Pay Attention: ADHD Through the Lifespan

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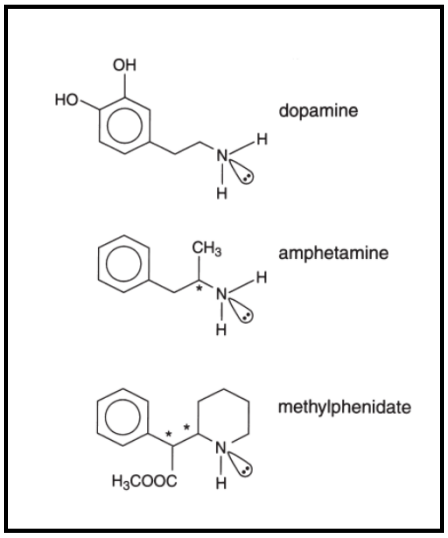
Week 9: Medical Treatment of ADHD (Part 1)



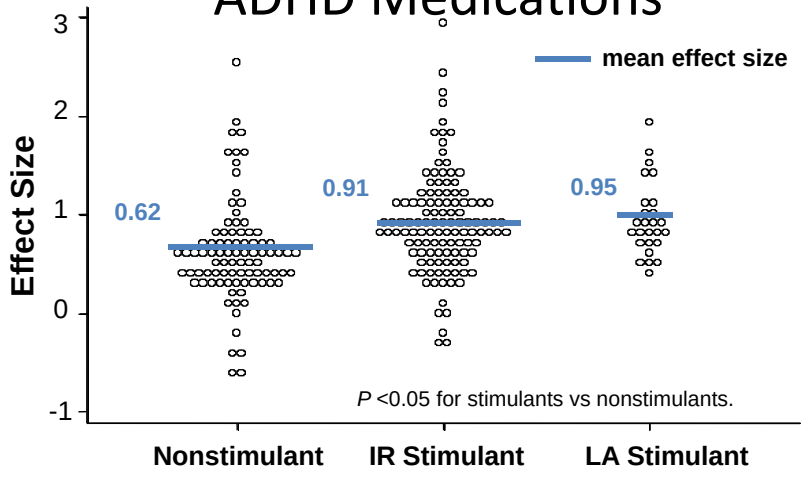
Homework Review

Medications for ADHD

Pharmacologic Treatments for ADHD

- *Stimulant Medications*
  - Methylphenidate-based
  - Amphetamine-based
- *Non-stimulant Medications*
  - Atomoxetine
  - ∝ adrenergic agonists
    - Clonidine
    - Guanfacine

Effect Size for Classes of ADHD Medications



IR = immediate-release

LA = long acting

Faraone. *Medscape Psychiatry and Mental Health*. 2003;8(2). Available at: http://www.medscape.com/viewarticle/461543.

Stimulants: Benefits

- Increased concentration & persistence
- Decreased impulsivity & hyperactivity
- Increased work productivity (~Accuracy)
- Decreased days absent from school
- Increased reading achievement by age 18
- Decreased likelihood of grade retention
- Better emotional control
- Decreased aggression & defiance
- Decreased antisocial activities

Stimulants: Benefits

- Improved compliance & rule following
- Better working memory
- Improved handwriting & motor control
- Improved self-esteem
- Decreased punishment from others
- Improved peer acceptance & interactions
- Better awareness of game in sports
- Improved attention and reaction time during driving performance

Stimulants: Side Effects

- All are dose-dependent; most are mild
- Most common:
  - Reduced appetite and consequent weight loss
  - Abdominal pain, nausea, constipation
  - Difficulty falling asleep
  - Mild increase in heart rate and blood pressure
  - Jitteriness, jumpiness
  - Motor tics
  - Dysphoria, moodiness, irritability
  - "Rebound effects" – worsening after medication wears off

Stimulants: Side Effects

- Frequency of side effects
  - Insomnia (50% +)
  - Loss of Appetite (50%+)
  - Headaches (20-40%)
  - Stomach Aches (20-40%)
  - Irritability, crying tendency (<10%)
  - Nervous habits & mannerisms (<10%)
  - Tics (<3%) & Tourette's (Rare)
- Mild failure to gain weight (mean = 1-4 lbs.; transient)
- Small effect on height in the 1st year (about 1 cm)
- Growth effects limited to first 1 - 3 years of therapy

Stimulants: Side Effects

- Increased heart rate (mean of 3-10 bpm)
- Increased blood pressure (mean of 1.5-14 mmHg)
- Risk of sudden death: not founded on the facts. Base rate is 1-7 in 100,000 patient years. Rate in stimulant cases is below this base.
- No evidence of chromosomal damage or increased cancer risk
- No discernible long-term adverse consequences found to date.

