AAFP Chapter Lecture Series: ADHD in Females

Presented By

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This AAFP sponsored CME course will include discussion of unapproved or investigational uses of products or devices.

• Various non-stimulant medications including antidepressants.
• Combinations of stimulants with non-stimulants.
• Herbal and OTC products.
• Non-medication interventions.

Program Disclaimer
The views and opinions expressed herein are those of the faculty/author/speaker and do not necessarily represent those of the American Academy of Family Physicians. Any recommendation made by the faculty/author/speaker must be weighed against the physician’s own clinical judgment, based on but not limited to such factors as the patient’s condition, benefits versus risks of suggested treatments, and evidence-based practice guidelines or practice recommendations supported by evidence, pharmaceutical compendia and other authorities.

Content Development
The AAFP would like to thank Scott Moser, MD, FAAFP for creating the content for this series.
Please select the most appropriate answer to each of the following questions by filling in the bubble next to the corresponding answer. Please be sure to fill in the bubble of your response completely.

**Pre-Assessment Questions:**

<table>
<thead>
<tr>
<th>Question # 1</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Question # 2</td>
<td>A</td>
<td>B</td>
<td>C</td>
<td>D</td>
<td>E</td>
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<tr>
<td>Question # 3</td>
<td>A</td>
<td>B</td>
<td>C</td>
<td>D</td>
<td>E</td>
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</tbody>
</table>

**Post-Assessment Questions:**

*NOTE: The orders of the questions and answers have been scrambled and are not in the same order as the pre-assessment questions.*

<table>
<thead>
<tr>
<th>Question # 1</th>
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<td>B</td>
<td>C</td>
<td>D</td>
<td>E</td>
</tr>
</tbody>
</table>
Overall, I would rate Kimberly Krohn, MD, MPH, FAAFP as excellent.

The content presented in this session covered the stated learning objectives.

The session was appropriately paced to sufficiently cover the amount of material presented.

The content of this session was of an appropriate level.

The course material content adequately supported the presentation.

Please provide any additional comments related to the faculty/session.

Based on the session content, my next step will be to (check all that apply):

1. Pursue additional education/reading
2. Discuss content with colleagues to obtain a consensus about a practice change
3. Continue current practice
4. Implement a change in practice from what I have learned in this session

If you intend to make a practice-based change(s) in patient care, please describe the change(s):
Objectives

- List the DSM-5 criteria for diagnosing ADHD with emphasis on female patients.
- Describe new developments in understanding etiology of ADHD and implications for care specific to females.
- Describe best evidence interventions and prognosis for ADHD in girls and women.

SORT

(Strength-of-Recommendation Taxonomy)

A. Consistent, good-quality, patient-oriented evidence
B. Inconsistent, limited-quality, patient-oriented evidence
C. Consensus, disease-oriented evidence, usual practice, expert opinion, or case series

Case: Stacy

CC: 27 yo woman who presents wondering if she has ADHD. She took an online inventory that suggested she has it after she noted similarities with her 7yo son who was diagnosed several months ago and has been doing much better since he started methylphenidate.

Stacy’s HPI

No “special ed” but struggled in school, especially once she started middle school. Dropped out of high school. Was often in trouble due to being late for class or talking. Remembers coming home in tears from being called “Spacy Stacy” by the other kids. Prescribed fluoxetine (Prozac®) for depression but quit taking it because she didn’t think it did anything for her.

Stacy’s Additional History

PMH: no meds or medical problems
FSH: Single mom of one child. Difficulty maintaining entry-level jobs; reprimanded at current job due to tardiness when she lost her car keys. Smokes 1 ppd. “ Recovering alcoholic and doper, sober for 4 yrs.”
ROS: Depression screen showed sleep latency difficulty and erratic eating, but otherwise negative.

Stacy’s Physical Exam

Vital Signs: normal
General: Overweight, multiple tattoos, talkative, occasionally interruptive, good eye contact
Other exam normal: specifically no thyroid abnormality or heart murmur
Stacy’s Lab/Assessment

Urine drug screen negative

Does Stacy have ADHD?

