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- Which disorders are common co-morbidities of ADHD in children?
- A-Learning disorders in Math
- B-Learning disorders in expressive language
- C-Oppositional defiant disorder
- D-Separation anxiety disorder
- E-Gender Identity Disorder of Childhood

Question 2

- Which of the following statements about bupropion is true?
- A-It should not be used in youth with a history of seizure disorder
- B-It should not be used in youth with a history of eating disorder
- C-It can be associated with serum sickness
- D-it is a second choice drug for ADHD
- E-All of the above

- Which of the following adverse events has been reported with atomoxetine in adults?
- A-Sexual side effects
- B-Stevens-Johnson syndrome
- C-QTc prolongation
- D-Hypotension
- E-None of the above

Question 4

- A diagnosis of ADHD in adults must include?
- A-retrospective history of ADHD symptoms before the age of 7-12 years
- B-History of school failure
- C-History of motor vehicle accidents
- D-History of failed multiple marriages
- E-History of substance abuse

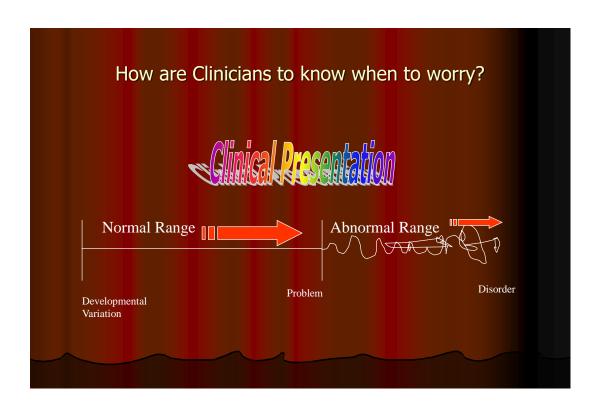
- Which of the following instruments are useful in diagnosing adult ADHD?
- A-CAARS
- B-CARS
- C-BAARS
- D-BARS
- E-CARBS

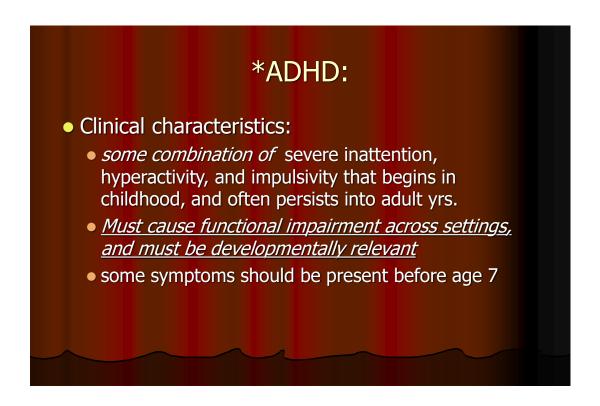
*Preview

- History of ADHD
- Subtypes of ADHD
- Co-morbidity
- NA and DA pathways
- MRI
- MTA study
- MedicationTreatments for children
- Adult ADHD

Teaching Points

- ADHD is a clinical diagnosis in both youth and adults
- There are several subtypes that have different presentations
- The DOC are psychostimulants, but there are several other medications that can be effective





Attention-Deficit Hyperactivity Disorder (ADHD)

- minimum brain dysfunction, hyperkinetic syndrome of childhood (1960s)
- 1980 DSM III: ADD(H)
- 1987 DSM IIIR: ADHD
- 1994 DSM IV: Subtypes
 - must meet 6 of 9 criteria in a particular category
 - Inattentive type (IA)
 - Hyperactive-Impulsive type (HI)
 - Combined type (CT)

*ADHD in Childhood:

- Epidemiology
 - 3-7% of school-age children
 - boys 4-9x > girls
 - girls get inattentive type much more than other subtypes

*ADHD-Inattentive type

- Failure to pay close attention to details / frequent careless mistakes
- Difficulty sustaining attention in tasks or play
- Not listening when spoken to
- Not following through on instructions, and failure to finish tasks (schoolwork, chores). Not due to oppositionality or failure to understand

*ADHD-Inattentive type

- Difficulty organizing tasks and activities
- Avoidance of tasks that require sustained mental effort
- Losing things necessary for tasks (toys, assignments, books)
- Easily distracted by external stimuli
- Often forgetful in daily activities

