Pharmacological Treatment of Attention Deficit Hyperactivity Disorder and its comorbidities

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History of stimulant treatment

- Benzedrine (a mixed salts amphetamine) first used in 1938
- Dextroamphetamine and methylphenidate (Ritalin) introduced in the 1960’s
- Hundreds of double blind, placebo controlled studies involving thousands of patients in last five decades
- The most extensively studied psychotropic medication

Methylphenidate (MPH)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concerta</td>
<td>Osmotic pump, small dose released in AM, the rest released gradually over the day- 10-12 hour action</td>
</tr>
<tr>
<td>Focalin</td>
<td>D-methylphenidate isomer only (+-methylphenidate is inactive, not absorbed into blood stream)- may have slightly longer action than d, l MPH</td>
</tr>
<tr>
<td>Focalin XR</td>
<td>Immediate and delayed release beads, gives 10-12 hour action in laboratory classroom</td>
</tr>
<tr>
<td>Ritalin</td>
<td>Immediate release d,l MPH, each dose last about 4 hours</td>
</tr>
<tr>
<td>Ritalin LA</td>
<td>Immediate and delayed release beads, gives 8 hour action</td>
</tr>
<tr>
<td>Daytrana</td>
<td>D,l MPH absorbed directly into bloodstream though skin, if patch worn 9 hours, gives 10-12 hour action</td>
</tr>
<tr>
<td>Metadate</td>
<td>D,l MPH, 30% released immediately, 70% release later in day, 8 hour action</td>
</tr>
</tbody>
</table>
Amphetamine (AMP)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Starting Dose</th>
<th>Maximum Dose</th>
<th>Usual Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPH</td>
<td>5 mg qd</td>
<td>2 mg/kg/day</td>
<td>bid (4h) bid (5h-6h)</td>
</tr>
<tr>
<td>Dex-MPH</td>
<td>2.5 mg</td>
<td>2 mg/kg/day</td>
<td>bid (5h-6h)</td>
</tr>
<tr>
<td>Dex-MPH XR</td>
<td>15 mg qd</td>
<td>2 mg/kg/day</td>
<td>bid (5h-6h)</td>
</tr>
<tr>
<td>Oros-MPH</td>
<td>2.5 mg-qd</td>
<td>1 mg/kg/day</td>
<td>bid (5h-6h)</td>
</tr>
<tr>
<td>MPH CD</td>
<td>5 mg</td>
<td>1 mg/kg/day</td>
<td>bid (5h-6h)</td>
</tr>
<tr>
<td>MPH LA</td>
<td>5 mg</td>
<td>1 mg/kg/day</td>
<td>bid (5h-6h)</td>
</tr>
<tr>
<td>Dex-MPH-XR</td>
<td>2 mg/kg/day</td>
<td>1 mg/kg/day</td>
<td>bid (5h-6h)</td>
</tr>
<tr>
<td>D-AMP, MAS</td>
<td>12.5 mg qd</td>
<td>1 mg/kg/day</td>
<td>bid (5h-6h)</td>
</tr>
<tr>
<td>LDX</td>
<td>2.5 mg-qd</td>
<td>1 mg/kg/day</td>
<td>bid (5h-6h)</td>
</tr>
<tr>
<td>MAS XR</td>
<td>5 mg</td>
<td>1 mg/kg/day</td>
<td>bid (5h-6h)</td>
</tr>
<tr>
<td>D-amphetamine</td>
<td>10 mg</td>
<td>20-30 mg qd</td>
<td>bid (5h-6h)</td>
</tr>
<tr>
<td>Dex Spansule</td>
<td>2.5 mg-qd</td>
<td>1 mg/kg/day</td>
<td>bid (5h-6h)</td>
</tr>
<tr>
<td>Lisdexamfetamine</td>
<td>5 mg</td>
<td>10 mg</td>
<td>bid (5h-6h)</td>
</tr>
<tr>
<td>MTS</td>
<td>10 mg-20 mg qd</td>
<td>bid (5h-6h)</td>
<td>bid (5h-6h)</td>
</tr>
<tr>
<td>MTX</td>
<td>10 mg-20 mg qd</td>
<td>bid (5h-6h)</td>
<td>bid (5h-6h)</td>
</tr>
<tr>
<td>MPH = methylphenidate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dex = dextroamphetamine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDX = lisdexamfetamine dimesylate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTS = methylphenidate transdermal system</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAS = mixed amphetamine salts</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D-AMP = dextroamphetamine</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Choosing stimulant

