Attention-Deficit Hyperactivity Disorder

Evidence-Based Practice Workforce Series
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Goals

- ADHD Phenomenology and Statistics
- Course of ADHD
- ADHD Treatments
Attention-Deficit Hyperactivity Disorder: Evolving Name and Focus

- Minimal Brain Dysfunction (MBD)
- Hyperkinesis
- Attention-Deficit Disorder (ADD)
  - With Hyperactivity
  - Without Hyperactivity
- Current ADHD with emphasis on evaluating:
  - Inattention/distractibility
  - Impulsivity
  - Increased motor activity
Epidemiology

- Prevalence in general elementary school age population generally 3-5%
- However, prevalence varies widely based on population studied, criteria used, etc
- Most studies in US elementary school age children yield rates of 6-12%
- In general, higher rates in post-industrialized countries
Evidence of both over and under-diagnosis and over and under-treatment

- Epidemiological study of 4 communities in US found that of youth meeting criteria for ADHD, only 12.5% had received a prescription for ADHD in the previous 12 months (Jensen, 1999)
- Survey in rural North Carolina found that only half on youth on stimulants clearly met criteria for ADHD (Angold, 2000)
Youth with ADHD, compared to those without:

- 2-4 times more likely to have a motor vehicle accident
- More likely to have repeat traffic citations
- More likely to have license suspended or revoked

Driving performance shown to improve with anti-ADHD medication
ADHD Gender

* Male: female
  * Clinical samples 9:1
  * General population 4:1
* Girls:
  * More likely to have inattentive subtype
  * Less likely to have impulsive subtype
  * Less disruptive behavior
ADHD Comorbidity

* Oppositional Defiant Disorder is commonly comorbid with ADHD
* 25-35% with a learning disorder (Pliszka, 1999)
* Anxiety disorders: up to 1/3
* Depression: up to 1/3—but generally less than anxiety
* Bipolar disorder: controversial
Comorbidity in the Multimodal Treatment of ADHD (MTA) Study (1993)
60-80% still meet criteria for disorder in adolescence (AACAP, 2007)
2-67% still meet criteria for disorder in adulthood, depending on who is reporting and criteria (AACAP, 2007)
National Comorbidity Study estimate: 4.4% prevalence of adult ADHD (Kessler, 2005)
Some consideration for altering criteria for older age groups in DSM-5
ADHD Presentation in Adolescents

- Decreased hyperactivity, but inner sense of restless may persist
- More interpersonal conflict
- Poor organization and follow through may lead to difficulty completing independent schoolwork
- May engage in high risk behaviors
Adult Outcomes of ADHD, Increased Rates of (AACAP, 2007):

- Antisocial and criminal behavior
- Injuries and accidents
- Employment and marital difficulties
- Health problems
- Substance use
- Risky sexual behaviors
Potential for Cascade of Negative Behaviors and Risk Factors

- Academic Problems
- Disruptive Behavior
- Harsh Discipline
- Peer Rejection
- Negative Outlook
- Substance Use
- Socialization with Antisocial Peers
- Disengagement from School

ADHD
Etiology of ADHD

- Heterogeneous disorder
- Genetics plays a role
- Multiple factors involved
- Known causes (lead toxicity, FAS, fragile X, etc) combined account for a small number of cases
- Subgroup of youth with ADHD due to CNS maturational delay
Etiology of ADHD
Deficits in Executive Functioning

* Response inhibition
* Vigilance
* Working memory
* Planning
Etiology of ADHD

* Brain imaging
  * A number of anatomical correlations reported
  * Growing number of functional neuroimaging studies
  * But understanding of ADHD and brain neuroimaging is in early stages
Food Colorings/Preservatives and ADHD

* (Will discuss briefly in treatment section too)
* Most studies show little, mixed or no effect
* Some researchers have demonstrated mild increase in motor activity in some youth with food coloring/preservative concoctions (Bateman, 2004; McCann, 2007)
* Some percentage of youth diagnosed with ADHD have been shown to improve with elimination diets (Stevens, 2011; Niggs, 2012)

* OK to try elimination diet first, or later if treatment response is inadequate
Assess clinically with
  * Interview of parent, child and school personnel
  * History
  * Observation

Adjunctive use of ADHD scales

No specific blood test

No specific paper and pencil test

No specific performance or computerized test

No specific brain imaging or functioning test
Neuroimaging and ADHD

* Research tool
* Not useful for making a diagnosis of ADHD or in predicting treatment response (AACAP ADHD Practice Parameters, 2007)
Attention-Deficit/Hyperactivity Disorder (ADHD)

