ADHD: Assessment and Treatment

+ Persistence of childhood vs. late-onset vs. late-identified
ADHD vs. misidentified diagnoses

William P. French, MD
February 1, 2020 | Bellevue, WA
Today’s Agenda

At the end of this session, participants will be able to describe:

- at least 3 clinical component that should be addressed when assessing youth, who may have ADHD.
- at least 3 components of a multimodal treatment plan for ADHD.
- at least 3 factors to consider when evaluating previously undiagnosed teenagers, who present with possible ADHD symptoms.
Introduction

Historical Considerations, Etiology, Prevalence, and Disease Course
ADHD Historical Timeline

- **1930**: Minimal Brain Damage
- **1937**: Efficacy of Amphetamine
- **1950**: Hyperactive Child Syndrome
- **1968**: Hyperkinetic Reaction of Childhood (DSM-II)
- **1980**: Attention Deficit Disorder + or - Hyperactivity (DSM-III)
- **1987**: ADHD (DSM-IV)
- **1994**: ADHD (DSM-V)
- **2014**: ADHD (DSM-VI)
Statistical Heritability—Liability risk for the disease

**Heritability Co-efficient of ADHD**

The diagram illustrates the average genetic contribution based on twin studies for various conditions, including ADHD. The heritability coefficients are as follows:

- **Breast cancer**: 0.2
- **Asthma**: 0.4
- **Schizophrenia**: 0.6
- **Height**: 0.76

The ADHD Mean is indicated at 1.

References:
Prevalence and Disease Course

- Prevalence 6-9% (2x boys); 4-5% in adults
- Adult prevalence approximately \( \frac{1}{2} \) of youth prevalence
- Many will have symptoms persisting into adulthood.
  - As many as 90% will still have some symptoms of ADHD, not necessarily meeting strict diagnostic criteria.
- Long-term consequences of ADHD:
  - Higher rates of traffic and other accidents, marital difficulties, unemployment, antisocial and criminal behavior, and obesity.
  - Lower household income attained
  - Higher rates of attempted and completed suicide

Prevalence across lifespan

ADHD Prevalence

70-85% persists into adolescence

60% persists into adulthood

Children with ADHD

5-8% of the population

Adolescents with ADHD

Adults with ADHD

>80% of adults with ADHD have never been diagnosed or treated

3-5% of the population

References:
Course of ADHD

Age
Inattention
Hyperactivity
Impulsivity
Comorbidity

Persistence of ADHD Over Time

Age-dependent Decline of ADHD Symptoms

Age-specific prevalence of remission from ADHD among 138 boys, according to definition of remission and symptom type

- Syndromatic remission
- Symptomatic remission
- Functional remission

Functional impacts across development

Developmental Impact of ADHD

- Pre-school
  - Behavioural disturbance
  - Plus: Academic problems, difficulty with social interactions, self-esteem issues

- School-age
  - Plus: Legal issues, smoking, drugs, injury/accidents, risky sexual behaviour, driving issues

- Adolescent
  - Plus: Occupational failure, numerous job changes, marital/relationship discord/separation/divorce

- College-age
  - Plus: Academic failure, occupational difficulties, relationship problems, substance abuse

- Adult
  - Plus: Occupational failure, numerous job changes, marital/relationship discord/separation/divorce
Etiology—Key Learning Points

- Heritability 76%
- Best conceptualized as a disorder of executive functioning
- Many different regions of the brain, including the prefrontal cortex, have been implicated in contributing to the manifestation of ADHD
- The principal neurotransmitters involved in ADHD are norepinephrine and dopamine
- Changing cultural practices/attitudes and environmental demands also should be taken into consideration
- Prenatal, perinatal, and post-natal environmental effects, such as, lead, nicotine, and alcohol exposure; low birth weight; psychosocial adversity (e.g., ACEs, including neglect; TBIs, etc., may be viewed as:
  1) potentiating a heritable risk (GxE interaction)
  2) a de novo etiologic factor (Narrow vs. Broad Phenotype)
Diagnostic Considerations

Work-up, DSM-5 Criteria, Role of Rating Scales and Impairment, Mimics, and Co-morbidities
Work-up

• In general, no testing or imaging is indicated.
• Clinical diagnosis
  • But some soft physical signs may be present, such as motor overflow and clumsiness.
• Rating scales can help elicit symptoms.
• Comparison to peers
  • Inattention/hyperactivity common in preschoolers.
  • At young ages, developmental gaps can be large even among same grade cohorts.
• Response to stimulants is not unique to individuals with ADHD
• Consider psychological or neuropsychological testing if low cognitive ability or low achievement relative to ability.