- On average MPH and AMP have equal efficacy and degree of adverse events
- Wide individual variation in how patients respond to stimulant class/formulations
- No clinical predictors of stimulant response exist
- Careful individual trials are needed

Side Effects with Methylphenidate and Amphetamine Therapy

Many side effects are characteristic of ADHD and improve with stimulant treatment.
Growth and Stimulants: Recent Studies (Cont.)

Estimated Reporting Rates (1992-2004): Pediatric Sudden Death (≤18 Years Old)

American Heart Association Guidelines

• Press release, article by Vetter et al. in Circulation, May 6, 2008
• While the article refers to stimulants in the title, it recommends EKG’s for all ADHD medications, including atomoxetine and alpha agonists, both at baseline and follow up
• No new data in article. Lengthy discussion in article of sudden death in athletes, yet AHA concludes that EKG screening of athletes is not feasible


• ~6000 children in atomoxetine trials
• QTc interval > 500 msec was exclusionary
• Only 7 subjects excluded
Winterstein et al., Pediatrics, 2007

- Florida Medicaid claims data 1994-2004
- 55,383 children placed on stimulants
- No cardiac deaths in 46,612 person-years
- 27 hospitalizations-
- 1091 children visited ER (8.7 per 100,000 person-years)
- ER visits associated with multiple med use, including concurrent use of bronchodilators
- "Incidence rates of cardiac events requiring hospitalization were small and similar to national background rates."

Psychiatric Side Effects of Stimulants?

<table>
<thead>
<tr>
<th>Drug</th>
<th>Type of trial</th>
<th>No. of</th>
<th>Duration of trials (range)</th>
<th>Category of exposure</th>
<th>N</th>
<th>Patient-years</th>
<th>Psychotic events</th>
<th>Suicidal events</th>
<th>Aggressive events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concerta</td>
<td>DB</td>
<td>4</td>
<td>9-25 dys</td>
<td>Placebo</td>
<td>317</td>
<td>12.23</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Ool</td>
<td>7</td>
<td>&lt;10 mos</td>
<td>Drug DB</td>
<td>424</td>
<td>12.23</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Metadate</td>
<td>DB</td>
<td>4</td>
<td>7-21 dys</td>
<td>Placebo</td>
<td>394</td>
<td>18.44</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ool</td>
<td>2</td>
<td>NS</td>
<td></td>
<td>Drug Ool</td>
<td>525</td>
<td>18.44</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Strattera</td>
<td>DB</td>
<td>6</td>
<td>1-5 wks</td>
<td>Placebo</td>
<td>356</td>
<td>23.62</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Ool</td>
<td>3</td>
<td>&lt;1 yr</td>
<td>Drug Ool</td>
<td>356</td>
<td>23.62</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Adderall</td>
<td>DB</td>
<td>7</td>
<td>1-4 wks</td>
<td>Placebo</td>
<td>510</td>
<td>26.13</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ool</td>
<td>5</td>
<td>&lt;1 yr</td>
<td></td>
<td>Drug Ool</td>
<td>510</td>
<td>26.13</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Atomoxetine</td>
<td>DB</td>
<td>20</td>
<td>&lt;7 wks</td>
<td>Placebo</td>
<td>349</td>
<td>56.95</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Ool</td>
<td>10</td>
<td>&lt;30 yrs</td>
<td>Drug Ool</td>
<td>349</td>
<td>56.95</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ritalin LA</td>
<td>DB</td>
<td>10</td>
<td>1-34 dys</td>
<td>Placebo</td>
<td>229</td>
<td>36.53</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Ool</td>
<td>1</td>
<td>NS</td>
<td>Drug Ool</td>
<td>229</td>
<td>36.53</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>DMPH</td>
<td>DB</td>
<td>5</td>
<td>4-8 dys</td>
<td>Placebo</td>
<td>500</td>
<td>13.55</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Ool</td>
<td>5</td>
<td>&lt;1 yr</td>
<td>Drug Ool</td>
<td>500</td>
<td>13.55</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>


