Attention Deficit Hyperactivity Disorder

Attention Deficit Hyperactivity Disorder
Treatment in Children and Adults
Clinical Aspects of Medication Management

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ADHD Talk Overview

• History
• Diagnostic criteria
• Epidemiology (Who has it?)
• Etiology (Why do they have it?)
• Making the diagnosis
• Treatment

History of ADHD

• Hyperkinetic reaction (1920s)
• Minimal brain damage
• Minimal brain dysfunction
• Psycho-neurologic integration deficit
• Hyperactive reaction of childhood (1968)
• Hyperactive child syndrome

Dole R. The history of adult attention-deficit disorder. Psychiatric Clinics of N. America 2004; 27:
201-14.
Attention-Deficit Hyperactivity Disorder

History of ADHD

- Attention-deficit disorder (1980)
- Attention-deficit disorder, residual type
- Attention-deficit hyperactivity disorder (1987)
- Inattentive type, hyperactive-impulsive type, and combined type (1994)

ADHD Diagnostic Criteria

Six (or more) of the following criteria are met for either inattention or hyperactivity-impulsivity

Inattention

- Often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities
- Often has difficulty sustaining attention in tasks or play activities
- Often does not seem to listen when spoken to directly
- Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (not due to oppositional behavior or failure to understand instructions)
- Often has difficulty organizing tasks and activities
- Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework)—AKA Procrastination
- Often loses things necessary for tasks or activities (e.g., toys, school assignments, pencils, books, or tools)
- Is often easily distracted by extraneous stimuli
- Is often forgetful in daily activities
Attention-Deficit Hyperactivity Disorder

Hyperactivity-Impulsivity

• Hyperactivity
  – often fidgets with hands or feet or squirms in seat
  – often leaves seat in classroom or in other situations in which remaining seated is expected
  – often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness)
  – often has difficulty playing or engaging in leisure activities quietly
  – is often “on the go” or often acts as if “driven by a motor”
  – often talks excessively

DSM-IV-TR, APA 2000

Hyperactivity-Impulsivity

• Impulsivity
  – often blurts out answers before questions have been completed
  – often has difficulty awaiting turn
  – often interrupts or intrudes on others (e.g., butts into conversations or games)

DSM-IV-TR, APA 2000

ADHD-Other Criteria

• Some hyperactive-impulsive or inattentive symptoms that caused impairment were present before age 7 years
• Some impairment from the symptoms is present in two or more settings (e.g., at school [or work] and at home).
• There must be clear evidence of clinically significant impairment in social, academic, or occupational functioning
• The symptoms do not occur exclusively during the course of a Pervasive Developmental Disorder, Schizophrenia, or other Psychotic Disorder and are not better accounted for by another mental disorder (e.g., Mood Disorder, Anxiety Disorder, Dissociative Disorder, or Personality Disorder)

DSM-IV-TR, APA 2000
Attention-Deficit Hyperactivity Disorder

ADHD Subtypes

- Predominantly inattentive type
- Predominantly hyperactive-impulsive type
- Combined type
- ADHD-not otherwise specified

Epidemiology (who has it?)

- 8-12% of school children worldwide
- Lower prevalence noted in some studies in other countries is criteria dependent (ICD-10 < DSM-IV)

Prevalence of ADHD


Attention-Deficit Hyperactivity Disorder

Epidemiology (Who has it?)

- More common in:
  - Men
  - Difference: Clinical > Non-clinical (females less likely to be referred for treatment)
  - ADHD may be less disruptive in women
  - Could be increased environmental exposure (head injury) in males
  - Lower economic strata
  - Under-identified and under-treated in minority groups


Co-morbidity (other diagnoses)

- 40% have oppositional defiant disorder
- 25% have an anxiety disorder
- 20-30% have a mood disorder
- 20-25% have a learning disorder
- 2% have Tourette’s disorder
  - 50% of patients with Tourette’s have ADHD