Work-up

• If other symptoms present, consider
  • Lead
  • Thyroid
  • Seizures
  • OSA
  • Anemia
  • Trauma
  • Substance abuse
  • Sensory impairment
  • Brain injury
  • Genetic syndrome

• Medication side effects may mimic ADHD.
  • Bronchodilators
  • Corticosteroids
  • Antihistamines
  • Antipsychotics
DSM 5 Diagnostic Criteria, the Role of Screening Tools, and Quantifying Impairment
Diagnosis

- Before 12 yo (versus prior to age 7 in DSM-IV)
- 6 months duration
- 2 or more settings
- Clinically significant impairment
- Not explained by other disorder
- 6 symptoms of inattention or hyperactivity or both
  - Other DSM-5 updates: 5 symptoms for adults, examples included to facilitate diagnoses across the life span, cross-situational requirement strengthened to include several symptoms in each setting, subtypes replaced with specifiers (which map to previous subtypes), autism is no longer an exclusionary comorbid diagnosis

### Lifetime Course of ADHD Symptoms: Inattention

<table>
<thead>
<tr>
<th>Childhood</th>
<th>Adulthood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difficulty paying attention in class</td>
<td>Difficulty paying attention at work or in conversations</td>
</tr>
<tr>
<td>Avoids homework</td>
<td>Avoids completing forms or reviewing lengthy papers</td>
</tr>
<tr>
<td>No follow-through</td>
<td>Fails to finish household chores or tasks in the workplace; inefficient</td>
</tr>
<tr>
<td>Incomplete assignments</td>
<td></td>
</tr>
<tr>
<td>Daydreaming</td>
<td>Paralyzing procrastination</td>
</tr>
<tr>
<td>Doesn’t listen</td>
<td>Late/misses appointments</td>
</tr>
<tr>
<td>Has difficulty organizing tasks</td>
<td>Disorganized</td>
</tr>
<tr>
<td>Works slowly</td>
<td>Messy</td>
</tr>
<tr>
<td>Loses things, such as school materials and books</td>
<td>Poor time management</td>
</tr>
<tr>
<td></td>
<td>Fail to meet deadlines</td>
</tr>
<tr>
<td></td>
<td>Loses things such as glasses, wallets, keys, mobile phones</td>
</tr>
</tbody>
</table>

### Lifetime Course of ADHD Symptoms: Hyperactivity-Impulsivity

<table>
<thead>
<tr>
<th>Childhood</th>
<th>Adulthood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Running, climbing, jumping</td>
<td>Restlessness</td>
</tr>
<tr>
<td>Can’t stay seated</td>
<td>Driving at high speed</td>
</tr>
<tr>
<td>Excessive talking</td>
<td>Can’t sit through meetings</td>
</tr>
<tr>
<td>On to go/driven by motor</td>
<td>Can’t relax</td>
</tr>
<tr>
<td>Squirming, fidgeting</td>
<td>Excessive talking</td>
</tr>
<tr>
<td>Can’t play/work quietly</td>
<td>Can’t tolerate frustration</td>
</tr>
<tr>
<td>Can’t wait turn</td>
<td>Impatient</td>
</tr>
<tr>
<td>Interrupts others/Blurs out answers</td>
<td>Inefficiencies at work</td>
</tr>
<tr>
<td></td>
<td>Self-selects very active job</td>
</tr>
<tr>
<td></td>
<td>Can’t wait in line</td>
</tr>
<tr>
<td></td>
<td>Interrupts others/intrudes</td>
</tr>
<tr>
<td></td>
<td>Makes inappropriate comments</td>
</tr>
<tr>
<td></td>
<td>Quits job</td>
</tr>
</tbody>
</table>

ACCURATE DIAGNOSES AND THE ROLE OF RATING SCALES

• Over-reliance on parent-, self-report- and teacher-completed rating scales during the assessment process may lead to inaccurate diagnoses.

• ADHD rating scales have only moderate sensitivity while their specificity ranges from low to moderate.

• Additionally, there is often poor agreement between parent and teacher responses. With these limitations in mind, it is important to remember that rating scales are best used as screening tools and to measure treatment response.

• Rating scales are best used as screening tools and to measure treatment response.
Central Role of Impairment in Assessment and Treatment

• **Impairment**—that is, problems in daily life functioning that result from symptoms (rather than symptoms themselves) are what should be targeted in treatment.

• **Assessment of impairment** in daily life functioning is a fundamental aspect of **initial evaluation**.

• **Ongoing assessment** of impairment in critical domains is necessary to determine the impact of and need for modifications in treatment.

• **Normalization or minimization of impairment** in daily life functioning is the **goal of treatment**.
ADHD “Mimics” and Comorbid Disorders
Psychiatric Mimics in children and adults

• Autism Spectrum Disorder
• Intellectual Disability (not obvious)
• Depression
• Anxiety and OCD
• Bipolar disorder (especially in adults)
• Eating Disorder
• Adjustment disorders
• ADHD personality (symptoms without impairment)
• Stimulant seeking (abuse, anorexia)
• Substance Use Disorders
• Borderline Personality Disorder
• Other Impulse Disorder/Problems
• OSA
• Early trauma and neglect (Bucharest Adoption Study)
Comparing ADHD and Anxiety Symptoms

ADHD Symptoms that mimic Anxiety

- Worrying about performance deficits
- Excessive mind-wandering
- Feeling overwhelmed
- Feeling restless
- Avoidance of situations due to ADHD symptoms, such as difficulty waiting in lines or social situations requiring focused attention
- Sleep problems linked to mental restlessness

