Attention Deficit Hyperactive Disorders

L. Eugene Arnold, MD, M.Ed.
Professor
Professor Emeritus of Psychiatry
The Ohio State University

Pre-test

Based on DSM-5 criteria, how many symptoms of inattention need to be present for a diagnosis of ADHD, predominantly inattentive presentation in a 23-year-old?

1. **3 or more**
2. **5 or more**
3. **6 or more**
4. **9**
5. **Unsure**

Pre-test

When treating ADHD, how do you choose the appropriate medication for each patient?

1. **Parental choice**
2. **Patient preference**
3. **Patient interview (parental input if child); needed dosing regimen; comorbidity**
4. **Check with pharmaceutical rep**
5. **Prefer not to recommend medication**

Diagnostic Procedure

- **Diagnosis requires 5 criteria:**
  1. **Symptom count and severity**
  2. **Impairment**
  3. **Pervasive across settings**
  4. **Chronicity**
  5. **Not better explained by other disorder**
- **Because of first criterion, ADHD is dimensional diagnosis, like hypertension**

DSM-5 Criteria for ADHD: Abbreviated

- **Six (5 for adults) or more symptoms of inattention, not developmentally appropriate for 6 months or more:**
  - **Often fails to [pay] attention, makes careless mistakes**
  - **Often has difficulty sustaining attention in tasks, play**
  - **Often does not seem to listen**
  - **Often does not follow through, finish schoolwork**
  - **Often has difficulty organizing tasks, activities**
  - **Often avoids, dislikes tasks requiring mental effort**
  - **Often loses things necessary for tasks or activities**
  - **Often easily distracted by extraneous stimuli**
  - **Often forgetful in daily activities**

Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (DSM-V). Washington, DC: American Psychiatric Association, 2013.

DSM-5 Criteria for ADHD: Abbreviated

- **Six (5 for adults) symptoms of hyperactivity-impulsivity, not developmentally appropriate for 6 months or more:**
  - **Often fidgets with hands or feet or squirms in seat**
  - **Often leaves seat when remaining seated is expected**
  - **Often runs or climbs excessively [inappropriately]**
  - **Often has difficulty playing quietly**
  - **Often "on the go" as if "driven by a motor" (for adolescents & adults, restless feeling)**
  - **Often talks excessively**
  - **Often blurts out answers before questions completed**
  - **Often has difficulty awaiting turn**
  - **Often interrupts, intrudes, butts in**

Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (DSM-V). Washington, DC: American Psychiatric Association, 2013.

Analogy to Hypertension

- **Everyone has some blood pressure (BP)**
- **Too much is problem**
- **How to set the threshold for problematic BP?**
- **Wherever it is set, some people on the cusp**
- **Stress, excess salt, obesity can nudge some over the BP threshold**
- **Stress, poor environment, poor nutrition, poor sleep can nudge some over the ADHD threshold**

Diagnostic Criteria for ADHD: DSM-5

- **Onset of symptoms before age 12**
- **Persistence of symptoms for at least 6 months**
- **Causes impairment in at least 2 settings**
- **Symptoms are**
  - **Pervasive: across settings**
  - **Protracted: chronic course**
  - **Pernicious: cause impairment**
- **Not due to other disorder**

Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (DSM-V). Washington, DC: American Psychiatric Association, 2013.

Associated Clinical Features

Outside the DSM criteria, but they express the core symptoms of ADHD, and may complicate Tx:

- **Low frustration tolerance**
- **Sleep problems (was DSM-III core symptom)**
- **Increased risk taking behavior**
- **Difficulty delaying gratification**
- **Over-reactivity**
- **Hasty, careless response style**

ADHD: Prevalence

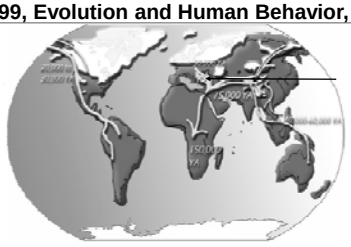
- **The most commonly diagnosed mental disorder in childhood**
- **5% to 8% in grade school children. Some epidemiologic surveys up to 10%**
- **In one survey 8% of U.S. children age 4-17 have ADHD by parent report**
- **Worldwide prevalence 3-12%, varying by country**

Centers for Disease Control and Prevention. Mental health in the United States: prevalence of diagnosis and medication treatment for attention-deficit/hyperactivity disorder-United States, 2003. *MMWR Morb Mortal Wkly Rep* 2005;54:842-847.