ADHD Presentation Specifiers in DSM-5 (not “types”)

- Attention-Deficit/Hyperactivity Disorder, Combined Presentation
- Attention-Deficit/Hyperactivity Disorder, Predominantly Inattentive Presentation
- Attention-Deficit/Hyperactivity Disorder, Predominantly Hyperactive-Impulsive Presentation
- (Other Specified ADHD; Unspecified ADHD)

ADHD is a Neurodevelopmental Disorder

- Strong inheritance evidence (A)
- Growing chromosomal/DNA evidence (B)
- Strong neurochemical evidence related to dopamine and norepinephrine pathways (A)
- Growing neuroanatomic evidence: prefrontal cortex and its connections (B)
- Growing environmental evidence (A,B)

Etiology: ADHD is a Neurodevelopmental Disorder

Heritability Comparisons

<table>
<thead>
<tr>
<th>Condition</th>
<th>Monozygotic Twin Concordance (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood type</td>
<td>100</td>
</tr>
<tr>
<td>Height</td>
<td>93</td>
</tr>
<tr>
<td>Weight</td>
<td>92</td>
</tr>
<tr>
<td>Eye color</td>
<td>80</td>
</tr>
<tr>
<td>Childhood asthma</td>
<td>65</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>60</td>
</tr>
<tr>
<td>Autism</td>
<td>50</td>
</tr>
<tr>
<td>Diabetes, type 2</td>
<td>50</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>46</td>
</tr>
</tbody>
</table>

Environmental Factors Associated With ADHD

- Maternal smoking
- Fetal exposure to alcohol
- Pregnancy and delivery complications
- Psychosocial adversity
- Exposure to environmental toxins such as PCBs or pesticides
- (NOT TV viewing)
- SORT: (A, B)

Syndrome Features

- Inattention
- Hyperactivity/Impulsivity
- Onset before age 12 (7 in DSM-IV)
- Impairment in at least 2 settings (school, work, home)
- Significantly impaired function (specify mild, moderate, severe)
- Not exclusively due to/better explained by another psychiatric disorder

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Inattention

6 of these 9 (5 of 9 for ≥ 17 yo): “Often…”
- Fails to give close attention to details
- Difficulty sustaining attention
- Doesn’t seem to listen
- Doesn’t follow through
- Difficulty organizing
- Avoids mental effort
- Loses things
- Easily distracted
- Forgetful in daily activities

Hyperactivity/Impulsivity

6 of these 9 (5 of 9 for ≥ 17 yo): “Often…”
- Fidgets
- Leaves seat
- Runs about or climbs excessively
- Difficulty playing quietly
- “On the go,” “Driven by a motor”
- Talks excessively
- Blurs answers before end of questions
- Difficulty awaiting turn/waiting in line
- Interrupts or intrudes on others

Prevalence

- 5% of school-age children in most cultures (2.5% of adults) per DSM-5 (1.7-17.8% reported)
- Males:females = 2:1 (true vs. false prevalence difference)

Evidence-Based (EB) Recommendation #1 (Diagnosis)

- Evaluate children/adolescents suspected of having ADHD based on (DSM-5) diagnostic criteria using consistent and appropriate diagnostic tools.
SORT: (A,C)
EB Recommendation #2 (Diagnosis)

Screen all patients for other primary conditions or comorbidities and appropriately refer to subspecialty consultation for further evaluation. 
SORT: (C)

Comorbid Conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Prevalence in ADHD</th>
<th>Prevalence in General Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conduct disorder</td>
<td>35-45%</td>
<td>3-4%</td>
</tr>
<tr>
<td>Oppositional defiant disorder</td>
<td>45-55%</td>
<td>4-5%</td>
</tr>
<tr>
<td>Depressive disorders</td>
<td>25-30%</td>
<td>4-5%</td>
</tr>
<tr>
<td>Bipolar I disorder</td>
<td>6-10%</td>
<td>1%</td>
</tr>
<tr>
<td>Anxiety disorder</td>
<td>25-35%</td>
<td>8-12%</td>
</tr>
<tr>
<td>Learning disorder</td>
<td>12-30%</td>
<td>5-7%</td>
</tr>
<tr>
<td>Tourette's disorder</td>
<td>0.1%</td>
<td>0.05-.1%</td>
</tr>
</tbody>
</table>

