ADHD: Assessment and Treatment across the Lifespan

Shashank V. Joshi, MD, FAAP
Director of Training in Child & Adolescent Psychiatry
Stanford University School of Medicine

Jessica R. Oesterheld, MD
Tufts University School of Medicine

Question 1

- Which of the listed disorders is the most common co-morbidity with 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 adverse events have been reported with atomoxetine in adults?
  - A-Sexual side effects
  - B-Stevens-Johnson syndrome
  - C-Bradycardia
  - D-Hypotension
  - E-None of the above

Question 3

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

Question 4

- 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 has off-label use for ADHD
  - E-All of the above

Question 5

- Which 2 of the following instruments are useful in diagnosing adult ADHD?
  - A-CAARS
  - B-CARS
  - C-BAARS
  - D-WRAADS
  - E-CARBS

Preview

- History of ADHD
- Subtypes of ADHD and co-morbidities
- NE and DA pathways
- MTA study
- Medication Treatments for pediatric ADHD
- Adult ADHD

Educational Objectives

- By the end of this session, participants should be able to:
  - Describe common features of ADHD and important aspects of history and diagnosis
  - List the 4 currently FDA-approved medications, and describe differences in duration, benefits and side effects
  - Incorporate psychological aspects of pharmacotherapy into daily practice
  - Refer parents and teachers to useful resources on ADHD

Teaching Points

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

ADHD:

- Clinical characteristics:
  - *some combination of* severe inattention, hyperactivity, and impulsivity that begins in childhood, and often persists into adult yrs.
  - *Must cause functional impairment across settings, and must be developmentally relevant*
  - some symptoms should be present before age 7

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

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 ***across settings*** (home, school)
- ***Clinically significant*** 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

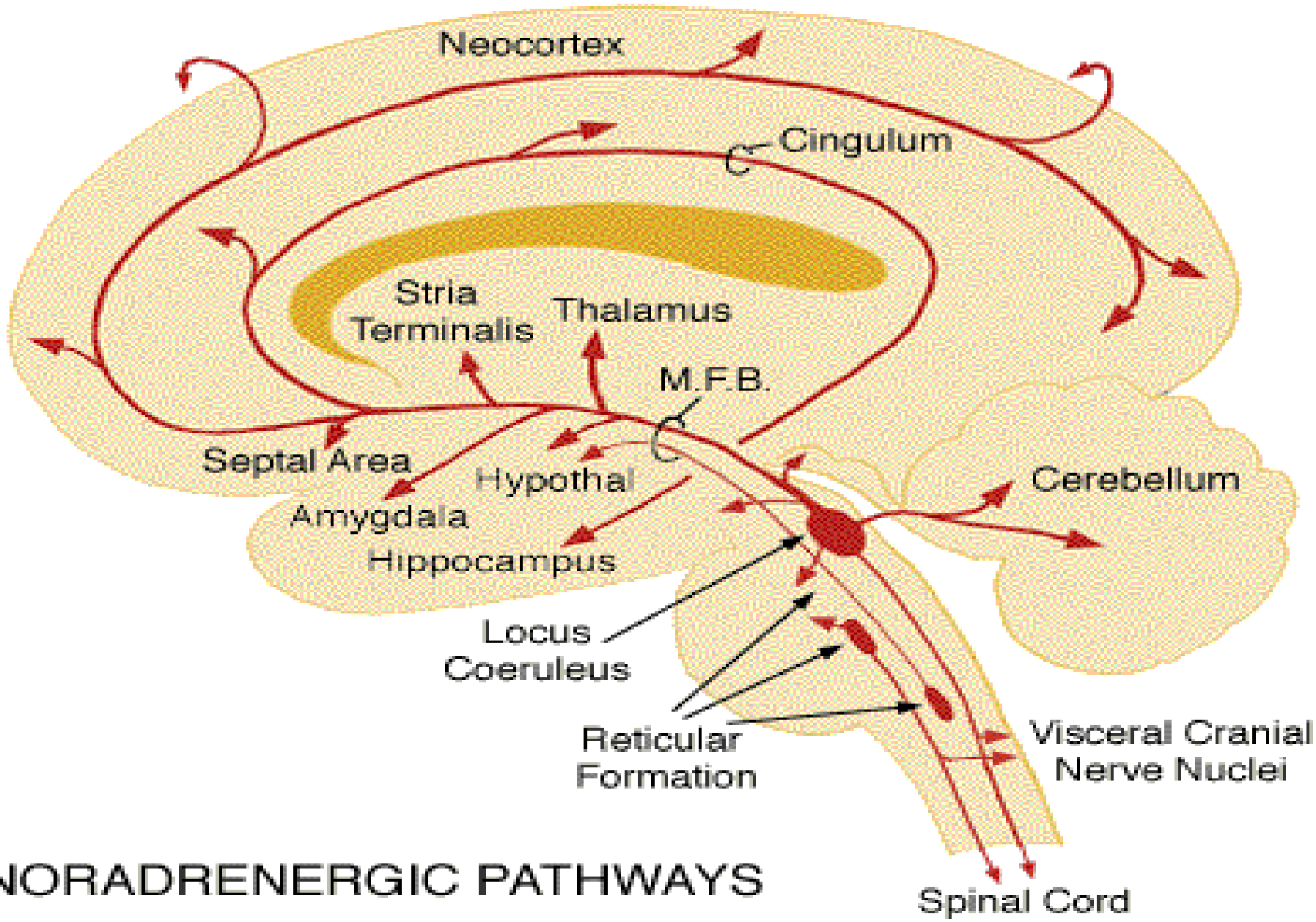
- In children who have good primary care, other diagnostic tests are not *routinely* indicated
  - EEG's indicated only if a history of seizure d/o or clinically significant lapses in consciousness exists
  - Continuous Performance Tests (CPT's) are useful in research settings only
    - measures of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

