Managing ADHD
Across the Lifecycle
Diagnostic Issues
DSM-5 ADHD
Changes from DSM-IV

• Impairing symptoms by 12 not 7 years old
• “Neurodevelopmental”- not “Disruptive”
• “Presentations” not subtypes
  – Inattentive/hyperactive-impulsive/combined
• Over 17: $\geq 5$ inattentive + or $\geq 5$ impulsive/hyperactive symptoms;
  Under 17: 6 or more of either
• Adult symptom-examples included
• Autism/PDD non-exclusionary
DSM-5 ADHD: Criteria Unchanged from DSM-IV

- Symptoms present in **2 or more settings**
  - (school, work, home)
- Not explained by another disorder
DSM-5 Inattention Symptoms Include Memory and Organization Deficits

5/6 of the following often apply:

- Easily distracted
- Careless mistakes
- Difficulty sustaining attention
- Poor listening
- Leaves tasks unfinished
- Avoids tasks requiring sustained attention
- Loses things
- Forgetful
- Difficulty organizing
DSM-5 Hyperactivity/Impulsivity Traits
Emphasize Internal Drive and Activity

5/6 of the following often apply:

• Fidgeting
• Inability to stay seated
• Moving excessively (restlessness)
• Difficulty doing quiet activities
• “On the go”
• Talks excessively
• Blurts out answers
• Difficulty awaiting turn
• Interrupting/intruding
**Collateral Information**

Gathering clinical information to make diagnosis varies based on developmental level; most adult patients rely on self-report; efforts must be made to gather collateral info as much as possible.

<table>
<thead>
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<th>AGE:</th>
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<th>12</th>
<th>18</th>
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<td>Child</td>
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<tr>
<td>Teacher</td>
<td>Teacher</td>
<td>Self</td>
<td>Self</td>
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<tr>
<td>Parent</td>
<td>Parent</td>
<td>Teacher</td>
<td>Spouse/Partner</td>
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<td>Parent</td>
<td>Sibling</td>
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<td>Grandparent</td>
<td>Grandparent</td>
<td>Friend</td>
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<td>Other adult</td>
<td>Other Adult</td>
<td>Co-worker</td>
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**Behavioral Observation**  **Self Report**

Primary source for information
Comprehensive Initial Adult Psychiatric Evaluation for ADHD

- Determine the specific current ADHD symptoms
- Determine presence of ADHD in childhood
- Determine level of daily impairments in multiple life domains
- Assess for history of and concurrent psychiatric comorbidities; differential diagnosis
- Assess family psychiatric history
- Assess medical history and current medications
- Evaluate risks for the use of ADHD medications
Does Neuropsychological Testing Diagnose ADHD?

NO!

“Most measures of EFs have good positive predictive power for ADHD (characterized by adequate sensitivity) but poor negative predictive power (poor specificity)."

That is:

Abnormal scores on measures of EF test are generally predictive of the diagnosis; however, normal scores cannot rule out the diagnosis.

Is There Any Test or Brain Scan That Confirms a Diagnosis of ADHD?

NO!

A wide range of brain structural differences and functional patterns have been found across studies in individuals with ADHD - but no tests have demonstrated specificity and sensitivity in replicated studies that received peer-review.

The diagnostic criteria does not include any test.
Utility of Neuropsychological Assessment in ADHD?

• May review DSM ADHD Criteria
  – (scales alone do not establish time-course)
• May identify extremes of brain function that are consistent with (not diagnostic of!) ADHD
• May clarify native strengths and challenges eg. learning disabilities, low processing speed
• May clarify level of functional impairment vs. norms
• Required by many entities to justify accommodation
Differential Dx & Complicating Conditions

- Mental health conditions (affective, anxious, substance, psychosis, eating, posttraumatic disorders, etc.)
- Learning or processing disorders
- Tourette's or tic disorder
- Chronic systemic medical conditions
- Developmental disorder/autism
- Asperger's/Social skill deficits
- Medication, substance, poison effects (e.g. lead)
- Nutritional deficiency (e.g. iron, B12)

Differential Dx & Complicating Conditions (cont.)

