10,000 patient-years
  - No significant association between MPH treatment and occurrence of psychotic events
  - Significant increased risk of psychotic events during the 90-day pre-MPH treatment period (incidence rate ratio = 4.64)

Risk of Suicide-Related Events
- Health Canada Warning for all ADHD medications (March 2015):
  - “There have been post-marketing reports of suicide-related events in patients treated with ADHD drugs, including cases of ideation, attempts, and very rarely, completed suicide. The mechanism of this risk is not known.”
  - “There is little evidence to establish that these drugs cause suicidal thoughts and behaviours, but it is possible that they may contribute to the risk.”

Risk of Priapism
- Warnings from FDA (December 2013) & Health Canada (April 2015):
  - Rare cases of priapism with MPH and atomoxetine
  - Risk not quantified, but appears to be greater with atomoxetine than with MPH
- Cases of priapism associated with ADHD medications reported as of May 15, 2014 (Eiland et al., 2014):
  - 15 cases in youth taking MPH
  - 4 cases in youth taking AMPH; however, these individuals were taking illicit or unspecified amphetamines, as well as other agents known to cause priapism
  - 1 case in an 11-year-old boy taking atomoxetine, risperidone, and aripiprazole
- Families should be counseled about the need for immediate medical attention if priapism occurs

Risk of Growth Suppression
- Evidence is mixed; for example:
  - Spencer et al., 2006: “The effects of prolonged OROS MPH therapy on growth were clinically insignificant and limited to slight decreases in weight during the first months of therapy.”
  - Charach et al., 2006: “Long-term use of high doses of stimulants during a period of 1 to 5 years is likely to have measurable effects on the rate of growth in school-age children with ADHD.”
- However, the preponderance of the evidence indicates that prolonged stimulant treatment is associated with generally modest vertical growth suppression in children (Vitiello, 2008)

Growth Rates in the MTA Follow-Up
- Swanson et al., 2007:
  - “Newly Medicated” (no stimulant before the MTA, then on stimulant for 3 years) vs. “Not Medicated” (never on a stimulant):
    - At MTA baseline: NewMed < NoMed by 1.1 cm
    - At 3 yrs: NewMed < NoMed by 3.0 cm
  - Growth suppression was maximal in the 1st year, attenuated in the 2nd year, and was absent in the 3rd year
  - Findings did not support the hypothesis of growth rebound when stimulants are continued; however, intermittent use was associated with less growth slowing
Final Height in the MTA (Swanson et al., 2017)

- Final height comparisons between the Negligible, Inconsistent, and Consistent groups:
  - *Consistent + Inconsistent < Negligible by 2.55 cm (p<0.0005)
  - *Consistent < Inconsistent by 2.36 cm (p<0.04)
  - **Consistent < Negligible by 4.66 cm (p=0.001)

*Planned comparison **Post hoc comparison

- Regression analysis found an association of cumulative stimulant dose with lower adult height:
  - Cumulative MPH equivalent dose of 100,000 mg predicted height suppression in adulthood of 2.4 cm

Swanson et al., 2017: Important Caveats!

- Because the findings are based on comparisons of naturalistic groups, they should be used to generate hypotheses and cannot establish causation
- It is unclear to what extent selection bias or confounding factors contributed to or accounted for the findings
- Other studies of naturalistic samples have not found an effect of prolonged stimulant treatment on final height; however, they were conducted in the 1960s, 1970s, and 1980s, when intensity of stimulant treatment was considerably lower (Kramer et al., 2000; Klein & Mannuzza, 1988; Harstad et al., 2014; Biederman et al., 2010)

Mechanism of Vertical Growth Suppression

- It is unclear how stimulants suppress vertical growth, but the two main hypotheses are (Vitiello, 2008):
  a) ↓ appetite → ↓ caloric intake → ↓ growth
  b) Effects on dopaminergic neurons in the pituitary → effects on growth hormone → ↓ growth

Recommendations for Addressing Risk of Growth Suppression

- Murray et al., 2008:
  - Discuss with families the possibility of relatively small long-term decrements in height and weight associated with consistent use of stimulant
  - Frequent follow-up (every 2 months) informed by school input
  - Monitor height and weight on a growth chart and review data every 6-12 months
  - Consider planned “drug holidays”
  - Assess medication efficacy annually through brief periods of medication discontinuation, and weigh risks vs. benefits of continued pharmacotherapy
Stimulant Controversy: Risk of Sudden Death?