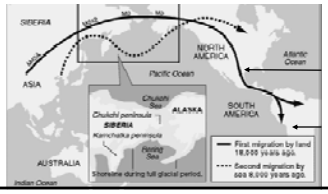
Genes, Geography, and Environment

- **Up to 80% heritable**
- **Does not equate to genetic determinism**
- **Genes expressed only in interaction with the environment**
  - **Example; PKU 100% hereditary and 100% environmental**
- **Geography important 2 ways**
  - **Migratory paths**
  - **Climate, flora, fauna**

MIGRATION PATHS "OUT OF AFRICA" INTO NEW WORLD (Chen et al., 1999, Evolution and Human Behavior, 20:309-324)



P(7R) = .15

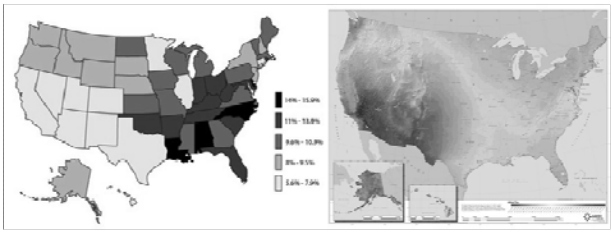


P(7R) = .26

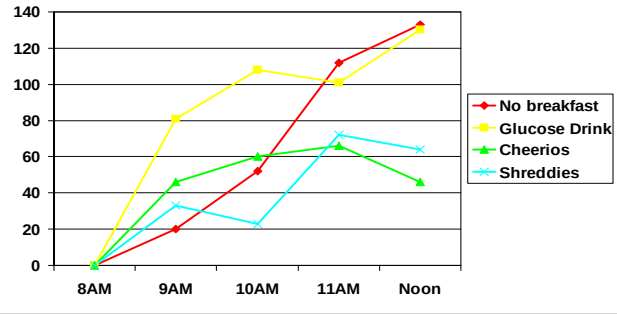
P(7R) = .63

2-FOLD VARIATION IN ADHD PREVALENCE BY STATE CORRELATES WITH SOLAR INTENSITY

Lightest states have lowest prevalence;
Red indicates highest solar intensity

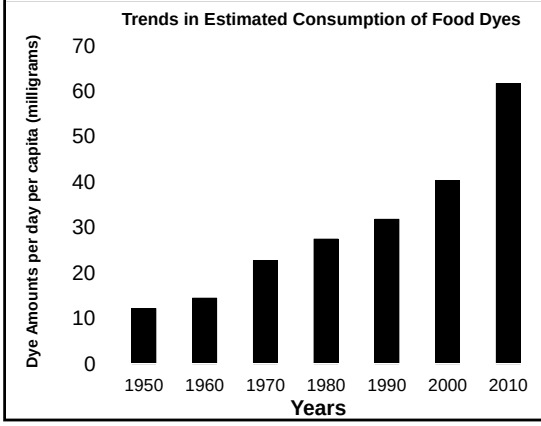


Breakfast Experiment: Attention Deterioration from 8 AM (Higher Score Worse) --Normal Kids

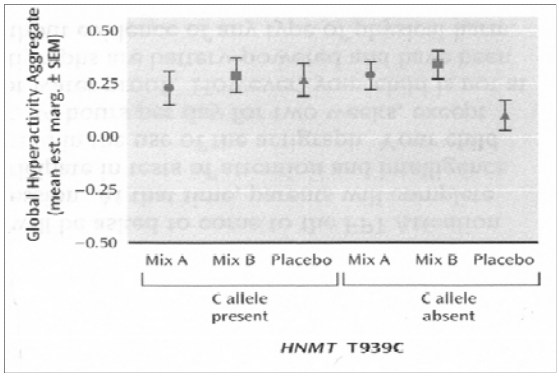


Wesnes et al (2003) Breakfast reduces declines in attention and memory over the morning in schoolchildren. *Appetite, 41*, 329–331