- Diagnosing
  - Symptoms in 2 settings
  - Don’t count on office evaluation
  - Obtain feedback from school
  - Use rating forms to help

- Double-blind placebo-controlled medication trials to assess medication effectiveness?
ADHD-Specific Rating Scales can help with Assessment, Course and Treatment Response

- Connors Rating Scales
- Vanderbilt ADHD Scale*
- SNAP IV*
- ADHD Rating Scale*
- ADHD-IV
- Child Attention Problems Scale
- ACTeRS

*free online
Consider

- Intellectual testing
- Achievement testing—rule out learning disorder
- Hearing test
- Vision test
Stimulants for ADHD

- Best studied psychiatric medication in children and adolescents
- Among the most effective psychiatric medications
- Treatment data base for ADHD is the largest in childhood-onset psychiatric disorders

- Stimulants are classified by the FDA as Schedule II medications, because of abuse potential
- Schedule II medications are monitored more closely, and prescribing is more restrictive
Stimulants: Over 175 Randomized Controlled Trials

- 8 involving preschoolers (241 subjects)
- >160 involving school-age children (5000 subjects)
- 7 with adolescents (120 subjects)
- 9 with adults (over 200 subjects)
- Improvement in 65-75% of treatment group versus 5-30% of placebo group
- Race and gender do not predict response
Historically, Short-Term Trials

* Of 160 trials, only 22 > 3 months

* Five well-designed studies lasting more than 1 year, demonstrating continued stimulant efficacy

* Given effectiveness, can no longer conduct long-term placebo-controlled research
Effect Size meta-analysis—up to 15 studies met criteria for inclusion (Van der Oord, 2007)

- methylphenidate compared to
- psychosocial treatment compared to
- combined methylphenidate and psychosocial treatment
Meta-Analysis Caveats (LoLorier, 1997)

- Large randomized controlled trials are considered the gold standard for evaluation clinical efficacy
- Metaanalysis combines a number of similar studies to increase data
- Metaanalysis limitations
  - Incorporates bias of original small studies
  - Introduces additional bias

- A metaanalysis of several small studies does not predict the outcome of a single large study
Goes beyond “statistical significance”

For following study, Cohen’s D used:
\[ ES = \frac{\text{pretreatment mean} - \text{post-treatment mean}}{\text{pooled standard deviation}} \]

Cohen’s guidelines for effect size:
- Small: 0.20
- Medium: 0.50
- Large: 0.80
ADHD Treatment Effect Size Meta-Analysis—up to 15 studies sampled (Van der Oord, 2007)

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Positive Stimulant Effects on Children with ADHD

- On-task behavior by all raters
- Compliance as rated by teachers
- Peer nominated rankings of social standing
- Parent-child interactions
- Attention during sports activities
- Performance on paper-and-pencil and computerized tests of attention, math, short term memory, problem-solving, accuracy
Long-Term Effects of Stimulants

- Continue to have positive effects 12+ months later
- Little evidence of tolerance
- No clear evidence of increased association with substance use disorders
Pre-Stimulant Work Up

- Good psychiatric evaluation
- Baseline blood pressure, pulse, height, weight, presence/absence of movement disorder
- Baseline ADHD symptoms in different settings
- Some debate regarding baseline EKGs; general consensus is to order EKG only if known cardiac risks
Contraindications for Stimulants

- History of stimulant drug abuse or dependence
- Psychosis
- Concomitant use of MAOI’s
- Glaucoma
Common Stimulant Side Effects

* Common in stimulant responders
  * Initial insomnia
  * Mild daytime appetite suppression—80%, 10-15% with significant but slight short-term weight loss
  * Mixed long-term findings of decreased growth—MTA study: average ~1 cm per year for 1-3 years (other studies suggest a plateau of height loss?) with individual variability
* Avoid with low initial dose; SE’s subside over time
  * Over-activation, agitation, irritability
  * GI symptoms
  * Headache
Management of Appetite Suppression

* Use minimum effective dose
* Change dosing times
* High calorie foods, shakes
* Increase oral intake before and after stimulant effect
* Decrease or stop dose on weekends
* Decrease or stop dose when school is not in session
Management of Initial Insomnia

- (Use minimal effective dose)
- Sleep hygiene and behavioral techniques
- Give stimulant earlier in day/evening
- Other medications?
  - Non-addictive sedating agents—antihistamines, alpha-agonists, trazodone, or other meds?
  - Stimulants?
“Rebound Hyperactivity”

