Pay Attention: ADHD Through the Lifespan

Anthony L. Rostain, MD, MA
Professor of Psychiatry and Pediatrics
Perelman School of Medicine at the
University of Pennsylvania

Week 10: Medical Treatment of ADHD (Part 2)

Homework Review

Misuse and Abuse of Stimulants

Definitions

Appropriate use: use of a controlled substance as prescribed for a defined condition with no signs of misuse or abuse

Misuse: use of a controlled substance for reason other than that for which it was prescribed or in dosage different than that prescribed; here, the pattern of misuse does not lead to disability or dysfunction

Abuse: use of a controlled substance outside normally accepted standards of use (e.g, "euphoriant" effects, enhancing alcohol or other substances), resulting in disability or dysfunction

Catastrophic use: use of a controlled substance that involves illegal activity or places patient in immediate harm

2001 College Alcohol Study Survey

McCabe, Knight et al, Addiction, 99:96-106, 2005

- 118 colleges participated, 215 students randomly selected from each school
- 10,904 students returned surveys (52%)
- Final sample represents a national cross-section of students enrolled in the US (region, size and type of institution, etc)
- 69% public institutions, 31% private
- Sample skewed: 64% female respondents

2001 College Alcohol Study Survey

McCabe, Knight et al, Addiction, 99:96-106, 2005

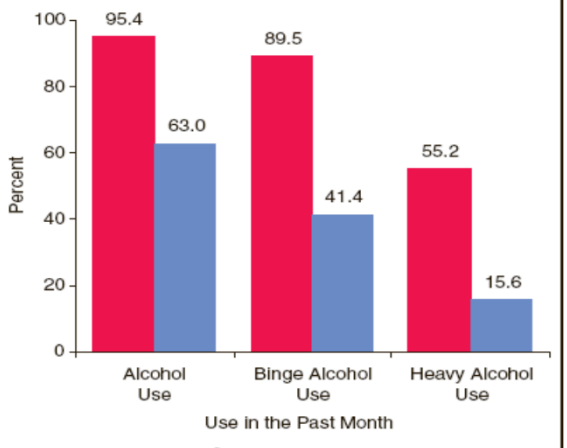
- Non medical use of prescription stimulants:
  - Lifetime rate: 6.9%
  - In past year: 4.1% (2.9% females, 5.8% males);
  - In past month: 2.1% (1.6% females, 2.8% males)
- Variation across campuses: 0 – 25%
  - 20 schools had 0% prevalence
  - 12 schools had 10% prevalence or higher

Illicit Stimulant Use Correlates with Alcohol and Other Drug Use

	- Stim	+ Stim
Alcohol use past month	72.8	97.1
Binge drinking past 2 weeks	48.4	83.5
Cigarette use past month	17.0	60.5
Marijuana use past year	32.7	88.2
Cocaine use past year	1.6	27.7
Ecstasy use past year	1.8	22.1
Amphetamine use past year	1.0	30.1

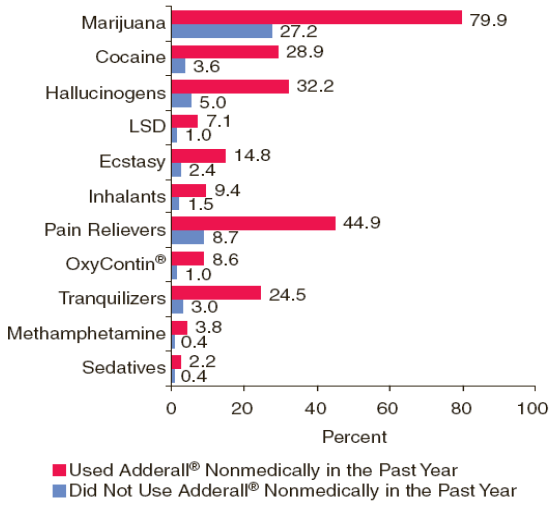
Teter, McCabe et al, J Amer Coll Health 53: 253-262, *2005*

Figure 3. Alcohol Use in the Past Month among Full-Time College Students Aged 18 to 22, by Past Year Nonmedical Use of Adderall®: 2006 and 2007



Source: 2006 and 2007 SAMHSA National Surveys on Drug Use and Health (NSDUHs).