Consumption of Dye over Time

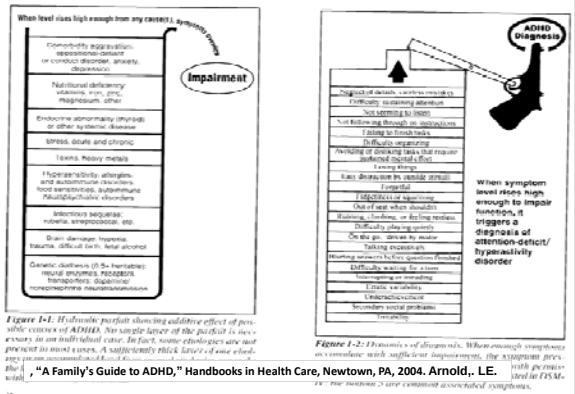


Interaction of Dye Effect with Histamine Genotype (8-9-yr-olds) --2



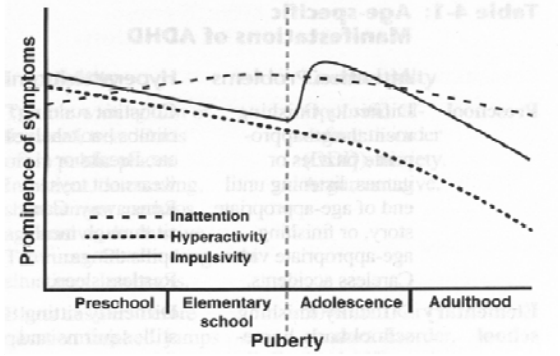
Stevenson et al, AJP, 2010

Multifactorial Hydraulic parfait for ADHD



, "A Family's Guide to ADHD," Handbooks in Health Care, Newtown, PA, 2004. Arnold,. LE.

ADHD Symptom Prominence by Age



"A Family's Guide to ADHD," Handbooks in Health Care, Newtown, PA, 2004. Arnold,. LE.

Clinical Presentation: Preschool Age

- ADHD can be recognized in children age 3
- At early age it can be difficult to distinguish ADHD symptoms from normal toddler activity
- Hyperactivity and impulsiveness most prominent at this age
  - Children are always
    - On the go
    - Getting into things
    - Acting as if driven by a motor
  - Tantrums are more severe and frequent than normal
  - Usual behavior management techniques often ineffective

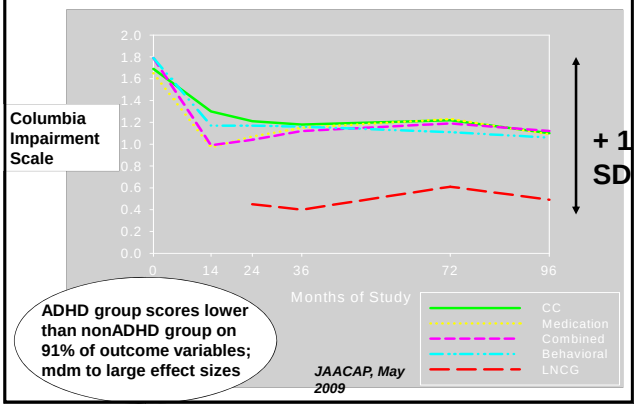
School Age (6 to 12 Years)

- Easily distracted
- Schoolwork poorly organized, careless errors, incomplete
- Blurts out answers, disruptive/talkative
- Interrupts or intrudes (difficulties in peer relationships)
- Impatient in waiting turn in games
- Often out of seat
- Perception of "immaturity"

Adolescence (13 to 18 Years)

- Sense of inner restlessness rather than hyperactivity
  - Hyperactivity wanes with maturity; inattention persists
- Struggling with increasing transition to middle school or high school
  - Schoolwork disorganized, poor follow through, can't work independently, unable to manage homework & projects
- Unable to deal with time management and growing distractions
  - Email, IM, jobs, sports, extracurricular activities
- Risky, impulsive behavior (dares, driving, drug/alcohol, sex)
- Poor self esteem (beginning of insight)
- Poor peer relations
- Difficulty with authority (high rate of comorbid oppositional-defiant and conduct disorder)

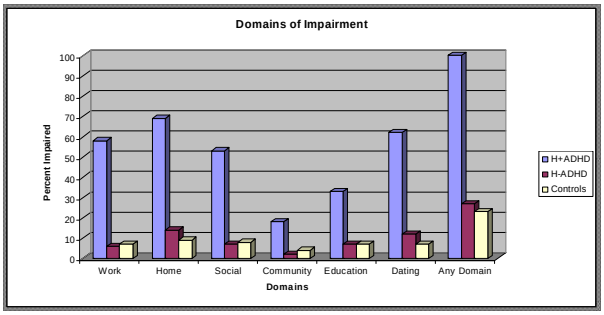
Follow-Up to 8 Years
Impairment by Original Randomly Assigned Treatment Grou