ADHD- Hyperactive/Impulsive type

- Fidgets with hands/ feet, or squirms in seat
- Leaves seat in classroom or other situations where sitting is expected
- Runs or climbs excessively in inappropriate situations
- Difficulty playing or engaging in leisure activities quietly
- Often "on the go" / "driven by a motor"
- Talks excessively

*ADHD- Hyperactive/Impulsive type

- Impulsivity
 - Blurts out answers before questions have been completed
 - Difficulty waiting turn
 - Interrupts or intrudes on others (conversations, games)

*Other criteria

- Some impairing symptoms were present before age 7
- Some impairment <u>across settings</u> (home, school)
- <u>Clinically significant</u> impairment in social, academic or work functioning
- Other conditions must be considered as source of symptoms

*ADHD

- Co-existing conditions must also be evaluated for
 - 30-50% of ADHD may be co-morbid with other dx
 - Oppositional Defiant Disorder (ODD)- Pervasive pattern of negativistic, defiant, disobedient, and hostile behaviors toward authority figures
 - Conduct Disorder (CD)- Repetitive pattern of violating the basic rights of others/ major age-appropriate social norms or rules are violated
 - Mood disorders (depression/bipolar disorder) check family history!
 - Poor outcome in co-morbid teens (higher risk for suicide)
 - Anxiety Disorders- 25% or more
 - Learning Disorders- up to 60% in non-PCP settings
 - Especially Reading Disorder

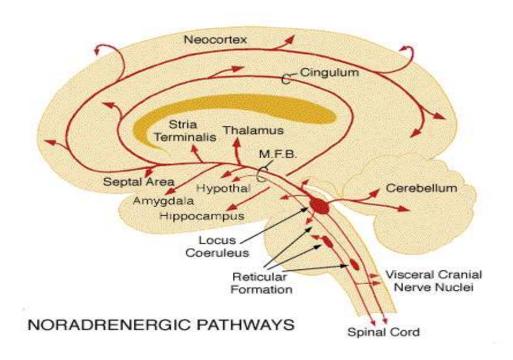
Practice Guidelines

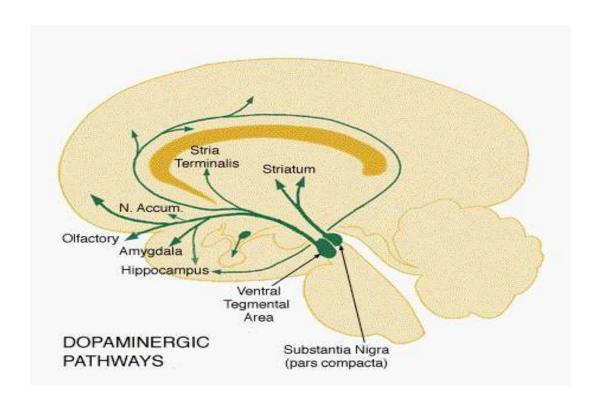
- In children who have good primary care, other diagnostic tests are not <u>routinely</u> indicated
 - EEG's indicated only if a history of seizure d/o or clinically significant lapses in consciousness exists
 - Continuous Performance Tests (CPT's) are useful in research settings only
 - measures of vigilance / distractibility which have low odds ratios in differentiating children with and without ADHD

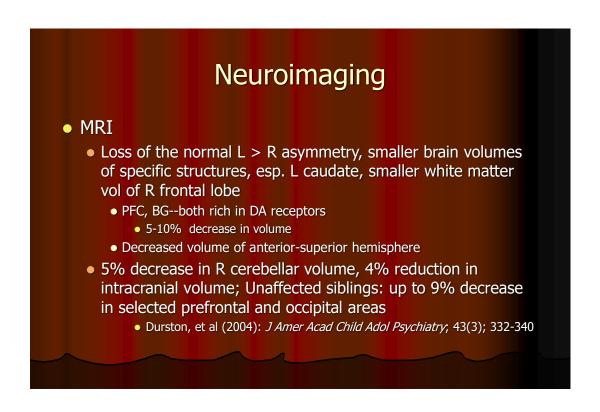
*Practice Guidelines

- Summary
 - Use explicit criteria for diagnosis
 - Obtain history from more than 1 setting
 - sx must be severe enough to cause functional impairment
 - Screen for co-existing conditions
- May need 2-3 visits for full work-up
 - parent and teacher questionnaires may be faxed for efficiency
 - Connor's scales, other ADHD rating scales