## Comparing ADHD and Borderline Personality Disorder Symptoms

### Distinguishing ADHD from Borderline Personality

<table>
<thead>
<tr>
<th>Overlapping Symptoms with ADHD</th>
<th>Borderline Distinct Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pattern of relationship challenges/impairments</td>
<td>Has intense relationships with often ‘black and white’ reactions and underlying intense fear of abandonment</td>
</tr>
<tr>
<td>Impulsivity and risky behavior (e.g., gambling, reckless driving, unsafe sex, spending sprees, binge-eating or drug abuse)</td>
<td>Rapid changes in self-identity and self-image</td>
</tr>
<tr>
<td>Mood swings</td>
<td>Periods of stress-related paranoia and loss of contact with reality</td>
</tr>
<tr>
<td>Inappropriate and intense anger</td>
<td>Suicidal threats, behaviours or self-injury</td>
</tr>
</tbody>
</table>

| | Ongoing feelings of emptiness |

## Comparing ADHD and Bipolar Disorder

### Distinguishing ADHD from Bipolar Disorder

<table>
<thead>
<tr>
<th>ADHD DISTINCT CHARACTERISTICS</th>
<th>BIPOLAR DISTINCT CHARACTERISTICS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial insomnia, sleep disorders</td>
<td>Decreased need for sleep</td>
</tr>
<tr>
<td>Chronic restlessness</td>
<td>Episodes of speediness, increased rate of speech</td>
</tr>
<tr>
<td>Impulsive sexual encounters</td>
<td>Hypersexuality</td>
</tr>
<tr>
<td>Chronic course</td>
<td>Episodic course</td>
</tr>
<tr>
<td>Chronic distractibility and/or impulsivity</td>
<td>Episode-related distractibility and/or impulsivity</td>
</tr>
<tr>
<td></td>
<td>Feeling &quot;high&quot;, or an overly happy mood</td>
</tr>
<tr>
<td></td>
<td>Grandiosity</td>
</tr>
</tbody>
</table>

Comorbidities in Youth

• Language or Learning problem (25-35%)
• ODD (55-85%)
• Substance abuse (20-40%)
• Conduct (10-20%)
• Anxiety (33%)
• Tic disorder Mood disorders
• Sleep problems
• PTSD
• Attachment issues

Tools to distinguish ADHD from other disorders

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Key Questions</th>
<th>Differentiating Symptom</th>
<th>Behavioral Health Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADHD</td>
<td>Does your child struggle with impulsivity, hyperactivity, or problems with attention?</td>
<td>Poor focus</td>
<td>Connors Early Childhood (ages 2-6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Connors 3 (ages 6-18); Vanderbilt (non-proprietary, ages 6-12)</td>
</tr>
<tr>
<td>Oppositional Defiant Disorder</td>
<td>Does your child often lose his or her temper, argue or behave defiantly with adults, or become resentful or vindictive when things do not go his or her way?</td>
<td>Context dependent emotional and behavioral reactivity</td>
<td>Child Behavior Check List (CBCL)</td>
</tr>
<tr>
<td>Conduct Disorder</td>
<td>Does your child have a history of being aggression to people or animals, destroying property, stealing, or staying out all night?</td>
<td>General disregard for and violation of the rights of others</td>
<td>CBCL</td>
</tr>
<tr>
<td>Trauma and PTSD</td>
<td>Does your child have a history of severe neglect, maltreatment, trauma or prolonged exposure to psychosocial adversity?</td>
<td>Recurring traumatic memories, hyperarousal, and avoidance behaviors</td>
<td>UCLA PTSD Index Trauma Screen, PCL-C CATS</td>
</tr>
<tr>
<td>Autism Spectrum Disorders</td>
<td>Does your child have poor social skills and a narrow range of interests?</td>
<td>Impaired social communication along with restricted interests and repetitive behaviors</td>
<td>Social Communication Questionnaire (SCQ)</td>
</tr>
</tbody>
</table>

Other disorders to consider: Intellectual Disability, Traumatic Brain Injury, Learning Disorders, Anxiety, Bipolar II
Comorbidities: ADHD and Completed Suicide in School-Aged Children. Is There a Connection?

Suicide in Elementary School-Aged Children and Early Adolescents

Arielle H. Sheftall, PhD,1,2 Lindsey Asti, MPH,1,2 Lisa M. Horowitz, PhD, MPH,1,2 Adrienne Felts, MA, PCC,1,2 Cynthia A. Fontanella, PhD,1 John V. Campo, MD,1 Jeffrey A. Bridge, PhD1,3

BACKGROUND AND OBJECTIVES: Suicide in elementary school-aged children is not well studied, despite a recent increase in the suicide rate among US black children. The objectives of this study were to describe characteristics and precipitating circumstances of suicide in elementary school-aged children relative to early adolescent decedents and identify potential within-group racial differences.

METHODS: We analyzed National Violent Death Reporting System (NVDRS) surveillance data capturing suicide deaths from 2003 to 2012 for 17 US states. Participants included all suicide decedents aged 5 to 14 years (N = 693). Age group comparisons (5–11 years and 12–14 years) were conducted by using the \( \chi^2 \) test or Fisher’s exact test, as appropriate.

RESULTS: Compared with early adolescents who died by suicide, children who died by suicide were more commonly male, black, died by hanging/strangulation/suffocation, and died at home. Children who died by suicide more often experienced relationship problems with family members/friends (60.3% vs 46.0%; \( P = .02 \)) and less often experienced boyfriend/girlfriend problems (0% vs 16.0%; \( P < .001 \)) or left a suicide note (7.7% vs 30.2%; \( P < .001 \)). Among suicide decedents with known mental health problems (n = 210), childhood decedents more often experienced attention-deficit disorder with or without hyperactivity (59.3% vs 29.0%; \( P = .002 \)) and less often experienced depression/dysthymia (33.3% vs 65.6%; \( P = .001 \)) compared with early adolescent decedents.