Atomoxetine Site of Action

1. NE concentration and duration increased
2. Forward transmission of impulse is enhanced
3. NE feedback inhibition to presynaptic neuron occurs, improving signal transmission efficiency

Atomoxetine

- Specific noradrenergic reuptake inhibitor
  - Affects dopamine in frontal lobes
  - Unscheduled, renewable
  - No addictive liability
  - >10 controlled trials demonstrating efficacy
  - Long-term studies: continued effectiveness

Neurotransmitter selective blocks NE transporter

NE Norepinephrine

Comparing stimulants and Atomoxetine

• Newcorn et al. (Am J Psychiatry, 2008; 165:721-730)
• Patients with ADHD (age 6-16 years) assigned randomly to:
  – Concerta (n = 220, 18-54 mg/day)
  – Strattera (n = 222, 1.2-1.8 mg/kg/day)
  – Placebo (n = 74)
• 6 week trial

Comparing stimulants and Atomoxetine

% Responders

Concerta
Strattera
Placebo

* Am J Psychiatry, 2008; 165:721-730)

Comparing stimulants and Atomoxetine

Atomoxetine

• Specific noradrenergic reuptake inhibitor (cont’d)

  – Rare hepatitis reported
    • One case confirmed/3.4 million exposures
    • One case suspected/3.4 million exposures
  – Possible slight increase in suicidal ideation reported in clinical trials
    • 0.37% atomoxetine vs 0.0% placebo
    • One suicide attempt/1,357 cases; no suicides

Dosing of Atomoxetine in ADHD

• Prescribing information (not a controlled substance)
  – Start = 0.5 mg/kg/day
  – Target 1.2 mg/kg/day with max of 1.4 mg/kg/day or 100 mg/day
• 8 yo boy
  – Start 18 mg for 4 days in AM after food
  – 25 mg for 4-7 days then increase to 40 mg
• If already on stimulant, typically stop stimulant, introduce atomoxetine then re-evaluate need for stimulant


MAOI = monoamine oxidase inhibitor.
Dosing of Atomoxetine in ADHD (cont’d)

- Available in 10 mg, 18 mg, 25 mg, 40 mg, 60 mg capsules
- Sprinkling not formally tested and may irritate GI tract
- Drug interactions (contraindicated with MAOIs)
  - Decrease dose if co-administering with strong 2D6 inhibitor (fluoxetine, paroxetine)
  - Co-administration with IV albuterol (600 mcg over 2 hours) is associated with mild increases in heart rate and blood pressure
  - Co-administration with methylphenidate appears well tolerated but has not been fully studied

Alpha Agonists in the treatment of ADHD

Clonidine and Stimulant Alone & Combined
Palumbo et al. JAACAP 47: 180

Extended Release Guanfacine: Change in ADHD RS

Biederman, J. et al. Pediatrics 2008;121:e73-e84

MAOI = monoamine oxidase inhibitor.

**Alpha Agonist Summary**

- **Clonidine**
  - Increasingly used in single dose in PM for insomnia secondary to stimulants (0.05 to 0.1 mg q HS)
  - Declining role for treatment of daytime ADHD due to efficacy issues as well as sedation

- **Guanfacine**
  - Both immediate release and XR (when available) used more ADHD itself
    - Non responders to stimulants and atomoxetine
    - Patients with stimulant-induced tics whose ADHD responds only to stimulants

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**Extended release Guanfacine**

\% of subjects with improvement in CGI-I scores

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**Dosing of clonidine and guanfacine**

<table>
<thead>
<tr>
<th>Week</th>
<th>Dosage (mg) of Alpha Agonist (Weight &lt; 45 kg)</th>
<th>Dosage (mg) of Alpha Agonist (Weight &gt; 45 kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Clonidine</td>
<td>Guanfacine</td>
</tr>
<tr>
<td>1-2</td>
<td>0.05 q.h.s.</td>
<td>0.5 q.h.s.</td>
</tr>
<tr>
<td>2-4</td>
<td>0.05 b.i.d.</td>
<td>0.5 b.i.d.</td>
</tr>
<tr>
<td>3-6</td>
<td>0.05 t.i.d.</td>
<td>0.5 t.i.d.</td>
</tr>
</tbody>
</table>

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**Stages of Medication RX for ADHD**

1. Trial of a single stimulant, try different formulations for duration action
2. Trial of stimulant in alternate class
   - MPH fail $\longrightarrow$ AMP
   - AMP fail $\longrightarrow$ MPH
3. Trial of atomoxetine or guanfacine XR (if approved)
4. No response to any the above: psychiatric consultation
When and how should PCP’s treat comorbidity in ADHD?