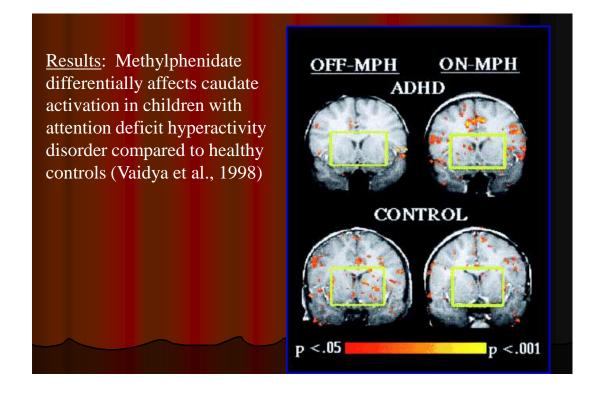
Heterogenous condition, many causes • Final common pathway • factors include: • brain structure / functional abnormalities • family / genetic factors • prenatal / perinatal factors • Maternal smoking and alcohol use • neurotoxins • psychosocial stressors and combined factors

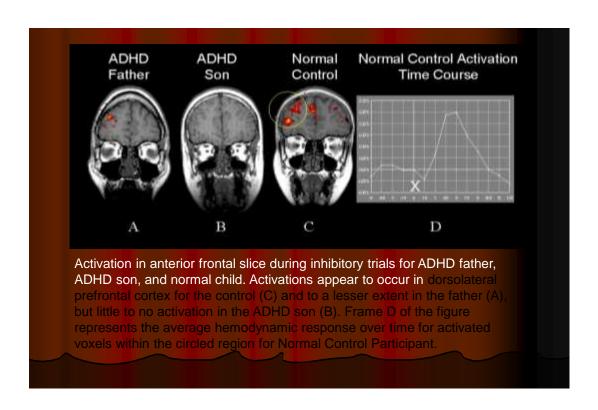






Neuroimaging • fMRI • lower blood flow in striatum, ant cingulate, PFC • MPH increases blood flow to striatum selectively (Vaidya, et al, 1998)







IDEA, Pt B

- Requires public schools in the US to provide a
 <u>free and appropriate education</u> for all
 children with disabilities
 - Evaluation must show that the child has one or more specific mental or physical impairments, and these must be severe enough to warrant special education

IDEA, Pt B

- Children/ teens with ADHD may get special ed services under 3 categories:
 - Specific LD
 - Emotional disturbance (ED)
 - Other health impaired (OHI)

Section 504

- Rehab Act of 1973: A civil rights law that prohibits discrimination, in fed. funded programs, solely based on disabilities, for otherwise qualified persons.
- No specific disability categories
 - Broadly defines disability as a "physical or mental impairment which limits one or more life activities", including learning.

Psychoeducational Interventions

- Cognitive-Behavioral Treatment
 - Impulse control
 - Anger management
- Classroom strategies and modifications
 - FBAs (Functional Behavior Assessments)
 - 504 / IEP specifics
- Parent Education and Empowerment
 - www.parentshelpingparents.com
 - www.schwablearning.org

*ADHD Treatments (Medication options)

- MTA study: <u>Arch Gen Psychiatry</u> Vol 56, 1073-1086, Dec 1999
 - 579 children with ADHD-CT; 7-9.9 yrs; 6 sites; 14 month parallel-design
 - 4 different treatment groups:
 - Medication mgmnt (titration plus 30" monthly visits)
 - Intensive behav treatment (parent, school, child components)
 - Optimal combination of both
 - "Usual" community care

*ADHD Treatments

- MTA study: conclusions
 - All 4 groups showed sizable reduction in symptoms over time
 - <u>ADHD symptoms</u>: Combo. and med-only groups had significantly greater improvement than those given intensive behav tx or "usual" community care (UCC)
 - ADHD with co-morbid anxiety disorder: behavioral treatment was similar to medication tx, and both were superior to UCC

MTA study: cont'd.