CONCLUSIONS: These findings raise questions about impulsive responding to psychosocial adversity in younger suicide decedents, and they suggest a need for both common and developmentally-specific suicide prevention strategies during the elementary school-aged and early adolescent years. Further research should investigate factors associated with the recent increase in suicide rates among black children.
Comorbidities: ADHD and Substance Abuse

- ADHD diagnosis increases the risk of substance use and nicotine dependence.
  - Early stimulant treatment may reduce or delay the onset of substance use disorder.
- Recent follow up data from the MTA revealed no harm or benefit from medication treatment in regard to rates of adolescent substance abuse.

Summary of Key Points in Screening and Diagnosing ADHD

- ADHD is both underdiagnosed and over-diagnosed in different populations and should be routinely screened for during regular office visits, especially if there are concerns for poor concentration and functional achievement below expected potential.

- Rating scales are best used as screening tools and to measure treatment response.

- Often exists with other co-morbid illnesses but symptoms may also represent a ADHD “mimic;” secondary gain may play a part in diagnostic picture.

- Determining level of functional impairment is critical.
Multimodal Treatment Considerations for Youth and Adults

Multimodal treatment, psychoeducation, psychosocial treatments, medication interventions (e.g., stimulants; non-stimulants), other treatment considerations
Psychoeducation on ADHD should include discussion of:

• Nature of disorder (causes, prevalence, clinical course)
• Establishing goals of treatment
• Importance of assessing level of impairment and response to treatment in terms of lowering impairment
• Safety issues (escalating doses, cardiac concerns, etc.)
• Importance of having a multimodal approach to treatment
• Role of behavioral interventions (e.g., parent management training in for children, cBT for adults)
• Importance of lifestyle modifications (e.g., sleep, exercise)
• Medication selection and monitoring of response
• Possible need for referrals (e.g., neuropsychological testing, specialty providers, vocational services and/or disability)
## Psychoeducation Components

### Psychoeducation

<table>
<thead>
<tr>
<th>Discover</th>
<th>Demystify</th>
<th>Instill Hope</th>
</tr>
</thead>
<tbody>
<tr>
<td>- What does the individual/family know about ADHD?</td>
<td>- Myths about ADHD</td>
<td>- Evidence-based treatments and interventions do exist and will promote a positive outcome</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Educate</th>
<th>Empathize</th>
<th>Encourage</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Importance of combining pharmacological and psychosocial interventions</td>
<td>- Acknowledge feelings of discouragement, grief, and frustration.</td>
<td>- A strength-based approach</td>
</tr>
<tr>
<td>- Risks and benefits</td>
<td></td>
<td>- Make more positive than negative comments</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Discourage criticisms</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recognize</th>
<th>Be Sensitive</th>
<th>Motivate</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Appropriate behavior, whether observed or reported</td>
<td>- Ethnic, cultural and gender issues may shape the perception and beliefs about ADHD and its treatment</td>
<td>- Nurture strengths and talents</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Encourage skills</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Promote</th>
<th>Humour</th>
<th>Give Resources</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Regular exercise</td>
<td>Humour can defuse awkward, tense situations and avoid or reduce conflict</td>
<td>- Websites</td>
</tr>
<tr>
<td>- Consistent sleep hygiene</td>
<td></td>
<td>- Local community resources</td>
</tr>
<tr>
<td>- Healthy nutrition routine</td>
<td></td>
<td>- Book lists</td>
</tr>
</tbody>
</table>

*CADDRA Guide to ADHD Psychoeducation Oct 2016; http://www.caddra.ca/pdfs/Psychosocial_October2016.pdf*
Examples of psychosocial interventions

Useful Psychosocial Interventions

**Behavioural**
- Social skills training
- Organization skills
- Anger management
- Parent training
- ADHD/ADD coaching

**Educational**
- Academic organizational and study skills
- Specific academic remediation
- Accommodations

**Lifestyle**
- Proper nutrition
- Good sleep hygiene
- Regular exercise
- Extracurricular activities
- Stress managements
- Screen time

**Psychoeducation**
- Regarding disorder and medication
- For patient and significant other/spouse

---

Evidence for Behavioral Interventions in Youth Depends on Age

**Behavioral Parent Training**
- ↓ oppositionality, aggression,
- ↓ negative parenting, family conflict,
- ↑ positive parenting, parent self-efficacy

**Behavioral Peer Interventions**
- ↑ prosocial behavior, peer acceptance, on-task time
- ↓ peer rejection, aggression

**Organization Skills Training**

**Behavioral Parent Training**

Preschool (2-5)

School Age (6-12)

Adolescence (13-18)

*Figure 1.* Functional Outcomes of “Well Established” Psychosocial Treatments for ADHD Throughout Development.

*Treatments to be prioritized for this developmental period*
cBT for ADHD (for teens and older)

cBT for ADHD focuses on helping to lay out specific functional treatment goals to help improve organizational, time-management, and problem-solving skills by:

- Chunking large tasks into smaller steps
- Introducing a daily planner and emphasizing use of one planner or notebook only
- Manage to-dos using assistive devices, such as mobile phones
- Starting tasks well in advance of their deadline
- Reducing distraction (i.e. clutter-free desktop, windowless and quiet space to work, etc.)
- List-making and task prioritization
- Self-monitoring with regular completion of behavioral check-lists and logging
- Target behaviors as they come up in session, such as arriving late for appointments or losing homework
Pharmacological Treatment—Stimulants

Treatment Hierarchy, Stimulant Characteristics, Monitoring Adherence and Treatment Response, and Stimulant Side Effects

