The Diagnosis and Treatment of ADHD

Learning Objectives

Pediatricians will be able to:
1. Identify symptom criteria for ADHD.
2. State the major rule-out diagnoses.
3. Identify the primary comorbidities.
4. Describe the diagnostic process.
5. Choose between various treatment options based upon their risk/benefit profiles.

History of ADHD

- Minimal Brain Dysfunction (damage): 1900 – 1950
- Diagnostic Criteria (DSM-III) and “ADD” with or without Hyperactivity: 1980
- ADD becomes ADHD (DSM-IIIR) w/mixed criteria: 1987
- ADHD (inattentive, hyperactive, combined subtypes) in DSM-IV: 1994

Differential Diagnosis (Psychiatric)

- Mood and/or Psychotic Disorder
- Anxiety Disorder
- Learning Disorder
- Mental Retardation/Borderline IQ
- ODD/Conduct Disorder
- Pervasive Developmental Disorder
- Substance Abuse
- Axis II Disorders
- Psychosocial Cx (e.g., abuse, parenting, etc.)
Differential Diagnosis (Medical)
- Seizure Disorder (e.g., Absence, Complex-Partial)
- Chronic Otitis Media
- Hyperthyroidism
- Sleep Apnea
- Drug-Induced Inattentional Syndrome
- Head Injury
- Hepatic Illness
- Toxic Exposure (e.g., lead)
- Narcolepsy

DSM-IV Diagnostic Criteria (Inattention)
- Makes careless mistakes/poor attention to detail
- Difficulty sustaining attention in tasks/play
- Does not seem to listen when spoken to directly
- Difficulty following instructions
- Difficulty organizing tasks/activities
- Avoids tasks requiring sustained mental effort
- Loses items necessary for tasks/activities
- Easily distracted by extraneous stimuli
- Often forgetful in daily activities

DSM-IV Diagnostic Criteria (Hyperactive/Impulsive)
- Fidgets
- Leaves seat
- Runs or climbs excessively (or restlessness)
- Difficulty engaging in leisure activities quietly
- “On the go” or “driven by a motor”
- Talks excessively
- Blurs out answers before question is completed
- Difficulty waiting turn
- Interrupts or intrudes on others

DSM-IV Functional Criteria
- 6 of 9 symptoms in either or both categories
- Code as: Inattentive; Hyperactive-Impulsive; or Combined Type
- Persisting for at least 6 months
- Some symptoms present before 7 y/o
- Impairment in 2 or more settings
- Social/academic/occupational impairment
AAP Changes

- 2011 guidelines from AAP
  - Can diagnose and treat as young as age 4 (old limits age 6)
  - Always assess for co-morbidities, developmental and physical conditions (sleep disorders)
  - Diagnosis can be made at anytime between age 4 to age 18

DSM 5-2013

- Reduce from 6 to 5 symptoms needed to diagnose for older adolescents
- Onset of symptoms used to be by age 7-now by age 12
- Must show reduction in quality of functioning and not requiring clinical significant dysfunction

Epidemiology (1)

- Most commonly diagnosed behavioral disorder of childhood (1 in 20 worldwide)
- 3 – 7% of school children are affected in U.S.
- Males:Females = 2 – 9:1
- Virtually all neurodevelopmental disorders are more common in boys prior to age 10 years; by adulthood, we get closer to 1:1 ratios
Epidemiology (3)

- At least 30 – 50% maintain diagnosis for ≥ 15 yr
- Strongest predictor of poor prognosis is pre-pubertal aggression
- Over 80% of psychotropics are Rx by PCPs: stimulants (>50%), antidepressants (30%), mood stabilizers (13%), anxiolytics (7%), & antipsychotics (7%)
- ADHD related outpatient visits to PCPs increased from 1.6 – 4.2 million between 1990 - 93

ADHD is Familial

- Family studies: (1) sibling risk increases 2-5x;
  (2) 3-5x increased likelihood that parent is affected (9 – 35%)

ADHD: Course of the Disorder

- Inattention
- Hyperactivity
- Impulsivity

Why More ADHD?

