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ADHD:
Fine Tuning Pharmacological Treatment

Martin T. Stein, M.D.
Professor of Pediatrics
University of California San Diego
Rady Children's Hospital San Diego

Disclosure

- *I have no relevant financial relationships with the manufacturer(s) of any commercial product(s) and/or provider of commercial services discussed in this CME activity.*
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Objectives

To maximized 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
  http://www.anthem.com/ca/provider/f4/s1/t0/pw_b135931.pdf
  http://dss.mo.gov/mhd/cs/psych/pdf/adhd_rating_teacher.pdf
- **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

Ref: Gephart H, Leslie L. ADHD Pharmacotherapy *Contemporary Pediatrics* 2006;23:46-54.

Medications for ADHD: A History

# FDA Approval		RCT's
#Amphetamine	1950s	*******
#Methylphenidate	1960	*******
#Atomoxetine	2003	**
#Lysdexamfetamine	2007	*
#Guanfacine ER	2009	*
#Clonidine ER	2010	*
Tricyclics		*
Bubroprion		*

[* 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

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)

Wender, EH. Managing Stimulant Medication for Attention Deficit/ Hyperactivity Disorder. *Pediatrics in Review*. (2001) 22:183-190.

Choosing medication: methylphenidate

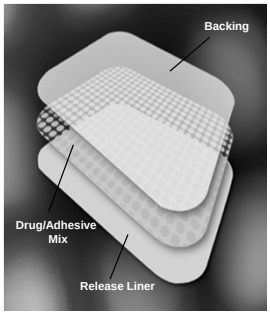
	Concerta	**Focalin XR**	**Metadate CD**	**Ritalin LA**
Duration	12 hrs	10-12 hrs 1/2 dose	8 hrs	8 hrs
Dosing	Once	Once	Once (BID)	Once (BID)
Onset	IR 22%	IR bead	IR bead	IR 50%
Ease of use	Large capsule	Capsule	Sprinkle	Sprinkle

Choosing Medication: amphetamine

	Adderall XR	Adderall	Dexedrine Spansules
Duration	10-12 hrs	6-8 hrs	6 hrs
Dosing	Once	BID	BID
Abuse Risk	Medium	High	High
Onset	Slower at lower dose		
Ease of use	Sprinkle	Grind	Sprinkle

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 cm^2 = 10 mg
  - 18.75 cm^2 = 15 mg
  - 25 cm^2 = 20 mg
  - 37.5 cm^2 = 30 mg



Shire Inc.—the only available MPH transdermal patch

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"

Michelson D et.al. 2001 Pediatrics 1089:5, e83.

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 track 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.

Biederman J et. al. Clin Ther. 2007;29:450-463.

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

Jensen P et al. *Arch Gen Psychiatry* (1999) 56:1073-1086.

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

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 atomoxitine)
- Stimulant and cognitive-behavioral therapy
- Atomoxitine and cognitive behavioral therapy
- Stimulant or atomoxitine 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

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