Practice Guidelines

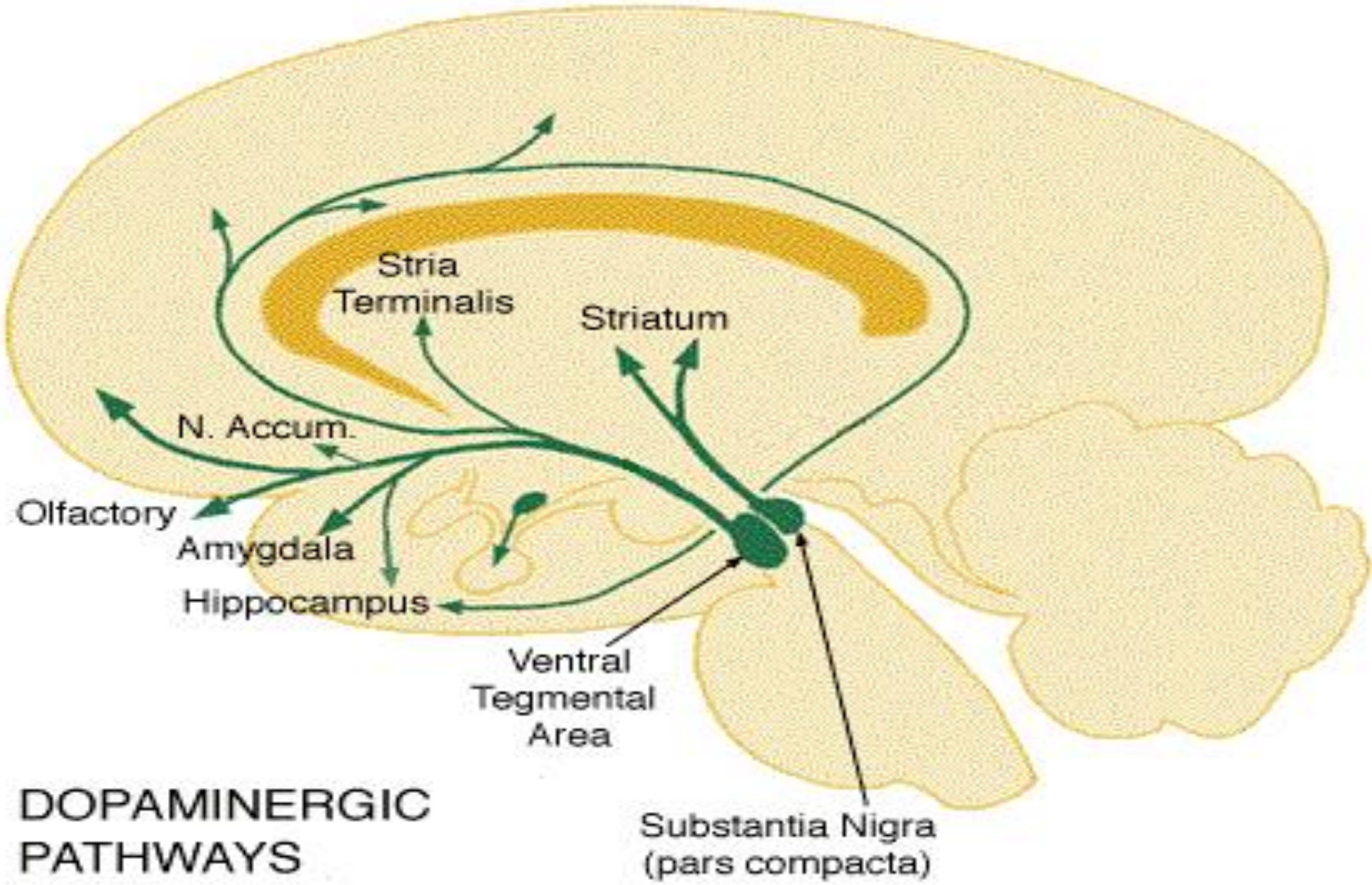
- Summary
  - Use explicit criteria for diagnosis
  - Obtain history from more than 1 setting
    - sx must be severe enough to cause functional impairment
  - Screen for co-existing conditions
- May need 2-3 visits for full work-up
  - parent and teacher questionnaires may be faxed for efficiency
 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



NORADRENERGIC PATHWAYS



DOPAMINERGIC PATHWAYS

Neuroimaging

- MRI
  - Loss of the normal L > R asymmetry, smaller brain volumes of specific structures, esp. L caudate, smaller white matter vol of R frontal lobe
    - PFC, BG--both rich in DA receptors
      - 5-10% decrease in volume
    - Decreased volume of anterior-superior hemisphere
  - 5% decrease in R cerebellar volume, 4% reduction in intracranial volume; Unaffected siblings: up to 9% decrease in selected prefrontal and occipital areas
    - Durston, et al (2004): *J Amer Acad Child Adol Psychiatry*; 43(3); 332-340

Legal Rights of the Student and Obligations of the School District (adapted from Robin, 1998)

- Section 504 of the Rehabilitation Act of 1973
- Americans with Disabilities Act (1990)
- IDEA / IDEIA: Parts B,C (1990, 1997; 2004, 2007)
- The PCP should obtain specific school history at each visit
  - Inquire about strengths, challenges, and school connections
  - Ask about specific classroom modifications and whether a 504 or individualized education plan (IEP) exists

IDEA, Pt B

- Requires public schools in the US to provide a ***free and appropriate education*** 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
  - www.schoolpsychiatry.org

ADHD Treatments (Medication options)

- Teaching Points
  - Warnings about ADHD drugs should NOT dissuade providers from using these drugs
  - Psychostimulants remain the drugs of choice for ADHD
  - It is important to “fine tune” medications by ascertaining effects over the day

Warnings about ADHD drugs

- 12/04 Strattera: black box warning about possible hepatitis following 2 reports of hepatitis
- 2/05 Adderall:FDA Alert- should not be used in individuals with underlying cardiac abnormalities following 12 sudden unexpected deaths over time Adderall in USA; only XR available in Canada and pulled from market
- 6/05 Ped Adv Com of FDA-Will delay labeling change to all MPH products of side effects of psychiatric (visual hallucination, psychosis, aggression) and cardiovascular until amphetamines and atomoxetine also evaluated in early 2006
- 6/05 Lilly observed increase in aggression and hostility “not statistically significant”, but will add information to Strattera label voluntarily

Warnings about ADHD drugs

- 10/05 Canada re-allowed Adderall XR back on market
- 11/05 FDA requires Black Box warning on Strattera for increased risk of suicidality 4/1000
- 2-3/06 FDA advisory committee recommends black box warnings for CV risk on psychostimulants
  - Committee votes only a parent guide and NOT a black box warning
- 3/06 European review highlights increased risk of seizures and QTc prolongation with Strattera

Special Issues: Pharmacotherapy in Youth

- Clinician must have good working alliance with both the patient AND the parents (a dual alliance)
- Children and (especially) teens may be reluctant consumers
- Children should be told that they may not recognize changes in themselves before the first medication trial
- Importance of school placement and teacher-doctor alliance
- Each school may have different requirements for medicating children
- From MTA study (discussed later), parents recognize side effects and teachers recognize efficacy

ADHD Treatments

- MTA study: *Arch Gen Psychiatry* 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
  - *ADHD symptoms*: 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*

- Note that the "medication management" in this study occurred for 30 minutes, 1x per month
  - *"usual community care" average for visit frequency was 1-2x per year*

ADHD Treatments

- MTA study: cont'd.
  - *Non-ADHD symptoms*: (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
- 13 % placebo response in MTA study
  - May have been related to alliance with MD and research team

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)

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ADHD Treatments (medication options)

- Established Treatments
  - Psychostimulants (1st line)
  - Atomoxetine (1st line)
  - Bupropion (2nd line)
  - Tricyclic antidepressants (TCAs: 2nd line)
  - Guanfacine extended release, recently FDA approved as Intuniv, for ages 6-17
- Probable Efficacy
  - Alpha-2 agonists (clonidine, guanfacine)
  - Modafinil

ADHD Treatments (medication options)

- Possible efficacy
  - Omega 3-6-9 Fatty Acids
    - For excellent review, see Freeman, et al. Jnl Clin Psychiatry 2006
- Effective, but impractical: MAOIs
- *Likely ineffective*
  - SSRIs
  - Caffeine
  - St. John's Wort

Stimulants

- “stimulate” certain areas of the brain to focus better
  - FDA classifies a substance as “psychostimulant” if nucleus accumbens is activated
- in use for “behavioral disorders” in children since 1930’s
- many studies to document safety and efficacy
- 70-85% response rate
  - do not use this to confirm diagnosis!