- Health Canada Advisory (May 2006):
  - “Theoretically there exists a pharmacological potential for all ADHD drugs to increase the risk of sudden/cardiac death”
  - “In patients treated with ADHD drugs, neither clinical studies nor post-marketing reports have shown to date that the incidence or reporting rates of serious cardiac adverse events, including fatalities, are greater than background rates”

Health Canada Advisory (cont.)

- “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.”

Stimulants & Sudden Death: Individual Cases

<table>
<thead>
<tr>
<th>Cases of Sudden Death Reported to the RDA Advisory Committee from the AMNE Database, N</th>
<th>n</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unmultifaceted Sudden Death</td>
<td>Care Meeting WHO Criteria for Sudden Death</td>
</tr>
<tr>
<td>Age, &lt; 18 yr</td>
<td>17</td>
<td>13</td>
</tr>
<tr>
<td>Age, 18-19 yr</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>18</td>
<td>17</td>
</tr>
</tbody>
</table>

* Data are from the Adverse Events Reporting System (AERS) of the Food and Drug Administration (FDA). Antiretrovirals include nevirapine, efavirenz, and dolutegravir. WHO criteria stated Health Organization.


N.B. Data are for the period 1999-2003, during which time about 2.5 million children and adolescents were taking stimulants (Perrin et al., 2008) (enlarged slide appended)

Individual Cases: Cardiac Risk Factors

- Of the 25 confirmed cases of sudden death, 19 had autopsies, and 12 of these were found to have structural heart defects (Batra et al., 2012)
  - Note that 2 of the 25 deaths occurred after 1 day of stimulant treatment (Hamilton et al., 2011):
    - 1 had idiopathic hypertrophic subaortic stenosis
    - 1 had a family history of ventricular arrhythmia

Individual Cases: Other Risk Factors

- Other risk factors identified among the cases of sudden death:
  - Presence of a medical illness
  - Strenuous exercise
  - Toxic levels of the stimulant (unexplained)
  - Concurrent medication
  - Concurrent cocaine use

Stimulants & Sudden Death: Controlled Data

- Several large cohort studies and a meta-analysis found that ADHD drugs were not associated with an ↑ risk of sudden death in youth:
  - Winterstein et al., 2007; Schelleman et al., 2011; Cooper et al., 2011; Olsson et al., 2012; Winterstein et al., 2012; Mazza et al., 2013 (meta-analysis)
  - However, a case-control study did find a significant association between stimulants and sudden death in youth:
    - Gould et al., 2009 (OR=7.4, 95% CI=1.4 to 74.9)
Controlled Data: Other CV Outcomes

- A large cohort study found that CV events involving hospital contact, though rare (84 events per 100,000 person-years), were twice as likely in children using stimulants vs. non-users (Dalsgaard et al., 2014).

- Findings of a self-controlled case series of 1224 young people (≤17 yrs) with ADHD who had started taking MPH and had a CV adverse event (Shin et al., 2016):
  - ↑ risk of arrhythmia associated with MPH (RR=1.61), especially in patients with congenital heart disease (RR=3.49).
  - ↑ risk of MI during the first 2 months of MPH treatment (RR=2.0-2.6).

- Nonetheless, the absolute risk of these cardiac adverse events is likely to be low.

Are Routine Baseline ECGs Necessary?

- April 21, 2008:
  - AHA Scientific Statement, original version (Vetter et al., 2008): “We are suggesting that an ECG be added [to patient and family history and physical exam] to increase the likelihood of identifying significant cardiac conditions … that might place the child at risk.”

- May 16, 2008:
  - AAP/AHA Clarification: “Acquiring an ECG is a Class IIa recommendation. This means that it is reasonable for a physician to consider obtaining an ECG … but this should be at the physician’s judgment, and it is not mandatory to obtain one.”