 Combined behavioral intervention and stimulant medication--(multimodal treatment), yielded no statistically significantly greater benefits than medication management "alone" for the core symptoms of ADHD

*ADHD Treatments

- MTA study: cont'd.
 - <u>Non-ADHD symptoms</u>: (social skills, parent-child relations, oppositional-aggressive behavior, internalizing symptoms, academic achievement)
 - The 3 MTA-delivered treatments were very similar, with the combined treatment arm being consistently superior to UCC.
- Highly anxious children with ADHD may represent a subgroup of children with unique treatment needs

ADHD Treatments

- MTA study: 2 year follow-up (PEDIATRICS, 113 (4); April 2004, pp. 762-769)
 - Consistent use of stimulant medication was associated with maintenance of effectiveness but continued "mild growth suppression" (1 cm per year over 2 years).
 - Further follow-up will help to address question of growth (ultimate ht. suppression vs. longer time to finish growing)
 - Medication holidays may be prudent clinical practice (summertime, holidays)

*ADHD Treatments (medication options)

- Established Treatments
 - Psychostimulants (1st line)
 - Atomoxetine (1st line)
 - Bupropion (2nd line)
 - TCAs (2^{nd-} 3rd line)
- Probable Efficacy
 - Modafinil
 - Alpha-2 agonists
 - Venlafaxine

ADHD Treatments (medication options)

- Possible efficacy
 - Beta-blockers
- Effective, but impractical: MAOIs
- Likely ineffective
 - SSRIs
 - Caffeine
 - St. John's Wort

Stimulants

- "stimulate" the brain to focus
- in use since late 1800's
- many studies document safety and efficacy
- 70-85% response rate
 - do not use this to confirm diagnosis!

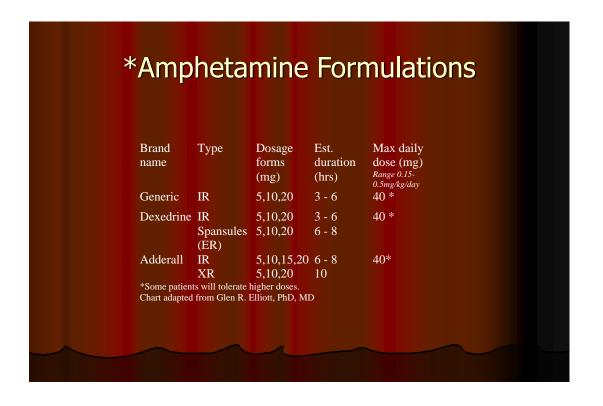
Stimulants

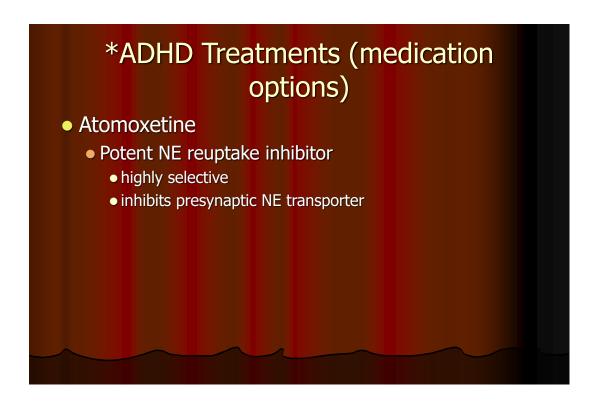
- benefits: improved focus, concentration, attn span; reduced hyperactivity, impulsivity, and fidgeting
- side effects: irritability, stomachache, headache, dysphoria, zoned-out effect, appetite suppression, sleep problems, height velocity slow-down (<10%)
- AMP/DEX may produce more sleep/ appetite probs, esp at higher doses

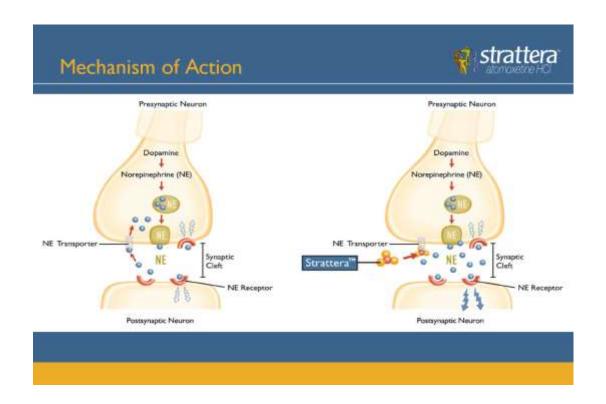
*Stimulants

- Special consideration
 - Motor tics
 - Depression
 - Anxiety d/o (children w/ co-morbid anxiety may improve on MPH, according to MTA study)
 - Seizure d/o (esp. in high doses in adults; treat with anticonvulsants first, then may add stimulant; Use AMPH 1st)
 - Children under 6 years old