Stimulants

- benefits: improved focus, concentration, attention span; reduced hyperactivity, impulsivity, and fidgeting
- side effects: irritability, stomachache, headache, dysphoria, zoned-out effect, appetite suppression, sleep problems, height velocity slow-down (<10%)
- Amphetamine formulations may produce more sleep/ appetite problems, especially 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
  - Children under 6 years old may be safely treated, starting with methylphenidate, once all psychosocial treatments have been implemented
    - PATS (Pre-school ADHD Treatment Study) is one of many to document safety and efficacy
      - Young children may be more sensitive to side effects
      - Consider weight-based dosing for children under 25 kg: 1mg/kg/day (MPH); 0.5 mg/kg/day (AMPH)

Methylphenidate Formulations

Brand	Type	Dosage forms (mg)	Est. duration (hrs)	Max daily dose [mg] *Range 0.3-1.0mg/kg/day*
Generic	IR	5,10,20	2.5 - 4	[60]
Ritalin	IR	5,10,20	2.5 - 4	[60]
	SR	20	6 - ?	
	LA***	20	8-10	
Methylin	IR*	5,10,20	2.5 - 4	[60]
	ER	5,10,20	6 -8	
Focalin	IR	2.5,5,10	3-5	[20-30]
	XR***	5, 10, 15, 20	8-10	
Metadate	ER	10,20	6-8	[60]
	CD***	20	8 -12	
Concerta	ER	18, 27,36,54	10 - 12	[72]
Daytrana	patch	10, 15, 20, 30	9-12	[30]

[ ] Some patients may tolerate higher doses.
* Available in chewable tablets and liquid
*** May be sprinkled on food
Chart adapted from Glen R. Elliott, PhD, MD

Amphetamine Formulations

Brand	Type	Dosage forms (mg)	Est. duration (hrs)	Max daily dose (mg) *Range 0.15-0.5 mg/kg/day*
Generic	IR	5,10,20	3-6	40 *
Dexedrine	IR	5,10	4-5	40 *
	Spansules**	5, 10, 15	5-9	
Adderall	IR	5, 7.5, 10, 12.5, 15, 20, 30	4-6	40*
	XR**	5-30 mg , (in 5-mg increments)	8-10	
Vyvanse	Lisdex-amfetamine	20, 30, 40, 50, 60, 70	8-12	70

*Some patients will tolerate higher doses. **may be sprinkled on food
Chart adapted from Glen R. Elliott, PhD, MD

Adderall XR
-delivers mixed salts using immediate and time-released beads:
50% immediate
50% delayed

Concerta
-delivers MPH using immediate release coating and delayed release osmotic mechanism:
22% immediate
78% delayed

Metadate CD
-biphasic delivery of MPH using immediate and delayed release beads in capsule:
30% immediate
70% delayed

Ritalin LA
-biphasic delivery of MPH using immediate and delayed release beads in capsule:
50% immediate
50% delayed

Focalin XR
-biphasic delivery of *dextro* MPH using immediate and delayed release beads in capsule
50% immediate
50% delayed

(note: only the *d*-version of MPH is active, thus only 1/2 the usual MPH dose is used)

Match the formulation with the needs of the patient and family

- Have to know when youth “needs” the psychostimulant (e.g., early in AM for school only, or including homework, peer activities, week-ends)
- Parent and teen sometimes have definite preferences for one or another, and so do HMOs
- Train parents to observe efficacy and side effects through the day and into the evening

How to initiate dosing

- Generally not by weight, unless patients are less than 25 kg (0.3- 1mg/kg/d for MPH)
  - (0.15 - 0.5 mg/kg/d for AMPH)
- Titrate to efficacy or intolerable side effects: start at 5 mg MPH or 2.5 mg AMP
  - Increase by 5 mg MPH, or 2.5 mg AMP every 3-5 days to first target dose, decided upon by doctor and family
  - Get weekly reports and adjust upward, checking for side effects and efficacy

The Art of Fine tuning

- Must have accurate info about child/teen's performance "over the day"; use scales and listen to teachers: titrate as needed

- Can combine short and long-acting preparations
  - if dysphoric at days end, add MPH to Concerta at the end of the school day (no later than 3:30PM); Dex to Dex-spansules at the start of the day because of delayed effect of spansules

The Art of Fine-tuning -II

- If only partial efficacy with stimulants, can "mix and match" with other anti-ADHD drugs (e.g., clonidine / guanfacine, bupropion, atomoxetine TCAs)
- Inform family, and be vigilant about checking for additive sympathomimetic side effects

Common errors in dosing psychostimulants

- Failure to increase dosing slowly to maximum if no side effects (MTA study showed lower dosing in community sample

- Beginning with a dose that is too high
  - “Start low and go especially slow” with patients who are developmentally delayed
- Not assessing the duration of action; (may need to “bunch up “ dosing with IR formulations)
- Failure to use another psychostimulant if the first or second trial fails
- Failure to use input from school

Serious side effects of psychostimulants

- Sudden cardiac death
  - Anecdotal, but not irrelevant
  - Cases thus far have been primarily in patients with pre-existing cardiac conduction defects
  - Ask about history of sudden tachycardia, fainting, and family history of sudden cardiac death prior to initiating
- 30+ cases of psychosis or formal hallucinations: discontinue the medication
- Growth Suppression (MTA 2004, 2009) effects are likely to be made up in late teens or by drug holidays; especially at risk, those with nausea and vomiting
  - Plot heights every 3 months to ensure proper growth velocity

Tics and ADHD (adapted from review by Plizska, 2006)

- Mild or moderate tics occur in a significant number of patients with or without ADHD pharmacotherapy
  - 5-18% of schoolchildren will experience a simple or complex tic in their lifetime
- Tics during ADHD treatment may improve even while psychostimulants are used; discontinue only if serious
- **Lipkin et al**, in a review of 122 children treated with stimulant medication found 9% developed transient tics and <1% developed chronic tics

Lowe et al. *JAMA* 1982;247:1729.
Sverd et al. *JAACAP* 1989;28:574.
Erenberg et al. *Neurology* 1985;35:1346.
Lipkin et al. *Arch Pediatr Adolesc Med* 1994;148:859.