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- Nonpsychiatric MDs tend to under-dose below doses used by psychiatrists or in research

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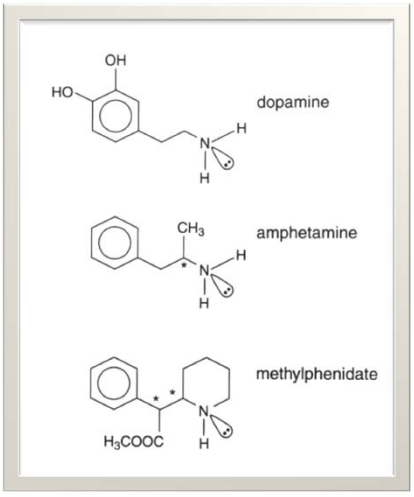
- No, 4.3 % on medication vs. 7.8% prevalence
- No, 15 studies find no such result; a few also found decreased risk if continued through teens
- Improves work productivity, classroom conduct and rule-following, peer interactions, grades, reduced punishment, fewer days absent, less likely to be retained in grade

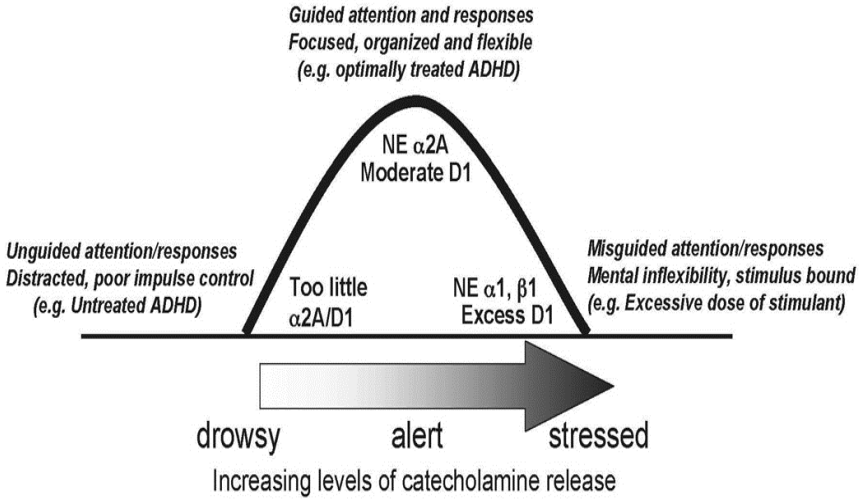
Mid-Lecture Questions

Mechanisms of Action: Stimulant Medications

Chemical Structure of Stimulants

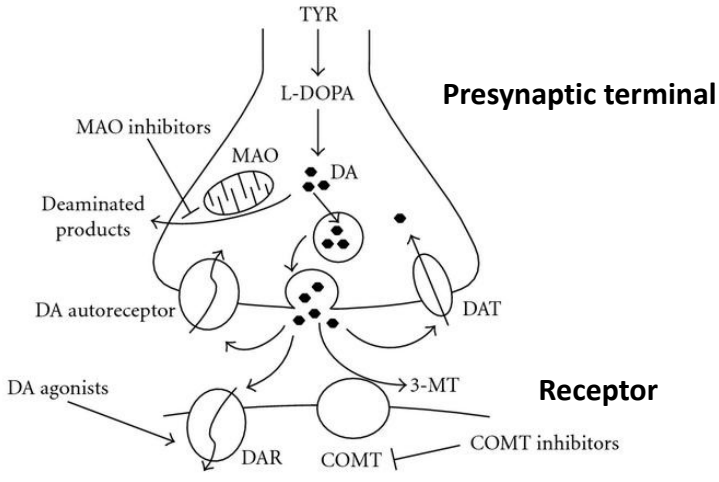


The Prefrontal Cortex Requires A Proper Level of Catecholamines for Optimal Function



Arnsten, A.F.T. *J Pediatr*. 2009 May 1; 154(5): I-S43.