ECG Controversy (cont.)

- Baseline ECGs in children without cardiac risk factors are generally considered unnecessary (AAP, AACP, CPS, CACAP, CCS).

- However, Elia & Vetter (2010) argue that:
  - Both Hx/PE and ECG have high specificity (Sp), but ECG has much higher sensitivity (Sn):
    - Hx/PE: Sp=97%, Sn=3-6%
    - ECG: Sp=85-97%, Sn=60-70%
  - Because Hx/PE has low sensitivity, it is often not useful in identifying cardiac pathology.
  - ECG may be more cost effective than Hx/PE.
Contraindications

- Significant cardiac problems
- Hyperthyroidism
- Glaucoma
- Psychosis
- Hypersensitivity to the drug
- Pregnancy
- Stimulants are not contraindicated in individuals with seizure disorders, autism spectrum disorder, or Tourette syndrome, but their use should be cautious in these populations

Drug Interactions

- No interaction with atomoxetine, but little evidence to support combining atomoxetine with a stimulant (Treuer et al., 2013)
- Conflicting information about the potential effect of SSRIs and antipsychotics on MPH levels:
  - Yorbik et al., 2014: MPH levels are not affected by sertraline, fluoxetine, risperidone, or aripiprazole
  - Frölich et al., 2014: MPH levels are increased by fluoxetine, aripiprazole, perphenazine, and thioridazine (through CES1 inhibition)

Drug Interactions (cont.)

- Sympathomimetics:
  - Stimulants potentiate other sympathomimetics (e.g., β2-agonists)
- Benzodiazepines and antihistamines:
  - Stimulants may counteract sedative effects
- Lithium:
  - Stimulatory effects of amphetamines may be inhibited
- Tricyclic antidepressants:
  - The combination may enhance the effects of both the TCA and the stimulant

Drug Interactions (cont.)

- Phenytoin and phenobarbital:
  - AMPH may act synergistically to increase anticonvulsant activity
- MAOIs:
  - Hypertensive crisis
- St. John’s wort:
  - Has some MAOI activity

Onset of Action: Instant Gratification!

- Stimulants have their full effect with the first dose!
- With the exception of Ritalin SR, stimulants start working ~30-90 min after ingestion:
  - Clinical benefits are often seen after ~30 min
  - Separation from PBO is reported after ~90 min
  - Ritalin SR starts working ~2 hrs after ingestion
### Duration of Action of Stimulant Formulations Available in Canada

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Duration of Action (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ritalin</td>
<td>3-5</td>
</tr>
<tr>
<td>Ritalin SR</td>
<td>Purportedly 8, but more likely ~4</td>
</tr>
<tr>
<td>Concerta</td>
<td>12</td>
</tr>
<tr>
<td>Biphentin</td>
<td>Purportedly 10-12, but more likely 8-10</td>
</tr>
<tr>
<td>Dexedrine tablet</td>
<td>4-6</td>
</tr>
<tr>
<td>Dexedrine Spansule</td>
<td>Purportedly 10-12, but more likely 6-8</td>
</tr>
<tr>
<td>Adderall XR</td>
<td>12</td>
</tr>
<tr>
<td>Vyvanse</td>
<td>13-14</td>
</tr>
</tbody>
</table>

#### Ritalin SR
- A wax-matrix vehicle is used in an attempt to achieve extended release
- However, the result is not extended release, but rather delayed release (Solanto, 2001):
  - Little or no benefit for ~2 hours, then clinical effect for ~4 hours, then little or no benefit again

#### Dexedrine Spansule
- Capsule containing 2 kinds of beads:
  - 50% d-amphetamine
  - 50% polymer-coated d-amphetamine
- Duration of action is unclear:
  - Estimates range from 4 hours (Brown et al., 1980) to 6-8 hours (Faraone et al., 2009) to 12 hours (James et al., 2001)

#### Concerta (OROS Delivery System)
- Concerta capsule must not be cut or chewed
- Concerta capsule shell is excreted in the stool
- Concerta capsule cannot be easily tampered with for purposes of drug abuse
- Although considered “bioequivalent,” generic versions of Concerta may not be therapeutically equivalent (Fallu et al., 2016; FDA, November 2014)
Biphentin (Multi-Layer Release MPH)

Adderall XR

Vyvanse

Vyvanse (cont.)