Tics and ADHD (adapted from review by Plizska, 2006)

- Many children with tics and ADHD can tolerate stimulants without an increase in tics
  - **Law & Schachar (1999):** 12-month study, 91 children
    - MPH treatment did not produce significantly more tics than placebo in children with or without mild-to-moderate preexisting tic disorder
  - **Gadow et al (1999):** 24-month study, 34 children with ADHD and tic disorder or Tourette's syndrome
    - stimulant treatment was effective in controlling ADHD symptoms without adversely affecting tics

Induction or Exacerbation of Tics (adapted from review by Plizska, 2006)

- Tics are usually transient
  - Rarely do patients develop a chronic tic disorder
- When tics do occur or are worsened
  - Decrease dose
  - Switch to another stimulant
  - Add adjunctive drug to treat tics
    - Clonidine / guanfacine
  - Try nonstimulant medication
    - Atomoxetine
    - Modafinil

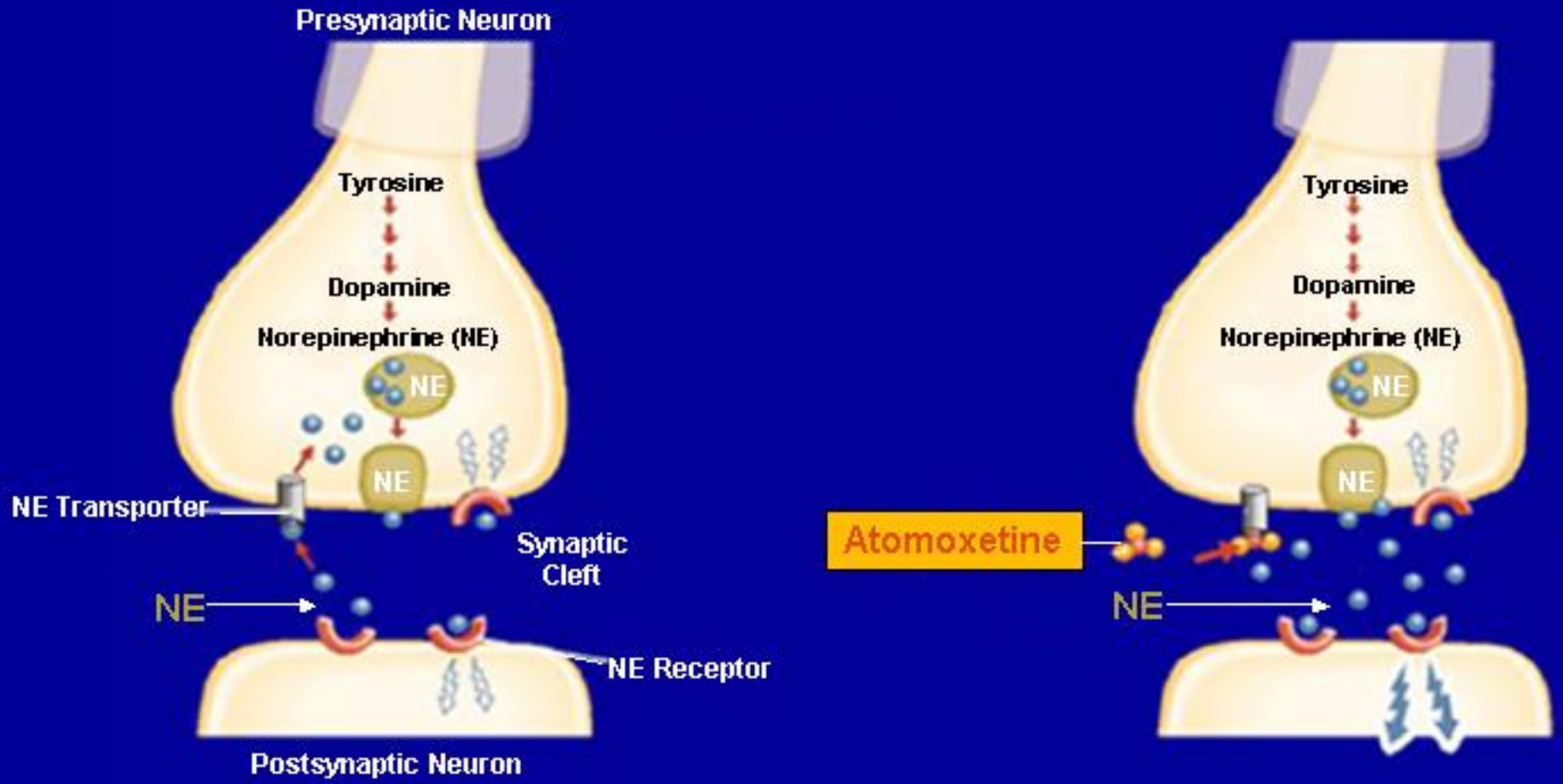
Pemoline (Cylert)
removed from US market 11/05

- Least abuse potential as a stimulant, but can cause insomnia, choreiform movements and tics: Must start low, go slow: may need BID dosing
- Onset of efficacy is rapid and dose-related
- Pemoline is efficacious for ADHD but does not have an impact on conduct disorder or substance abuse in the absence of specific treatment for substance use disorders
- Labeling change; 13 cases of acute hepatic failure since 1975 (4-17 times the expected rate)
  - Pre-check LFTs, educate parents on signs and symptoms of hepatitis:FDA requires biweekly LFTs (impractical)
- Chewable form

ADHD Treatments (other medication options)

- Atomoxetine
  - Potent norepinephrine (NE) reuptake inhibitor
    - highly selective
    - inhibits presynaptic NE transporter

Atomoxetine: Site of Action



ADHD Treatments (medication options)

- Atomoxetine *(not to be confused with 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
  - Total database (Lilly) of several million pediatric and adult patients with ADHD
  - 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 (no activation of dopamine in nucleus accumbens)

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)
  - Assessment of liver function prior to start is optional; monitor for hepatotoxicity

- **Black Box warning** re: teen patients with suicidal thinking
  - 5/1357 patients with suicidal thinking during initial trials
    - 1 of these 5 actually attempted suicide (unsuccessfully)

- Monitor height, weight, pulse and BP
  - Potential exists for decreases in growth (up to 0.5cm per year, 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 (medication options)

- Guanfacine extended release (Intuniv)
  - Released in U.S. Nov 2009; FDA indicated for ADHD (6-17y.o.)
  - Alpha-2a agonist, non-stimulant; non-schedule II
  - T ½ = 17 hours (5 hours to Cmax)
  - Dose range 1-4 mg total daily dose
    - consider 0.05-0.08 mg/kg/day (max 0.12 mg/kg/day)
    - 1mg QD to start, then increase by 1mg weekly, if needed, to 4mg QD
  - Common side effects: **drowsiness, dyspepsia, fatigue
    - Monitor BP and HR for hypotension and bradycardia
- CYP3A4/5 substrate
  - Use cautiously when other medicines are used (potential additive CNS effects, drug interactions)
  - Assess cardiac function with good history

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
  - weaker cognitive benefits than stimulants
  - Dosing/ monitoring
    - Use gradual 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

Cardiovascular parameters for TCAs: When to Call A Cardiology Consult !