- Commonly reported
- Occurs after stimulants wear off
- Try reducing doses later in the day
- Conversely, try adding dose of stimulant
- Use additional non-stimulant anti-ADHD medications
Less Common but More Problematic Stimulant Side Effects

- Tachycardia/fast heart rate
- Hypertension/high blood pressure
- Movement disorders/tics
- Obsessive-compulsive symptoms
- Psychosis—typically in overdose/abuse, not at therapeutic doses
- Seizures (lowers seizure threshold)
Stimulants and Tics

* Significant comorbidity
  * 50-80% of kids with Tourette’s have ADHD
  * But most youth with ADHD don’t have tics
* History of contraindication, but reexamined
* Better controlled studies have not found that stimulants increase tics in Tourette’s
* Therapeutic doses do not cause motor tics in children with ADHD without Tourette’s
* Some tics get worse initially, then subside to baseline
* Current recommendation is to treat dysfunction-associated ADHD in children with Tourette’s or tics; if tics worsen, try changing agents
Diversion of Stimulants

* 62% of college students prescribed stimulants for ADHD reported diverting their stimulants at least once in their life (Garnier, 2010)
* 23% of middle & high school youth reported being asked to give, sell or trade medications (McCabe, 2004)
* Use of non-prescribed stimulants—metaanalysis (Wilens, 2008)
  * 5-9% of grade school students
  * 5-35% of high school students
  * 16-19% requested to divert
Medication Adherence

Need to Develop Plans to Assure Youth Receives Medication Every Single Day Medication is Prescribed!
Stimulant Preparations

- Methylphenidate
  - Immediate release (Ritalin)
  - SR (Ritalin SR, Metadate CD)
  - LA (Ritalin LA)
  - OROS-methylphenidate (Concerta®)
- Dexamphetamine (Focalin, Focalin XR)
- Dextroamphetamine (Dexedrine)
  - Immediate release
  - Spansules
- Racemic mixture amphetamine salts (MAS)—Adderall, Adderall XR
Relatively Newer Long-Acting Stimulants

* Daytrana (methylphenidate patch) (2006)
  * Slower onset of action—apply early in the day
  * Can be taken off to stop action at some point
  * Must remember to take off!
  * Can be taken off and
    * Reattached (on someone else?)
    * Extract methylphenidate?
      * To deliver 30 mg, 82.5 mg in patch
Relatively Newer Long-Acting Stimulants

* Vyvanse (lisdexamfetamine) (2007)
  * Prodrug—must be ingested and metabolized before it becomes active
  * Less likely to be diverted and taken by alternative route (snorted or injected)?
  * Still classified as a Schedule II medication
  * Long-acting
    * However, may have delayed onset of action
Treatment Response to Stimulants

* ~40% will respond to any one agent
* ~80% will respond if tried on all
* For many youth, no clear difference in positive or negative effects among methylphenidate, dextroamphetamine or mixed salts amphetamine
  * Individual responses may vary, so may try different stimulants to assess positive and negative effects
Non-Stimulant Medications for ADHD

- In general not as effective as stimulants for most youth
- However, some youth will respond better to non-stimulants
- Youth may tolerate non-stimulants better
- Delayed onset of effect—weeks
- No abuse potential
- Some evidence for combining stimulants with non-stimulants
**Atomoxetine (Strattera)**

* FDA Approved for ADHD in children >5-years old
* Better tolerated with twice-a-day (versus once) dosing and titrating over 2 weeks
* May interact with other medications
* Less growth suppression compared to stimulants
* Common side effects: nausea, GI distress, moodiness, fatigue, sedation, dizziness,
* Warnings: new-onset suicidality, severe liver damage
Atomoxetine

- Average effect size in efficacy (laboratory) trials: 0.7 (AACAP, 2007)
- Comparison to stimulant, one meta-analysis of effect sizes (Faraone, 2006)
  - Atomoxetine: 0.62
  - Immediate release (IR) stimulants: 0.91
  - Extended release (XR) stimulants: 0.95
Alpha 2-Adrenergic Agonists for ADHD

* Originally tested and marketed as anti-hypertension agents
* Appear to treat hyperactivity and impulsivity more than inattention
* Possible use in association with stimulants for hyperactivity/aggression, rebound or tics
* Not as effective as stimulants
* Sudden deaths with MPH and clonidine combination
* One report of additional anti-ADHD effects when guanfacine XR added to stimulant (Wilens, 2012)
Alpha-2 Agonist Side Effects

- Sedation/sleepiness
- Irritability
- Throat pain
- Headache
- Abdominal pain
Alpha-2 Agonist Side Effects