ADHD group scores lower than nonADHD group on 91% of outcome variables; mdm to large effect sizes

JAACAP, May 2009

Domains of Impairment
(self-reported by interview at age 27 follow-up; MKE Study)



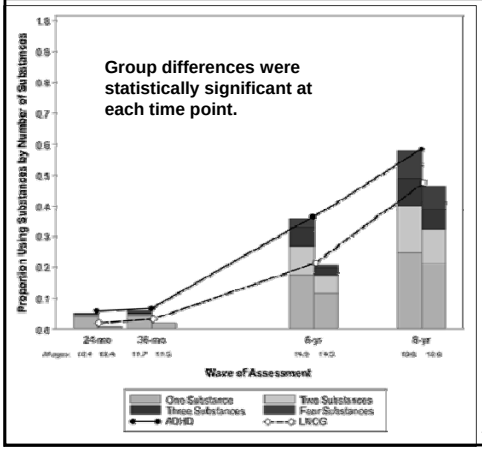
H+ADHD = Hyperactive as a child and still ADHD at adult outcome (4+ symptoms and 1+ impairments);

H-ADHD = Hyperactive as a child but is not diagnosable as ADHD at adult outcome;

Controls = Community control group

Barkley by Hechtman

Substance Use to the 8 Year Follow-Up of the MTA Children



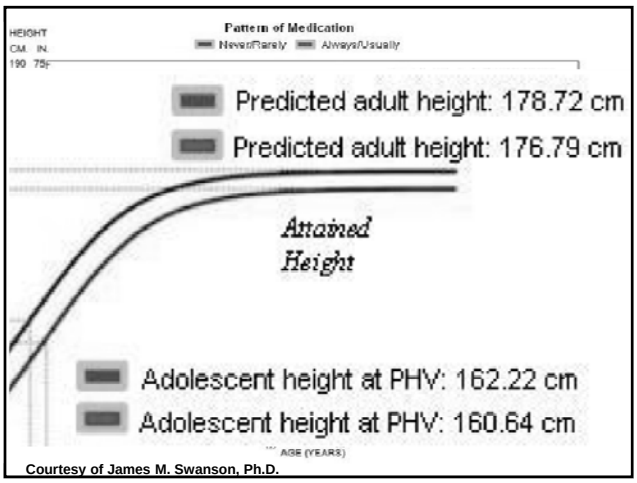
Mean Age = 17 at 8 Year F-Up

Daily Smoking: 16.7% vs 7.9%

Molina, MTA, 2013, JAACAP

Stimulant Treatment and Adolescent Substance Use in the MTA

- **Treatment with stimulants between ages 7 and 9.9 did not predict later substance use.**
- **Treatment in the past year was not associated with substance use in adolescence.**
- **Total days treated from childhood into adolescence did not predict later substance use.**
- **less substance use at 2-year follow-up for children in behavior therapy groups**



Courtesy of James M. Swanson, Ph.D.

Deceased Male Subjects

- ✓ **198 of the 207 Male Probands were located and contacted. Of these, 15 (8%) were identified as ***Deceased*****.**
- ✓ **173 of the 178 Male Controls were located and contacted. Of these, 5 (3%) were identified as *Deceased.***

8% vs. 3%, Chi-Square = 3.97, p = .05

Klein et al

ADHD Diagnosis: AACAP Practice Parameter

- **Clinical interviews with parent(s) and patient[1]**
  - **School or daycare functioning**
  - **Evaluation for comorbid or mimicking disorders**
  - **Review of medical, social, and family histories**
  - **Interviewing child helps to identify signs or symptoms inconsistent with ADHD or suggestive of other serious disorders**
- **If medical history & PE are unremarkable, laboratory or neurological testing is not necessarily needed**

Pliszka S, et al. *J Am Acad Child Adolesc Psychiatry* 2007;46:894-921.
. Pliszka S, et al. *J Am Acad Child Adolesc Psychiatry* 2000;39:908-919.

Examples of ADHD Rating Scales

- **Rating scales do NOT make or refute the diagnosis**
- **Quantify how behavior deviates from the norm**
- **Helpful in monitoring response to treatment**
- **SNAP (adhd.net)**
- **Conners' ADHD Rating Scales: www.mhs.com**
- **ADHD-IV-RS: www.guilford.com**
- **Adult ADHD Self-Report Scale (ASRS): www.med.nyu.edu/psych/assets/adhdscreen18.pdf**
- **NICHQ Vanderbilt Assessment Scale Parent and Teacher form: www.qualitytools.ahrq.gov/summary/summary.aspx?doc_id=6191**

Mid-Term Exam

To ensure safety for patients with ADHD taking stimulant medication, which of the following should be monitored at each visit?