	*Met	hylphe	nidate	Formul	ations
Ш	Brand	Type	Dosage forms (mg)	Est.	Max daily dose (mg) Range 0.3- 1.0mg/kg/day
	Generic	IR	5,10,20	2.5 - 4	60 *
ш	Ritalin	IR SR LA***	5,10,20 20 20	2.5 - 4 6 - ? 8-10	60 *
ш	Methylin	IR ER	5,10,20 5,10,20	2.5 - 4 6 -8	60*
	Focalin	IR	2.5,5,10	3-5	20
Ш	Metadate	ER CD***	10,20 20	6-8 8 -12 10 - 12	60*
				ypatch expected *may be sprinkle	







ADHD Treatments (medication options)

- Atomoxetine (cf. Tamoxifen)
 - Michelson, et al (2001): n=297, ages 8-18, 71 % male; 67% ADHD-CT; 8-week randomized prospective controlled study
 - Participants were moderately -to-severely impaired prior to tx.
 - Results showed superior response to placebo (65% response rate)
 - ADHD symptoms
 - Measures of social and family functioning

*ADHD Treatments (medication options)

- Atomoxetine (cf. Tamoxifen)
 - Total database (Lilly) of several thousand pediatric patients; 2300+ total patients with ADHD (including Adults)
 - Common side effects: Dizziness, drowsiness, dyspepsia, decreased appetite
 - Less common, but not rare (>2%)
 - Depression, tremor, early AM awakening, pruritus (generalized itching)
 - Adult patients: Possible Sexual dysfunction; No abuse potential

*Atomoxetine, cont'd

- CYP2D6 substrate
 - Use cautiously when other medicines are used (eg. paroxetine, fluoxetine, quinidine)
 - Dose: 0.5 mg/kg/day—1.2 mg/kg/day; Max dose 1.4 mg/kg/day or 100mg (whichever is less)
 - Assess liver function prior to start; monitor for hepatotoxicity
- Monitor height, weight, pulse and BP
 - Potential exists for decreases in growth, and increases in HR and BP
- May be used QD or BID
 - Time to Cmax is 1-2 hours
 - Duration of action is 6-10 hours (may be up to 24 hours)
 - Allow 6-8 weeks for full effect!

ADHD Treatments (other medication options)

- Tricyclic Antidepressants (TCAs)
 - *30+ randomized controlled studies show efficacy in children
 - imipramine, amitryptiline, desipramine, clomipramine
 - uncontrolled studies show benefit of nortryptiline, protryptiline

ADHD Treatments (medication options)

- Tricyclic Antidepressants (TCAs)
 - strong effects on H/I symptoms
 - wkr cognitive benefits than stimulants
 - Dosing/ monitoring
 - Use grad dose elevation/ LOTSA drug interax!
 - Imipramine most widely used
 - Most will respond to less than 5mg/kg/day
 - many to 1-2mg/kg/day
 - start at 50 mg @ HS// level @ 7-10 days
 - Do not exceed 300 ng/ml
 - Monitor BP, EKGs:
 - QTc < 0.44ms, PR < 200ms, QRS < 120ms

Tricyclic Antidepressants (TCAs)

- Clomipramine (<u>non-routine in kids</u>)
 - non-selective SRI
 - data to show efficacy, but side effects limit use
 - possible use in co-morbid OCD
 - High sz risk (1.5% annual risk in adults)
- Desipramine
 - Still used in adults
 - 6 published cases of sudden death in children

*Other medication options

- Bupropion (Wellbutrin/ Zyban)
 - Minimal 5-HT effects
 - Inhibits NE, DA uptake
 - May have special use with comorbid depression or substance abuse
 - 1 open and 3 controlled studies in children
 - not quite as robust an effect as stimulants

Bupropion, cont'd.