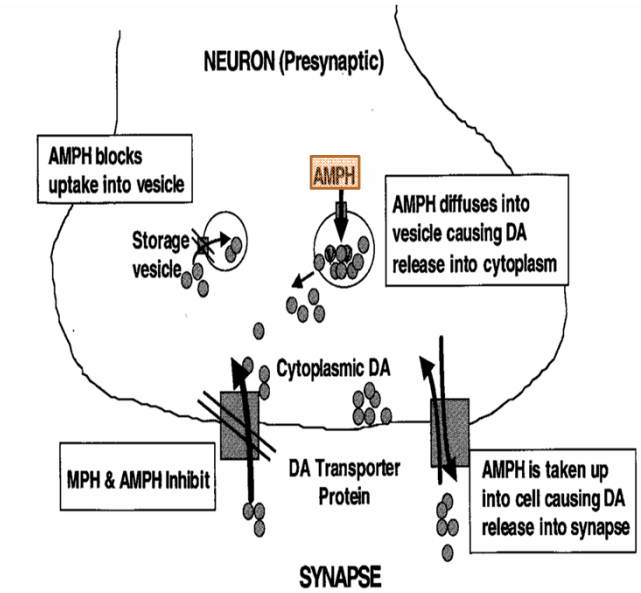
Dopamine Neurotransmission



Presynaptic terminal

Receptor

Stimulants and Dopamine Neurotransmission



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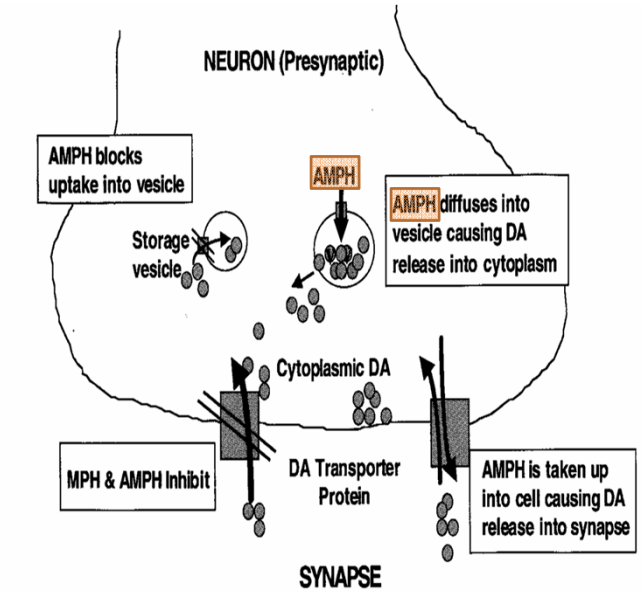

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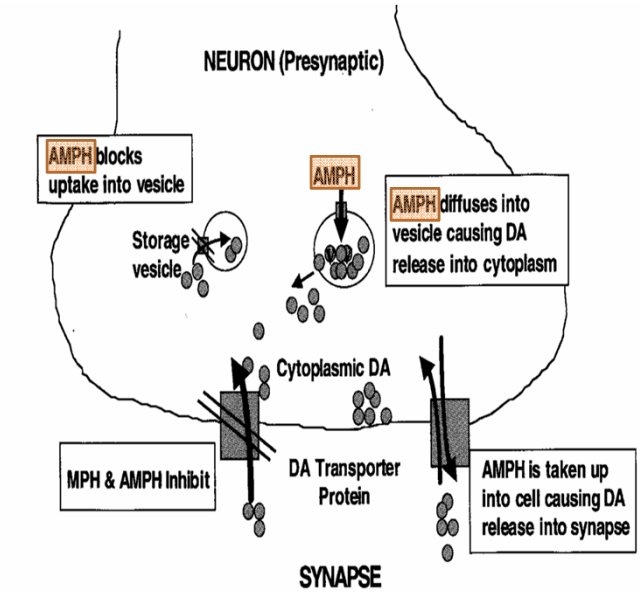

