ADHD: Fine Tuning Pharmacological Treatment

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• I do not intend to discuss an unapproved/investigative use of a commercial product/device in my presentation.

Objectives

To maximize understanding of medications used for ADHD in these areas:
• Start by getting the diagnosis right
• What are treatment goals/target symptoms?
• Benefits and side effects of stimulant and non-stimulant medications
• Is it ADHD-Simplex or ASHD-Complex?
  Co-existing conditions often guide med choice
• Stimulants and non-stimulants
• Maximizing use of long-acting stimulants
Getting the diagnosis right

- **Interview parents and child** and/or ADHD specific behavioral checklist
  - Vanderbilt Assessment Scale

- **Teacher narrative** or behavior checklist
  - “Tell me about Joey in class...about his behavior and learning style”

- Screen for **mental health disease and LD**
- Knowledge about the **family**

ADHD: AAP Treatment Guideline

Treatment Strategies

*Pediatrics (2011) 128:1007*  
doi: 10.1542/peds.2011-2654

- Education (parents and child)
- Setting target outcomes
- **Behavioral management**
  - Classroom and home accommodations
- **Medication**
  - Systematic follow-up plan

ADHD:

**Selecting an initial medication**

- Effectiveness (RCTs)
- Side effect profile
- Duration of action
- Child-friendly formulation
- Co-existing behavioral conditions
- Cost
- Risk for diversion and abuse
- Family history of ADHD medication
- History of substance abuse
- History of cardiac disease (pt/family)
Treatment Goals

- Improve organizational skills and executive functions
- Enhance self-esteem
- Prepare child/adolescent with ADHD to successfully function and competently manage strengths and weaknesses with ADHD as an adult


Medications for ADHD: A History

<table>
<thead>
<tr>
<th>Medications</th>
<th>FDA Approval</th>
<th>RCT's</th>
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<tbody>
<tr>
<td>Amphetamine</td>
<td>1950s</td>
<td>**</td>
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<tr>
<td>Methylphenidate</td>
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<td>**</td>
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<tr>
<td>Atomoxetine</td>
<td>2003</td>
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<tr>
<td>Lisdexametamine</td>
<td>2007</td>
<td>*</td>
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<tr>
<td>Guanfacine ER</td>
<td>2009</td>
<td>*</td>
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<tr>
<td>Clonidine ER</td>
<td>2010</td>
<td>*</td>
</tr>
<tr>
<td>Tricyclics</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Buproprion</td>
<td>*</td>
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</tr>
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</table>

[* Relative # RCT's]

Case #1: 8 yo male with ADHD/C w/o Learning Disability, co-existing mental health condition or major psychosocial/family problems

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Stimulant Medication: 1st line Rx
Methylphenidate and amphetamines
(Regulation of dopamine)

- Equivalent head-to-head responses in reducing core symptoms of ADHD
- >200 RCT’s of stimulants
- 70% of children respond to 1 stimulant
- Half who fail 1st stimulant or who have intolerable side effects, respond to 2nd stimulant
- Short-acting, intermediate-acting and extended release preparations

Titrating Stimulant Medications

- Not weight dependent
- Begin low and titrate upward
- Variability in dose response
- Initial positive response may not be optimal dose to improve function
- Goal: optimal effects with minimal SE’s
- Schedule depends on target outcomes (5 or 7 days/week; holidays; afternoon dose)


Choosing medication: methylphenidate

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<tr>
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<th>Metadate CD</th>
<th>Ritalin LA</th>
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<td>Once</td>
<td>Once (BID)</td>
<td>Once (BID)</td>
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<td>IR 22%</td>
<td>IR bead</td>
<td>IR bead</td>
<td>IR 50%</td>
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<tr>
<td>Ease of use</td>
<td>Large capsule</td>
<td>Capsule</td>
<td>Sprinkle</td>
<td>Sprinkle</td>
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</table>
Choosing Medication: amphetamine

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<th>Dexedrine Spansules</th>
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<tr>
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<td>Medium</td>
<td>High</td>
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<tr>
<td>Onset</td>
<td>Slower at lower dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ease of use</td>
<td>Sprinkle</td>
<td>Grind</td>
<td>Sprinkle</td>
</tr>
</tbody>
</table>

Methylphenidate ER Patch

- Evenly dispersed, concentrated drug cells within adhesive layer
- Concentration gradient between drug and skin allows efficient diffusion
- Precise content ratios control rate of delivery
- Patch size conversion to MPH dose delivered over 9 hours:
  - $12.5 \text{ cm}^2 = 10 \text{ mg}$
  - $18.75 \text{ cm}^2 = 15 \text{ mg}$
  - $25 \text{ cm}^2 = 20 \text{ mg}$
  - $37.5 \text{ cm}^2 = 30 \text{ mg}$

Atomoxetine: Strattera

2nd line ADHD medication
Inhibitor of presynaptic norepinephrine transporter (SNRI)
Non-stimulant medication

- Treatment failure or intolerable side effects with stimulant
- Substance abuse potential for stimulant
- Co-existing anxiety disorder
- Significant sleep disturbance
- Tic disorder
- Parent against use of a "stimulant"


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Titrating Atomoxetine

- Starting dose: 0.5 mg/kg/day (3-5 days)
- Increase to 1.2-1.5 mg/kg/day
- Side effects similar to stimulants
- Fatigue and nausea: less w/ evening dosing
- Single daily dose or BID
- May take 3-6 weeks to have detectable effects

Lisdexamfetamine

*Vyvanse*

- Objective for development of drug: reduce the potential for abuse
- Inactive *prodrug* in which d-amphetamine is bound to l-lysine (inactive)
- Converted in GI tract to the active form of d-amphetamine by cleaving lysine
- 30 mg, 50 mg and 70 mg produced functional improvements comparable to 10 mg, 20 mg and 30 mg of mixed amphetamine salts.