Risk Factors for ADHD

Biological

- Brain injuries
- Low birth weight
- Fetal alcohol exposure
- Maternal smoking in pregnancy
- Lead exposure


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Attention-Deficit Hyperactivity Disorder

Risk Factors for ADHD
Psychosocial
- Marital or family discord
- Neglect/deprivation
- Reduced family cohesion
- Low socioeconomic status
- Large family size
- Parental psychopathology
- Foster placement

Etiology (What caused it?)
- ADHD diagnosis does not imply any specific etiology
- No one theory accounts for all cases
- Most likely multifactorial

Etiology (What caused it?)
- Localized brain dysfunction
  - Frontal-subcortical circuits
    - Executive function: inhibition, working memory, set-shifting, interference control, planning, sustained attention
    - Reduced volume size in these regions on structural imaging
    - Less activation in these areas on functional imaging
  - Striatum (subcortical structure)
    - Many dopamine synapses
    - Vulnerable to perinatal hypoxia
    - Related to hyperactivity and impulsivity if not intact


Attention-Deficit Hyperactivity Disorder

Etiology (What caused it?)

- Genetic factors
  - Heritability: 75%
  - 4-5x greater probability if full sibling has ADHD
  - Genes with small effect:
    - Dopamine D4 + D5 receptor
    - Dopamine transporter SLC6A3
    - Serotonin transporter SLC6A4
    - Serotonin receptor HTR1B
    - Synaptic vesicle transporter SNAP25
  - Genes with large effect:
    - None


Etiology (What caused it?)
Evolution in a complex society

Prehistoric hunter/gatherer needed impulsivity and quickly shifting attention
One-room schools, small classes, individual attention, chores, tight community
Same biological capacity now overwhelmed in demanding society

Diagnosis of ADHD

- History
  - Patient
  - Family
  - School/teachers
  - Standardize and quantify symptoms
    - Connors Series
    - Achenbach Child Behavior Checklist
    - Teacher Observation of Classroom Adaptation (TOCA)
    - Quay Problem Checklist

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Diagnosis of ADHD

- Rule out other diagnoses
  - Conduct and oppositional defiant disorders
  - Mood disorders (depression, bipolar disorder)
  - Anxiety disorders (panic, OCD, generalized)
  - Post-traumatic stress disorder
  - Learning and developmental disorders
  - Psychosis
  - Parenting problems (limits, structure, consistency)
  - Medications (asthma, anti-seizure, other)

Diagnosis of ADHD

- Tests
  - Not necessary or sufficient for a diagnosis
  - Psychometric and neuropsychological tests
    - Quotient Test
    - Continuous Performance Test
    - Matching Familiar Figures
    - Reaction time tests
    - Wisconsin Card Sorting Test (older patients)
    - Paired Associate Learning
    - Porteus Mazes
    - Stroop Color Word Test
    - Wechsler Intelligence Scale for Children


Adult ADHD

- Age-dependent decline in symptoms
- People develop better impulse control, better attention spans and more sedate habits as they grow older.
- Rely on history from the patient, significant other and occasionally an employer

Untreated ADHD Complications

- Prone to accidents:
  - 50% ↑ bike accidents
  - 33% ↑ ER visits
  - 2-4x more MVA’s
- Increased likelihood of:
  - Depressive disorders
  - Anxiety disorders
  - Alcohol and drug abuse
  - Poor team performance
  - Academic failure and grade retention
  - Social ineptness, unpopularity, and peer rejection
  - Missed development of life-long good work habits and attitude


Treatment of ADHD

- Medications
- Behavioral treatments
  - Cognitive behavioral skill training
  - Parent training
  - Teacher consultation and school-based interventions

Attention Deficit Hyperactivity Disorder

Medication Treatment

- Stimulants
  - Methylphenidate; amphetamine compounds; dextroamphetamine
- Noradrenergic reuptake inhibitors
  - Atomoxetine
- Antihypertensives
  - Extended-release guanfacine (not approved)
- Antidepressants
  - Bupropion; tricyclics; venlafaxine
- Other
  - Mood stabilizers and Neuroleptics