Differential Diagnosis

- Cognitive Problem: intellectual disability, learning disability*, autistic disorders
- Medical Problem: allergies, sleep disorders*, lead toxicity, fragile X**
- Neurological Problem: seizure disorder, Tourette’s
- Psychological Problem: depression*, bipolar*, conduct disorder, drug abuse, adjustment disorder
- Family/Social Problem: chaotic or abusive environment*, parental substance abuse

Evaluation: History Sources

- Child/Patient
- All Parents (Spouse)
- School Teachers, Counselor, Nurse
- Coaches, Scout Leaders, Coworkers, Others

Evaluation: History Content

- Detailed medical, developmental, neurologic, family, sleep, and school history
- Specific examples of problem behaviors
- School evaluations, report cards, achievement tests, class work

Evaluation: Physical Exam

- General Medical
- Detailed Neurologic
- Detailed Developmental for Age (verbal and math skills, backward alphabet)
- Height, weight, blood pressure before starting meds
Evaluation: Lab Tests

- Hearing and vision screen
- Consider CBC or ferritin
- Consider TSH
- Consider lead level
- EEG if H&P suspicious for seizure
- EKG before stimulants or tricyclics
- Drug screen in teens and adults
- Pregnancy test

Evaluation: Standardized Questionnaires

- Conners’ Rating Scales-Revised
  - Teacher and Parent versions
  - Short and Long versions
- Barkley’s Home Situations and School Situations Questionnaires
- ACTers, NICHQ Vanderbilt Assessment Scale, Achenbach, others

Stacy’s Evaluation

- Barkley adult symptom checklists for childhood and current symptoms to Stacy, her mom and aunt
- Barkley adult checklist for current symptoms to coworker/friend and to aunt
- Lead, thyroid, iron, vitamin D screens (?)
- EKG (?)
- Continuous Performance Testing in office (?)

Stacy’s Assessment

- ADHD, inattentive presentation, adult, moderate
- Smoking
- History of multi-drug abuse, not active

How would you treat her?

EB Recommendation #3 (Treatment)

Establish appropriate use of medication in both initial and ongoing management of patients with ADHD.

SORT: (A,C)

EB Recommendation #4 (Treatment)

ADHD is rarely a singular diagnosis. Multimodal intervention is commonly needed for other concomitant conditions and comorbidities (special ed, mental health, etc.).

SORT: (A,C)
EB Recommendation #5
(Treatment)
Provide consistent and comprehensive monitoring and care coordination for all patients with ADHD including pharmacologic and non-pharmacologic interventions, identification and management of emerging comorbidities, and the impact of ADHD condition on patients, their families, and schools.
SORT: (A,C)

Family/Social Consequences to Address
- Family/classroom chaos
- Parental guilt/comorbidity
- Ineffective discipline; abuse
- Social isolation
- Academic underachievement
- Dangerous impulses

Behavior Management
Psychotherapy
- Children: Behavior training for parents/teachers (A), insight therapy/support groups for parents/teachers (C)
- Teens/adults: Cognitive behavioral therapy (A), coaching (B), insight therapy/support groups (C)
Environmental/educational modification
- Classroom accommodations vs. special education interventions (B,C)
- Remove distractions (C)
- Supervise closely/parent-teacher communication (C)
- Individualized sports (C)

Medications
- Stimulants
  - Methylphenidates
    - Methylphenidate: Concerta®, Daytrana®, Metadate®, Methylin®, Quillivant®, Ritalin®
    - Dexamphetamine: Focalin®, generic
- Amphetamines
  - Dextroamphetamine: Dexedrine®, ProCentra®
  - Amphetamine mixture: Adderall®
  - Lisdexamfetamine: Vyvanse®

Stimulant Effects
- Motor activity decreases
- Certain cognitive processes improve
- Motivation improves
- Academic performance improves
- Oppositional and aggressive behaviors decrease
SORT: (A)
Common Methylphenidate Side Effects