- Brain trauma (e.g. post-concussive syndrome)
- Delirium
- Degenerative neurologic condition (e.g. dementia)
- Endocrine disorder (e.g. thyroid disorder)
- Seizure disorder
- Sleep disorder (e.g. insomnia, phase delay, apnea)
- Dietary allergy or sensitivity
- Major life stress (loss, trauma)
- Familial/genetic disorders
- Other Encephalopathies (e.g., fetal alcohol)
Developmental Course
ADHD Prevalence and Treated by Age

Persistence of 30-60%

Child and Adolescent

Treated
~60%
2.5 million

8% prevalence rate in US
54 million age<18
~4.3 million with ADHD

Adult

Treated
10-15%
1.6 million

4.4% prevalence rate in US
250 million age≥18
~11 million with ADHD
Adult ADHD Prevalence in Older Adults: Longitudinal Aging Study Amsterdam (LASA)

- First epidemiological study on ADHD in older persons (age 55-85)
  - 1494 participants screened with ADHD questionnaire
  - 231 respondents administered structured diagnostic interview
  - 6 out of 9 ADHD symptoms must be present in childhood for ADHD diagnosis (relying solely on respondents’ recollection of childhood symptoms)
  - Other psychiatric diagnoses not included
- Prevalence of syndromatic ADHD in older adults: 2.8%
- Prevalence of symptomatic ADHD in older adults: 4.2%
- Men and women reported similar levels of symptoms
- Prevalence rates of inattentive and hyperactive-impulsive subtypes were the same

Developmental course of attention-deficit/hyperactivity disorder in persistent cases

Behavioral disinhibition, emotional ability and emergence of diagnosis in preschool years

Prodrome: hyperactivity; and speech, language and motor coordination problems

Full expression of ADHD, psychiatric co-morbidity, school failure, peer rejection and neurocognitive dysfunction

Inattention persists and hyperactive-impulsive symptoms wane

Smoking initiation

Substance abuse, low self-esteem and social disability

In utero

Childhood

Adolescence

Adulthood

Genetic predisposition

Psychosocial influences, chaotic family environments, peer influences and mismatch with school and/or work environments

Different genetic risk factors affect the course of ADHD at different stages of the lifespan

Frontal–subcortical–cerebellar dysfunction via structural and functional brain abnormalities and downregulation of catecholamine systems that regulate attention, reward, executive control and motor functions

Persistence of cortical thickness, default-mode network and white matter tract abnormalities

Clinical presentation of ADHD changes across development and is related to interplay among environmental demands, external supports available, and typical symptom trajectories.
Neurobiology of ADHD

• Significant advances have been made over the years in understanding the neurobiology of ADHD in children and adults

• Receptors
  – DAT density differences in striatum

• Cerebral/cerebellum morphology
  – Volumetric differences

• Neurodevelopment
  – Regional maturational delays

• Neural network activation
  – Different activated networks for tasks
Predictors of Poor Transitions to Adulthood

- Risk factors for persistent ADHD and a poor outcome in adolescence may include
  - Severity of ADHD
  - Comorbidity
  - Low social competence
  - Peer rejection

Mrug et al., 2012; Murray-Close et al., 2010; Weiss & Hechtman, 1993; Schei et al. 2015
Higher Risks by Age for Untreated ADHD

- Smoking
- Sex/Pregnancy
- H.S. drop-out
- College drop-out
- Work Issues/Loss of Job
- Marital problems/Divorce

Age: 11, 13, 15, 17, 19, 22+

Substance Use
Driving problems

Treatment
Managing Transition Age Youth

- Adolescents: not little adults / not big children – unique clinical considerations
- Get perspective of a caregiver based on adolescent’s developmental level
  (younger or less mature adolescents = more parental input)
- Attend to social influences and function more than other age groups
- Be aware of development and environmental demands faced by all adolescents (e.g. more academic work; sleep phase delay; exploration of independence; higher risk-taking)
- Beginning of higher risk period for substance involvement: anticipate misuse/diversion risks, educate parents
Understanding the Role of Stimulants in a Comprehensive Treatment Plan