- Improved recognition by physicians?
- Increase in prevalence?
- An easing of standards for making the diagnosis?
- An easing of standards for prescribing medication?...or the "Prozac" connection?
- Increased scholastic demands?
- Changing parental habits?
- Managed care and the pharmaceutical industry?
- 1991 amendments to IDEA?
### Potential Areas of Impairment

- ADHD
- Low self-esteem
- Academic limitations
- Relationships
- Legal difficulties
- Motor vehicle accidents
- Injuries
- Smoking and substance abuse
- Adolescents
- Adulthood

### Comorbidities (1)

- 2/3 of children with ADHD present with ≥ 1 comorbid Axis I disorder:

### Comorbid Conditions in Children with ADHD

<table>
<thead>
<tr>
<th>Comorbidities</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety disorder</td>
<td>6% – 30%</td>
</tr>
<tr>
<td>Conduct disorder</td>
<td>5% – 25%</td>
</tr>
<tr>
<td>Oppositional-defiant disorder</td>
<td>45% – 64%</td>
</tr>
<tr>
<td>Affective disorder</td>
<td>15% – 15%</td>
</tr>
<tr>
<td>Tic disorder</td>
<td>8% – 14%</td>
</tr>
<tr>
<td>Manic/hypomania</td>
<td>0% – 22%</td>
</tr>
<tr>
<td>Learning/academic problems</td>
<td>15% – 92%</td>
</tr>
</tbody>
</table>

#### Natural History

- Rule of “thirds”:
  - 1/3 → complete resolution
  - 1/3 → continued inattentive, some impulsivity
  - 1/3 → early ODD/CD, poor academic achievement, substance abuse, antisocial adults

- Age related changes:
  - Preschool (3-5 y/o) – hyperactive/impulsive
  - School age (6-12 y/o) – combination symptoms
  - Adolescence (13-18 y/o) – more inattentive/restlessness
  - Adult (18+) – largely inattentive with periodic impulsivity
Specific Genes Associated w/ADHD
- Rare mutations in the human thyroid receptor β gene on chromosome 3
  - Symptoms suggestive of ADHD are found among those w/a general resistance to thyroid hormone (Hauser et al, NEJM, 1993)
- Dopamine Transporter gene (DAT) on chromosome 5
  - A “hyperactive” presynaptic DAT (Gill et al, Mol Psych, 1997)
- Dopamine Receptor D4 gene (DRD4) on chromosome 11
  - Postsynaptic malfunction do not allow signal transmission (Swanson et al, Mol Psych, 1998)

Potential Non-Genetic Causes
- Non-genetic causes of ADHD are also neurobiological in nature
  - Perinatal stress
  - Low birth weight
  - Traumatic brain injury
  - Maternal smoking during pregnancy
  - Severe early deprivation (extreme)

Executive Functioning
- Most children with ADHD have impairments in executive functioning, including:
  - Response inhibition
  - Vigilance
  - Working memory
  - Difficulties with planning

Establishing a Convincing Diagnosis (1)
- There is no single test to identify ADHD
- Available “tests” are primarily Continuous Performance Tests (CPTs):
  - TOVA (Test of Variables of Attention)
  - Conner’s CPT
  - Gordon Computerized Diagnostic System
  - I.V.A. CPT
- Diagnosis must be multi-factorial
Establishing a Convincing Diagnosis (2)

- Clinical Interview:
  - Diagnostic Assessment of Primary Complaint
  - Review of Psychiatric Systems (e.g., attention, hyperactivity/impulsivity, oppositional & conduct difficulties, mood, anxiety, psychosis, trauma, neurovegetative systems, tics, substance abuse, etc.)
  - Medical, Psychiatric, & Developmental History
  - Detailed Educational History
  - Detailed Family & Social History

Establishing a Convincing Diagnosis (3)

- Collateral interviews:
  - Patient
  - Primary Caregivers (parents, grandparents, etc.)
  - Teachers
  - School Counselors
  - Sunday School Teachers
  - Coaches
  - Music Teachers
  - Camp Counselors (e.g., Boys & Girls’ Club)

Establishing a Convincing Diagnosis (4)

- “Some” symptoms by age 12 years
  - This criterion has been maintained in 3 versions of the DSM, despite a lack of empirical support
  - Likely leads to increased false-negatives
  - DSV-IV field trials demonstrated that inattentive subtype exhibited a later onset (Applegate et al, 1997)
  - An adult population survey found that only 50% of individuals with clinical features of ADHD retrospectively reported symptoms by age 12, but 95% reported symptoms before age 12 & 99% before 16 (Kessler et al, 2005)

Establishing a Convincing Diagnosis (5)

- Symptoms in ≥ 1 setting:
  - Never diagnose ADHD in a 1:1 interview
  - Individuals with ADHD can often function well in certain settings with no signs of symptoms when they are interested and maintain total focus (e.g., playing Nintendo, watching videos, etc.)
  - Symptoms in group settings are a must!
Establishing a Convincing Diagnosis (6)

- Rating scales:
  - SNAP – IV (for parents & teachers)
  - Conners (for teachers, parents, and affected adults)
  - ACTeRS (for teachers & parents)
  - Child Behavior Checklist
  - Behavior Assessment System for Children (BASC)
  - ADHD Rating Scale – IV
  - Brown ADD Scales

Establishing a Convincing Diagnosis (7)

- Treatment trial:
  - Risk of adverse effects is significant
  - Not necessarily “diagnostic” even if effective
  - At least 2 – 3 medications should be attempted before patient deemed non-responder
  - Very low placebo response with treatment of ADHD

Who “Gets” ADHD?