* Anti-hypertension meds—may lower blood pressure and/or cause dizziness upon standing
* Potential for rebound hypertension if abruptly discontinued
* EKG changes, typically of no clinical significance if normal cardiac status when taken as prescribed
* History of reports or rare sudden death when combined with stimulants
  * However, combination with stimulants currently studied
Alpha-2 Agonists

- Clonidine (Catapress)*
- Clonidine XR (extended release) (Kapvay)**
- Guanfacine (Tenex)*
- Guanfacine XR (Intuniv)**

- *FDA approved for ADHD
- **Available in generic form
**Guanfacine XR**

- FDA approved for ADHD, based on 8-week and 9-week studies
- Based on 2 studies, effect size: 0.43-0.86 (Biederman, 2008; Sallee, 2009)
- Response rates:
  - Guanfacine XR: 43-56%
  - Placebo: 26-30%
Clonidine

- Effect size of clonidine immediate release based on meta-analysis (Choi, 2006): 0.58
- Clonidine XR (Kapvay) dosing is twice-a-day
- In one study, effect size of clonidine XR in a 3 week study estimated to be ~0.713-0.766
- 8 week clonidine XR add-on (to stimulant) study (Kollins, 2011)
  - Effect size: 0.34
  - Response rate (wk 7): clonidine XR 42%, placebo 25%
Bupropirion for ADHD

- Not FDA Approved for ADHD
- Limited controlled research and demonstrated effectiveness in youth
- In one adult controlled trial, effect size estimated to be ~0.60 (Wilens, 2008)
- Do not use in patients with seizures or eating disorders
Complementary and Alternative Approaches to ADHD

- Studies indicate that upwards of 2/3 of families try complementary or alternative treatments for ADHD (Chan, 2002; Karpouzis, 2010)
- Most studies have methodological problems (no control, no blinding, large dropout rates, small sample sizes, limited standardized measures for inclusion/response, selection bias) limiting interpretation of results
Complementary and Alternative Approaches to ADHD

* Restriction diet: remove food colorings and preservatives—in one meta-analysis (Nigg, 2012):
  * ~33% of youth with ADHD may respond to elimination diets removing various foods and additives
  * Up to 8% of youth with ADHD may have symptoms related to food colors
  * Effect size ~0.27 (Hedge’s g) when including only studies using FDA-approved food colors
  * Authors noted methodological problems with individual studies, and call for more research
Complementary and Alternative Approaches to ADHD

- Omega-3 fatty acid meta-analysis (Bloch, 2011)
  - Effect size ~0.31
    - Higher doses of eicosapentenoic acid (EPA) significantly associated with increased efficacy for ADHD symptoms
  - Omega 3 fatty acids have relatively benign side effect profile—look for mercury-free preparations
  - Low effect size compared to medications, ?use as supplemental treatment?
  - Authors note problems with study design of individual studies, call for more research
ADHD Requires Multimodal Approach
Family Psychosocial Interventions

- Family and parent education about ADHD: psychiatrist, psychologist, books, Children and Adults with Attention Deficit/Hyperactivity Disorder (CHADD), internet (variable quality)
- Parent Management Training
- Contingency Management Training
- Prioritize goals
- Effective communication
School Psychosocial Interventions

- Appropriate academic placement/program
- Structured classroom with predictable schedules
- Clearly stated rules/expectations and consequences
- May benefit more individualized behavioral program and proximity to teacher at times
- Behavioral program coordinated with home
- Daily contact with home via tracking sheet
Child-Focused Psychosocial Interventions

- Assess and treat comorbid anxiety or depression, if present
- Impulsivity and anger management training
- Social skills, conversational skills training
- Expand range of problem-solving skills
- Shape behavior with attention to reinforcing desired behavior
Screen everyone for ADHD
Interview youth, parent and school
If medical history is unremarkable, no laboratory or neurological testing is indicated
Psychological and neurological testing only if low cognitive ability, low achievement or suspected learning disorder
AACAP ADHD Recommendations

- Evaluate for comorbid disorders
- Comprehensive treatment plan
- Mild ADHD may be treated with behavior therapy alone
- If there is a good response to medications, may treat with medications only
- Periodically assess need for medication
Conclusions

* ADHD is a common youth mental/behavioral health problem
* It is critical to obtain feedback from the school to diagnose ADHD and assess medication response
* Treating ADHD with medication generally enhances the effects of psychosocial interventions for disruptive behavior
For most youth, stimulants are generally the best medications for treating ADHD, but some youth will respond better to non-stimulants.

There is no evidence that treating ADHD with stimulants increases the likelihood of substance use disorders.

Developing systems to assure the youth is receiving medication every day is critical.