FDA Approved for ADHD

Attention-Deficit Hyperactivity Disorder

Treatment of ADHD
Medications: Stimulants

- Stimulants
  - Best documented efficacy in controlled trials
  - Most specific for ADHD symptoms
  - Linear benefit with dosage until side effects
  - Fast acting and safe (although Schedule II)
  - Dexedrine (dextroamphetamine) developed in 1920s and Ritalin (methylphenidate) developed in 1950s

MTA Study: Multimodal Treatment Study of Children with ADHD
NIMH and US Department of Education

Follow-up at 14 and 24 months found all treatment arms to be effective, on an absolute basis.

Nearly equally effective and superior to both:
- Behavioral treatment alone
- Community-based treatment

NIMH Multimodal Treatment of ADHD

Attention-Deficit Hyperactivity Disorder

### Stimulant Mechanisms of Action

Presynaptic Neuron

**AMPH** diffuses into vesicle, causing DA release into cytoplasm

**AMPH** is taken up into cell, causing DA release into synapse

**Cytoplasmic DA**

**DA Transporter Protein**

**Stimulant Neurons**

- **NEpi and DA Receptors**

**Presynaptic Neuron**

- **AMPH** diffuses into vesicle, causing DA release into cytoplasm
- AMPH blocks uptake into vesicle
- AMPH blocks storage vesicle
- AMPH transport into cell, causing DA release into synapse

**Stimulant Mechanisms of Action**

**NEpi and DA Receptors**


**Slide Courtesy of Jeff Prince, MD**

### Treatment of ADHD Medications: Stimulants

- **Stimulants**
  - Amphetamines
    - Mixed-amphetamine salts
      - Adderall
      - Adderall XR
    - Dextroamphetamine
      - Dexedrine
      - Dexedrine Spansules
    - Lisdexamfetamine
      - Vyvanse
  - Methylphenidates
    - Mixed-methylphenidate salts
      - Ritalin, Ritalin LA, Ritalin SR
      - Concerta, Daytrana patch
      - Metadate CD, Metadate ER
      - Methylin, Methylin ER
    - Dexmethylphenidates
      - Focalin, Focalin XR

### Stimulant Dosing

<table>
<thead>
<tr>
<th>Stimulant</th>
<th>Duration (hours)</th>
<th>Child Start Dose</th>
<th>Adult Start Dose</th>
<th>FDA Max Dose</th>
<th>Max Dosing*</th>
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<tbody>
<tr>
<td>Adderall</td>
<td>4-5</td>
<td>5-10 mg/d</td>
<td>10-20 mg/d</td>
<td>60 mg/d</td>
<td>1.0 mg/kg/d</td>
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<tr>
<td>Adderall XR</td>
<td>6</td>
<td>5-10 mg/d</td>
<td>10-20 mg/d</td>
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<td>10-20 mg/d</td>
<td>60 mg/d</td>
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</tr>
<tr>
<td>Vyvanse</td>
<td>13</td>
<td>10 mg/d</td>
<td>30 mg/d</td>
<td>70 mg/d</td>
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<tr>
<td>Ritalin LA</td>
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<td>20 mg/d</td>
<td>80 mg/d</td>
<td>2.0 mg/kg/d</td>
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<tr>
<td>Ritalin</td>
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<td>10 mg/d</td>
<td>20 mg/d</td>
<td>1.0 mg/kg/d</td>
</tr>
<tr>
<td>Focalin</td>
<td>3-4</td>
<td>2.5-5 mg/d</td>
<td>10 mg/d</td>
<td>20 mg/d</td>
<td>1.0 mg/kg/d</td>
</tr>
</tbody>
</table>

*Maximum dosing may exceed FDA approved dose limits


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Stimulant Dosing Instructions