- Children without insurance receive less attention (e.g., care) in all domains
- Latino and black children are less likely to be diagnosed with ADHD by parent report than are white children
- Black children with ADHD are less likely to receive stimulants than white children

*1997 – 2001 National Health Interview Surveys
*1997 – 2000 Medical Expenditure Panel Survey

Treatment (1)

- Medication
- Behavioral Therapy
  - Cognitive/Behavioral Therapy
  - Parent Management Training
  - Social Skills Training
- Educational Support
  - 504
  - Individual Educational Plan (IEP)
**Treatment (2): The MTA Study of 1999**
- Over 550 school-aged children with ADHD were followed for 14 months:
  1. Community Treatment
  2. Rigorous Medication Protocol
  3. Rigorous Behavioral Protocol
  4. Combined Behavioral and Medication Protocols

**Treatment (3)**
- The MTA Study demonstrated:
  - Medication (stimulants) treatment effective
  - Behavioral treatment not effective for core ADHD symptoms (useful for some related impairments)
  - More frequent & higher dosing led to greater responses
  - Increased physician contact improved outcome

**Stimulants (1): Mechanism of Action**
- Reuptake inhibition of NE & DA
- Cause increased release of presynaptic NE/DA
- Amphetamine promotes passive diffusion of NE and DA into synaptic cleft
- Amphetamine promotes release of NE and DA from cytoplasmic pools
- Amphetamine & Methylphenidate are mild inhibitors of MAO

**Stimulants (5): Dosage & Administration**
- Routine PE prior to initiation of stimulants; Vitals checked periodically
- Long-acting treatments (e.g., Concerta, Ritalin LA, Adderall XR, Metadate CD) are good options given concerns about tachyphylaxis
- Dosing averages: 30 mg/d MPH, 20 mg/d AD
- Ritalin LA & Adderall XR are good long-acting choices for those with difficulty swallowing pills
Stimulants (6): Dosage and Administration Continued

- Weight based dosing (not generally utilized)
  - Methylphenidate @ 1 mg/kg
  - Adderall @ 0.6 mg/kg
- Dose to clinical response
- Forced Dosage Titration
  - E.g., for a 100+ pound child: Concerta: 18 mg/d week #1; 36 mg/d week #2; and 54 mg/d week #3
  - E.g., for a 50 pound child: Adderall XR: 5 mg/d week #1; 10 mg/d week #2; and 15 mg/d week #3

Long Term Effects on Academic Success

- Mayo Clinic 18 year study (2008) of >5,000 children from birth (370 with ADHD, 277 boys & 93 girls) found that treatment with prescription stimulants is associated with improved long-term academic success of children with ADHD.
- Girls and boys with untreated ADHD were equally vulnerable to poor school outcomes.
- By age 13, on average, stimulant dose was modestly correlated with improved reading achievement scores.
- Both treatment with stimulants and longer duration of medication were associated with decreased absenteeism.
- Children with ADHD who were treated with stimulants were 1.8 times less likely to be retained a grade than children with ADHD who were not treated.  
  – Barbaresi et al, 2008

Are Stimulants Protective?

- Certainly with regard to SUDS
- 10-year, prospective study of 112 white males with ADHD ages 6 to 17 years
- 82 (73%) had received stimulant treatment, with a mean treatment duration of six years
- In comparison with those who never took stimulants, participants who had received stimulant medication were significantly less likely to subsequently develop MDD (24% versus 69% for those who were stimulant naïve), conduct disorder (22% versus 67%), oppositional defiant disorder (40% versus 88%) and multiple anxiety disorders (7% versus 60%)
- Children receiving stimulant therapy also had significantly lower lifetime rates of grade retention as compared to their counterparts who never received stimulants (26% versus 63%)  
  –Biederman et al, 2009

Stimulants (9): Pros & Cons

- Methylphenidate (Ritalin), Adderall, Dexedrine
- Pros:
  - Highly effective
  - Long history of use
- Cons:
  - Limited duration of action
  - Side effects [e.g., Nausea, headache, insomnia, decreased appetite, tics (up to 65% w/MPH), anxiety, HTN/tachycardia, psychosis]
  - Contraindications [HTN, symptomatic cardiovascular disease, glaucoma, hyperthyroidism, tics/Tourette’s (relative), drug abuse (relative), psychosis (relative)]
Stimulants (10): Standard Care

