

Attention-Deficit/ Hyperactivity Disorder (ADHD) in Female Patients

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Disclosure of Unlabeled/Investigational Uses of Products

The following faculty have returned forms declaring that the content of their presentation(s) at 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.

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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.

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Pre-Assessment

Please complete your answers
on the sheet provided in your syllabus.

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Pre-Assessment Question #1

Girls with ADHD are more likely than boys to exhibit which of the following?

- A. Butting into conversations, games, or activities
- B. Blurting out an answer before the question is completed
- C. Running or climbing in inappropriate situations
- D. Easily distracted by extraneous stimuli

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Pre-Assessment Question #2

Which of the following is true regarding treatment of ADHD in female patients compared to their male counterparts?

- A. Female patients are less likely to respond to methylphenidate.
- B. Female patients are more likely to require the addition of an antidepressant.
- C. Female patients are more likely to respond to an SSRI than an SNRI antidepressant.
- D. Pregnancy is an important contraindication to ADHD treatment with most available medications.

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Pre-Assessment Question #3

Which of the following is true regarding prognosis in female vs. male patients with ADHD?

- A. Female patients are more likely to be diagnosed early due to their tendency to "act out."
- B. Female patients are more likely to "outgrow" their symptoms than male patients.
- C. Female patients are more likely to "suffer in silence" than male patients.
- D. Girls are less likely to have intellectual impairments along with their ADHD than boys.

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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

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(SORT) from American Family Physician¹

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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.

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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.

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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 dooper, sober for 4 yrs."

ROS: Depression screen showed sleep latency difficulty and erratic eating, but otherwise negative.

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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

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Stacy's Lab/Assessment

Urine drug screen negative

Does Stacy have ADHD?

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DSM-5 Definition

Mental Disorder:

- **Syndrome:** pattern of psychological, biological, or developmental dysfunction
- **Outcome:** significant distress or disability in social, occupational, or other important activities
- **Individual dysfunction:** not just cultural or social differences

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DSM-5, Am Psychiatric Assoc, 2013.²

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DSM-5 Presentation Specifiers (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)

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DSM-5, Am Psychiatric Assoc, 2013.²

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DSM-5 vs. DSM-IV RE: ADHD

- “Disorders Usually First Diagnosed in Infancy, Childhood, or Adolescence” category removed
- ADHD grouped with “Neurodevelopmental Disorders”
- ADHD not grouped with “Disruptive, Impulse-Control, and Conduct Disorders”

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Etiology: 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)

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Heritability Comparisons

ADHD
75%
→

Condition	Monozygotic Twin Concordance (%)
Blood type	100
Height	93
Weight	92
Eye color	80
Childhood asthma	65
Schizophrenia	60
Autism	50
Diabetes, type 2	50
Coronary artery disease	46

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JAMA, May 7, 2014.³

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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)
- (A, B)

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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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DSM-5, Am Psychiatric Assoc, 2013.²

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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

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DSM-5, Am Psychiatric Assoc, 2013.²

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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
- Blurts answers before end of questions
- Difficulty awaiting turn/waiting in line
- Interrupts or intrudes on others

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DSM-5, Am Psychiatric Assoc, 2013.²

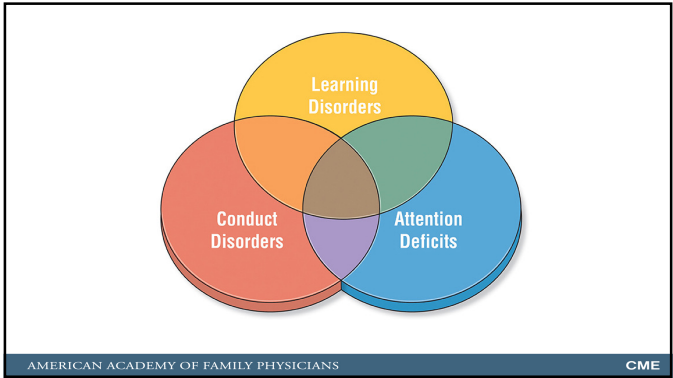
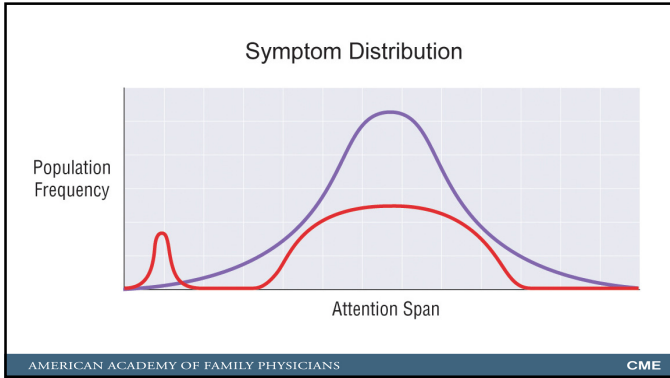
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Prevalence