1. Height, weight, blood pressure, and pulse
2. Routine EKG
3. Neuropsychological testing
4. Routine labs
5. All of the above

Mid-Term Exam

According to the AACAP Practice Parameter, which of the following is/are always necessary for diagnosis?

1. Laboratory testing
2. Neurological testing
3. Psychological testing
4. Clinical interviews with parent(s) and patient
5. 3 & 4

PsychoEducation of Family about:

- **ADHD and medications**
- **Rewarding positive behaviors**
- **"Choosing battles" appropriately**
- **Techniques for "time outs"**
- **Effectively issuing commands**
- **Establishing home "token economy"**
- **Being the child's advocate at school**
- **Contingency plans for behavioral disruptions and crises**

Helping the Child with Structure

- Routine schedules (sleep, meals, meds)
- Organize everyday items
  - "A place for everything and everything in its place"
- Homework and notebook organizers
- Plan and prepare for the next day
- One good habit at a time: "Habits are the best friend of people with ADHD."

Or refer to MH professional

School

- Rule out learning disability first
- Assess educator awareness of ADHD and its treatment
  - Individuals with Disabilities Act (IDEA) and Section 504 of the Rehabilitation Act of 1973 plans
- Systematic positive reinforcement
  - Daily Report Card --parent and teacher allied
- Organized, well managed classroom
  - Seating charts, limiting distractions

ADHD Treatment: AACAP Practice Parameter

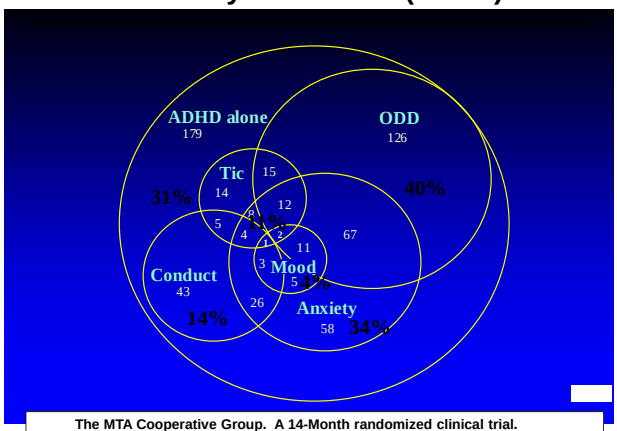
- If medicating, initial trial should be an FDA-approved agent
- Monitor for side effects
- If outcome is not satisfactory: review diagnosis, add behavior therapy if not already implemented and/or a different medication
- Patients treated with medication should have height and weight (as well as pulse and BP) monitored throughout treatment
- Concomitant behavior therapy can reduce the optimal dose of drug and reduce side effects.

Pliszka S, et al. *J Am Acad Child Adolesc Psychiatry* 2007;46:894-921

AACAP Practice Parameter

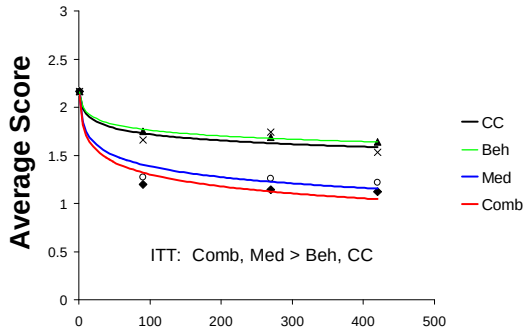
- If less than optimal response, presence of comorbid disorder(s), or stressors in family life, psychosocial treatment indicated
- Assess periodically
- Treatment of ADHD should continue as long as symptoms cause impairment

Comorbidity in the MTA (n=579)



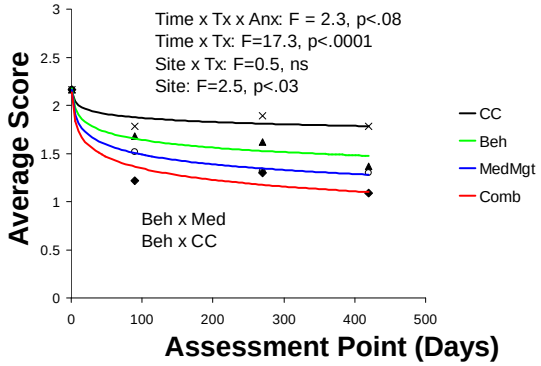
The MTA Cooperative Group. A 14-Month randomized clinical trial. Archives of General Psychiatry, 56:1073-1086, Dec. 1999.