Figure 2. Other Drug Use in the Past Year among Full-Time College Students Aged 18 to 22, by Past Year Nonmedical Use of Adderall®: 2006 and 2007



Source: 2006 and 2007 SAMHSA National Surveys on Drug Use and Health (NSDUHs).

Misuse and Diversion of Prescribed ADHD Medications by College Students

Rabiner, Anastopoulos, et al, *J Atten Disord* 13:144-153, 2009

Method: 115 students at two universities completed a Web Survey in Spring 2007

Results:

- 69% took medications as prescribed
- 31% misused (took larger or more frequent doses than prescribed or used someone else's medication)
- 8% used intranasal route in prior 6 months
- 26% diverted medications to peers
- Misuse associated with impulsivity and other substance use
- Primary motive: studying outside class
- Most who misused felt that doing so was helpful

Summary of survey studies

Findings

- Between **4 - 16 %** of students report using stimulants without prescription; males tend to have higher rates than females; rates vary from school to school and among racial groups
- Major motives – improve attention, perform better on tests, improve study habits, stay awake, party drug
- High correlation between nonprescription stimulant use and alcohol and other drug use
- Substantial percentage of students report snorting (!!)

Summary of survey studies

Limitations

- Samples may not be representative (e.g. women respond more than men)
- Survey response rates vary – not clear what this means about the validity of the study
- Survey respondents may not be reporting the full extent of their involvement
- Qualitative studies are not readily available

Mid-Lecture Questions

Factors contributing to the rise in non-prescription stimulant use

- Pre-college access to prescription drugs
- Greater availability of prescription drugs
- Higher rates of ADHD diagnosis in young adults
- Increased pressures to achieve in college
- Perception that "everybody does it…"
- More frequent recreational use (peer culture)
- Marketing / media messages (mass culture)

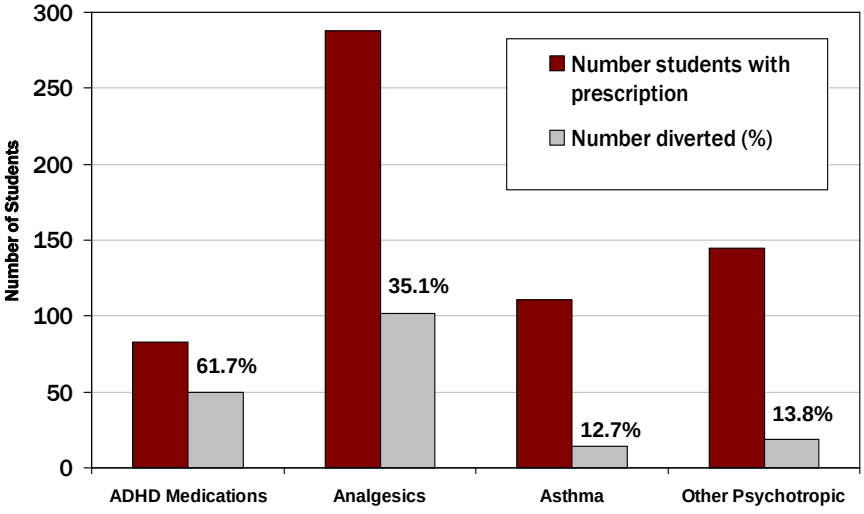
Sharing and Selling of Prescription Medications in a College Student Sample

Garnier LM, Arria AM, et al (2010) *J Clin Psychiatry* 71:262-269

- Method
  - Cross sectional analysis of personal interview data collected between 8-06 and 8-07 at U.MD.
  - Information gathered on a wide set of variables
- Results
  - Among 483 students prescribed a medication, 35.8% diverted a medication at least once
  - Sharing was most common type of diversion
  - Stimulants were diverted at rate of 61.7%