Guanfacine: alpha 2-agonist

- Short acting: used off-label in ADHD (often with a stimulant) when significant disruptive behaviors or tics
- New extended release form: *Intuniv* (FDA approval 2009)
- 345 patients (6-17 yo: M=10.5 yo) with ADHD randomized to the extended-release guanfacine (2, 3, or 4 mg/day) or a placebo.
- Similar improvement c/w stimulants in hyperactivity and impulsivity but not inattention.
- Children had better response than adolescents
- Side effects: fatigue, sedation, minimal decr. BP and pulse

Biederman J. *Pediatrics* Jan 2008 121:e73-e84
Clonidine: alpha 2-agonist

- Extended-release tablets
- 0.1-mg and 0.2-mg (Kapvay)
- Treatment of ADHD (6-17 yo)
- FDA approval Oct. 2010 for monotherapy or w/ stimulant
- 2 RCTs: 0.1-0.2 mg BID (max. 0.4 mg)

MTA Study
Multimodal Treatment Study of Children w/ADHD
Study of long term treatment for ADHD
6 sites/579 children ages 7-9
Randomly assigned groups
Medication management
Behavior treatment
Combined (medication and behavior)
Standard community care


MTA Study
Multimodal Treatment Study of Children w/ADHD

- Started with methylphenidate
- Non-responders: amphetamine or non-stimulant
- Short-acting dosing (TID)
- Behavior treatments
  - Parent training
  - Intensive summer school program
  - Teacher training w/ aid in classroom
  - Daily home/school behavior report cards
MTA Study
Multimodal Treatment Study of Children w/ADHD

- Combined treatment *did not* yield significantly greater benefits than medication-only management for core ADHD symptoms
- Combined treatment outcomes were achieved with lower medication doses than medication alone
  (mean dose: 37 vs. 31 mg/day MPH)

MTA Study
Multimodal Treatment Study of Children w/ADHD

In several non-ADHD domains of functioning, *combined treatment* was superior to MTA medication management, behavioral treatments and community care
  - Oppositional defiant disorder
  - Symptoms of depression and anxiety
  - Teacher rated social skill deficits
  - Parent-child relationships
  - Reading achievement

Case # 2:
12 yo girl with ADHD
(primarily inattentive type)
associated with Anxiety

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ADHD: Co-existing Conditions

- Oppositional Defiant Disorder 25%
- Anxiety Disorder 15-20%
- Conduct Disorder 10%
- Depressive Disorder 5-10%
- Learning disorders 20-30%
- OCD, PTSD, Tourette’s Syndrome
- Environmental stressors

Case # 2:
12 yo girl with ADHD (I) + Anxiety

- Stimulant alone (or atomoxetine)
- Stimulant and cognitive-behavioral therapy
- Atomoxetine and cognitive behavioral therapy
- Stimulant or atomoxetine w/ SSRI

Case # 3:
15 yo boy with ADHD and depression

Stimulants and atomoxetine are generally not effective with depression
Bupropion (aminoketone)
    Dopamine and norepi reuptake inhibitor
    3 RCTs: effective with ADHD + depression
    Off-label when prescribed for ADHD alone
Stimulant or Atomoxetine + SSRI
  • CBT, IPT

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Tailoring ADHD Medications

- Co-existing Anxiety: Stimulant; Atomoxetine
- Co-existing Depression: Bupropion
- Co-existing aggression-increased impulsiveness:
  Alpha-2 agonist (guanfacine/Intuniv; clonidine/Kapvay)
- Atomoxetine may be beneficial w/ co-existing
  Delayed sleep onset
  Concern with substance abuse (patient/family)
  Parent refuses a “stimulant”

Common Side Effects with Stimulants

- Emotional lability at 3-5 PM (LA)
- Weight loss (or not gaining weight)
- Decrease height velocity
- Tics
- Sleep problems

Controversial/Uncommon Side Effects

- Stimulants
  Sudden unexplained death (cardiac)
- Atomoxetine
  Suicidal ideation (Black box warning)
ADHD: 2 special categories

Emerging evidence for benefit of stimulant medication in these children with ADHD:
- Preschool children *(Behavioral Therapy 1st)*
- Children and adolescents with developmental disabilities

ADHD Tool Kit
American Academy of Pediatrics and NICHQ

- Includes checklist of ADHD Behaviors and co-existing mental health and learning disabilities
- Medication table
- Parent Information
- Tool kit available at
  American Academy of Pediatrics
  (888) 227-1770
  www.aap.org/bookstore
  http://www.nichq.org/resources/toolkit/

- AAP: ADHD: What Every Parent Needs to Know
  Michael Reiff, M.D. ed. 2011  (800) 433-9016

To write a prescription is easy, but to come to an understanding with people is hard.
Franz Kafka