Adult ADHD: Assessment and Treatment

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Question 1

- 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 2

- 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 3

- Which of the following statements about bupropion is true?
  - A-It should not be used in patients with a history of seizure disorder
  - B-It should not be used in patients 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

Educational Objectives

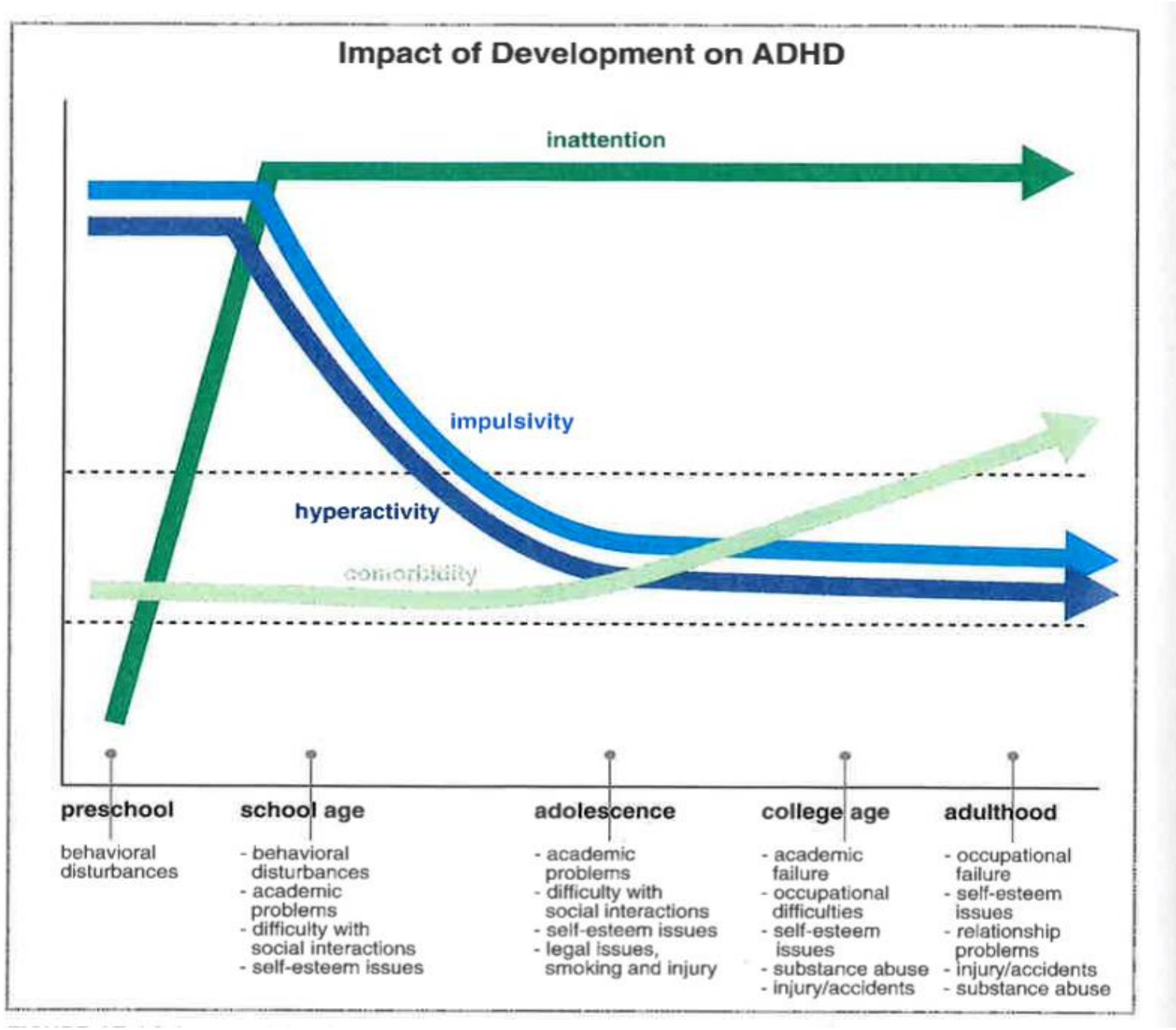
- By the end of this session, participants should be able to:
  - Describe common features of ADHD and important aspects of history and diagnosis
  - List the currently FDA-approved medications, and describe differences in duration, benefits and side effects
  - Refer to useful resources on ADHD