Sharing and Selling of Prescription Medications in a College Student Sample

Garnier LM, Arria AM, et al (2010) *J Clin Psychiatry* 71:262-269



Other factors influencing misuse and abuse of stimulants

- Greater availability of stimulants
  - **Friends, acquaintances (>80%)**
  - Physicians
  - Other sources
- Cultural expectations and norms (casual acceptance of stimulant use)
- Consumer marketing of pharmaceuticals
- Increased rates of "faking" ADHD symptoms to obtain prescriptions

Health Risks of Stimulants

- Cardiovascular
- Psychiatric
- Stimulant intoxication
- Stimulant withdrawal
- Interactions with other substances (medications, alcohol, recreational drugs)

Mid-Lecture Questions

Non-Stimulant Medications

Why Nonstimulant Treatments?

Advantages of non-stimulants

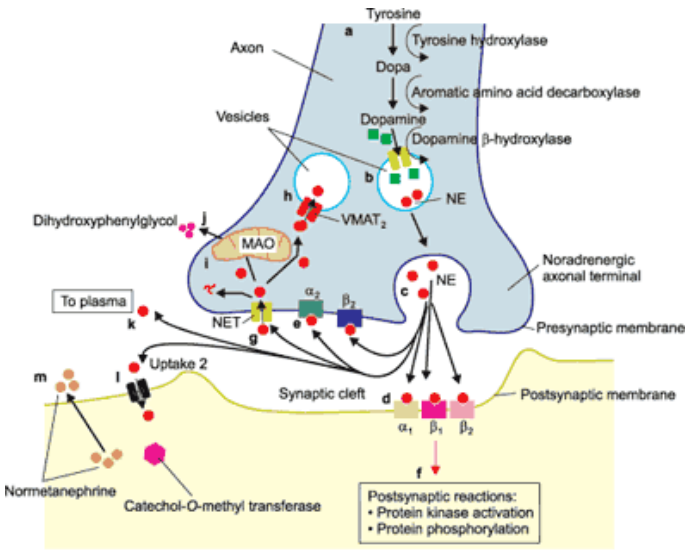
- No drug abuse or diversion potential
- Longer duration of action – different mechanisms
- May treat several existing co-occurring conditions (e.g. anxiety, depression, tics, sleep disturbances, morning or evening oppositional behavior)
- Different side effects profile as compared to stimulants (i.e. don't lead to reduced sleep and appetite, personality suppression, accentuation of tics, cardiovascular issues)

FDA Approved Non-stimulants Medications for ADHD

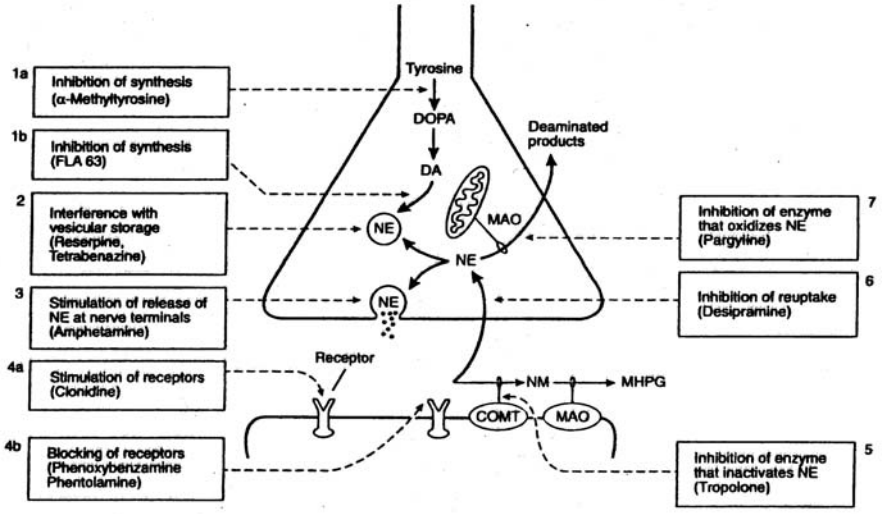
Medication	Starting dose	Target dose*	Usual daily dosing	Duration of effect
Norepinephrine reuptake inhibitor				
Atomoxetine (Strattera)	0.5 mg/kg/d	1.2 mg/kg/d	Once	Up to 24 hours
Alpha-2a receptor agonist				
Guanfacine XR (Intuniv)	1 mg/d	1 to 4 mg/d	Once	About 12 hours
Clonidine Extended Release (Kapvay)	0.1 mg	0.1 to 0.2	BID	About 12 hours