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Odds Ratio vs. Placebo</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>5.29</td>
<td>2.51-11.15</td>
</tr>
<tr>
<td>Dizziness</td>
<td>7.50</td>
<td>1.93-29.13</td>
</tr>
<tr>
<td>Stomachache</td>
<td>7.0</td>
<td>3.29-14.89</td>
</tr>
<tr>
<td>Appetite loss</td>
<td>19.0</td>
<td>9.18-39.31</td>
</tr>
<tr>
<td>Insomnia</td>
<td>3.1</td>
<td>1.80-5.42</td>
</tr>
</tbody>
</table>

Other Stimulant Side Effects

- **Less common**: depression, irritability, rebound problems
- **Infrequent**: tics, OCD, palpitations
- **Rare**: “Zombie effect,” growth suppression, psychosis, seizures, sudden death

Stimulants and Sudden Death

- Screen for cardiac risk with standard pre-participation sports exam questions:
  - Spontaneous syncope
  - Exercise-induced syncope
  - Exercise-induced chest pain/discomfort
  - Sudden death in family member <30yo
  - Fam hx of cardiac abnormality (structural or electrical)
- Further evaluation of +’s
- Document risk discussion

Ritalin Diversion/Abuse

<table>
<thead>
<tr>
<th>Substance Use Disorder in ADHD Youth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unmedicated ADHD (n=19)</td>
</tr>
<tr>
<td>75%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Substance Use Disorder in ADHD Youth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ritalin</td>
</tr>
<tr>
<td>Been drunk, alcohol</td>
</tr>
<tr>
<td>Marijuana</td>
</tr>
<tr>
<td>Cocaine</td>
</tr>
<tr>
<td>Steroids</td>
</tr>
<tr>
<td>Heroin</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>12th Grader Prevalence, non-medicinal/illicit use</th>
<th>2001</th>
<th>2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ritalin</td>
<td>5.1</td>
<td>2.3</td>
</tr>
<tr>
<td>Been drunk, alcohol</td>
<td>53.2</td>
<td>43.5</td>
</tr>
<tr>
<td>Marijuana</td>
<td>37.0</td>
<td>36.4</td>
</tr>
<tr>
<td>Cocaine</td>
<td>4.8</td>
<td>2.6</td>
</tr>
<tr>
<td>Steroids</td>
<td>2.4</td>
<td>1.5</td>
</tr>
<tr>
<td>Heroin</td>
<td>0.9</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Monitoring the Future study, University of Michigan (www.monitoringthefuture.org) as of 8-28-14.
Pearls for Stimulant Administration
• First line in patients of all ages and both genders unless there is a specific contraindication
• Use caution < 6 yo or > 12 yo
• Give enough, often enough
• Measure benefit
• Follow up at least every 3-6 months
• Consider annual discontinuation
• Keep good prescription records

Atomoxetine (Strattera®)
• Appears safe and effective (liver toxicity rare)
• Once daily dosing, usually
• Convenient (not DEA Schedule II)
• Full effect may take 4 weeks
• Second line at present

SORT: (B)

Atomoxetine vs. Methylphenidate

<table>
<thead>
<tr>
<th></th>
<th>Atomoxetine (N=222)</th>
<th>Osmotic-Release Methylphenidate (N=220)</th>
<th>Placebo (N=74)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response rate</td>
<td>45%*</td>
<td>56%**</td>
<td>24%</td>
</tr>
<tr>
<td>Response rate in primary failures</td>
<td>43%</td>
<td>42%</td>
<td></td>
</tr>
<tr>
<td>Side effects &gt; placebo:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>14%</td>
<td>6%</td>
<td>17%</td>
</tr>
<tr>
<td>Somnolence</td>
<td>6%</td>
<td>17%</td>
<td>8%</td>
</tr>
<tr>
<td>Insomnia</td>
<td></td>
<td></td>
<td>3%</td>
</tr>
</tbody>
</table>

Antidepressants Effective for ADHD
• TCAs
  – Imipramine (Tofranil®, generic)
  – Desipramine (Norpramin®, generic)
  – Nortriptyline (Pamelor®, generic)
• Bupropion* (Wellbutrin®, generic)
• SNRIs
  – Venlafaxine (Effexor®, generic)
  – Duloxetine (Cymbalta®, generic)
• (SSRIs not effective)
  SORT: (A,B) *FDA-approved for ADHD