- 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)

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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. (evidence classes: C, R)

AMERICAN ACADEMY OF FAMILY PHYSICIANS ICSI Guideline: Diagnosis and Management of ADHD, March 2012 (www.icsi.org) CME

EB Recommendation #2 (Diagnosis)

Screen all patients for other primary conditions or comorbidities and appropriately refer to subspecialty consultation for further evaluation.

AMERICAN ACADEMY OF FAMILY PHYSICIANS ICSI Guideline: Diagnosis and Management of ADHD, March 2012 (www.icsi.org) CME

Comorbid Conditions

Condition	Prevalence in ADHD	Prevalence in General Population
Conduct disorder	35-45%	3-4%
Oppositional defiant disorder	45-55%	4-5%
Depressive disorders	25-30%	4-5%
Bipolar I disorder	6-10%	1%
Anxiety disorder	25-35%	8-12%
Learning disorder	12-30%	5-7%
Tourette's disorder	0.1%	.05-.1%

AMERICAN ACADEMY OF FAMILY PHYSICIANS Am J Psychiatry 2005 CME

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

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Evaluation: History Sources

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

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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

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Evaluation: Physical Exam

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

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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

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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

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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 (?)

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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.

(evidence classes: A, C, R)

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.).

(evidence classes: A, C, M)

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.

(evidence classes: A, C, D, M, R)

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
- Atomoxetine
- Antidepressants
- Alpha-2 agonists
- Others

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Stimulants

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

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Stimulant Effects

- Motor activity decreases
- Certain cognitive processes improve
- Motivation improves
- Academic performance improves
- Oppositional and aggressive behaviors decrease (A)

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Common Methylphenidate Side Effects

	Odds Ratio vs. Placebo	95% Confidence Interval
Headache	5.29	2.51-11.15
Dizziness	7.50	1.93-29.13
Stomachache	7.0	3.29-14.89
Appetite loss	19.0	9.18-39.31
Insomnia	3.1	1.80-5.42

AMERICAN ACADEMY OF FAMILY PHYSICIANS SORT: (A)

Pediatrics. 1993 Jun;91(6):1101-6. ⁸

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Other Stimulant Side Effects

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

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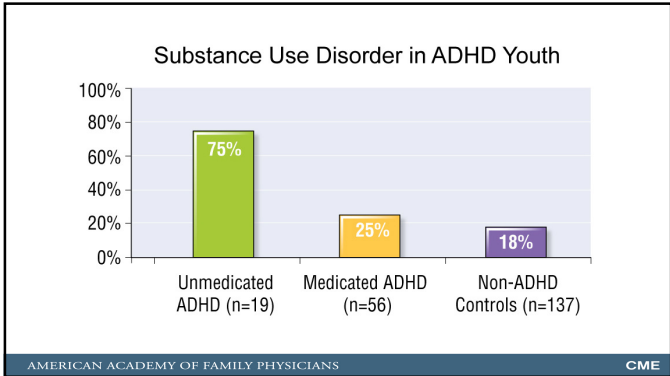
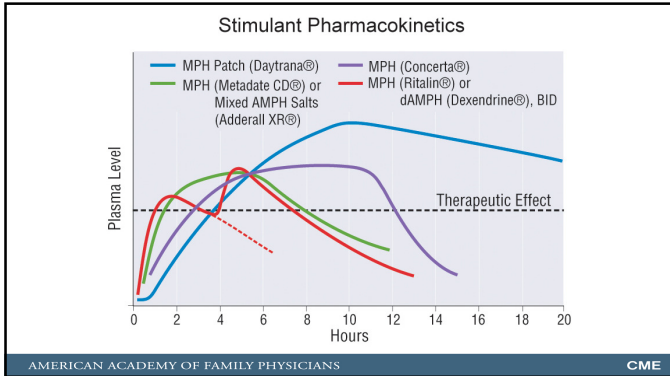
Stimulants and Sudden Death

- 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

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SORT: (C)

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Ritalin Diversion/Abuse

12 th Grader Prevalence, non-medical/illicit use	2001 %	2013 %
Ritalin	5.1	2.3
Been drunk, alcohol	53.2	43.5
Marijuana	37.0	36.4
Cocaine	4.8	2.6
Steroids	2.4	1.5
Heroin	0.9	0.6

Monitoring the Future study, University of Michigan (www.monitoringthefuture.org) as of 8-29-14.