Seattle Children's®
Hospital • Research • Foundation
Medication Treatments: Take Your Pick

Stimulants

Methylphenidate

- Short Acting
  - Ritalin
  - Methylin
  - Focalin

- Intermediate
  - Ritalin SR

- Long Acting
  - Concerta
  - Metadate CD
  - Ritalin LA
  - Focalin XR
  - Daytrana
  - Quillivant
  - Aptensio
  - Jomay

Amphetamine

- Short Acting
  - Zenedi
  - Dextrostat
  - Dexedrine tabs

- Intermediate
  - Dexedrine Spansule

- Long Acting
  - Adderall
  - Vyvanse
  - Evekeo
  - ProCentra

Non-Stimulants

- Approved
  - Strattera
  - Intuniv
  - Kapvay

- Not Approved
  - Tricyclic Antidepressants
  - Wellbutrin, Zyban
  - Effexor
  - Clonidine
  - guanfacine

†††††††††††

- dextmethylphenidate
- dextroamphetamine sulfate
- mixed amphetamine salts
- atomoxetine
- guanfacine
- clonidine
- tricyclic antidepressants
- modafinil
- bupropion
- venlafaxine
How do stimulants work?

Stimulants: First-Line Agents

Methylphenidate and amphetamine block reuptake of norepinephrine and dopamine

Amphetamine also promotes release of norepinephrine and dopamine
The Potential Power of Psychopharmacology: Relative Efficacy of ADHD Therapies in terms of Effect Size

Effect size: a statistical measurement of the magnitude of effect of a treatment. Large = 0.8 (Swanson et al, 2001)

- Nonstimulant
- Stimulant
- Long-acting Stimulant

Large (0.8)  Moderate (0.5)  Small (0.2)

Faraone et al. Poster presented at APA; May 17–22, 2003; San Francisco, CA.
Stimulants

• Can start with either a methylphenidate or an amphetamine product
  • Amphetamines FDA approved $\geq \text{3 yo}$
  • Methylphenidates FDA approved $\geq \text{6 yo}$
• Similar efficacy
• Side effects may be more pronounced with amphetamine products, especially in younger children
• Push a stimulant dose before moving on to next trial.

Treatment Hierarchy

- If IR is not tolerated or ineffective, try XR and vice versa.
- If first stimulant class is unsuccessful, try the other class.
- If stimulants are ineffective, revisit diagnosis before proceeding to non-stimulants.
- Use a single medication when possible.
- Consider adding alpha agonists if response is suboptimal but increasing stimulant not possible due to side effects.
- Adding atomoxetine to stimulant generally not advised but may be useful in certain cases.
Responses to AMP and MPH vary from individual to individual

Patients May Respond Differently to Amphetamines or Methylphenidates

- CADDRA recommendations:\(^1\)
  - Patients who do not respond to one stimulant may respond to another
    - Eg, methylphenidate vs. amphetamine
    - Patients who do not tolerate one medication may tolerate another

  **Patients respond differently to each molecule (n=174)^2**

![Bar Chart]

**AMP = amphetamine; MPH = methylphenidate**

# Immediate Release Stimulants

<table>
<thead>
<tr>
<th>Name</th>
<th>Duration of Action</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylphenidate (Ritalin, Methylin)</td>
<td>4-6 h</td>
<td></td>
</tr>
<tr>
<td>D-methylphenidate (Focalin)</td>
<td>4-6 h</td>
<td>*2x potency of methylphenidate</td>
</tr>
<tr>
<td>Mixed amphetamine salts (Adderall)</td>
<td>4-6 h</td>
<td></td>
</tr>
<tr>
<td>D-amphetamine (Zenzedi, ProCentra)</td>
<td>4-6 h</td>
<td>Liquid 5 mg/5 ml Approved ages 3-5</td>
</tr>
<tr>
<td>Methamphetamine Desoxyn</td>
<td>4-6 h</td>
<td>FDA-indicated for ADHD and obesity</td>
</tr>
<tr>
<td>Amphetamine (Evekeo)</td>
<td>4-6 h</td>
<td>Approved ages 3-5 FDA-indicated for ADHD, obesity, and narcolepsy</td>
</tr>
<tr>
<td>Name</td>
<td>Mode of Delivery</td>
<td>Duration of Action</td>
</tr>
<tr>
<td>------------------------------------------</td>
<td>-----------------------------------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>Ritalin SR, Metadate ER, Methylin ER</td>
<td>Gradual release</td>
<td>4-8 h</td>
</tr>
<tr>
<td>Metadate CD</td>
<td>30% IR, 70% 3 h later</td>
<td>7-9 h</td>
</tr>
<tr>
<td>Ritalin LA</td>
<td>50% IR, 50% 4 h later</td>
<td>7-9 h</td>
</tr>
<tr>
<td>Quillivant XR</td>
<td>20% IR, 80% gradual release</td>
<td>8-10 h</td>
</tr>
<tr>
<td>Focalin XR</td>
<td>50% IR, 50% 4 h later</td>
<td>Up to 12 h</td>
</tr>
<tr>
<td>Concerta</td>
<td>22% IR, pump</td>
<td>Up to 12 h</td>
</tr>
<tr>
<td>Daytrana patch</td>
<td>Gradual release</td>
<td>3-5 h after removal</td>
</tr>
<tr>
<td>Adderall XR</td>
<td>50% IR, 50% 4 h later</td>
<td>8-12 h</td>
</tr>
<tr>
<td>Dexedrine spansule (dextroamphetamine)</td>
<td>50% IR, 50% gradual</td>
<td>10 h</td>
</tr>
<tr>
<td>Vyvanse</td>
<td>Activated in GI tract</td>
<td>10 h</td>
</tr>
<tr>
<td>Aptensio XR (methylphendiate)</td>
<td>40% IR, 60% ER (may be sprinkled)</td>
<td>12 h</td>
</tr>
</tbody>
</table>
Ballpark dosing guidelines for Youth