- **PATIENT NAME:**
- **DATE:**
- **MEDICATION NAME:**
- **TABLET STRENGTH:**

**INSTRUCTIONS**
- Take ____________ each morning for five (5) days. After five (5) days, if there is no benefit and no side effects,
  - Then increase the dose to ____________ each morning for five (5) days. After five (5) days, if there is no benefit and no side effects,
  - Then increase the dose to ____________ each morning until we meet again.
- Do not exceed a dose of ____________ each morning.
  - If you have side effects at a particular dose, then reduce the dose by one tablet each morning and stay on that dose until we meet again, or stop the medication.
- **Return to see Dr. Tom Weigel in three weeks for a 1/2-hour appointment to discuss how things are going with the medication.**

Treatment of ADHD Stimulants

- **Side effects**
  - Appetite loss
  - Sleep disturbance
  - Restlessness/anxiety
  - Cramps
  - Rebound/Crash
    - Irritability
    - Depression
  - Tics
  - Growth slowing

Stimulant Controversies

- **Growth suppression in children receiving consistent medication**
  - 2 cm in 2 years in MTA study (20% reduction)
  - No further reduction if treated 1 additional year
  - Catch-up or rebound growth may be possible
  - Growth Chart with height every 3-4 months if concern

- **Development of tics**
  - Tics are usually transient; only 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 non-stimulant medication


Stimulant Controversies:
Diversion / Misuse

- Study design: meta-analysis of 7 studies (N = 1195)
- Stimulant exposure at 10 and 11 years old
- Follow-up 4 to 15 years later
- Findings:
  - Treatment of ADHD significantly decreases the risk for subsequent substance abuse (protective odds ratio = 2.0)
  - Twice the risk for substance abuse with untreated ADHD


Stimulant Controversies-CV
FDA analysis of amphetamines and methylphenidates from 1992-2005

- 38 cases of sudden death on stimulants (28 in children)
  - 12/28 children had structural cardiovascular abnormalities
  - 4 in 38 cases in patients aged 12 years or younger
- General population (not on stimulants)
  - Sudden death rate in children/adolescents: 6.6 per million per year
  - Rate in pre-exercised with cardiomyopathy similar to basal rate
  - Rate in pre-exercised with attherosclerosis similar to basal rate
  - Fibrillation rate in sudden death in children
- Sudden death rate for unexplained CV abnormalities with sudden death (about 30% have CV structural abnormality)


Treatment of ADHD
atomoxetine (Strattera)

- Approved in 2002 for ADHD treatment
- Noradrenergic re-uptake inhibitor
- > 10 controlled trials demonstrating efficacy
- Long term studies: continued effectiveness
- Once-daily dosing
- Benefit in 1-4 weeks
- No on/off effect
- May help with anxiety
- No abuse potential

Attention-Deficit Hyperactivity Disorder

**Treatment of ADHD**

*atomoxetine* (Strattera)

- **Dosing** (4-6 weeks)
  - Adult: 40 mg/d x3 days then 80 mg/d (max. 100/d)
  - Kids: 0.5 mg/kg/d x3 days, then 1.2 mg/kg/d starting dose; 1.4 mg/kg/d max
- **Side effects**
  - Abdominal pain
  - Insomnia
  - Decreased appetite
  - Constipation
  - Fatigue
  - Dizziness
  - Sexual side effects
  - Depression


- Possible slight increase in suicidal ideation reported in clinical trials
  - 0.37% Atomoxetine vs. 0.0% placebo
  - One suicide attempt/1557 cases; no suicides
- Rare hepatitis reported
  - One case confirmed/3.4 million exposures
  - One case suspected/3.4 million exposures

**Extended-Release Guanfacine (Intuniv)* for ADHD**

- FDA approved for children ages 6-17 to treat ADHD (*will be released in November)
- **Dosing**: 1-4 mg qam
- **Pharmacology**:
  - half-life = 18 hours
  - alpha-2a adrenergic agonist
- **Efficacy**:
  - improvement in hyperactivity/impulsivity as well as inattention
  - may be less effective with inattentive-subtype
- **Side effects**:
  - somnolence, dizziness, abdominal pain, dry mouth and constipation
  - use with caution in patients at risk for bradycardia, hypotension, heart block or syncope


Attention-Deficit Hyperactivity Disorder

**Treatment of ADHD**

**Other Medications**

- bupropion (Wellbutrin)
- clonidine (Catapres)
- Tricyclic antidepressants
- Mood stabilizers
- Neuroleptics/anti-psychotics

*Not FDA approved for treatment of ADHD.