Antidepressants vs. Stimulants
• Advantages
  – No abuse potential
  – Mood stabilizers
  – No appetite loss
• Disadvantages
  – Cardiac toxicity, seizures
  – Less dependable ADHD treatment
  SORT: (A,B)

Alpha-2 Agonists
• Clonidine (Kapvay®, Catapres®) and Guanfacine (Intuniv®)
• Mostly behavioral effect rather than cognition
• Adjuncts to stimulants for hyperactive and oppositional symptoms
• Useful for ADHD + Tics or ADHD with insomnia
• Side effects: hypotension, rebound hypertension, sedation (give at night), headache, depression
  SORT: (A,B)
ADHD Meds in Pregnancy/Lactation

<table>
<thead>
<tr>
<th>Medication</th>
<th>Pregnancy Risk</th>
<th>Lactation Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylphenidate, Dexamphetamine</td>
<td>C</td>
<td>Probably safe</td>
</tr>
<tr>
<td>Dextroamphetamine, Mixed Amphetamines</td>
<td>C</td>
<td>Safety conditional</td>
</tr>
<tr>
<td>Atomoxetine</td>
<td>C</td>
<td>Safety unknown</td>
</tr>
<tr>
<td>Bupropion</td>
<td>C</td>
<td>Possibly unsafe</td>
</tr>
<tr>
<td>Desipramine</td>
<td>C</td>
<td>Safety unknown</td>
</tr>
<tr>
<td>Imipramine, Nortriptyline</td>
<td>D</td>
<td>Probably safe</td>
</tr>
<tr>
<td>Duloxetine, Venlafaxine</td>
<td>C</td>
<td>Safety unknown</td>
</tr>
<tr>
<td>Guanfacine</td>
<td>B</td>
<td>Safety unknown</td>
</tr>
</tbody>
</table>

Source: ePocrates

Non-Prescription Remedies

- Caffeine: mild stimulant, helps some but with greater side effects than other stimulants
- Herbal remedies: unproven in children, lack consistency, cause potential harm
- Sugar restriction: no benefit, no harm
- Few foods diet: no benefit, potential harm
- Cognitive training: possible benefit may not be sustained

SORT: (B)

Stacy’s Plan:
Which Medication to Start?

- Long-acting methylphenidate (Concerta®), 18-36 mg q AM, vs.
- Lisdexamfetamine (Vyvanse®) 30 mg q AM, vs.
- Atomoxetine (Strattera®), 40 mg q AM x3 then 80 mg q AM, vs.
- Bupropion (Wellbutrin®) 100 mg q AM x7 then 200 mg q AM

F/U every few weeks with titration of meds to effectiveness (define means to measure), or side-effects, or maximum FDA-approved dose.

Stacy’s Plan:
Behavioral/Ancillary Interventions

- Coaching/observation agreement with girlfriend and aunt
- Reading assignments
  - [www.ncgiadd.org](http://www.ncgiadd.org), resources from Dr. P Quinn
  - ADD-Friendly Ways to Organize Your Life, Kolberg & Nadeau
- Offer counseling for her, parenting skills, family as necessary
- Smoking cessation

When to Refer

- Uncertain diagnosis
- Not responding to treatment
- Complication of treatment or of disorder

Pearls for ADHD Diagnosis in Females

- Harder to recognize than in males due to higher incidence of inattentive presentation alone and lack of acting out
- Delayed diagnosis common:
  - Often diagnosed with depression before ADHD
  - Bring it up with parents of ADHD children
- Girls have greater intellectual impairments and more internalizing problems than boys
- Use standardized questionnaires with age/gender norms

SORT: (B,C)
Pearls for ADHD Treatment in Females

- As with males, stimulants are first line
- Stimulant dose may need to be lowered at menarche and peri-menopause
- Non-stimulants appropriate as alternatives and adjuncts, especially in comorbid situations
- Keep potential pregnancy in mind

Sources