- Side effects
 - skin rash
 - seizures (lower with SR preparation)
 - 0.3%-0.4%; risk increases with doses> 450 mg Total Daily Dose
 - psychosis, agitation
 - sleep problems
 - appetite suppression
 - ?paradoxical effect in combo. with stimulants
 - Callaghan, *JAACAP*, July 1999

*Venlafaxine (Effexor)

- Selective Inhibition of NE and 5-HT
- Adults: 3 open series and a case report suggest therapeutic effects
- Youths: 1 case series (n=16), 1 case report
 - more benefits on behavioral than cognitive symptoms
 - anecdotal reports: useful in OCD, perseveration, depression, anxiety, agitation
 - Recently fallen out of favor due to concerns about suicidal thinking

*Clonidine (Catapres)

- alpha-2 adrenergic agonist
- may have role for H-I symptoms and aggression (not inattention)
 - special utility in DD population
- placebo-med differences have been found in small controlled studies
- side effects often limit its usefulness
 - CV, sedation

*Clonidine (Catapres)

- Dose:
 - Start with 0.05 mg @ HS
 - Typical range is 0.05-0.2 mg, BID-QID
 - max daily dose 0.9 mg
- Must monitor BP, other CV parameters
 - Possible bradycardia
 - rebound tachycardia and HTN
 - children between doses
 - if d/c'd abruptly
 - if tx'd for more than 1 month, d/c at a rate of 0.05 mg q3-7 days

*Clonidine (Catapres)

- Relative contraindication: Depression
- MPH/ CLON combination
 - may be very helpful, esp. w/ comorbid insomnia
 - 1994: 40% of pts w/ ADHD tx'd with CLON were also on stimulants.
 - 3 fatalities, 1 LTE in kids on MPH/ CLON
 - See <u>JAACAP</u> 38:5, May 1999, pp614-622, for debate on this oftenused combination
- Recent prospective studies from the Neurology literature
 MPH/CLON combo for tx of ADHD and tics Neurology 2002;58:527-536
 - Total n= 160; no major safety issues in cross-over studies of up to 4 months
 - Mean daily doses CLON 0.25 mg; MPH 25 mg

*Guanfacine (Tenex)

- Similar MOA to clonidine, with some impt receptor diffs:
 - alpha 2A agonist, but weaker alpha 1, alpha 2B, alpha 2C activity
 - less beta-adrenergic, histamine, 5-HT, beta-endorphin, and DA effects
- Less hypotension, sedation, rebound HTN
- Longer duration, so less frequent dosing necessary (T 1/2= 17 hrs.); pks in 2-3 hrs
 - start with 0.5 mg qD, then increase 0.5 mg q3-4 days if necessary
 - optimal dosing: 2.5-3.5 mg TDD, div TID or QID.
 - MDD=4 mg/day
- May have role in inattention, impulsivity, tics

*Guanfacine (Tenex)

- Sedation, BP changes are common (25-30%), but usually transient
- No reports of sudden death thus far.
- Monitor for behavioral activation/ disinhibition
- Controlled studies underway
 - See Scahill, et al: Am J Psychiatry 158:7, July 2001

Modafinil (Provigil, Sparlon)

- Wakefulness promoter
- MOA: Possible modulation of glutamate and GABA, and/or an effect on orexin/hypocretin receptors
 - Results in an increase in extracellular DA, NE, 5-HT
 - Different MOA than stimulants
- Schedule IV (cf. schedule II), thus fewer prescribing restrictions
- Therapeutic Dose range: 100-400 mg qAM

*Modafinil (Provigil)

- Benefits: Improved mood, reaction time, logical reasoning, short term memory
- Side effects: Headache, nausea, rhinitis, pharyngitis, dizziness, dry mouth, anorexia, insomnia
- FDA Indications: Narcolepsy in Pts 16 and older
- Duration 12-15 hours
- Rugino Study (2003): 6 weeks; n=22;RPCT
 - 100mg QD: Significant improvement vs. placebo; minimal side effects; no anorexia
 - Independent study (No Cephalon funding)
- Submission to FDA in 2006 for Pediatric and Adult ADHD indication (Sparlon)