- Routine Treatment with Stimulants and Atomoxetine
  - Prior to treatment
    - Height, weight, Blood Pressure & Heart Rate
    - Cardiac Exam
    - Family history of sudden cardiac death and/or personal or family history of syncope, chest pain, shortness of breath, or exercise intolerance warrants an ECG and pediatric cardiology referral for an echo
  - During Treatment
    - At least annual height & weight (compare to published norms); if height for age decreases by > 1 standard deviation while on stimulants, refer to a pediatric endocrinologist (re: possible growth hormone deficiency or hypothyroidism)
    - Repeat blood pressure and heart rate at least twice annually and anytime prior and subsequent to a dosage increase

Tic Disorders

- Up to 65% of children initiating Rx with MPH may develop a transient tic
- Simple Motor, Complex Motor, or Vocal
- Stimulants may cause or “unmask” tics

Treatment: Alteration in stimulant dose, discontinuation of stimulant, change of stimulant, α-2 agonists, antipsychotics, CBT, Strattera(?)

Vyvanse (lisdexamfetamine)

- Dextro-Amphetamine
  - Contrast to Adderall (25% L-Amp & 75% D-Amp)
  - Pro-drug Stimulant (20, 30, 40, 50, 60, & 70 mg dosages)
  - 10-12 hour duration
  - Lower “drug liking effects” among drug abusers than amphetamine (diminishing at higher doses)
  - Once daily dosing; can be dissolved in water
  - Side Effx = as amphetamine

Daytrana (The “patch”)

- Methylphenidate
- 10-12 hour duration
- One patch per day worn for 9 hours
- Dosages: 10 mg (27.5 mg @ 1.1 mg/hour), 15 mg (41.3 mg @ 1.6 mg/hour), 20 mg (55 mg @ 2.2 mg/hour), & 30 mg (82.5 mg @ 3.3 mg/hour)
- Side Effx = as methylphenidate
Texas Medication Algorithm

- Revised (JAACAP, June 2006)
- Uncomplicated ADHD:
  1. Stimulant
  2. 2nd Stimulant
  3. Atomoxetine
  4. Bupropion or TCA
  5. Alternate (BPA/TCA)
  6. Alpha-2 agonist

Other Treatments

- Focalin (dex-MPH), use at 50% MPH dose
- Focalin XR
- Pemoline (Cylert)
- Methamphetamine (Desoxyn)
- Reboxetine

Strattera: Pharmacokinetics/Pharmacodynamics

- Rapidly absorbed following oral administration
- Maximal plasma concentrations reached 1–2 hrs p dose
- Metabolized via hepatic CYP P450 2D6
- Half-life (t½) ~ 5 hours
  (~ 20+ hours in poor metabolizers)
- Observed duration of action with once-daily dosing suggests:
  - Therapeutic effects may persist after drug is cleared and/or
  - Brain concentration may differ from plasma concentration

Strattera: Efficacy in Children & Adolescents

- 24-hour duration of action with once-daily dosing
- Incidence of insomnia comparable with placebo (for children/adolescents)
- Not contraindicated in patients with tics and anxiety
- Nonstimulant/noncontrolled substance
- May improve some measures of functional outcome (not just core ADHD symptoms)
Patients in Whom You Might Consider Strattera

- History of adverse effect to stimulants
- Comorbid anxiety, depression, tics, enuresis or Tourette’s
- Require 24 hour symptom relief
- Severe stimulant rebound
- Personal or family history of substance abuse
- Concern about insomnia or appetite suppression
- Monthly prescriptions are a major hassle
- Any newly diagnosed patient for whom you determine the treatment to be appropriate

Organizational Skills Training

- Manualized Treatment, Flexibly Applied to Individual Needs
- 20 sessions conducted in 10 weeks
- Meet with child and parents
- Consult with teachers
- Focus on practical routines that children can use over and over again
- Rewards and reinforcement used to motivate students to change

Treatment Areas for Organizational Skills Management

- Tracking Assignments
- Organization of Settings
- Materials Management
  - Collection
  - Storage
  - Transfer
- Time Management
  - Time Estimation
  - Scheduling
- Planning
  - Single Time Period
  - Long-Term Projects
  - Setting Priorities
  - Determining Breaks

Parent Problems Related to ADHD

- Parents of children w/ADHD are 3-5x more likely to become separated or divorced
- Parents of children w/ADHD have a higher incidence of depression & family discord
- Majority of parents of children w/ADHD report making changes in work status
- 9 – 35% risk that a parent of a given patient has ADHD