Anxiety Comorbidity as Moderator: Parent-Inattention, No Baseline Anxiety



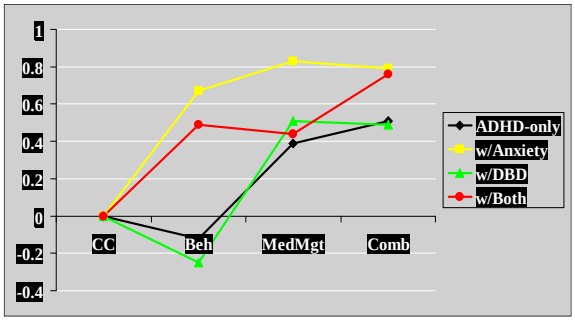
The MTA Cooperative Group. Moderators and mediators. *Archives of General Psychiatry*, 56:1088-1096, 1999.

Anxiety Comorbidity as Moderator: Parent-Inattention, With Baseline Anxiety



The MTA Cooperative Group. Moderators and mediators. *Archives of General Psychiatry*, 56:1088-1096, 1999.

Effect Sizes -SNAP Total (parent) cf. CC
Differential Score Outcomes By Comorbidity Type

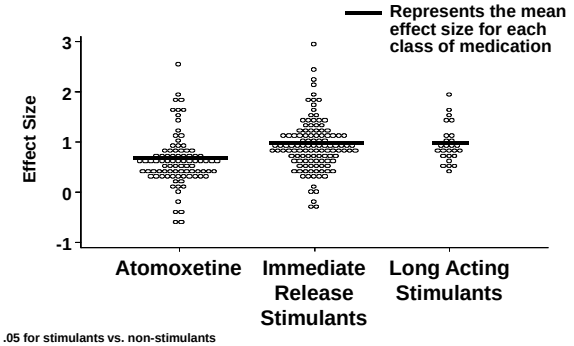


Jensen PS et al. *J. Amer. Acad. Child & Adolesc. Psychiatry*, 40:147-158, 2001.

ADHD Medication Options

- Stimulants
  - Amphetamine
  - Methylphenidate
- Atomoxetine
- Alpha-2 agonists
  - Guanfacine
  - Clonidine

Effect Sizes for FDA-Approved ADHD Meds (Guanfacine XR near Atomoxetine)



$p < .05$ for stimulants vs. non-stimulants

Faraone SV, et al. *Medscape General Medicine* 2006;8:4. Available at: www.medscape.com/viewarticle/543952.

Relative Advantages Two Stimulants

AMPHETAMINE

- Longer half-life
- Better for aggression?
- Safer w. seizure Hx; Low doses slightly anticonvulsant
- Not likely to cause depression
- May work when MPH does not

METHYLPHENIDATE

- Better for LD?
- Better for tics?
- Less SE in general?
- Less stigma; possibly less growth delay
- May work when amphetamine does not

Arnold LE. Methylphenidate vs. Amphetamine: Comparative Review. J. Attention Disorders, 3(4):200-211, 2000.

Special Option: Methylphenidate Transdermal Patch

Advantages

- Customize treatment to daily needs
- All day efficacy with 1 patch
- Almost infinite flexibility & control of dose and duration
- Smoother absorption curve
- Bypasses first pass metabolism, no effect of food
- Helpful for children with trouble swallowing pills
- May have less abuse potential than oral preparations

Disadvantages

- Onset in 2 hrs
- Specific removal time
- Requires skin hygiene
- Temperature can affect storage and application of patch
- Skin sensitization
- Size of patch increases with dose
- Noticeable by peers in gym and pool locker room
- Can be removed prematurely

Pelham WE, et al. *J Am Acad Child Adolesc Psychiatry* 2005;44:522-529.
Arnold LE, et al. *Pediatrics* 2007;120:1100-1106.