*Adult ADHD

- Still regarded as "controversial", despite presence of continued morbidity in 50% or more of teens transitioning to young adulthood
- Diagnosis is primarily clinical
 - Useful tools include Connors Adult ADHD Rating Scales (CAARS), and Wender-Reimherr Adult ADD Scale (WRAADS)
 - DSM is only partially useful
 - Valid for children and teens only
 - Some items irrelevant for adults: "runs/climbs excessively; difficulty playing quietly"
 - Adult dx "relies" on ADHD NOS, or "Residual type"

*Adult ADHD (McGough & Barkley, 2004)

- Shortcomings of DSM-IV criteria: Do not take "additional major life settings" into account which may produce impairment yet would not be evident in children.
 - General functioning within the larger organized community (e.g., participating in government, cooperating with others, abiding by laws, driving)
 - Financial management (e.g., banking, establishing and using credit, forming contracts)
 - Child rearing (providing protection, sustenance, financial and social support, appropriate education, etc.)
 - Marital functioning
 - Routine health maintenance activities

*Adult ADHD

- Laboratory-based measures in the diagnosis of ADHD
 - SPECT, fMRI, CPT, PET useful currently for research purposes only
- <u>ADHD remains a clinical diagnosis</u> that is best determined through careful history taking, adherence to well-described clinical criteria, and training in the differential diagnosis of adult disorders (McGough & Barkley, 2004)

*Summary for diagnosis: Adult ADHD (McGough & Barkley, 2004)

- Use rating scales that have been well standardized in groups of adults (eg, WRAADS; CAARS)
- Given the lack of empirical support for 7 years as the age-of-onset criterion, clinicians should establish some evidence of symptoms and impairment before age 12 or initiation of puberty
- In assessing functional impairment, consider all available information to confirm evidence of pervasive impairments over the lifespan, even if current complaints are limited to a single domain

*Summary for diagnosis: Adult ADHD (McGough & Barkley, 2004)

- Clinicians must maintain a high suspicion for <u>coexisting psychiatric conditions</u> and should provide rational polytherapy when justified
- Ongoing research and clinical input on the criteria for ADHD in adults, including <u>long-term follow-up</u> <u>studies of DSM-diagnosed children</u> and field trials of symptoms in adults, are essential for subsequent revisions of DSM-IV.

Summary for diagnosis: Adult ADHD (McGough & Barkley, 2004)

- Clinicians can be comfortable treating adults with childhood histories of ADHD, evidence of current ADHD-related impairment, and a <u>minimum of four</u> (4), and not six (6) current hyperactive-impulsive or inattentive symptoms
- Clinicians should make efforts to <u>obtain third-party</u> <u>corroboration</u> whenever available and should carefully document the evidence of the disorder as justification for treatment
- Clinicians who prescribe medication should <u>carefully monitor</u> <u>treatment response</u> and the possibility of stimulant abuse and illicit diversion

Summary for diagnosis: Adult ADHD (WRAADDS)

- 7 primary symptom areas
 - 4 mirror DSM: Attention difficulties, Disorganization, Hyperactivity/Restlessness, Impulsivity
 - 3 cover Emotional Dysregulation: Temper, Affective lability, Emotional overreactivity
- May more accurately describe adult phenotype
- Requires subject to give retroactive history
- Critiques: may exclude inattentive type, excludes comorbid dx, requires further (other) assessment of current functioning (?possibly a strength)

Summary for diagnosis: Adult ADHD (CAARS)

- Based on large normative database (n=2000)
- For use in ages 18 and over
- Excellent reliability and validity
- Self-report and observer (friends, co-workers, family members) report
 - Long version: 66 items/ short version 26 items
 - Focuses more on current symptoms than WRAADDS
- ADHD Index and Inconsistency Index provide useful clinical data
- Easy to score and obtain (see references)

Adult ADHD Cognitive-Behavioral Treatment Manualized Treatment Safren, et al (2005) Mastering Your Adult ADHD: A cognitive-behavioral treatment program Client workbook: ISBN#0-19-518819-5 Therapist guide: ISBN#0-19-518818-7 Patient Empowerment ADD.org CHADD.org