Pliszka SR et al. *J Am Acad Child Adolesc Psychiatry*. 2007;46(7):894-921. http://www.aacap.org/galleries/PracticeParameters/JAACAP_ADHD_2007.pdf. Accessed September 19, 2008 Sallee et al. *J Am Acad Child Adolesc Psychiatry*. 2009;19(3):215-226. Sallee et al. *J Am Acad Child Adolesc Psychiatry*. 2009;48(2):155-165.

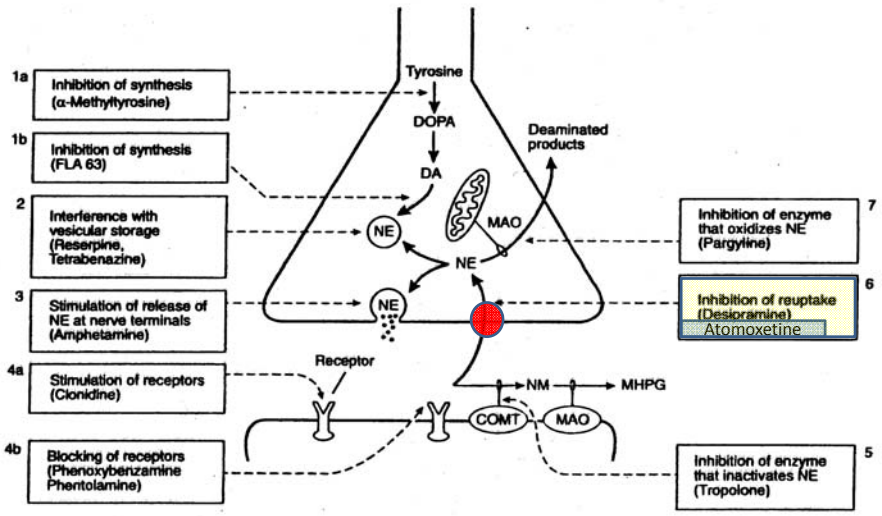
Norepinephrine Neurotransmission



Norepinephrine Neurotransmission



Norepinephrine Neurotransmission

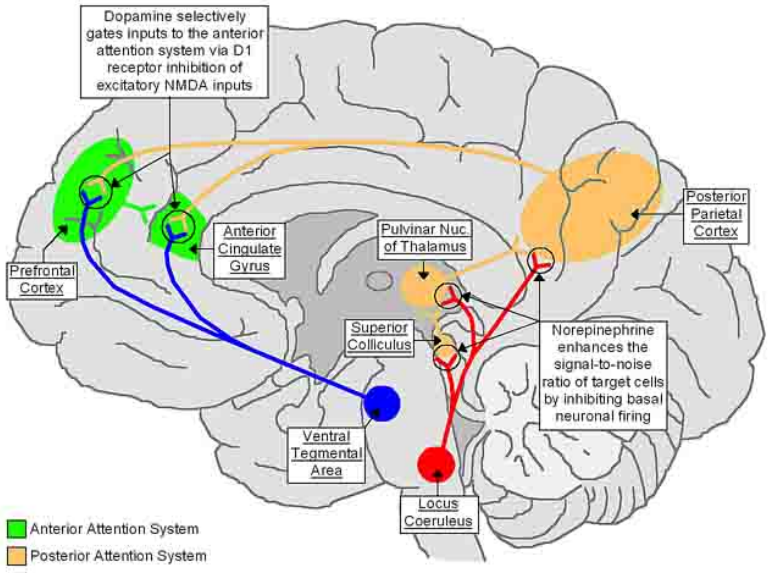


Atomoxetine: Selective Norepinephrine Reuptake Inhibitor (NRI)