Choosing a Stimulant, Decision #1: MPH or AMPH?

- Absorption and bioavailability of d-amphetamine from LDX are unlikely to be affected by GI factors (e.g., taking it with food, gastric pH, transit time)
- Reportedly low interpatient variability in pharmacokinetic parameters
- May take a little longer in the morning to start working
- Low abuse potential (because LDX is a pharmacologically inactive prodrug)
- Purportedly higher effect size (up to 1.6), at least in children 6-12 years old, compared to other AMPH formulations and MPH (Biederman, 2007; Faraone, 2008 [review])

- Lisdexamfetamine dimesylate (LDX) is a pharmacologically inactive prodrug
- LDX is converted, mainly in the blood, to L-lysine (a naturally occurring amino acid) and pharmacologically active d-amphetamine
- Whereas other long-acting stimulants achieve extended duration of action through "engineering," Vyvanse achieves it through chemical conversion (hydrolysis of the covalent bond between L-lysine and d-amphetamine)

- Recall that MPH and AMPH have similar benefit and adverse effect profiles (although on average, AMPH appears to be somewhat more efficacious)
- There are no clinical predictors as to which child will respond better to which type of stimulant (Pliszka et al., 2006)
- Overall, there is no compelling evidence to support starting with one type of stimulant over the other, and most guidelines (e.g., AACAP, AAP) indicate that either MPH or AMPH may be tried first

©Daniel Gorman, Amy Cheung, Elia Abi-Jaoude 2017
Choosing a Stimulant, Decision #2: Long-Acting or Short-Acting?

- Advantages of long-acting formulations:
  - ↑ convenience,
  - ↑ adherence (?)
  - ↓ abuse potential for some formulations (Vyvanse, Concerta)

- Advantages of short-acting formulations:
  - ↑ control and flexibility (timing and dose)
  - ↓ cost

Long-Acting vs. Short-Acting (cont.)

- According to some guidelines (CPS, CADDRA), long-acting formulations should be first-line "because they are more effective and less likely to be diverted" (Feldman & Bélanger [CPS], 2009)

- However, other guidelines (AACAP, AAP) indicate that any approved ADHD medication may be started first

Long-Acting vs. Short-Acting (cont.)

- Meta-analysis of long-acting vs. short-acting formulations (Punja et al., 2013):
  - Similar efficacy, with teachers slightly favouring short-acting and parents slightly favouring long-acting
  - No difference in adverse effects
  - Only 3 studies assessed adherence; 1 found greater adherence with long-acting (Steele et al., 2006), but the other 2 found no difference (Pelham et al., 2001; Schachar et al., 2008)

So How Do You Choose?

- The initial choice of stimulant formulation should be based on the clinical circumstances and family preference, especially regarding the desired duration of action:
  - Does the child require coverage in the evenings?
  - How concerned is the family regarding potential interference with sleep and appetite?
  - Does the family prefer convenience or control/flexibility?
  - How would the child feel about taking medication at school?
  - Is there a risk of abuse or diversion of the stimulant?
  - What is the family’s financial/insurance situation?

What if the Type of Stimulant You Choose Doesn’t Work Out?

- Arnold, 2000:
  “The clearest lesson gleaned from the controlled studies is that … nonresponse or intolerable side effects with one stimulant [MPH or AMPH] does not preclude a good response to the other … each should be tried before giving up on stimulant treatment, and patients and parents should be forewarned of this.”
Consider Trying Different Formulations of the Same Type of Stimulant (MPH or AMPH)

• A review of head-to-head studies of long-acting MPH formulations came to the following conclusion (Coghill et al., 2013):
  “At a group level, efficacy across the day generally follows the PK profile of the MPH formulation. No formulation is clearly superior to another; careful consideration of patient needs and subtle differences between formulations is required to optimize treatment. For patients achieving suboptimal symptom control, switching long-acting MPH formulations may be beneficial.”