Potential Adverse Effects of Psychostimulants

Most Common

- Appetite suppression and weight loss
- Sleep delay
- Mild growth delay
- Mood lability and irritability (esp. as medication effect wanes)
- Affective blunting "Zombie look"
- Exacerbation of tics
- Agitation or Lethargy

Less Common

- Nail/skin picking
- Hypertension
- Tachycardia
- Depression
- Headaches
- Hallucinations
- Suicidal thoughts (rare)

Psychostimulant Safety

- **Reports of sudden death in children with underlying cardiac abnormalities[1]**
  - **Document any family history of cardiac abnormalities or sudden death, patient history of cardiac abnormalities, and auscultate for worrisome murmurs prior to treatment. ECG if anything suspicious.**
  - **Routine EKG screening is not recommended for all children**
- **Dependence not reported in children taking therapeutic doses**
- **Possible protective effect[2,3] against substance abuse not upheld by most recent data**
- **NIH MTA[4] and PATS[5,6] trials found growth deceleration in some children treated with stimulants**

1. Wilens TE, et al. *Pediatrics* 2003;111:179-185.
2. Biederman J, et al. *Am J Psychiatry* 2008;165:597-603.
3. Mannuzza S, et al. Am J Psychiatry 2008;165:604-609.
4. MTA Cooperative Group. *Arch Gen Psychiatry* 1999;56:1073-1086.
5. Greenhill L, et al. *J Am Acad Child Adolesc Psychiatry* 2006;45:1284-1293.
6. Swanson J, et al. *J Am Acad Child Adolesc Psychiatry* 2006;45:1304-1313.

Addressing Safety Issues

- **Document height, weight, blood pressure, and pulse at every visit**
- **Assess for substance abuse**
- **Check for persistent and pervasive changes in mood and o ask about suicidality when suspected**

CDC/ Debora Cartagena

Norepinephrine Reuptake Inhibitors: Atomoxetine

- **Blocks norepinephrine reuptake**
  - **Increases both norepinephrine and dopamine in prefrontal cortex**
  - **Does not affect dopamine in nucleus accumbens**
- **Unscheduled, renewable prescription, no addiction**
- **>10 controlled trials demonstrating efficacy[1]**
- **Effects last 24 hrs[2], but splitting dose in the beginning reduces side effects, later once daily.**
- **Gradual onset, ~4 to 6 wks at target dose for full effect[2]**
- **Long term (2 yrs) treatment well tolerated**

1. Michelson D, et al. *Am J Psychiatry* 2002;159:1896-1901.
2. Atomoxetine. Full Prescribing Information. Available at: www.fda.gov/cder/pediatric/labels/Atomoxetine.pdf. Accessed April 4, 2008.
3. Kratochvil CJ, et al. *J Am Acad Chld Adolesc Psychiatry* 2006;45:919-927.
4. Wilens TE, et al. *J Pediatr* 2006;149:112-119.

Atomoxetine: Adverse Effects and Safety

- Adverse effects
  - Abdominal distress, appetite suppression, cough, dizziness, growth deceleration, headache, hepatotoxicity (rare), hypertension, insomnia, irritability, moodiness, lethargy, nausea, suicidality (rare), tachycardia, vomiting, weight loss
- Reports of hepatotoxicity in two patients prompted FDA warning in 2004 about potentially severe liver injury, reversible
- In 2005 the FDA required a boxed warning about small increased risk of suicidal thinking in children and adolescents taking atomoxetine

Atomoxetine information. Available at: www.fda.gov/cder/drug/infopage/atomoxetine/default.htm.

Alpha$_2$ Adrenergic Agonists

- May reduce hyperactivity, impulsivity, and inattention (probably to a lesser degree). XR forms FDA-approved.
- Clonidine: a nonselective 2A, 2B, and 2C agonist; sedating and hypotensive effects
- Guanfacine, immediate and extended release: is selective for alpha$_{2A}$ subtype and potentiates PFC regulation of attention and behavior[1]. May have lower rates of side effects than nonselective agonists such as clonidine[3]
- Both agents inhibit norephinephrine induced arousal

1. Arnsten AF, et al. *J Child Adolesc Psychopharmacol* 2007;17:393-406.
2. Wang M, et al. *Cell* 2007;129:397-410.
3. Biederman J, et al. *Pediatrics* 2008;121:e73-e84.

Adherence to Treatment

- 50% of patients stopped taking medication within first 3 months of treatment, and 80% stopped by 18 months. 10%/yr stop during adolescence
- Symptom severity, increasing age, and oppositional symptoms negatively impact adherence
- Characteristics of ADHD predict poor treatment adherence:
  - Poor motivation
  - Forgetfulness
  - Impulsiveness
  - Family instability
- Many adolescents don't like how it makes them feel, and friends complain they are too serious when taking med.