• Medications often manage attention and behavioral symptoms well
• Other modalities may be needed for common related challenges
  – Time management
  – Planning
  – Decision making
  – Spatial sense
  – Social skills
Reasons for Discontinuing Pediatric ADHD Medication After 1 Year

- Own wish/remission/don't need: 20%
- Withdrew consent: 16%
- Adverse effects: 15%
- Suboptimal effect: 15%

Adverse Effects of ADHD Medications Leading to Pediatric Non-Adherence


Bar chart showing percentages of adverse effects:
- Reduction in weight/appetite: 19%
- Aggressive behavior/irritability: 17%
- Sleeping difficulties: 11%
- Abdominal pain: 8%
- Motor tics: 7%
- Worsening of ADHD: 6%
- Depression: 6%
Adult ADHD & Comorbidities
Prevalence Rates of Psychiatric Disorders in Adults

Comorbidity Is The Rule in Adult ADHD:
MUST CAREFULLY ASSESS COMORBIDITY

Any mood disorder 38.3%

National Comorbidity Survey Replication: Anxiety Disorders in Adult ADHD

Any anxiety disorder 47%
ADHD and SUD

- Adults with ADHD are at elevated risk of other disorders
- High rates of misuse of stimulants in some populations
- 15%-25% of adults with substance use disorder have concurrent ADHD
- Consistent treatment of ADHD may lower SUD risk in adolescents and young adults – less so later
- Adults with both diagnoses have:
  - Earlier onset
  - A longer course
  - Greater severity with more relapses
  - Greater difficulty remaining abstinent

Diagnostic Prioritization for Pharmacotherapy

Alcohol and substance abuse
Mood disorders
Bipolar and MDD
Anxiety disorders
Obsessive-compulsive disorder, generalized anxiety disorder, panic
ADHD

Order of treatment also considers the severity of the concurrent disorders.

Evaluate Opportunity Cost of Rx vs. no Rx

Unclear Diagnosis
Hx of agitation
Hx of sub. use disorder
Sympathetic vulnerability
Subpopulation specific risk
Misuse/diversion
Lack of outcome measure

Clear Diagnosis
No comorbid history
Typical effects
Medically healthy agenda
Clear adaptive improvement
Clear outcome measure
Clinical Assessment of Cardiac Risk

• ECGs are not routinely required
• Obtain cardiac clearance if:
  – Spontaneous syncope or unexplained lightheadedness
  – Exercise-induced syncope
  – Exercise-induced chest pain
  – Sudden death in family member under age 30
  – History of cardiac abnormalities (structural or electrical) in self or family members

Medications for ADHD
## Methylphenidate Preparations

<table>
<thead>
<tr>
<th>Methylphenidate Formulations</th>
<th>Duration</th>
<th>Form</th>
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<tbody>
<tr>
<td>Generic methylphenidate</td>
<td>2-3 hrs</td>
<td>tablet</td>
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<tr>
<td>Methylin liquid</td>
<td>2-3 hrs</td>
<td>liquid</td>
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<tr>
<td>MPH SR</td>
<td>4 hrs</td>
<td>wax matrix</td>
</tr>
<tr>
<td>MPH LA</td>
<td>8 hrs</td>
<td>beaded (50:50)</td>
</tr>
<tr>
<td>OROS MPH*</td>
<td>12 hrs</td>
<td>OROS</td>
</tr>
<tr>
<td>MPH ER</td>
<td>6-8 hrs</td>
<td>beaded</td>
</tr>
<tr>
<td>MPH CD</td>
<td>8 hrs</td>
<td>beaded (30:70)</td>
</tr>
<tr>
<td>MPH XR</td>
<td>12 hrs</td>
<td>multilayer bead (40:60)</td>
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<tr>
<td>DexMPH*</td>
<td>3 hrs</td>
<td>tablet</td>
</tr>
<tr>
<td>DexMPH XL</td>
<td>10 hrs</td>
<td>beaded</td>
</tr>
<tr>
<td>MPH ER liquid</td>
<td>12 hrs</td>
<td>liquid</td>
</tr>
<tr>
<td>MPH transdermal patch</td>
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<td>patch</td>
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</tbody>
</table>