	Resting heart beats/min = or >	Resting BP = o r>	PR = or >	QTc = or >
< 10 yrs	110	140/90 or 135/85 > 1/2 time 3 wks	0.18	0.44
>10 yrs	100	150/95 or 140/85 > 1/2 time 3 wks	0.20	0.44

Adapted from Rye and Ryan: *Child and Adolesc Psychiatric Clinics NA* 4:275, 1995

Tricyclic Antidepressants (TCAs)

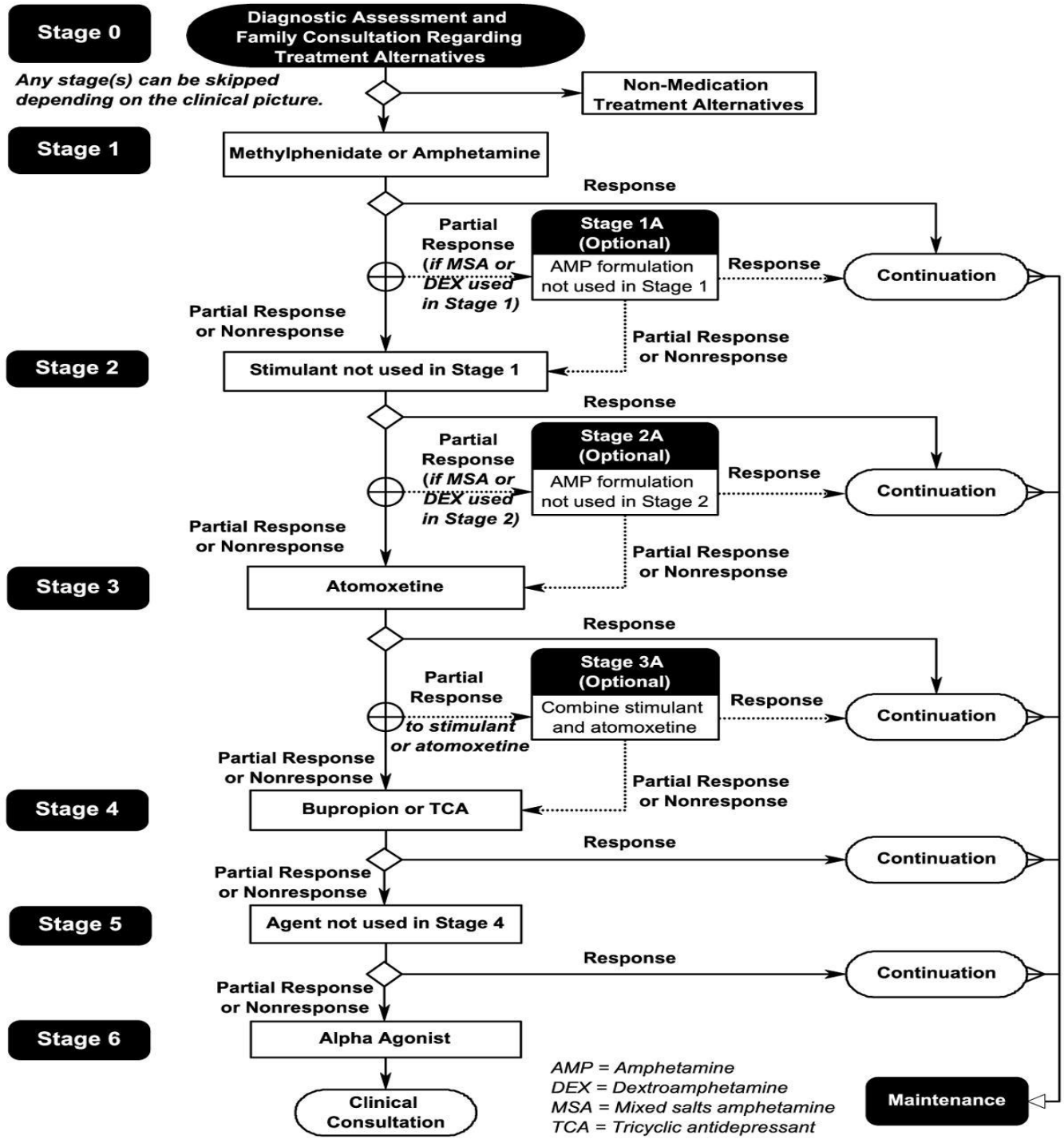
- Clomipramine (*non-routine in kids*)
  - non-selective SRI
  - data to show efficacy, but side effects limit use
  - possible use in co-morbid OCD
  - High seizure risk (1.5% annual risk in adults)
- Desipramine
  - Still used in adults
  - 6 published cases of sudden death in children