- Tics
- Impulsive/severe aggression
- Autism Spectrum Disorders
  - Deferred to separate module
- Depression and Anxiety
  - Deferred to separate module

Tics and ADHD

- Many children with tics and ADHD can tolerate stimulants without an increase in tics
  - Law and Schachar (1999): 12-month study, 91 children
    - MPH treatment did not produce significantly more tics than placebo in children with or without mild-to-moderate pre-existing tic disorder
  - Gadow et al. (1999): 24-month study, 34 children with ADHD and tic disorder or Tourette’s syndrome
    - Stimulant treatment was effective in controlling ADHD symptoms without adversely affecting tics
  - Lipkin et al. (1994), in a review of 122 children treated with stimulant medication found 9% developed transient tics and <1% developed chronic tics


Induction or Exacerbation of Tics

- Tics are usually transient; only very rarely do patients develop a chronic tic disorder
- When tics occur or increase
  - Decrease dose
  - Switch to another stimulant
  - Adjunct agent to treat tics
  - Try nonstimulant medication

Controlled Trial of MPH and Clonidine

[Graph showing the change in Y-GTSS over weeks for PLA, MPH, CLON, and MPH + CLON conditions]

Y-GTSS = Yale Global Tic Severity Scale; Tourette Syndrome’s Study Group (2002), Neurology 58(4):527-536
Aggression

• First line for children with ADHD and aggression
• Treatment of ADHD
  – Stimulants show striking efficacy in controlled trials of the treatment of aggression 1,2
  – Behavior therapy by SUPPORT counselor
  – If aggressive outbursts with prolonged (> 10 min) rage, attacks on others or destruction of property, in spite of treatment of ADHD and psychotherapy, adjunctive psychopharmacology may be needed


When should PCP’s treat aggression pharmacologically?

• SUPPORT therapist consults with psychiatrist, determines if bipolar/psychosis is ruled out
• If necessary, PCP consults directly with psychiatrist

How far should PCP’s go?

• Monotherapy with one or two second generation antipsychotics (SGA’s) [alone or in combination with stimulant], if no response after that, transfer to psychiatry
• Classic mood stabilizers (lithium, divalproex) will have limited use, no combinations with SGA

SGA Antipsychotics

• Current agents*  
  – Risperidone (Risperidal)  
  – Quetiapine (Seroquel)  
  – Aripiprazole (Abilify)  
  – Olanzapine (Zyprexa)  
  – Ziprasidone (Geodon)

• Powerful  
• Sometimes necessary  
• Limit use because of ...  
  – Sedation  
  – Weight gain

*Listed in order of common usage/number of studies

Efficacy of Risperidone in Conduct Disorder: Change in Aggression Score

Snyder R et al. (2002), J Am Acad Child Adolesc Psychiatry 41(9):1026-1036
### Combination of Stimulant and SGA

**On Aggression scale, no difference between placebo and risperidone; placebo effect suggest effect of psychosocial intervention**

*Armenteros et al. (2007) JAACAP 46: 558-565*

![Combination of Stimulant and SGA](image)

### SGA’s and bipolar disorder in children

- **Risperidone**- FDA approved for treatment of bipolar in adolescents age 10-17 years, extensive studies in aggression
- **Aripiprazole**- FDA approved for treatment of bipolar in adolescents age 10-17 years, small studies in aggression
- **Quetiapine**- studies in children with bipolar and aggression, no FDA approval yet, but extensive clinical experience
- **Olanzapine**- studies in teens with bipolar, serious weight gain, viewed as drug of last resort
- **Ziprasidone**- one positive study in children with bipolar, EKG issues