For Kids Who Won’t Swallow Pills…

• Dexedrine Spansule, Adderall XR, and Biphentin:
  – Capsules may be opened up and the beads inside sprinkled on soft foods (e.g., apple sauce, yogurt, ice cream)

• Vyvanse:
  – Capsules may be opened up and the powder inside mixed into water (taste is slightly sweet), orange juice, or yogurt

Stimulant Dosing Summary

<table>
<thead>
<tr>
<th>Stimulant</th>
<th>Starting Dose (mg)</th>
<th>Dose Frequency</th>
<th>Usual Single Dose Range</th>
<th>Usual Daily Dose Range</th>
<th>Max Single Absolute Dose (mg)</th>
<th>Max Daily Absolute Dose (mg)</th>
<th>Off-Label Max Daily Absolute Dose (mg)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ritalin</td>
<td>5 bid-tid</td>
<td>0.3-0.7</td>
<td>0.6-2.1</td>
<td>20</td>
<td>60</td>
<td>100</td>
<td>(&gt;50 kg)</td>
</tr>
<tr>
<td>Ritalin SR</td>
<td>(20 mg is the only tablet available)</td>
<td>qam-bid</td>
<td>0.6-1.4</td>
<td>40</td>
<td>80</td>
<td>160</td>
<td>(&gt;50 kg)</td>
</tr>
<tr>
<td>Concerta</td>
<td>18 qam</td>
<td>0.6-2.1</td>
<td>0.6-2.1</td>
<td>54-72</td>
<td>54-72</td>
<td>108</td>
<td>(enlarged slide appended)</td>
</tr>
<tr>
<td>Biphentin</td>
<td>10 qam</td>
<td>0.6-1</td>
<td>0.6-1</td>
<td>60-80***</td>
<td>60-80***</td>
<td>N/A</td>
<td>(enlarged slide appended)</td>
</tr>
<tr>
<td>Dexedrine</td>
<td>(tablet)</td>
<td>2.5-5 bid-tid</td>
<td>0.15-0.5</td>
<td>0.3-1.5</td>
<td>20</td>
<td>60</td>
<td>(&gt;50 kg)</td>
</tr>
<tr>
<td>Dexedrine</td>
<td>(spansule)</td>
<td>qam-bid</td>
<td>0.3-1.5</td>
<td>40</td>
<td>100</td>
<td>100</td>
<td>(&gt;50 kg)</td>
</tr>
<tr>
<td>Adderall</td>
<td>XR 5-10 qam</td>
<td>0.3-1.5</td>
<td>0.3-1.5</td>
<td>30</td>
<td>60</td>
<td>60</td>
<td>(&gt;50 kg)</td>
</tr>
<tr>
<td>Vyvanse</td>
<td>20-30 qam</td>
<td>N/A†</td>
<td>N/A†</td>
<td>60-70†</td>
<td>60-70‡</td>
<td>“Not yet known”</td>
<td>(enlarged slide appended)</td>
</tr>
</tbody>
</table>

* According to the AACAP Practice Parameter for ADHD (Pliszka et al., 2007)
** Per Health Canada, 54 mg in youth ≥6 yrs and 72 mg in adults; however, the FDA allows up to 72 mg (not to exceed 2 mg/kg/day in adolescents 13-17 yrs and 72 mg (no weight-based max) in adults 18-65 yrs
*** 60 mg in youth ≥6 yrs and 80 mg in adults (not to exceed 1 mg/kg/day)
† Dose ranges by weight have not been described, but note that 1 mg of Vyvanse (lisdexamfetamine) is converted into about 0.3 mg of d-amphetamine (Boellner et al., 2010)
‡ Per Health Canada, 60 mg in youth ≥6 yrs and adults; per the FDA, 70 mg in youth ≥6 yrs and adults

Titration “Mindset”

• Try to emulate the “Medication” arm of the MTA, not “Community Care”!