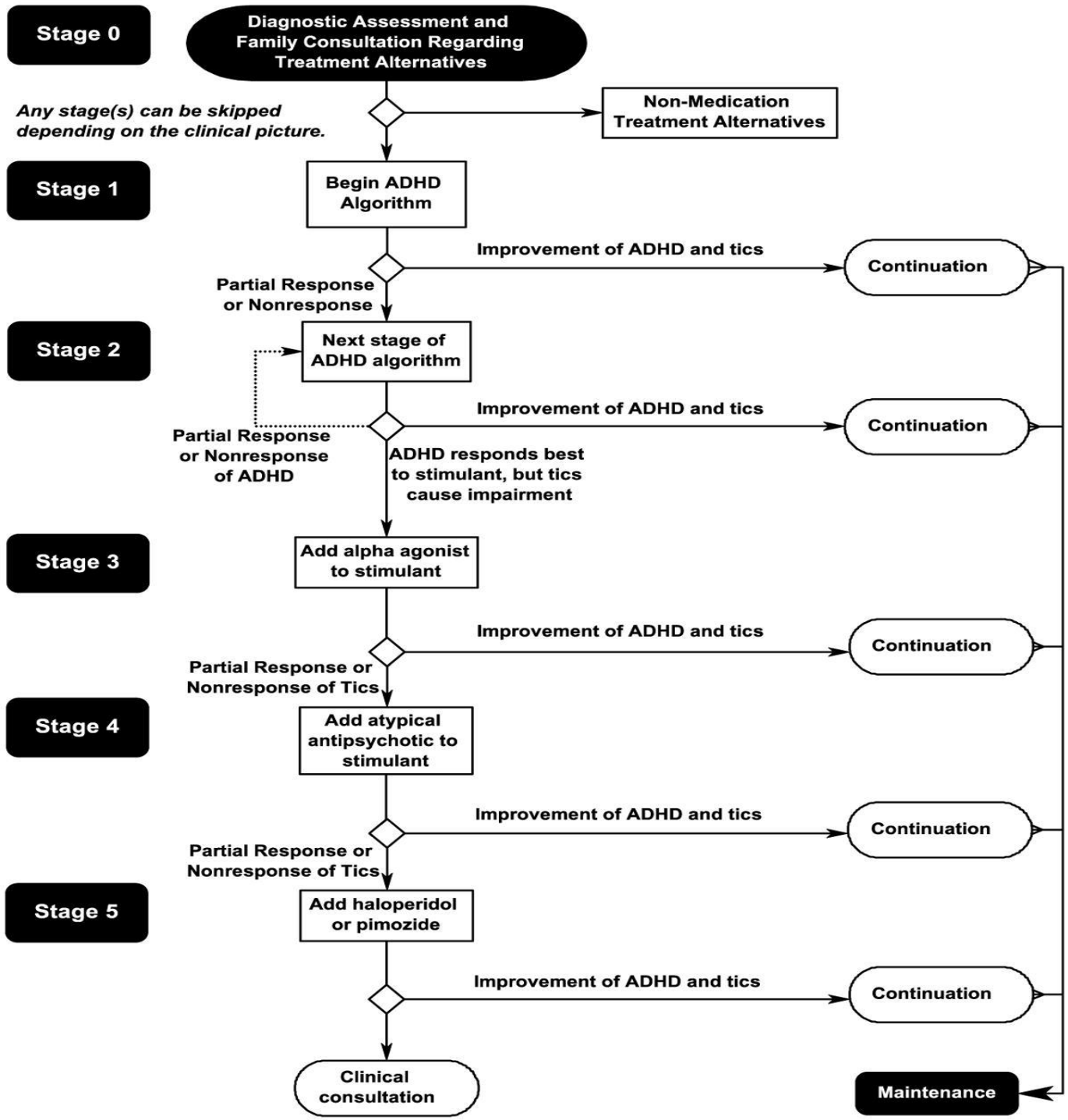
TCAs drug interactions

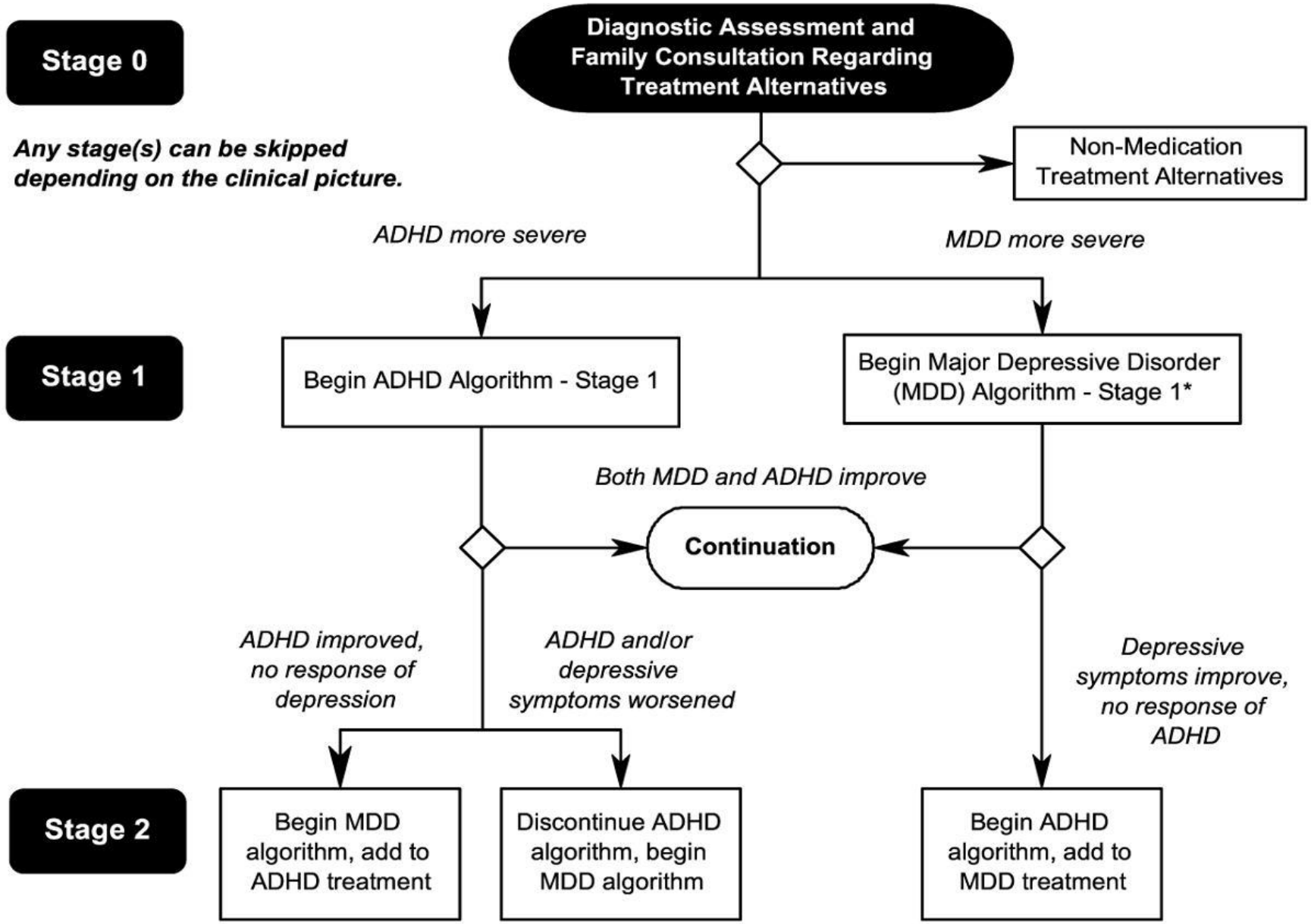
- Very complicated, must be vigilant when using polypharmacy
- TCAs demethylated by variety of CYPs and then hydroxylated via CYP2D6
- Paroxetine/ fluoxetine inhibit CYP2D6, thus decrease clearance up to 400% of CYP2D6 substrates, including TCAs
- Sertraline/citalopram decrease clearance 25% of CYP2D6 substrates