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**Bupropion (Wellbutrin) in ADHD**

- Dopamine/norepinephrine reuptake inhibitor
- Stimulant-like structure
- No cardiac conduction delays
- Superior to placebo in children
  - N=3 controlled studies (104 subjects)
- Improvement in attention and behavior
- Dosing to 6 mg/kg/d (approximately 300-450 mg/d)
- Delayed onset of therapeutic action
  - 1 to 6 weeks

*Not FDA approved for treatment of ADHD.

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**Tricyclic Antidepressants**

- Advantages
  - Long duration of action
  - Potential benefits on mood and anxiety
  - Positive effects on sleep
- Disadvantages
  - Efficacy < Stimulants
  - Serious potential cardiac effects in children
  - Need for cardiac monitoring

*Not FDA approved for treatment of ADHD.

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Biederman J. J Clin Psychiatry. 1998;59(suppl 7:S4-S16.

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Clonidine (Catapres) for ADHD*

• Pharmacology: Alpha-2a-noradrenergic agonist
• Dosing: 0.05 mg to 0.2 mg up to TID
• Also transdermal (patch) dosing
• Efficacy
  – helpful for hyperactivity and impulsivity
  – not helpful with attention deficit
  – 3 controlled trials – efficacy for ADHD
  – Multiple open trials – efficacy in aggression, impulsivity, ADHD-related sleep disorders
• Side effects: sedation, headaches, depression, rebound hypertension; controversy of use with stimulants (4 deaths in 1990’s but no causal link)

*Not FDA approved for treatment of ADHD.

Summary:
Pharmacotherapy for ADHD

• Stimulants, atomoxetine and extended-release guanfacine are FDA approved first-line agents
• Antidepressants (bupropion and TCAs) are second-line agents
• Clonidine is an alternative agent typically used adjunctively with other medications
• Combined pharmacotherapy for incomplete response:
  – Stimulant plus atomoxetine, bupropion, tricyclics, clonidine, or guanfacine

Treating Refractory ADHD

• Evaluate for co-morbidity
• Referral for
  – Behavioral therapy
  – Coaching/study skills
  – Family therapy/parental coaching
• Higher doses of medication(s)
• Other Medicines not approved by FDA


Attention-Deficit Hyperactivity Disorder

Treatment of ADHD
Behavioral Strategies

- Parent training
  - Track behavior
  - Reward system
  - Catch good behavior
  - Issuing clear commands
  - Establishing house rules
  - Time out procedures
  - Structure time

- Teacher/School
  - Build teacher/student bond
  - Extra structure, consistency and organization
  - Decrease distractions
  - Extra time for tests
  - Reminders
  - Rules / Target behaviors
  - Effective commands
  - Rewards/punishments
  - Tutoring
  - Daily report card


ADHD and DSM-V
work group identified research questions relating to three broad areas:

1. Diagnostic coverage and exclusions
2. Adjusting criteria for key patient characteristics, especially age
3. Accounting for severity, heterogeneity, and subtypes—a more “dimensional approach” to substitute the rigid “categorical approach”

ADHD and DSM-V
Possible Changes

- Eliminate ADHD subtypes
- Create ADD diagnosis
- Add 4 more impulsivity criteria
- Increase age of onset to before age 12 (rather than 7)
- Lower threshold for ADHD combined dx in adults
- Remove autism-spectrum d/o and PDD from excluders
- Elaborate ADHD criteria descriptions (more examples)

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