• That means…
  – Start low
  – Monitor closely
  – Titrate the dose by small increments
  – Continue titration until 1 of 3 things happens:
    (1) Optimal response is achieved
    (2) Intolerable adverse effects develop
    (3) Maximum dose is reached

Titration Tips

• Start on a weekend so that parents can observe the child and monitor closely for response and adverse effects
• Allow about a week to assess the effects of medication at each dose (kids can have good days and bad days for other reasons)
• Frequent phone contact or visits (e.g., weekly) in the first 1-2 months after starting medication to assess benefits and adverse effects, and make dose adjustments

Titration Tips (cont.)

• Use patient/parent and teacher rating scales to help monitor response and adverse effects at each dose
• As long as the medication is well tolerated and the maximum dose hasn’t been reached, don’t stop titrating after partial improvement
• Consider “drug holidays” on weekends or school vacations depending on the clinical circumstances (e.g., degree of social impairment from ADHD symptoms, concerns about appetite/growth)
Monitoring

• Response and adverse effects (preferably using rating scales)
• HR & BP at baseline and regularly thereafter, especially with dose increases
• Height and weight plotted on a growth chart

Common Pitfall #1

• Giving up on a stimulant too soon because of inadequate response or mild adverse effects:
  – If response is inadequate and the stimulant is well tolerated, continue titrating towards the maximum dose
  – Mild adverse effects can often be addressed without discontinuing the stimulant (see slides on “Troubleshooting”)

Common Pitfall #2

• Abandoning the stimulant class too soon:
  – If the first type of stimulant you try (MPH or AMPH) does not work out because of poor response or tolerability, try the other type
  – Consider trying different formulations of the same type of stimulant (Coghill et al., 2013), especially if problems with one formulation relate to its duration of action (too long or too short)

Common Pitfall #3

• Not thinking about stimulants in the first place because ADHD symptoms are overshadowed by other problems (e.g., ODD, aggression, irritability):
  – Careful history and differential diagnosis
  – Consider whether other problems may be secondary to ADHD
  – Comorbid oppositional/aggressive behaviour and irritability often improve with appropriate stimulant treatment for ADHD:
    • Pringsheim et al., 2015 [meta-analysis]; Fernandez de la Cruz et al., 2015 [MTA analysis]

Troubleshooting #1: “She won’t fall asleep”

• Assess and optimize sleep hygiene
• Assess for other causes of sleep disturbance
• If using a short-acting formulation: ↓ or eliminate the last dose, or give it a little earlier
• If using a long-acting formulation: give it earlier in the morning, or consider switching to a shorter-acting formulation
• Last resort: consider adding a sleep medication (e.g., melatonin, clonidine, diphenhydramine, trazodone, mirtazapine)

Troubleshooting #2: “He won’t eat”

• Assess parenting and routines related to eating
• Assess for other causes of poor eating
• Encourage big breakfasts (before morning dose of medication), later dinners, and big bedtime snacks
• Encourage high-calorie foods that kids like
• Consider “drug holidays”
• Consider a shorter-acting stimulant formulation
• Last resort: consider adding a medication to ↑ appetite (e.g., cyproheptadine, mirtazapine)
Troubleshooting #3: “She’s worse”

• Assess for other possible causes of behavioural or emotional problems
• When is she worse?
  – If she’s consistently worse at the medication peak, consider lowering the dose or switching to a different stimulant formulation
  – If she’s consistently worse during the medication wear-off, consider giving short-acting doses closer together, switching to a different stimulant formulation, or adding a small dose of the short-acting formulation of the same stimulant (i.e., short-acting Ritalin or Dexedrine) during the wear-off period at the end of the day (to “soften the landing”)

Troubleshooting #4: “He’s a zombie”

• Assess for other causes of social withdrawal (e.g., depression, social anxiety)
• Is he really withdrawn, or are the parents just not used to seeing him alert but calm?
• Consider lowering the dose
• Consider switching to a different stimulant formulation

Troubleshooting #5: “She Won’t Stop Twitching”

• Note that stimulants do not exacerbate or cause new onset of tics on average (Pringsheim et al., 2011; Cohen et al., 2015), but may do so in certain individuals
• Note that tics are common and usually transient in children, and they wax and wane on their own
• If after careful evaluation the stimulant is clearly causing tic exacerbation, then weigh the benefits of improved ADHD symptoms vs. the degree of distress and impairment associated with the tics
• Consider ↓ stimulant dose, switching to a different stimulant formulation, adding or switching to an α2 agonist, or switching to atomoxetine
Hyperactive-Impulsive Symptoms (Teacher Report)

- Community Care
- Behavioral Treatment
- Medication Management
- Combined Treatment

Reference: MTA Group, 1999
Fig. 1 Average ADHD and ODD Symptoms and Columbia Impairment Scale scores through 36 months. Comb = combination of medication management and behavior therapy; Med = medication management; Beh = behavior therapy; CC = usual community care.