Capone NM, et al. *Persistence with common pharmacologic treatments for ADHD*. 17th Children and Adults with Attention Deficit/Hyperactivity Disorder (CHADD) Annual Conference. Dallas, TX; 2005.

American Academy of Pediatrics ADHD Toolkit

- Diagnosis - Checklists for teachers and parents, as well as diagnostic tools for clinical use
- Treatment - Guidelines for selecting and implementing appropriate therapy plans, setting and evaluating treatment goals, plus medication dosing and side effect information
- Parent Information and Support - AAP booklet "Understanding ADHD," ADHD evaluation timeline, information about school issues, and other parenting resources
- Resources - Information on practice management pertaining to ADHD, plus Internet resources of interest to parents, teachers, and clinicians

Caring for children with ADHD: A resource toolkit for clinicians. Available at: www.aap.org/pubserv/adhdtoolkit

Nutritional Support

- Most ADHD meds reduce appetite
  - Meal timing: breakfast, h.s. snack
- Micronutrients
  - RDA/RDI multivitamin/mineral
- Omega-3 long-chain fatty acids (EPA & DHA)
  - Small but significant effect: ES=0.4 for triple combo
  - EPA probably most critical
  - A gram/day; 3 mo. to effect

Arnold L.E. Fish Oil is not Snake Oil. *J. Amer. Acad. Child & Adolesc. Psychiatry* 2011, 50(10):969-971.

Bloch MH & Qawasmi A. Omega-3 Fatty Acid Supplementation for ADHD: Systematic Review and Meta-analysis.. *J. Amer. Acad. Child & Adolesc. Psychiatry*, 2011, Vol. 50, #10.

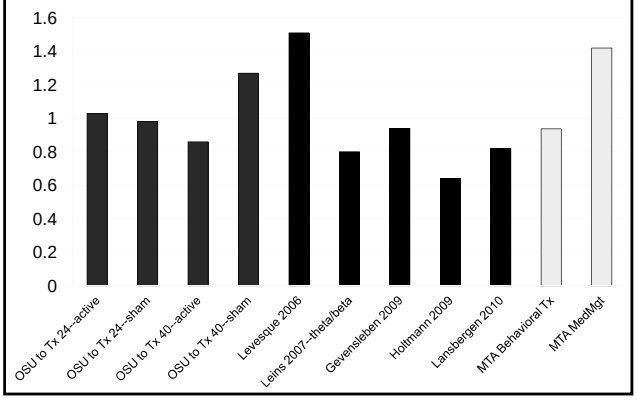
Arnold,. LE. Contemporary Diagnosis and Management of ADHD. Handbooks in Health Care, Newtown, PA 18940. WWW.HHCbooks.com

Lifestyle Complementary Tx/Support: Minimal promising evidence at present

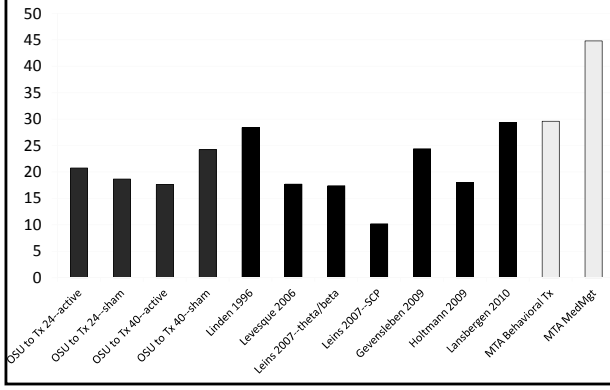
- Exercise
- Outdoor time
- Cerebellar-vestibular practice
- Meditation, Yoga
- Sleep hygeine
- Control of allergies
- Slow food
- Minimal food dyes

Arnold,. LE. Contemporary Diagnosis and Management of ADHD. Handbooks in Health Care, Newtown, PA 18940. WWW.HHCbooks.com

Pre-post ES (Cohen's d) for parent-rated ADHD inattentive symptoms in various NF studies



Pre-post % change in parent-rated ADHD inattentive symptoms in various NF studies



Advantages of participating in studies

- **Prompt appointments –no waiting**
- **Free evaluation with summary to Dr. of choice**
- **Free treatment**
- **Some reimbursement for travel & time; free parking, prize for child**
- **Possible placebo benefit without risk**

Kristina.Zottola@osumc.edu

614-561-1429