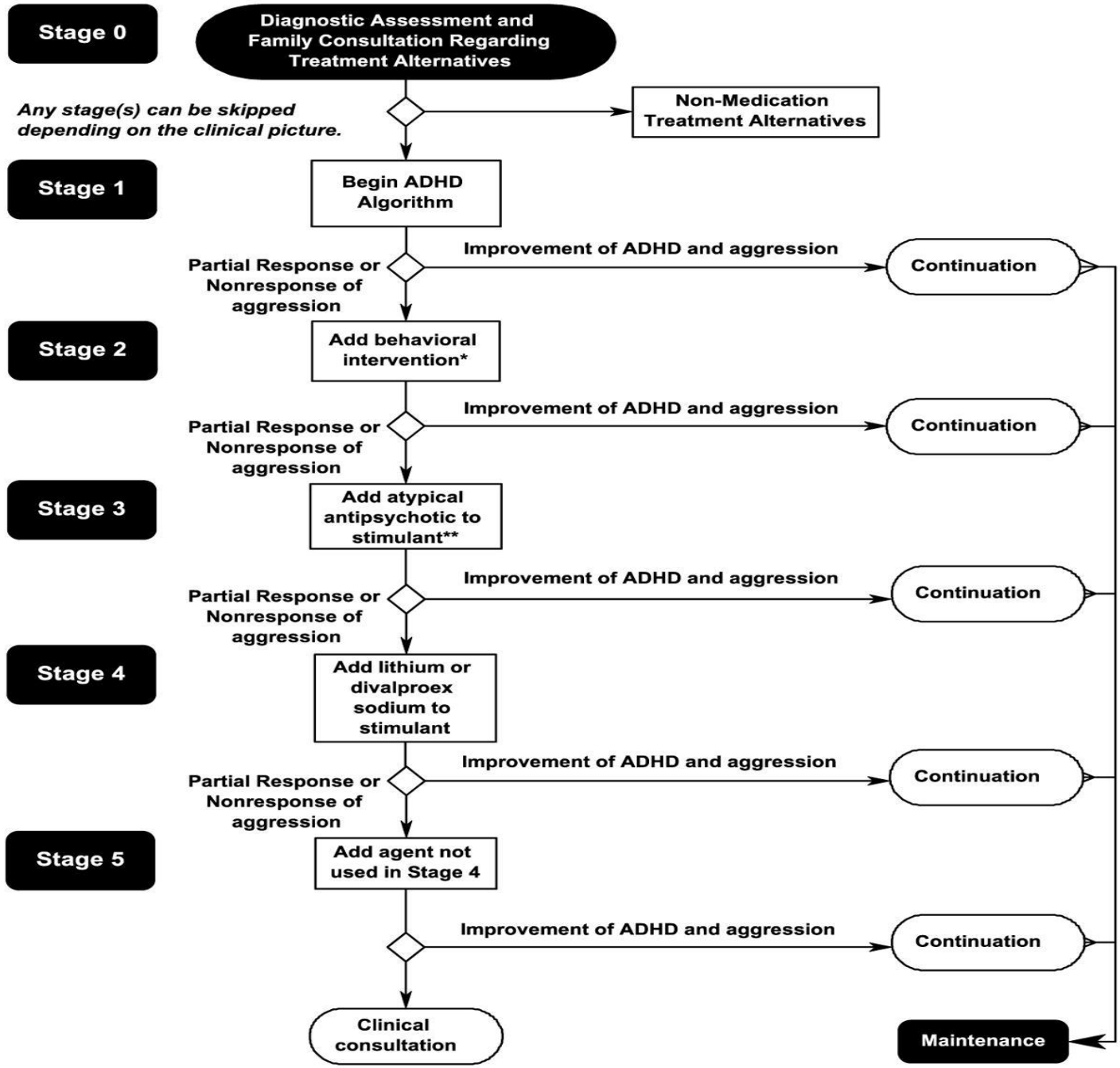
CMAP-ADHD

- http://www.mhmr.state.tx.us/centraloffice/medicaldirector/adhdalgo.pdf
- 4 algorithms: ADHD, with tics, with MDD and with IED
- Tactic Tables: Dosing schedules for Stimulants,TCAs,Bupropion, Alpha Agonists and SSRIs


Stage 0
Diagnostic Assessment and Family Consultation Regarding Treatment Alternatives
Any stage(s) can be skipped depending on the clinical picture.
Non-Medication Treatment Alternatives
Stage 1
Methylphenidate or Amphetamine
Response
Partial Response (if MSA or DEX used in Stage 1)
Stage 1A (Optional)
AMP formulation not used in Stage 1
Response
Continuation
Partial Response or Nonresponse
Partial Response or Nonresponse
Stage 2
Stimulant not used in Stage 1
Response
Partial Response (if MSA or DEX used in Stage 2)
Stage 2A (Optional)
AMP formulation not used in Stage 2
Response
Continuation
Partial Response or Nonresponse
Partial Response or Nonresponse
Stage 3
Atomoxetine
Response
Partial Response to stimulant or atomoxetine
Stage 3A (Optional)
Combine stimulant and atomoxetine
Response
Continuation
Partial Response or Nonresponse
Partial Response or Nonresponse
Stage 4
Bupropion or TCA
Response
Continuation
Partial Response or Nonresponse
Stage 5
Agent not used in Stage 4
Response
Continuation
Partial Response or Nonresponse
Stage 6
Alpha Agonist
Clinical Consultation
AMP = Amphetamine
DEX = Dextroamphetamine
MSA = Mixed salts amphetamine
TCA = Tricyclic antidepressant
Maintenance


Stage 0
Diagnostic Assessment and Family Consultation Regarding Treatment Alternatives
Any stage(s) can be skipped depending on the clinical picture.
Non-Medication Treatment Alternatives
Stage 1
Begin ADHD Algorithm
Improvement of ADHD and tics
Continuation
Partial Response or Nonresponse
Stage 2
Next stage of ADHD algorithm
Improvement of ADHD and tics
Continuation
Partial Response or Nonresponse of ADHD
ADHD responds best to stimulant, but tics cause impairment
Stage 3
Add alpha agonist to stimulant
Improvement of ADHD and tics
Continuation
Partial Response or Nonresponse of Tics
Stage 4
Add atypical antipsychotic to stimulant
Improvement of ADHD and tics
Continuation
Partial Response or Nonresponse of Tics
Stage 5
Add haloperidol or pimozide
Improvement of ADHD and tics
Continuation
Clinical consultation
Maintenance


Stage 0
Diagnostic Assessment and Family Consultation Regarding Treatment Alternatives
Any stage(s) can be skipped depending on the clinical picture.
Non-Medication Treatment Alternatives
ADHD more severe
MDD more severe
Stage 1
Begin ADHD Algorithm - Stage 1
Begin Major Depressive Disorder (MDD) Algorithm - Stage 1*
Both MDD and ADHD improve
Continuation
ADHD improved, no response of depression
ADHD and/or depressive symptoms worsened
Depressive symptoms improve, no response of ADHD
Stage 2
Begin MDD algorithm, add to ADHD treatment
Discontinue ADHD algorithm, begin MDD algorithm
Begin ADHD algorithm, add to MDD treatment



* Evaluate adequacy of behavior treatment after inadequate response at any stage.
**If patient is an imminent threat to self or others, atypical antipsychotic may be started with behavioral teatment.

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
    - May have paradoxical beneficial effect on appetite when combined 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 *JAACAP* 38:5, May 1999, pp614-622, for debate on this often-used 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

Pre-treatment workup for Clonidine

- Check for history of arrhythmias, relatives' early sudden death
- Check for Raynaud's Disease, Diabetes Mellitus
- ECG if indicated (Biederman 1999, Kofoed 1999, Oesterheld 1996)
- Orthostatic blood pressure
- Pulse

Clonidine: Adverse effects

Common

- Sedation, dry mouth, dizziness
- Nighttime awakenings, nightmares, night terrors

Serious

- Idiosyncratic aggravation of cardiac arrhythmias
- Danger of rebound hypertension if stopped suddenly
- Depression in about 5%
- *Hyper*glycemia

- ***No contraindication to use with psychostimulants***, as of 2008

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
- Long-acting form of guanfacine (Intuniv) was approved in Nov 2009, and has FDA indication for pediatric ADHD

Modafinil (Provigil)

- 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
- Current 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)

Modafinil in ADHD (adapted from review by Pliszka, 2006)

- Double blind, placebo controlled trial
- 190 patients, ages 6-17 years
- 7 week trial, 2:1 randomization assignment to modafinil or placebo
- Dose: < 30 kg: 340 mg
  - 30kg or heavier: 425 mg-fixed titration

Modafinil in ADHD

- Submission to FDA in 2006 for Pediatric and Adult ADHD indication with new trade name, “Sparlon”, and 2 additional positive studies
  - Rejected due to safety concerns over possible Stevens-Johnson syndrome in 3 pediatric and 5 adult patients

Adult ADHD

- Still regarded as “controversial”, despite presence of continued morbidity in 30-40% of children diagnosed, and 50% + of teens transitioning to young adulthood; Prevalence in adults = 4-5% (Rostain, 2008)
- Diagnosis is primarily clinical
  - Useful tools include Connors Adult ADHD Rating Scales (CAARS), and Wender-Reimherr Adult ADD Scale (WRAADS)
  - Self-assessment, Adult ADHD Self Report Scale (NYU)
    - http://www.med.nyu.edu/psych/assets/adhdscreen18.pdf
  - 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 TR criteria: Adult ADHD is classified as ADHD NOS in DSM-IV TR; 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*

- *ADHD remains a clinical diagnosis* 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,CAARS (Connors Adult ADHD Rating Scales), and WRAADS (Wender-Reimherr Adult ADD Scale)
- 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 ***coexisting psychiatric conditions*** and should provide rational polytherapy when justified