Reference: Jensen et al., 2007
MTA Outcomes at 3 Years (cont.)

Reference: Swanson et al., 2007
Fig. 2 Selected outcome variables for MTA children, graphed by originally randomized treatment group assignment and LNCG. Beh = behavior therapy; CC = community care; CIS = Columbia Impairment Rating Scale; Comb = combined; LNCG = local normative comparison group; MedMgt = medication management; ODD = oppositional defiant disorder; SNAP = Swanson, Nolan, Pelham Rating Scale.

Reference: Molina et al., 2009
Long-Term Injury Outcomes

• Several large studies found that treatment with ADHD medication reduced the risk of injury (Dalsgaard et al., 2015; Mikolajczyk et al., 2015; Merrill et al., 2016; Chen et al., 2017)

Reference: Dalsgaard et al., 2015
Swanson et al., 2007 (cont.)

LNCG = local normative comparison group
Stimulants & Sudden Death: Individual Cases

### Cases of Sudden Death Reported to the FDA Advisory Committee from the AERS Database.*

<table>
<thead>
<tr>
<th>Patients</th>
<th>Amphetamines</th>
<th>Methylphenidate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjudicated Sudden Deaths</td>
<td>Cases Meeting WHO Criteria for Sudden Death</td>
</tr>
<tr>
<td>Age, 1–18 yr</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>Age, &gt;18 yr</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>28</td>
<td>17</td>
</tr>
</tbody>
</table>

* Data are from the Adverse Event Reporting System (AERS) of the Food and Drug Administration (FDA).<sup>1</sup> Amphetamines include mixed amphetamine salts (Adderall), amphetamine, biphentamine, and dextroamphetamine. WHO denotes World Health Organization.


**N.B.** Data are for the period 1999-2003, during which time about 2.5 million children and adolescents were taking stimulants (Perrin et al., 2008)
FIGURE 1
Cardiac evaluation of children and adolescents receiving or being considered for stimulant medications.

Reference: American Academy of Pediatrics Policy Statement on Cardiovascular Monitoring and Stimulant Drugs for ADHD (Perrin et al., 2008)
### Table 1. Screening Tool for Identification of Potential Cardiac Risk Factors for Sudden Death in Children Starting Stimulant Medication

*Answering “yes” to any of these questions should prompt further investigation or review by a specialist in pediatric cardiology.*

<table>
<thead>
<tr>
<th>Item</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>History</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shortness of breath with exercise (more than other children of the same age) in the absence of an alternate explanation (e.g. asthma, sedentary lifestyle, obesity)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor exercise tolerance (in comparison with other children) in the absence of an alternate explanation (e.g. asthma, sedentary lifestyle, obesity)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fainting or seizures with exercise, startle or fright</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palpitations brought on by exercise</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family history of sudden or unexplained death including sudden infant death syndrome, unexplained drowning or unexplained motor vehicle accidents (in first or second degree relatives)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Personal or family history (in first or second degree relatives) of non-ischemic heart disease such as:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long QT syndrome or other familial arrhythmias</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wolff-Parkinson-White syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart Transplant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary Hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unexplained motor vehicle collisions or drowning</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Implantable defibrillator</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical Examination</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Organic (not functional) murmur present</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sternotomy incision</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other abnormal cardiac findings</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Reference:** Cardiac Risk Assessment Before the Use of Stimulant Medications in Children and Youth, A Joint Position Statement by the CPS, CCS, and CACAP (Bélanger et al., 2009)
Biphentin (Multi-Layer Release MPH)
Adderall XR

(50%)
Vyvanse

- Lisdexamfetamine dimesylate (LDX) is a pharmacologically inactive prodrug.
- LDX is converted, mainly in the blood, to L-lysine (a naturally occurring amino acid) and pharmacologically active d-amphetamine.
- Whereas other long-acting stimulants achieve extended duration of action through "engineering," Vyvanse achieves it through chemical conversion (hydrolysis of the covalent bond between L-lysine and d-amphetamine).
**Figure 1.** The standardized mean difference [a measure of effect size] predicts the probability that a drug will lead to a better outcome than placebo for a random patient.