Teaching Points

- ADHD is a *clinical* diagnosis
- 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

Adult ADHD

- Occurs in 50% or more of teens with ADHD transitioning to adulthood
- Prevalence in adults = 4-5% (Rostain, 2008)



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Adult ADHD:

- Clinical characteristics:
  - *Some combination of* severe inattention, hyperactivity, and impulsivity that begins in childhood, and often persists into adult years

ADHD-Inattentive type

- Failure to pay close attention to details / frequent careless mistakes
- Difficulty sustaining attention in tasks
- Not listening when spoken to
- Not following through on instructions, and failure to finish tasks

ADHD-Inattentive type

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

ADHD- Hyperactive/Impulsive type

- Fidgets with hands/ feet, or squirms in seat
- Leaves seat when sitting is expected
- 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)

Adult ADHD (McGough & Barkley, 2004)

- ***Minimum of five*** (5) 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

Other criteria

- Some impairing symptoms were present before age 12
- Impairment ***across several settings*** (home, school, work)
- ***Clinically significant*** impairment in social, academic or work functioning
- Other conditions must be considered as source of symptoms

Wender-Reimherr Adult Attention Deficit Disorder Scale(WRAADDS)

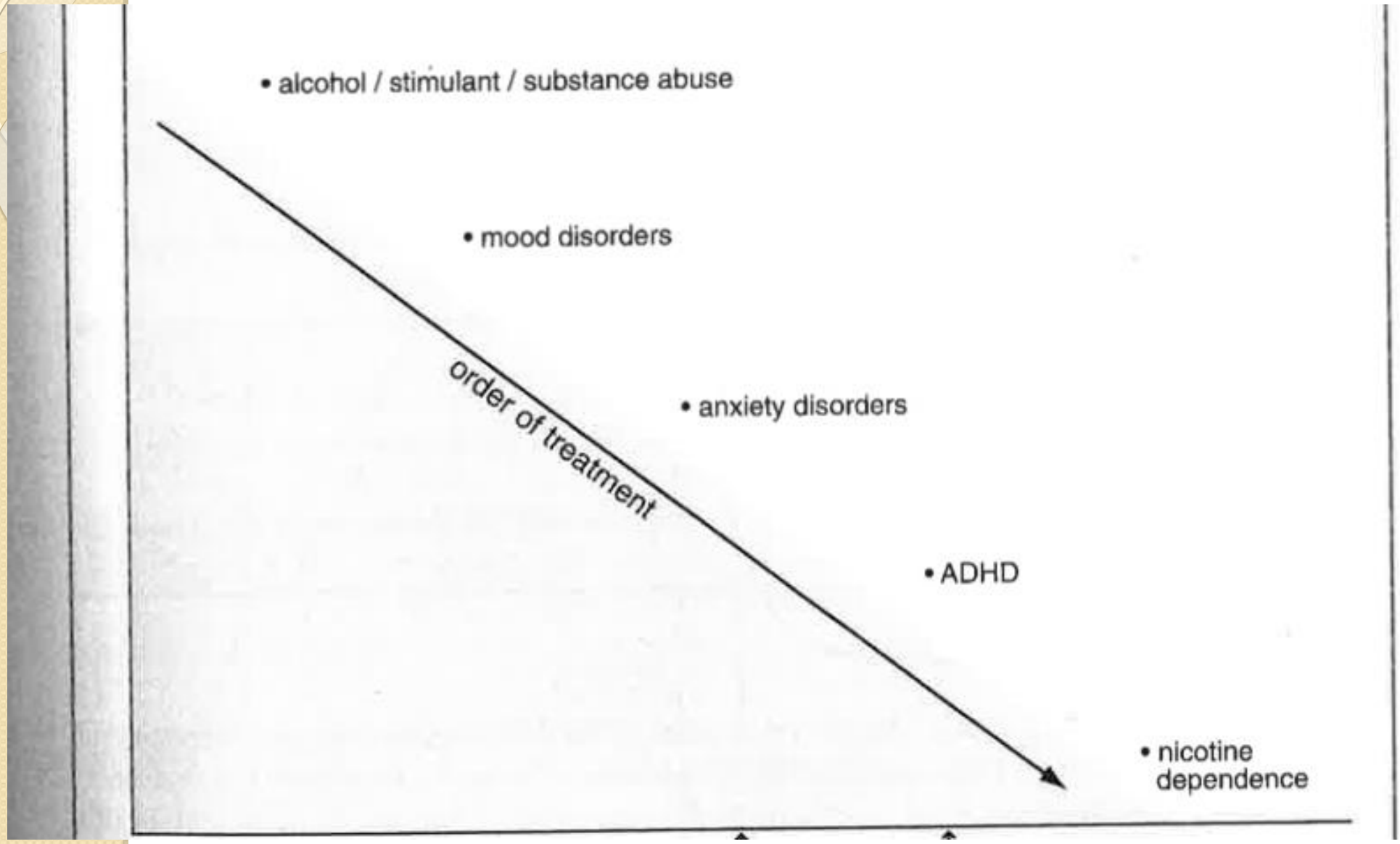
- 7 primary symptom areas
  - 4 mirror DSM: Attention difficulties, Disorganization, Hyperactivity/Restlessness, Impulsivity
  - 3 cover Emotional Dysregulation: Temper, Affective lability, Emotional over-reactivity
- May more accurately describe adult phenotype
- *Requires subject to give retrospective history*
- Critique: may exclude inattentive type