- Ongoing research and clinical input on the criteria for ADHD in adults, including ***long-term follow-up studies of DSM-diagnosed children*** 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 ***minimum of four*** (4), and not six (6) current hyperactive-impulsive or inattentive symptoms
- Clinicians should make efforts to ***obtain third-party corroboration*** whenever available and should carefully document the evidence of the disorder as justification for treatment
- Clinicians who prescribe medication should ***carefully monitor treatment response*** 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 over-reactivity
- 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

Medications used in Adult ADHD

- Use pediatric and adolescent guidelines to start treatment, as in slides 42-50
- Most Adults will tolerate larger doses than typical doses used in pediatrics
  - Dosing of Adult ADHD does not typically need to exceed FDA maximums for pediatric dosing, though some exceptions exist
    - 40 mg Amphetamine (70 mg lis-dexamfetamine)
    - 60-72 mg Methylphenidate
    - 100 mg Atomoxetine
  - May be more responsive to TCAs than children/teens
  - See Rostain article (2008) for recent update

Adult

Wilens, et al, 2004

Table. Medications Used in Adults With Attention-Deficit/Hyperactivity Disorder

Medication	Daily Dose, mg*	Daily Dosage Schedule	Common Adverse Effects
Stimulants			
Methylphenidate	20-100	Twice to 4 times	Insomnia Decreased appetite/weight loss Headaches Edginess
Amphetamine			
Dextroamphetamine and mixed amphetamine salts†	10-60	Twice to 3 times	Insomnia Decreased appetite/weight loss Headaches Edginess Mild increases in pulse/blood pressure
Magnesium pemoline	75-150	Once or twice	Insomnia Decreased appetite/weight loss Headaches Edginess Abnormal liver function test results
Noradrenergic agents			
Atomoxetine	40-120	Once or twice	Sleep disturbance Gastrointestinal tract distress, nausea Headache Mild increases in pulse/blood pressure
Antidepressants			
Tricyclics			
Desipramine; imipramine	100-300	Once or twice	Dry mouth Constipation Vital sign and electrocardiographic changes
Nortriptyline	50-200	Once or twice	Dry mouth Constipation Vital sign and electrocardiographic changes
Bupropion	150-450	Once or twice	Insomnia Risk of seizures (in doses >6 mg/kg) Contraindicated in bulimia

*Denotes typical daily doses, which may exceed US Food and Drug Administration–approved dosing.
†US Food and Drug Administration approved for adults with attention-deficit/hyperactivity disorder.

Psychological issues in pharmacologic management

- 30-70 % of all pediatric psychiatric prescriptions are not filled or are taken improperly (Joshi, 2006)
- Why is psychological management important?
- Parent issues:
  - Ambivalence re: need for meds or having “caused” the illness
  - Inadequate parental surveillance of adherence
  - Misunderstanding of doses, serum levels, and onset of effects
  - Internet information and misinformation
- Child/Teen issues:
  - May feel “damaged” or very different because of need to take medication
  - Often ascribe particular meaning and significance to both benefits and side effects
- School issues:
  - Pharmacotherapist should strive for ongoing communication with teachers and any other involved school staff
  - Staff should be coached on how to ascribe improvement/benefits from treatment more to student effort than to medication

Psychological issues in pharmacologic management

- All of our actions have potential meaning to the patient and family
  - What language do we use to explain the theoretical nature of their child's illness?
  - How well do we attend to the ***Dual Alliance*** in the office, and ***Supporting Alliance*** in the community? (see Lecture on Therapeutic Alliance in Pediatric Pharmacotherapy in this series)
- Many patients (especially teens) attach meaning to the medication itself
  - Once taken, it may become 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***

Question 1

- Which of the listed disorders is the most common co-morbidity with 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 adverse events have been reported with atomoxetine in adults?
  - A-Sexual side effects
  - B-Stevens-Johnson syndrome
  - C-Bradycardia
  - D-Hypotension
  - E-None of the above

Question 3

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

Question 4

- 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 has off-label use for ADHD
  - E-All of the above

Question 5

- Which 2 of the following instruments are useful in diagnosing adult ADHD?
  - A-CAARS
  - B-CARS
  - C-BAARS
  - D-WRAADS
  - E-CARBS

Answers

- 1-c
- 2-a
- 3-a
- 4-e
- 5-a, d

Resources

- Kaye DL, et al: Child and Adolescent Mental Health; 2003; Philadelphia: Lippincott

  excellent guide for both medical and non-medical providers, about the cost and size of the Harriet Lane Handbook

- Wilens, Timothy: Straight Talk about Psychiatric Medications for Kids, revised edition, Guilford Press, 2004

  well-written and recently revised; among the best medication resources for parents, teachers, nurses, and therapists

- Martin A, Scahill L, and Kratochvil C (eds.), Pediatric Psychopharmacology: Principles and Practice, 2nd ed., 2010 , NY: Oxford Univ Press

  ** The standard textbook of pediatric psychopharmacology, well-written and updated in 2010**

Resources

- **Connors (CPRS, CTRS, 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.**

- Vanderbilt Scales for rating ADHD are available for *free* through http://www.brightfutures.org/mentalhealth/pdf/tools.html

- **Wender-Reimherr Adult ADD Scale can be obtained through http://www.add-pediatrics.com/add/wender.html**
  - **Ref- Ward MF, Wender PH, Reimherr FW: The Wender Utah Rating Scale: an aid in the retrospective diagnosis of childhood attention deficit hyperactivity disorder *Am J Psychiatry*. 1993 Jun;150(6):885-90.**

- **Golstein S & Ellison AT: Clinician's Guide to Adult ADHD, 2002; London, Academic Press**

- **Barkley RA: Attention Deficit Hyperactivity Disorder: A Handbook for Diagnosis and Treatment, 3rd Ed. 2007; NY, Guilford**

References:

- Slides 22 and 23 are courtesy of H. Brent Solvason, MD, PhD

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- MTA Cooperative Group
  National Institute of Mental Health Multimodal Treatment Study of ADHD Follow-up: Changes in Effectiveness and Growth After the End of Treatment**;** *Pediatrics*, Apr 2004; 113: 762 - 769.

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  - **Revision and update of the above in Pliszka et al. : *JAACAP*. 2006 Jun;45(6):642-57**

- Pliszka SR, and the AACAP Work Grp on Quality Issues: Practice parameter for the assessment and treatment of children and adolescents with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry*. 2007 Jul;46(7):894-921

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- Greenhill, LL, et al. A Randomized, Double-Blind, Placebo-Controlled Study of Modafinil Film-Coated Tablets in Children and Adolescents with Attention-Deficit/Hyperactivity Disorder, *JAACAP*, 45(5), May 2006

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Resources:

- Classroom strategies and modifications
  - www.schoolpsychiatry.org
- Parent Education and Empowerment
  - www.parentshelpingparents.com
  - www.schwablearning.org / www.greatschools.net
  - www.chadd.org
  - www.aacap.org (Amer Acad of Child & Adol Psychiatry: Facts for Families)
  - *www.parentsmedguide.org* (antidepressants)
  - www.add.org
  - NAMI (www.nami.org)