Reference: Faraone, 2003 (meta-analysis)
<table>
<thead>
<tr>
<th>Medication</th>
<th>Starting Dose (mg)</th>
<th>Dose Frequency</th>
<th>Usual Single Dose Range by Weight (mg/kg/dose)</th>
<th>Usual Daily Dose Range by Weight (mg/kg/day)</th>
<th>Max Single Absolute Dose (mg)</th>
<th>Max Daily Absolute Dose (mg)</th>
<th>Off-Label Max Daily Absolute Dose (mg)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ritalin</td>
<td>5</td>
<td>bid-tid</td>
<td>0.3-0.7</td>
<td>0.6-2.1</td>
<td>20</td>
<td>60</td>
<td>100 mg (&gt;50 kg)</td>
</tr>
<tr>
<td>Ritalin SR</td>
<td>(20 mg is the only tablet available)</td>
<td>qam-bid</td>
<td>0.6-1.4</td>
<td>0.6-2.1</td>
<td>40</td>
<td>60</td>
<td>100 mg (&gt;50 kg)</td>
</tr>
<tr>
<td>Concerta</td>
<td>18</td>
<td>qam</td>
<td>0.6-2.1</td>
<td>0.6-2.1</td>
<td>54-72**</td>
<td>54-72**</td>
<td>108 mg</td>
</tr>
<tr>
<td>Biphentin</td>
<td>10</td>
<td>qam</td>
<td>0.6-1</td>
<td>0.6-1</td>
<td>60-80***</td>
<td>60-80***</td>
<td>N/A</td>
</tr>
<tr>
<td>Dexamphetamine tablet</td>
<td>2.5-5</td>
<td>bid-tid</td>
<td>0.15-0.5</td>
<td>0.3-1.5</td>
<td>20</td>
<td>40</td>
<td>60 mg (&gt;50 kg)</td>
</tr>
<tr>
<td>Dexamphetamine spansule</td>
<td>10</td>
<td>qam-bid</td>
<td>0.3-1.5</td>
<td>0.3-1.5</td>
<td>40</td>
<td>40</td>
<td>60 mg (&gt;50 kg)</td>
</tr>
<tr>
<td>Adderall XR</td>
<td>5-10</td>
<td>qam</td>
<td>0.3-1.5</td>
<td>0.3-1.5</td>
<td>30</td>
<td>30</td>
<td>60 mg (&gt;50 kg)</td>
</tr>
<tr>
<td>Vyvanse</td>
<td>20-30</td>
<td>qam</td>
<td>N/A†</td>
<td>N/A†</td>
<td>60-70†</td>
<td>60-70†</td>
<td>“Not yet known”</td>
</tr>
</tbody>
</table>

* According to the AACAP Practice Parameter for ADHD (Pliszka et al., 2007)

** Per Health Canada, 54 mg in youth ≥6 yrs and 72 mg in adults; however, the FDA allows up to 72 mg (not to exceed 2 mg/kg/day) in adolescents 13-17 yrs and 72 mg (no weight-based max) in adults 18-65 yrs

*** 60 mg in youth ≥6 yrs and 80 mg in adults (not to exceed 1 mg/kg/day)

† Dose ranges by weight have not been described, but note that 1 mg of Vyvanse (lisdexamfetamine) is converted into about 0.3 mg of d-amphetamine (Boellner et al., 2010)

‡ Per Health Canada, 60 mg in youth ≥6 yrs and adults; per the FDA, 70 mg in youth ≥6 yrs and adults

©Daniel Gorman, Amy Cheung, Elia Abi-Jaoude 2017