Conners Adult ADHD Rating Scale (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

Co-morbidity

- Co-existing conditions must also be evaluated
- 30-50% of ADHD may be co-morbid with other mental disorders:
  - Mood disorders (depression/bipolar disorder)
    - Poor outcome in co-morbid states (higher risk for suicide)
  - Anxiety Disorders- 25% or more
  - Learning Disorders- up to 60% in non-PCP settings



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Medications used in Adult ADHD

- 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 lisdexamfetamine
    - 60-72 mg Methylphenidate
    - 100 mg Atomoxetine
  - May be more responsive to TCAs than children/teens

ADHD Treatments (medication options)

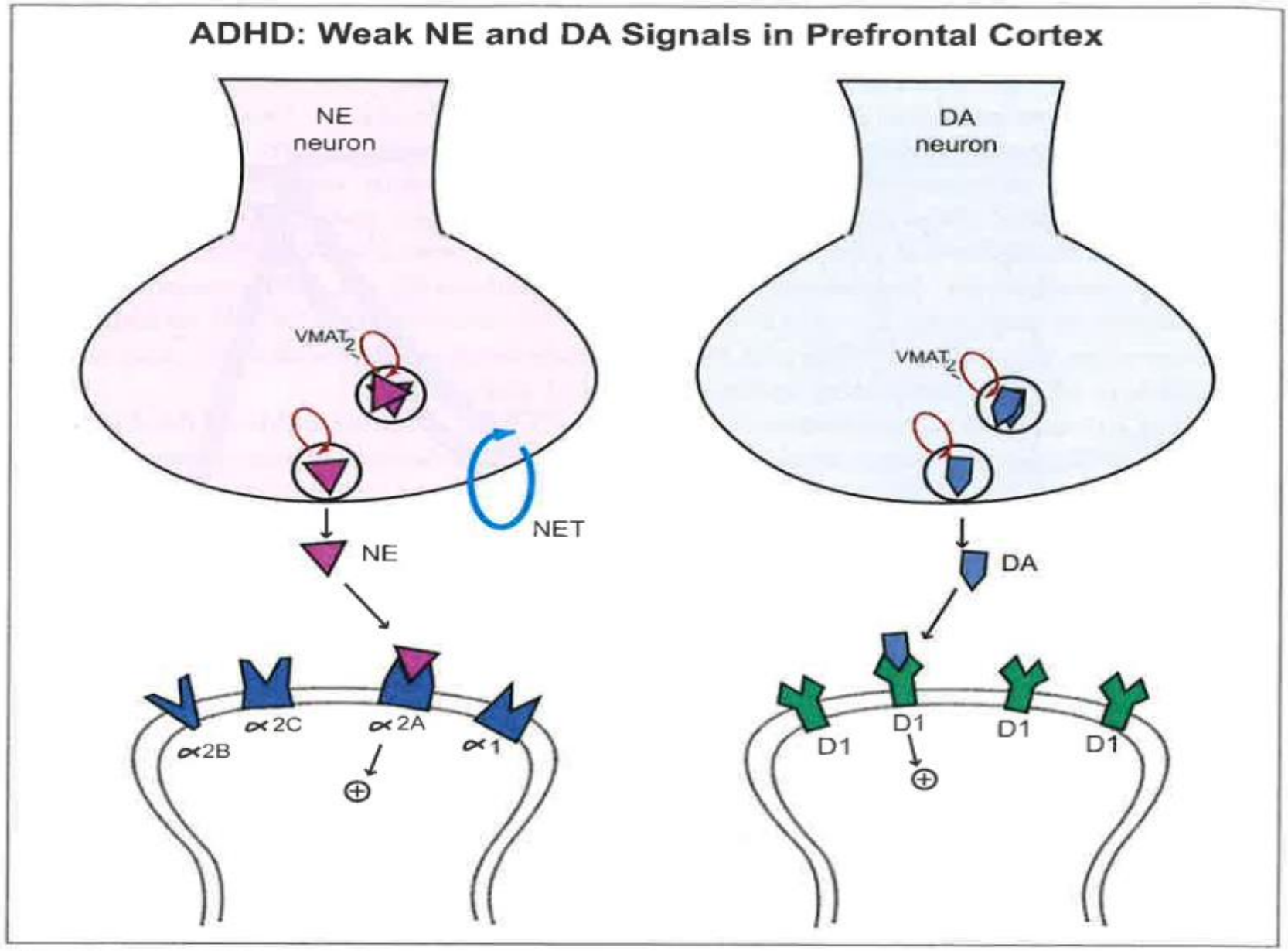
- Established Treatments
  - Psychostimulants (1st line)
  - Atomoxetine (1st line)
  - Bupropion (2nd line)
  - Tricyclic antidepressants (TCAs: 2nd line)
  - Guanfacine extended release, recently FDA approved as Intuniv, for ages 6-17
- Probable Efficacy
  - Alpha-2 agonists (clonidine, guanfacine)
  - 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 1930s
- Many studies to document safety and efficacy
- 70-85% response rate