Effects on Attention: Improved Signaling

- Posterior Attentional System
  - Increased NE
    - Improved alerting and orienting
    - Reduced "startle" and over-reactivity
- Anterior Attentional System
  - Increased NE and DA
    - Improved focusing
    - Improved executive functioning

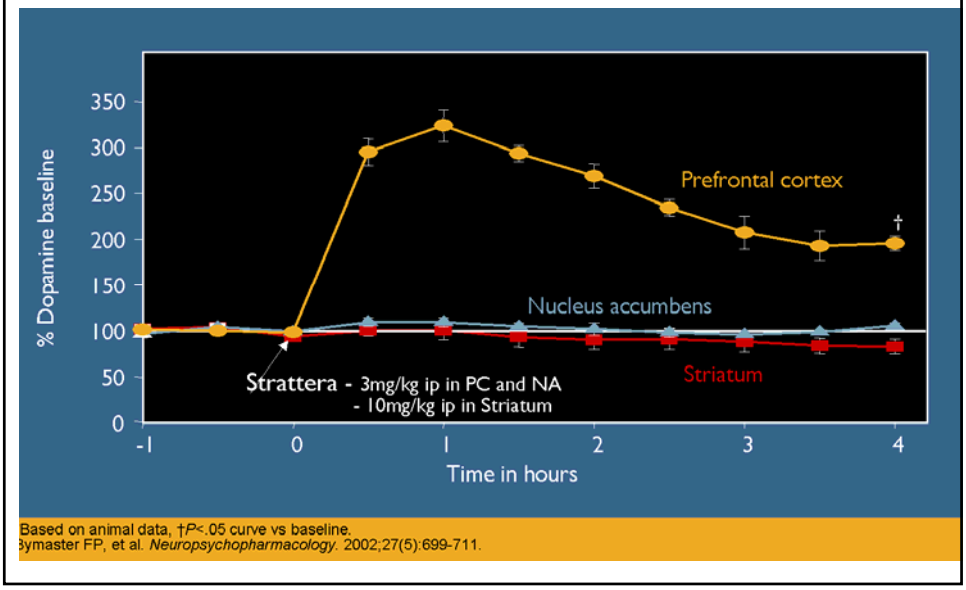
Dual Systems of Attention



Atomoxetine: Effects on Dopamine

- Downstream increase in dopamine activity in the prefrontal cortex
  - Consistent with improved executive functioning
- No increase in dopamine activity in the nucleus accumbens (reward center)
  - Not associated w/ abuse liability
- No increase in dopamine in the striatum
  - Not associated w/ abnormal motor activity (tics)

Atomoxetine: Dopamine Activity in Select Brain Regions



Based on animal data, †$P<.05$ curve vs baseline.
Bymaster FP, et al. *Neuropsychopharmacology.* 2002;27(5):699-711.

Atomoxetine – Side Effects

- Dizziness, high blood pressure
- Headache, irritability, nervousness
- Abdominal pain, nausea, vomiting, loss of appetite, weight loss
- Dry mouth, constipation, urinary hesitancy
- Decreased sexual desire
- Very slight chance of hepatic insufficiency

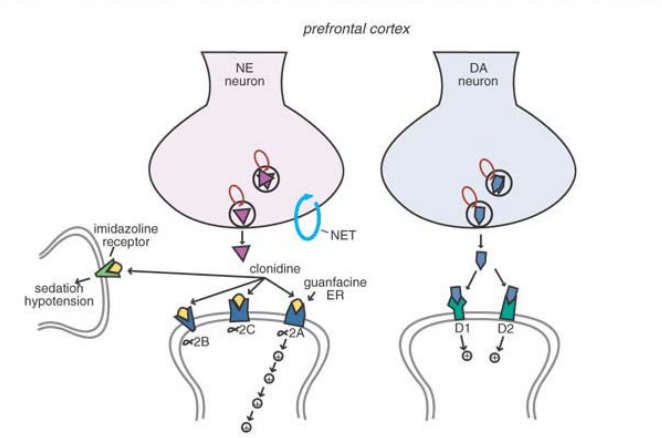
Mid-Lecture Questions

Non-Stimulant Medications: Alpha adrenergic agonists

Alpha 2A Adrenergic Agonists (clonidine, guanfacine)