- Multimodal Treatment of Attention-Deficit/Hyperactivity Disorder Study (MTA)
  - About 1 mg/kg optimal
  - Those in combination treatment ended up on lower doses of medication than medication treatment alone group.
    - Medication management 32.3 mg/day
    - Combined care 28.7 mg/day

- Preschool ADHD Treatment Study (PATS)
  - Outcomes: Stimulants were effective, but
    - lower end doses (mean optimal methylphenidate dose 14.2 mg/day or 0.7 mg/kg)
    - lower effect sizes
    - higher rates of side effects (crabbiness, proneness to crying, irritability)
Monitoring Adherence, Side Effects, and Treatment Response
# Adverse Effects of ADHD Medications

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>MPH(^1\text{-}^5)</th>
<th>Amph.(^5\text{-}^7)</th>
<th>ATX(^8\text{-}^11)</th>
<th>Alpha-2 Agonists(^12\text{-}^15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appetite/anorexia</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>-</td>
<td>-</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Irritability</td>
<td>++</td>
<td>++</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Somnolence/asthenia</td>
<td>-</td>
<td>-</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Sleep problems/Insomnia</td>
<td>++</td>
<td>++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Emotional lability</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Depressed mood</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Tics</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Light-headed/Dizzy</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Increased heart rate</td>
<td>++</td>
<td>++</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td>Increased blood pressure</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>-</td>
</tr>
</tbody>
</table>

What are the risks of stimulant medication misuse?

**ADHD Stimulant Medication Diversion**

- Stimulant medication misuse in the general population
  - 5-9% in school-age children (all grades)
  - 5-35% in college-age students
  - 8% in adults (aged 18-49)
  - Many obtained the stimulants through friends or family

- A large proportion of ADHD patients divert their stimulant medication from their prescriptions
  - About 54% of college students prescribed stimulant medication are approached to divert their medication
  - About 28% of college students and 16% of adults with ADHD give or sell their medication to someone else

- The most common reason among college students, was the desire to enhance academic functioning (to study more effectively)\(^4,5\)
  - Studies suggest that students who misuse stimulants have poorer academic outcomes compared to nonusers\(^4\)

---

Pharmacological Treatment—Non-Stimulants

Atomoxetine, Alpha-agonists, Bupropion, and Alternative and Complementary Treatments
Atomoxetine

• Brand name: Strattera
• Noradrenergic reuptake inhibitor
• Once daily or twice daily dosing
• Start at 0.5 mg/kg/day for at least 3 days; increase to 1.2 mg/kg/day (unless on 2D6 inhibitor, such as fluoxetine).
• Maximum 100 mg or 1.4 mg/kg (whichever is less).
• Metabolized by P450 2D6 pathway
• Approved > or = 6 yo

**Atomoxetine**

- Can be helpful to anxiety

- Can take up to 6 weeks for benefit
  - Counsel family on delayed effect compared to stimulants.

- Effect size 0.6 (similar to guanfacine)
  - For comparison, effect size of stimulants approximately 0.9
  - For reference, effect size 0.2 is mild, 0.6 is moderate, and 0.8 is high.

**Fig. 1** Temporal course of changes in the Attention-Deficit/Hyperactivity Disorder Rating Scale–IV–Parent Version: Investigator Administered and Scored (ADHD-RS total score). Unlike moderate/nonresponders (filled diamonds), much improved responders (filled squares) experienced sharp decreases (i.e., improvements) in the ADHD-RS total score within the first 1 to 4 weeks, with continued divergence at later time points. *p < .001 at each time point across response groups by week.

Alpha agonists
(Only ER is FDA approved)

• May be more effective for hyperactivity than inattention
• Clonidine more soporific; guanfacine may be better for inattention
• Soporific effect may wane after 2-3 weeks
• May not see full benefit for 4-6 weeks
• Sedation, dizziness, hypotension, bradycardia
• Review personal and family cardiac history
• Review risk of rebound hypertension
Bupropion (Off Label)

• Brand name: Wellbutrin
• Combined dopaminergic/noradrenergic mechanism of action
• Consider when primary treatments have failed or in patients with co-occurring mood disorders, substance abuse, or smoking.