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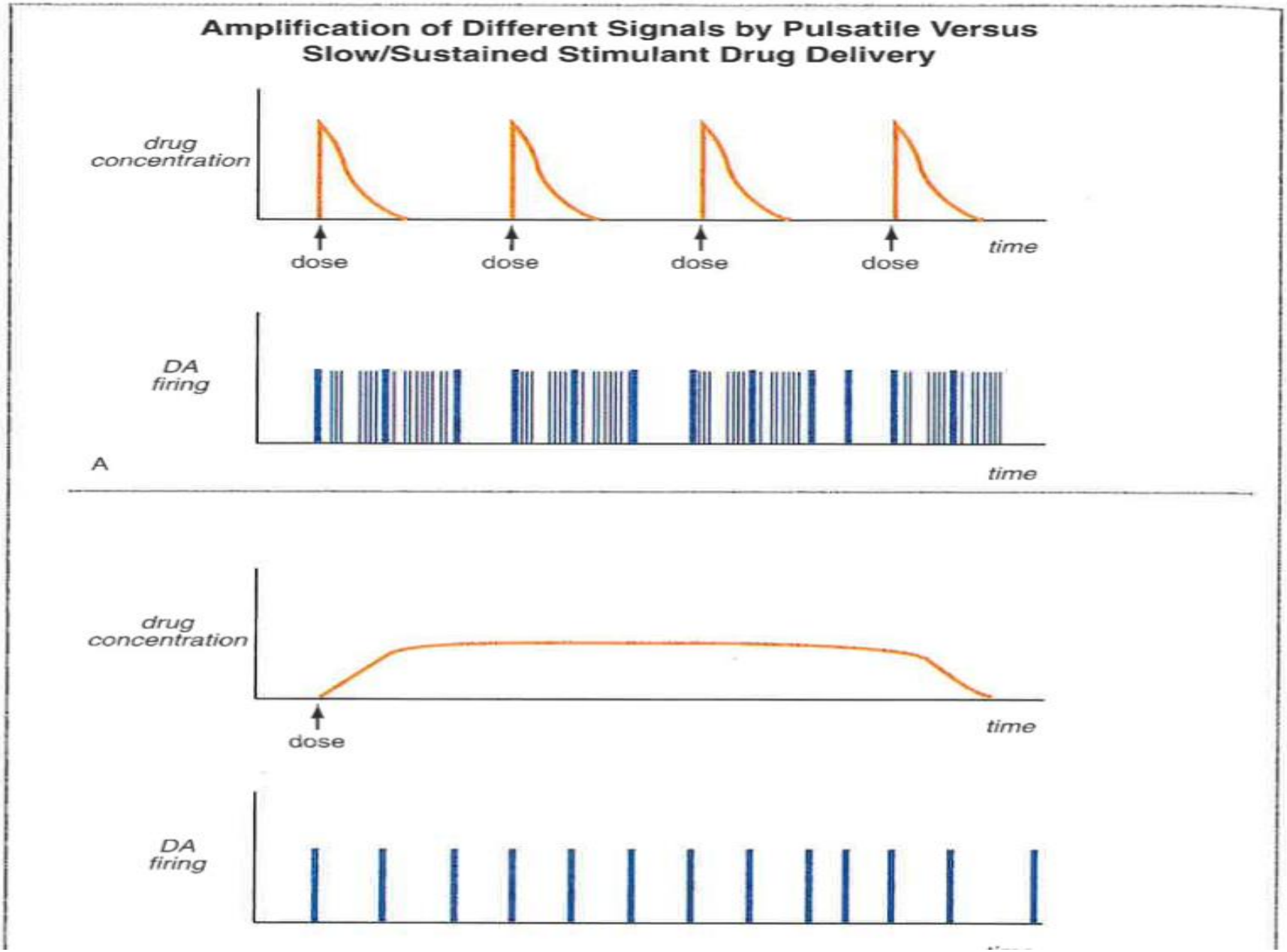
Stimulants

- 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



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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)

Lisdexamfetamine dimesylate

- Pro-drug of dextroamphetamine
- Approved for ADHD and binge eating disorder
- May have less diversion potential
- Half life of 10-14 hours
- Starting dose of 30mg/day, can titrate in intervals of 20mg/day to a maximum dose of 70mg/day

Common errors in dosing psychostimulants

- Failure to increase dosing slowly to maximum if no side effect
- Beginning with a dose that is too high
- Not assessing the duration of action (may need to combine IR and ER formulations)
- Failure to use another psychostimulant if the first or second trial fails
- Failure to use input from collateral sources

The art of fine-tuning

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

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

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 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**

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

Tics and ADHD (Plizska, 2006)

- Mild or moderate tics occur in a significant number of patients with or without ADHD pharmacotherapy
- Tics during ADHD treatment may improve even while psychostimulants are used; discontinue only if serious

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.

Induction or Exacerbation of Tics (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

ADHD Treatments (other medication options)

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

ADHD Treatments (medication options)

- Atomoxetine
- Michelson, et al (2001) : n=297, ages 8-18, 71 % male; 8-week randomized prospective controlled study
  - Participants were moderately-to-severely impaired prior to treatment.
  - 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

- CYP2D6 substrate
- 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)

ADHD Treatments (other medication options)

- Tricyclic Antidepressants (TCAs)
  - 30+ randomized controlled studies show efficacy:
    - imipramine, amitryptiline, desipramine, clomipramine
  - Uncontrolled studies show benefit of nortryptiline, protryptiline

ADHD Treatments (medication options)

- Tricyclic Antidepressants (TCAs)
  - Use gradual dose elevation/ careful of drug interactions
  - Most will respond to less than 5mg/kg/day
    - Do not exceed 300 ng/ml
  - Monitor BP, EKGs:
    - QTc < 0.44ms, PR< 200ms, QRS < 120ms