- First introduced as anti-hypertensive agents in the 1970s
- Mechanism of action: “Partial agonists” of Norepinephrine
- Decrease tonic and phasic activity of the locus ceruleus (LC)
- Increase efficiency of neurotransmission in prefrontal cortex
- Helpful for patients who are highly aroused, impulsive, emotionally labile, irritable and explosive
- Reduce anxiety, defiance and aggression
- Useful in controlling tics

Mechanism of Action of Alpha 2A Agonists



Alpha 2A Adrenergic Agonists: Mechanism of action

<u>Stimulation of α2A-adrenergic receptors</u>

- Inhibits cAMP production which closes nearby HCN channels
- Increases pyramidal dendritic cell excitability
- Strengthens connectivity of DLPFC microcircuits
- Reduces distractibility and improves working memory in monkeys and humans
- Enhances DLPFC perfusion in monkeys during working memory tasks

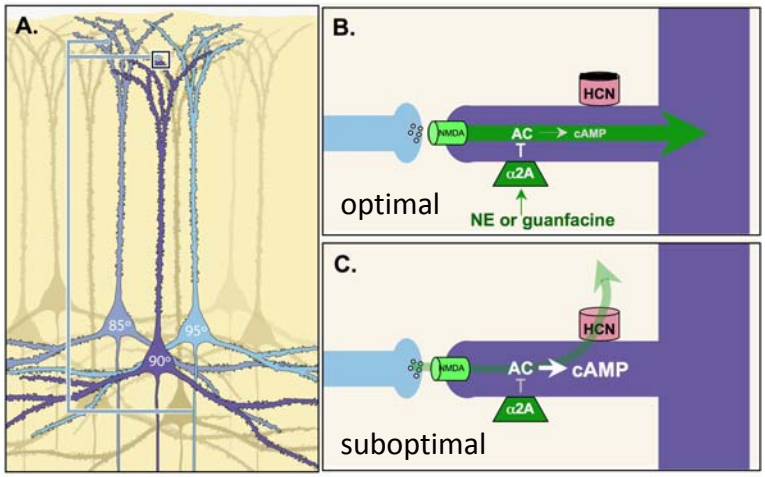
Alpha 2A Adrenergic Agonists: Mechanism of action

Stimulation of α2A-adrenergic receptors

- The right amount of NE will properly stimulate postsynaptic alpha-2A receptors to inhibit cAMP (cyclic adenosine monophosphate) in PFC dendritic spines, protrusions where neurons communicate.

- When there is inadequate NE stimulation of alpha-2A receptors, cAMP opens ion channels that weaken neuronal inputs. With sufficient NE, the cAMP pathways are inhibited and the neuronal networks connect more effectively

Mechanism of Action of Alpha 2A Agonists



PFC dendritic spines

Alpha 2A Adrenergic Agonists: (Clonidine, guanfacine)

Side effects

- Sedation, fatigue
- Dizziness
- Dry mouth, indigestion, nausea
- Slowed heart rate, low blood pressure
- Nightmares, insomnia
- Anxiety, depression
- Hallucinations (rare)
- Hypertensive crisis with sudden discontinuation

Medications for ADHD: Summary

- Stimulants and non-stimulants are effective in reducing symptoms of ADHD in children and adolescents
- Medication choice should be based on efficacy and tolerability
- High variability in optimal dosage
  - Many pharmacologic agents need dose adjustments as children develop and gain weight
- Obtain pretreatment measure of potential side effects (eg, sleep latency, appetite, irritability)
- Begin medication trial 7 days per week
- Consider dosing strategies to allow for evening activities
- Use self-reports of symptoms to determine effectiveness

Wilens T, et al. *Ann Rev Med.* 2002;53:113-131.
Zametkin AJ, Ernst M. *N Engl J Med.* 1999;340:40-46.
Steinhoff KW. *Am J Manag Care*. 2004;10(4 suppl):S99-106.
Wilens T, et al. *Arch Pediatr Adolesc Med.* 2006;160:82-90.

Quiz Questions