### Controversy over use of SGA’s in children

- Eli Lilly paid $1.4 billion to settle federal charges that it downplayed risks of olanzapine to physicians and encouraged off label use in children and the elderly
- Concerns that the diagnosis of bipolar disorder is made too frequently in children and adolescents
- Are we exposing children to long term risk of cardiovascular disease and/or diabetes?
- SGA’s should never be used for treatment of ODD alone, only severe aggression and mood lability

### Antipsychotic Weight Gain: Meta-Analysis

*Allison DB et al. (1999), Am J Psychiatry 156(11):1686-1696*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Weight Change (kg)</th>
<th>95% CI for weight change after 10 weeks on standard drug doses, estimated from a random effects model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Conventional antipsychotics</td>
<td>-2.1 (2.7)</td>
<td></td>
</tr>
<tr>
<td>Novel antipsychotics</td>
<td>-3.3 (0.9)</td>
<td></td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>4.7</td>
<td></td>
</tr>
<tr>
<td>Haloperidol</td>
<td>5.3</td>
<td></td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>6.4</td>
<td></td>
</tr>
<tr>
<td>Risperidone</td>
<td>4.1</td>
<td></td>
</tr>
<tr>
<td>Olanzapine</td>
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<tr>
<td>Clozapine</td>
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<tr>
<td>Clozapine</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>Conventional antipsychotics</td>
<td>1.5 (2.9)</td>
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</table>
### SGA dosing: Risperidone

<table>
<thead>
<tr>
<th></th>
<th>Preadolescents</th>
<th>Adolescents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weeks 1-2</td>
<td>.5 qhs</td>
<td>1 mg q hs</td>
</tr>
<tr>
<td>Weeks 3-4</td>
<td>.5 mg bid</td>
<td>1 mg bid/tid</td>
</tr>
<tr>
<td>Weeks 5-6</td>
<td>1 mg bid/tid</td>
<td>2 mg bid/tid</td>
</tr>
</tbody>
</table>

Specific side effects: Sedation, EPS, drooling, increased prolactin, weight

### SGA dosing: Quetiapine

<table>
<thead>
<tr>
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<th>Preadolescents</th>
<th>Adolescents</th>
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</thead>
<tbody>
<tr>
<td>Weeks 1-2</td>
<td>25 mg Q D/25 mg bid</td>
<td>50 mg bid</td>
</tr>
<tr>
<td>Weeks 3-4</td>
<td>50 mg bid</td>
<td>200 mg bid</td>
</tr>
<tr>
<td>Weeks 5-6</td>
<td>100-200 mg bid</td>
<td>300 mg bid</td>
</tr>
</tbody>
</table>

Specific side effects: Sedation, increased weight, some street value for sedating effect

### SGA dosing: Aripiprazole

<table>
<thead>
<tr>
<th></th>
<th>Preadolescents</th>
<th>Adolescents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weeks 1-2</td>
<td>2.5-10 mg/day*</td>
<td>5-10 mg/day</td>
</tr>
<tr>
<td>Weeks 3-4</td>
<td>10-15 mg/day</td>
<td>15-20 mg day</td>
</tr>
<tr>
<td>Weeks 5-6</td>
<td>20 mg/day**</td>
<td>30 mg/day**</td>
</tr>
</tbody>
</table>

*Use 2.5-5 mg starting dose in children < 30 kg
**Caution, watch for EPS

Specific side effects: EPS, weight gain

### SGA’s safety monitoring

- **Baseline measures**
  - Comprehensive metabolic panel
  - Lipid panel
    - Triglycerides
    - Total cholesterol
    - High density cholesterol (HDL)
    - Low density cholesterol (LDL)
  - Height, weight and BMI
- Repeat in 3 months, then every 6 months
Excessive weight gain

- First, assess risk/benefit ratio
- Is the SGA really provide benefit? The parent saying that he “seems” better is not sufficient. Look for:
  - Drop of 50% in Aggression questionnaire score
  - Now has 1-2 weeks completely free of physical aggression
- Consider switch to alternative SGA

Summary

- Algorithm for treatment of uncomplicated ADHD is well established
- Presence of ODD or CD does not change medication management
- ADHD with tics: trial of atomoxetine or guanfacine alone or stimulant combined with guanfacine
- Impulsive, explosive aggression: treat ADHD, engage behavior therapy, if this fails add SGA monotherapy to ADHD medication treatment (Do not combine alpha agonist with SGA)