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

Other medication options

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

Bupropion

- 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

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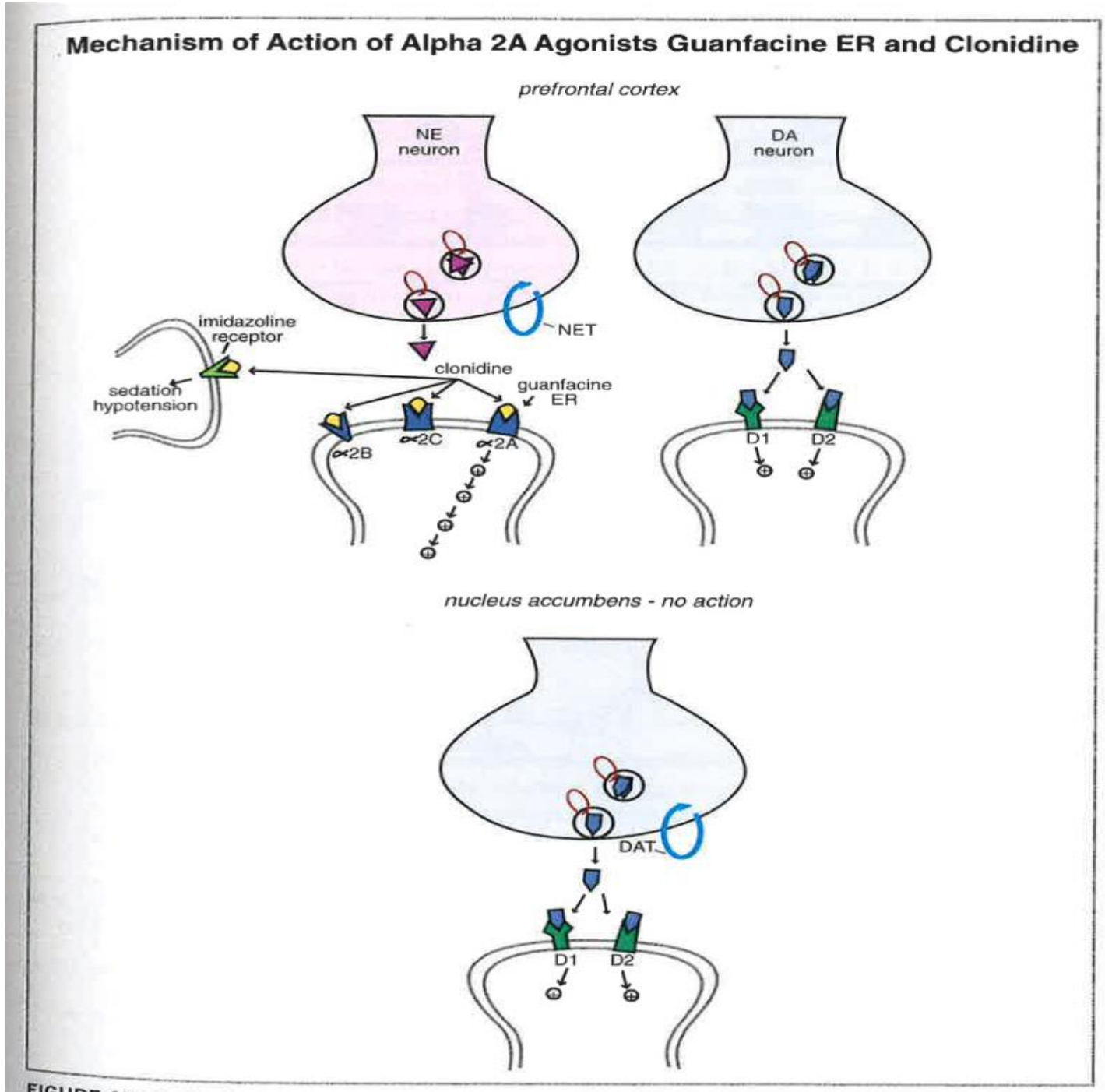

FIGURE 17-24

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

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
  - *if tx'd for more than 1 month, discontinue 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***

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

- 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

- 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

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.**

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