Non-pharmacological interventions for cognitive difficulties in ADHD: A systematic review and meta-analysis

• Evidence synthesizing the effects of ADHD interventions on cognitive difficulties is limited

• The neuropsychological effects of non-pharm interventions for ADHD were examined across 18 studies (1980-2017)

• Four categories of intervention:
  - **Neurofeedback** (visualization of brain activity → teach pts to increase attention/impulse control)
  - **Cognitive-behavioral therapy** (skills = organization, planning, and time management skills)
  - **Cognitive training** (employing adaptive schedules hypothesized to strengthen working memory)
  - **Aerobic physical exercise**

• Only included interventions w/ cognitive tasks as outcome measures (no parent training or classroom interventions)
Results

- Physical exercise = highest effect size (Morris d=0.93)
- Effect sizes on 5 categories: attention, inhibition, flexibility, and working memory.
- Analyses showed a homogenous, medium to large, effect size of improvement across interventions (inhibition largest on average 0.685)
Alternative treatments

• Omega-3s: some evidence for benefit based upon meta-analyses (effect size: 0.31)

• Dietary: Elimination of food dye may provide small benefit in sensitive patients
Monarch external Trigeminal Nerve Stimulation (eTNS) System

• Indicated for children aged 7 to 12 years who aren’t already taking prescription medication for ADHD. Available by prescription only
• Intended for home use during sleep under a caregiver’s supervision
• Delivers mild stimulation to branches of the trigeminal nerve
• Projects directly or indirectly to specific brain regions involved in ADHD
• In blinded trial after 4 weeks, children receiving the treatment had significantly improved symptoms and functioning compared to children receiving a sham treatment
Why are optimal treatment outcomes difficult to achieve in ADHD?

• Comorbidities: ODD, anxiety, learning disorders, etc.
• Mimics: OSA, anxiety, in utero exposure, borderline intellectual functioning
• Overlapping diagnostic criteria
• Problems with treatment adherence and variability in ADHD care
• Over-reliance on medication only treatment and uncertainty about the sequencing of treatment modalities
• Underestimating the difficulty of achieving long-term success in treatment
• Symptom and functional changes over time
• Our changing environments
• Over-reliance on symptom scales
• Drop out due to care burden and side effects
Some questions to ask if ADHD symptoms are refractory to treatment?

- Is the diagnosis accurate? Consider taking another history, contacting additional informants and, in general, collecting more data.

- Is there an important comorbidity that’s been missed? A missed comorbidity could lead to suboptimum response to ADHD medication treatment. Adequate treatment of the comorbidity may lead to a better medication response for the ADHD symptoms/impaired functioning.

- Are non-pharmacological treatments being utilized? Organizational skills classes, CBT (in older teens and adults), coaching, physical exercise, mindfulness training, etc. can all help decrease the need for dose escalation.
Some questions to ask if ADHD symptoms are refractory to treatment? (continued)

- Has a tolerance to the current medication developed? Consider switching classes (e.g., switch from MPH to an amphetamine product).
- Is the medication the patient is currently taking at the maximum recommended dose? If not, dose optimization may be needed, even possibly beyond recommended maximum-daily doses.
- Is augmentation of a stimulant with a non-stimulant ADHD medicine (e.g., guanfacine ER) warranted?
- For stimulants, is there possibility that the medication is being diverted or misused?
- Is the patient adherent with the medication and receiving adequate follow-up and outcomes monitoring?
Late-onset ADHD: Fact or Fiction?

Maggie Sibley, Ph.D.
Associate Professor of Psychiatry & Behavioral Sciences
University of Washington
Center for Child Health, Behavior, & Development
Seattle Children’s Research Institute
Should We Be Thinking of Adult ADHD By Comparing It to Type-2 Diabetes?

Is Adult ADHD a Childhood-Onset Neurodevelopmental Disorder? Evidence From a Four-Decade Longitudinal Cohort Study

Terrie E. Moffitt, Ph.D., Renate Houts, Ph.D., Philip Asherson, M.D., Daniel W. Belsky, Ph.D., David L. Corcoran, Ph.D., Maggie Hammerle, B.A., HonaLee Harrington, B.A., Sean Hogan, M.S.W., Madeline H. Meier, Ph.D., Guilherme V. Polanczyk, M.D., Richie Poulton, Ph.D., Sandhya Ramrakha, Ph.D., Karen Sugden, Ph.D., Benjamin Williams, B.A., Luis Augusto Rohde, M.D., Avshatam Caspi, Ph.D.

Objective: Despite a prevailing assumption that adult ADHD is a childhood-onset neurodevelopmental disorder, no prospective longitudinal study has described the childhoods of the adult ADHD population. The authors report follow-back analyses of ADHD cases diagnosed in adulthood, alongside follow-forward analyses of ADHD cases diagnosed in childhood, in one cohort.

Method: Participants belonged to a representative birth cohort of 1,037 individuals born in Dunedin, New Zealand, in 1972 and 1973 and followed to age 38, with 95% retention. Symptoms of ADHD, associated clinical features, comorbid disorders, neuro-psychological deficits, genome-wide association study-derived polygenic risk, and life impairment indicators were assessed. Data sources were participants, parents, teachers, informants, neuropsychological test results, and administrative records. Adult ADHD diagnoses used DSM-5 criteria, apart from onset age and cross-setting corroboration, which were study outcome measures.

Results: As expected, childhood ADHD had a prevalence of 6% (predominantly male) and was associated with childhood comorbid disorders, neurocognitive deficits, polygenic risk, and residual adult life impairment. Also as expected, adult ADHD had a prevalence of 3% (gender balanced) and was associated with adult substance dependence, adult life impairment, and treatment contact. Unexpectedly, the childhood ADHD and adult ADHD groups comprised virtually nonoverlapping sets; 90% of adult ADHD cases lacked a history of childhood ADHD. Also unexpectedly, the adult ADHD group did not show tested neuropsychological deficits in childhood or adulthood, nor did they show polygenic risk for childhood ADHD.