	Medication	Daily Dose, mg*	Daily Dosage Schedule	Common Adverse Effects
	Stimularits Methylphenidate	20-100	Twice to 4 times	Insomnia Decreased appetite-weight loss Hectaches Edginess
	Amphetamine Destroamphetamine and mixed amphetamine sats†	10-60	Twice to 3 times	Insomnia Decressed appeths/weight loss Headachos Edginass Mild incresses in pulse/blood pressure
	Magnesium pemoline	75-150	Once or twice	Insomnia Decreased appetite/weight loss Headaches Edginess Abnormal liver function test results
/ilens, et al, 2004	Noradionergic agents Atomoxetine	40-120	Once or twice	Seep disturbance Gastrointestinal tract distress, nausea Headache Mild increases in pulse/blood pressure
	Antidepressants Thoyclics Despremine: impramine	100-300	Once or twice	Dry mouth Constitution Vital sign and electrocardiographic changes
	Nortriptyline	50-200	Once or twice	Dry mouth Constitution Vital sign and electrocardiographic changes
	Bupropion	150-450	Once or twos	Insomnia Risk of selcures (in doses >-6 mg/kg) Contraindicated in bulinia

Psychological issues in pharmacologic management

- 30-70 % of all pediatric psychiatric rx are not filled or are taken improperly (Joshi, 2006)
- Why is psychological management important?
- Parent issues:
 - Ambivalence re: need for meds
 - Inadequate parental surveillance of adherence
 - misunderstanding of doses, serum levels, and onset of effects
 - Internet information and misinformation

Psychological issues in pharmacologic management

- All of our actions have meaning to the patient and family
 - What language do we use to explain the theoretical nature of their child's illness?
- Many patients (esp teens) attach meaning to the medication itself
- Once taken, it b/c psychologically incorporated into the patient's view of himself/herself, and can change their sense of identity
- The meaning and significance of a drug can affect the way patients view the drug, the prescriber, and themselves (Lieberman & Tasman, 2000)

Conclusions

 Remember that all of our actions have potential meaning to the patient, from the pens we write with, to the language used to explain about mental illness, to the way we offer realistic hope for the future

- Which disorders are common co-morbidities of ADHD in children?
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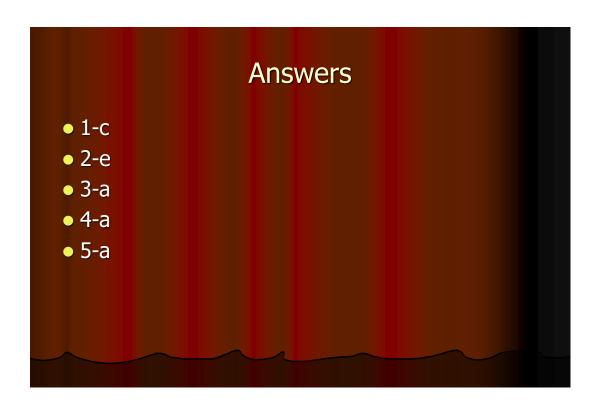
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- E-History of substance abuse

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- A-CAARS
- B-CARS
- C-BAARS
- D-BARS
- E-CARBS





Resources

- Kaye DL, et al: <u>Child and Adolescent Mental Health</u>; 2003; Philadelphia: Lippincott
 - *excellent guide for both medical and non-medical providers, about the cost and size of the Harriet Lane Handbook*
- Wilens, Timothy: <u>Straight Talk about Psychiatric Medications for Kids</u>, revised edition, Guilford Press, 2004
 - *well-written and recently revised; among the best medication resources for parents, teachers, nurses, and therapists*
- Steiner, Hans (ed.): <u>Handbook of Mental Health Interventions in Children and</u> Adolescents: An Integrated Developmental Approach, 2004; SF, Jossey-Bass
 - *excellent evidence-based text for working with children, families, & systems*

References:

- Connors forms may be obtained through Multi-Health Systems (along with instructions for scoring): 908 Niagara Falls Blvd., North Tonawanda, NY 14120-2060, (800) 456-3003.
- Martin T. Stein
 Attention-Deficit/Hyperactivity Disorder: The Diagnostic Process From Different Perspectives
 Pediatrics, Nov 2004; 114: 1453 - 1457.
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Resources

- Connors (CPRS, CAAARS) rating scales may be obtained through Multi-Health Systems (along with instructions for scoring): 908 Niagara Falls Blvd., North Tonawanda, NY 14120-2060, (800) 456-3003.
- Wender-Reimherr Adult ADD Scale can be obtained through http://www.add-pediatrics.com/add/wender.html
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