*FDA approved for ADHD in Adults*
## Amphetamine Preparations

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Duration of Action</th>
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<tbody>
<tr>
<td>Dextroamphetamine</td>
<td>2-3 hrs liquid</td>
</tr>
<tr>
<td>Dextroamphetamine</td>
<td>2-3 hrs tablet</td>
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<tr>
<td>Dextroamphetamine spanules</td>
<td>4 hrs tablet</td>
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<tr>
<td></td>
<td>6 hrs beaded</td>
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<tr>
<td>Amphetamine racemic</td>
<td>6 hrs tablet</td>
</tr>
<tr>
<td>Mixed AMPH salts XR*</td>
<td>6 hrs tablet</td>
</tr>
<tr>
<td></td>
<td>Up to 12 hrs beaded</td>
</tr>
<tr>
<td>AMPH XL liquid</td>
<td>12 hrs liquid</td>
</tr>
<tr>
<td>AMPH XR ODT*</td>
<td>12 hrs Orally disintegrating tablet</td>
</tr>
<tr>
<td>AMPH XR</td>
<td>Tablet</td>
</tr>
<tr>
<td>Lisdexamfetamine*</td>
<td>Up to 13 hrs prodrug</td>
</tr>
</tbody>
</table>

*FDA approved for ADHD in Adults
Lisdexamfetamine Withdrawal

LDX ~6 mos; 6 wk blinded withdrawal phase; Relapse ≥50% increase ADHD score And ≥2 point CGI-S

Brams et al, J Clin Psych 2012; 73 (7), 977-983
Useful Things to Know To Optimize Stimulant Treatments

- Side effects differ between agents & release patterns
  - Peak or valleys may create side effects
  - Different side effect profiles may be evident across different ages
- Adult methylphenidate studies separated from placebo when dosing allowed > 1 mg/kg/day
  - Many patients benefit from higher than FDA limit dosing but little safety guidance
- Methylphenidate approx. 50% potency of amphetamine
- Taking breaks to overcome “tolerance” more appropriate than dose escalation
Side Effects Of Stimulant Medication

- Insomnia
- GI upset
- Decreased appetite
- Weight loss
- Headaches
- Dry mouth
- Constipation
- Hand tremors
- Jittery

- Research on individual stimulants has generally shown no dose relationship with side-effects in group data
- Some research has shown side effects may be more likely in stimulant-naive patients
- Children may be more sensitive to side effects than adults

Nonstimulants

- Atomoxetine*
- Guanfacine ER
- Clonidine ER

Off-label:
- Bupropion (positive controlled adult trials)
- Desipramine (positive adult trial)
- Modafinil (although adult study negative)
- Memantine (open label study only)

Not FDA approved in adult ADHD

*FDA approved in adult ADHD
Pregnancy and Stimulants

• Category C
  – Amphetamines, methylphenidate, atomoxetine
  – Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks

Breast Feeding and Stimulants

• Amphetamine
  – Detectable in breast milk
  – Amphetamine in infants’ urine

• Methylphenidate
  – Detectable in breast milk

• American Academy of Pediatrics considers amphetamines and methylphenidate a contraindication for breastfeeding

Clinical Presentations ADHD Rx May Exacerbate:

• Extreme states (psychosis, bipolar)
  – Stimulants, atomoxetine, ? others
• Seizure risk (e.g. bulimia nervosa, binge drinking)
  – bupropion
• Birth control • Modafinil reduces levels
• Orthostatic vulnerability • Guanfacine, clonidine
• Tics or Tourette syndrome • Stimulants may exacerbate