Conclusions: The findings raise the possibility that adults presenting with the ADHD symptom picture may not have a childhood-onset neurodevelopmental disorder. If this finding is replicated, then the disorder’s place in the classification system must be reconsidered, and research must investigate the etiology of adult ADHD.

Cohort studies: Dunedin Study

- New Zealand Birth Cohort (N=1037)
- Followed from birth to age 38
- At age 38, 3% of sample had adult-onset ADHD—90% of adults with ADHD showed onset after age 15.
- Only 5% of children with ADHD showed persistence of ADHD at age 38

Moffitt et al., 2015
Potential study flaws:
Only a snapshot of childhood

• Some studies considered only one assessment in childhood to determine ADHD status
• Symptoms may have occurred outside of that assessment
Potential study flaws: Long follow-up periods

- Some studies had a decade or more between assessments
- Made it unclear when symptom onset occurred
Potential study flaws: Failure to rule out comorbidities or substance use

- Studies did not rule out ADHD diagnosis when symptoms were caused by non-ADHD sources:
  - Cognitive effects of substance use
  - Anxiety
  - Depression
  - Illness
  - Brain injury
  - Drug side effects
  - Poor nutrition, sleep hygiene, or exercise habits
  - Stress
  - Deprivation
  - Trauma
  - Mood Disorders
  - Cognitive overload compared to task demands
Late-Onset ADHD Reconsidered With Comprehensive Repeated Assessments Between Ages 10 and 25

Margaret H. Sibley, Ph.D., Luis A. Rohde, M.D., James M. Swanson, Ph.D., Lily T. Hechtman, M.D., Brooke S.G. Molina, Ph.D., John T. Mitchell, Ph.D., L. Eugene Arnold, M.D., Arthur Caye, Traci M. Kennedy, Ph.D., Arunima Roy, Ph.D., Annamarie Stehli, M.P.H., for the Multimodal Treatment Study of Children with ADHD (MTA) Cooperative Group
Sample

- Local Normative Comparison Group (LNCG) of the Multimodal Treatment of ADHD (MTA) Study
- Subsample of children who did not have ADHD at baseline in childhood (N=239)
- Average age at BL: $M=9.89, SD=1.22$
- Drawn from classrooms of ADHD participants
- Matched for sex with ADHD group
- Average age at final follow up: $M=24.40, SD=1.36$
Goal of Analyses

- To assess the extent to which late-onset ADHD cases remain valid after accounting for methodological limitations of birth cohort studies
### Results

<table>
<thead>
<tr>
<th></th>
<th>Adolescent-Onset</th>
<th>Adult-Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Meets DSM-5 ADHD symptom criteria</td>
<td>40.2%</td>
<td>96</td>
</tr>
<tr>
<td>+ clinically significant impairment</td>
<td>13.4%</td>
<td>32</td>
</tr>
<tr>
<td>+ late-onset</td>
<td>8.8%</td>
<td>21</td>
</tr>
<tr>
<td>+ not due to substance abuse</td>
<td>7.5%</td>
<td>18</td>
</tr>
<tr>
<td>+ not attributable to other mental disorder</td>
<td>5.4%</td>
<td>13</td>
</tr>
<tr>
<td>+ cross-situational symptoms</td>
<td>2.5%</td>
<td>6</td>
</tr>
<tr>
<td>Absence of subthreshold childhood symptoms (less than 3 childhood symptoms of IN and H/I)</td>
<td>1.3%</td>
<td>3</td>
</tr>
</tbody>
</table>

**Note.** Symptom criteria were counted using an “or” rule that considered information from all available informants (e.g., parent, self, teacher). Designated period was either adolescence or adulthood. Cross-situationality was inferred from multiple raters and consulting interview questions about context as needed. \(^a\)One case was first assessed at age 12, at which point there were not subthreshold symptoms.
Adolescent-Limited Case Example
Adolescent-Onset/Persistent Case Example
Conclusions from Sibley et al.:

- 95% of 239 cases that initially screened positive based on symptom count were excluded from late-onset characterization upon careful review
- Important to track symptoms and functioning over an extended period of time
- 53% (adolescents) and 83% (adults) of individuals who met all symptom, impairment, and onset criteria were excluded because symptoms were better explained by other sources
- Late-onset ADHD prevalence may be overestimated in birth-cohort studies
- Late-onset cases tended to be adolescent-limited or complex (i.e., possessing several previous diagnoses)
- Look for evidence that the individual may have had evidence of some (3 or more subthreshold symptoms) in childhood which could support a late-identified situation, especially if cognitive capacity (i.e., high IQ) enabled the individual to be able to compensate with functional demands when younger
Conclusions from Sibley et al.:

- Clinicians should obtain thorough assessment of past and present functioning when assessing first-time late-onset ADHD diagnoses; it is important to rule out better explanations for presentation (e.g., mimics and/or comorbid conditions).

- Without clear exclusionary methods, late-onset ADHD may become a catchall diagnosis for executive dysfunction from any source.

- However, there is still a debate whether there needs to a differentiation from narrow phenotype (e.g., childhood onset) vs. broad phenotype (e.g., trauma, TBI) ADHD if treatment with stimulants can improve functioning.

- Important to track symptoms and functioning over an extended period of time.

- Field needs to decide what can count as an acceptable form of ADHD?
  - Co-morbidity
  - High demand, achievement-oriented lifestyle with multiple competing priorities in a fast-paced world driven to distraction
  - Negative life experiences and trauma
  - Drug use
  - Temporary changes due to adolescent brain development
Any Questions?