AMERICAN ACADEMY OF FAMILY PHYSICIANS CME

- ### 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
- AMERICAN ACADEMY OF FAMILY PHYSICIANS Sources ^{9, 10} Listed in back of handout CME

- ### Atomoxetine (Strattera®)
- Appears safe and effective
 - Once daily dosing, usually
 - Convenient (not DEA Schedule II)
 - Full effect may take 4 weeks
 - Second line at present
- Prescriber's Letter Detail Document #220214. 2006 (B)
- AMERICAN ACADEMY OF FAMILY PHYSICIANS Biological Psychiatry 2003; 53:112-120¹¹ CME

Atomoxetine vs. Methylphenidate

	Atomoxetine (N=222)	Osmotic-Release Methylphenidate (N=220)	Placebo (N=74)
Response rate	45%*	56%**	24%
Response rate in primary failures	43%	42%	
Side effects > placebo:			
Decreased appetite	14%	17%	3%
Somnolence	6%	8%	4%
Insomnia			1%

AMERICAN ACADEMY OF FAMILY PHYSICIANS Am J Psychiatry 165:6, June 2008 (A)¹² CME

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)
- (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
 - 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
- (A,B)

ADHD Meds in Pregnancy/Lactation

Medication	Pregnancy Risk	Lactation Risk
Methylphenidate, Dexamethylphenidate	C	Probably safe
Dextroamphetamine, Mixed Amphetamines	C	Safety conditional
Atomoxetine	C	Safety unknown
Bupropion	C	Possibly unsafe
Desipramine	C	Safety unknown
Imipramine, Nortriptyline	D	Probably safe
Duloxetine, Venlafaxine	C	Safety unknown
Clonidine	C	Safety unknown
Guanfacine	B	Safety unknown

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

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, 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

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When to Refer

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

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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
- (B,C)

AMERICAN ACADEMY OF FAMILY PHYSICIANS Sources 18, 19, 20, 21, 22 Listed in back of handout CME

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

SORT: (A,B,C)

AMERICAN ACADEMY OF FAMILY PHYSICIANS Treating adolescent girls and women with ADHD: gender-specific issues 23, 24 CME

Pearls for ADHD Prognosis in Females

- Girls and women more likely to suffer in silence due to personal and community lack of awareness
- May or may not have worse problems with self-esteem
- Rates of symptom continuation/impairment in adolescence and adulthood similar to males (about 2/3)

SORT: (B)

AMERICAN ACADEMY OF FAMILY PHYSICIANS Perceptions of girls and ADHD: results from a national survey 25 CME

Post-Assessment

Please complete your answers
on the sheet provided in your syllabus.

Note: The questions are not in the same
order as the pre-assessment.

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Post-Assessment Question #1

Which of the following is true regarding treatment of ADHD in female patients compared to their male counterparts?

- A. Female patients are less likely to respond to methylphenidate.
- B. Female patients are more likely to require the addition of an antidepressant.
- C. Female patients are more likely to respond to an SSRI than an SNRI antidepressant.
- D. Pregnancy is an important contraindication to ADHD treatment with most available medications.

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Post-Assessment Question #2

Which of the following is true regarding prognosis in female vs. male patients with ADHD?

- A. Female patients are more likely to be diagnosed early due to their tendency to "act out."
- B. Female patients are more likely to "outgrow" their symptoms than male patients.
- C. Female patients are more likely to "suffer in silence" than male patients.
- D. Girls are less likely to have intellectual impairments along with their ADHD than boys.

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Post-Assessment Question #3

Girls with ADHD are more likely than boys to exhibit which of the following?

- A. Butting into conversations, games, or activities
- B. Blurting out an answer before the question is completed
- C. Running or climbing in inappropriate situations
- D. Easily distracted by extraneous stimuli

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Resources/References

- DSM-5 (www.dsm5.org)
- CHADD: Children and Adults With ADHD (www.chadd.org)
- ADD Warehouse 1-800-233-9273 (www.addwarehouse.com)
- National Institute of Mental Health (www.nimh.nih.gov/)
- Am Acad Pediatrics NICHQ ADHD toolkit (<http://www.nichq.org/childrens-health/adhd/resources>)
- ICSI Health Care Guideline on ADHD (www.icsi.org)
- MyADHD (www.MyADHD.com)
- American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Arlington, VA, American Psychiatric Association, 2013.

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Presentation Sources Listed in the
Back of the Handout

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Thank you!

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Sources

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Sources-con't

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