<table>
<thead>
<tr>
<th>Company</th>
<th>Mechanism</th>
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<tr>
<td>Shire</td>
<td>AMPH Triple beaded-duration 16 hours</td>
</tr>
<tr>
<td>Purdue</td>
<td>MPH Triple beaded-duration 16 hours</td>
</tr>
<tr>
<td>Ironshore</td>
<td>MPH –onset starts 8 hrs after ingestion (Delexis technology) taken at bedtime for am coverage</td>
</tr>
<tr>
<td>Neos</td>
<td>Oral dissolving (ODT) long acting MPH</td>
</tr>
<tr>
<td>Rhodes</td>
<td>MPH Multilayered bead (IR40:ER60)</td>
</tr>
<tr>
<td>Neurovance</td>
<td>Triple reuptake inhibitor</td>
</tr>
<tr>
<td>Alcobra</td>
<td>Metadoxine (high dose Vit B6)</td>
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<tr>
<td>Lilly</td>
<td>Edivoxetine- norepinephrine reuptake inhibitor</td>
</tr>
<tr>
<td>Sunovion</td>
<td>Dasotraline- triple reuptake inhibitor</td>
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</tbody>
</table>
Dasotraline for ADHD in Adults: A Randomized, Double-Blind, Placebo-Controlled, Proof-of-Concept Trial

Inhibits Dopamine and Norepinephrine Transporters more than Serotonin

- N=331 with post baseline efficacy assessment
- Discontinuation due to adverse events: 10.3% (4 mg), 27.8% (8 mg), and 1.8% (placebo)

**Figure 2**  LS mean change in ADHD RS-IV total scores (MMRM).

Koblan et al., Neuropsychopharm, 2015
Dasotraline Pediatric ADHD Study

6–12 years olds, rated on home version of ADHD-RS
Intent to treat analysis
Adverse event discontinuation rate: 2mg: 6.3%, 4 mg: 13%, Placebo: 1.7%

Goldman R, et al. APSARD, 2017
Dasotraline May Enter Brain Slower Than Methylphenidate

Bolus/Infusion in 3 Rhesus Monkeys of 0.1 / 0.2 mg/kg dasotraline OR 0.1 / 0.5 mg/kg methylphenidate

Estimated brain entry rates: mean (±SD) estimated
Dasotraline: 0.1 mg/kg: 23.0 ± 4.9 minutes; 0.3 mg/kg: 14.7 ± 2.6 minutes
Methylphenidate: 0.1 mg/kg: 2.8 ± 0.1 minutes; 0.5 mg/kg: 2.5 ± 0.7 minutes

Do Other Interventions Reduce ADHD Symptoms?
Oxford Center for Evidence-Based Medicine Rankings

• Mechanism-based reasoning
• Case series, case-control studies, or historically controlled studies
• Non–randomized controlled studies
• Single randomized trial or observational study with clear effect
• Systematic review of randomized trials

Faraone and Antschel, 2014
Effect Size

\[
\frac{\text{[Mean of experimental group]} - \text{[Mean of control group]}}{\text{Standard Deviation}}
\]
Evidence for Treatment Effect on ADHD Symptoms

**Fig. 2.** ADHD treatment effect sizes.

- Stimulant Medication
- Non-Stimulant Medication
- Restricted Elimination Diets
- Artificial Food Color Exclusions
- Neurofeedback
- Computer Cognitive Training
- Omega-3 Fatty Acids
- Behavioral Parent Training

* OCEBM level is at right of bar

Faraone & Antshel, 2014
Behavioral Interventions May Reduce ADHD Symptoms in Adults

- Behavioral interventions may improve related behaviors and coping, particularly in conjunction with medication
- Two RCT’s in adults demonstrated positive effects of cognitive-behavioral therapy

Clinical Implementation

- Systematically identify whether individuals meet full ADHD criteria
- Establish healthy, adaptive function as a mutual goal with your patients
- Track change in ADHD symptoms and role function
- Steer to additional supports for coping strategies, accommodations, comorbid challenges
- Re-evaluate need for, adherence to, and benefit / risk of interventions
Resources

• For consumer education:
  – CHADD National Resource Center; CHADD.org
  – ADD.org
  – CADDAC.ca

• Screening Tools
  – Adult: ASRS
    https://www.hcp.med.harvard.edu/ncs/asrs.php

• For professional training:
  – APSARD.com
  – CADDRA.ca