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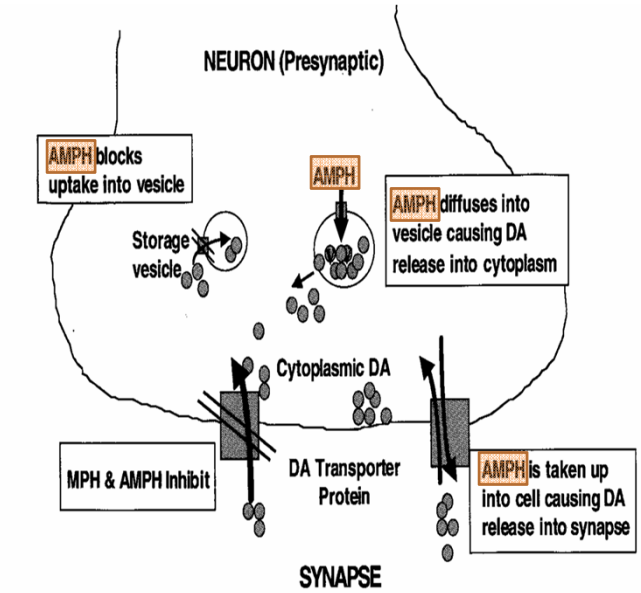

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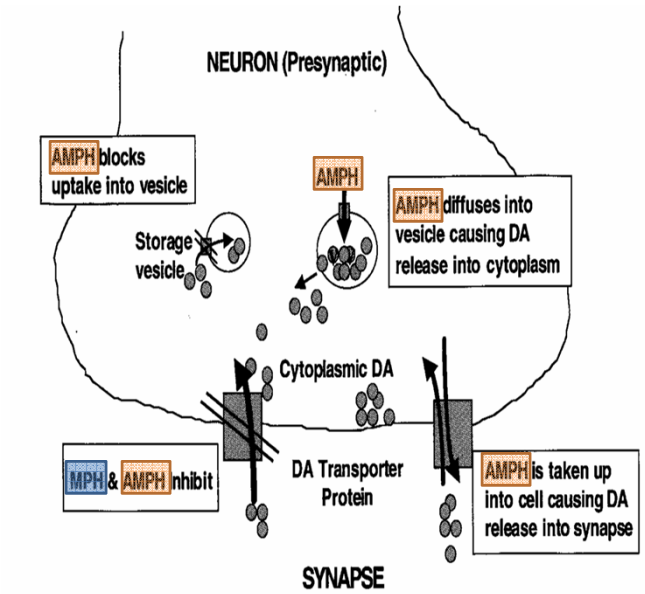

Summary of Stimulant Action

- Methylphenidate
  - Blocks reuptake of transmitter into pre-synaptic terminal
- Amphetamine
  - Releases transmitter from vesicle
  - Blocks reuptake of transmitter into vesicle
  - Blocks reuptake of transmitter into pre-synaptic terminal
  - Induces release of transmitter when it is absorbed into the pre-synaptic terminal
  - D- form acts on DA neurons; L-form acts on NE neurons

Mid-Lecture Questions

FDA Approved Stimulant Treatments

Methylphenidate-based formulations	Duration of effect
Concerta®	~12 hours
Ritalin®	3 - 4 hours
Metadate® CD	8 - 10 hours
Ritalin® LA	~8 hours
Focalin ®	3 - 4 hours
Focalin ® (XR)	8 - 10 hours
Daytrana® (Patch)	~12 hours (worn for 9)
Quillivant XR® (Liquid)	10 - 12 hours
Amphetamine-based treatments	
Adderall XR®	~12 hours
Adderall®	4 - 6 hours
Dexedrine® Tablet /Spansule	5 - 6 / 6 - 8 hours
Vyvanse®	~12 hours

Methylphenidate

- First synthesized in 1944.
- Identified as a stimulant in 1954.
- Beginning in the 1960s, it was used to treat children with ADHD known at the time as hyperactivity or minimal brain dysfunction (MBD).
- Today methylphenidate is the most commonly prescribed ADHD medication.

Methylphenidate (cont)

- Multiple formulations available:
  - Immediate release
  - Delayed release
  - Extended release (i.e. Metadate CR™ and Concerta™)
  - Methylphenidate transdermal system (Daytrana™)
  - Dextro-isomer (Focalin™)
  - Liquid preparation (Quillivant ™)

Amphetamine

- Synthesized in 1887 in Berlin.
- Related to ephedrine, a plant derivative isolated from Ma-Huang
- Initially sold by Smith, Kline and French in a volatile base form as a decongestant inhaler, Benzedrine.
- 1935: CNS drug effects identified as "a sense of well being and a feeling of exhilaration" and "lessened fatigue in reaction to work".
- Soldiers extensively used in WWII to diminish fatigue and increase alertness.
- 2003: Still used by US Air Force for pilot fatigue.

Amphetamine (cont)

- 1965: The FDA banned Benzedrine inhalers and limited amphetamine use to prescriptions.
- 1971: Amphetamine became a schedule II drug under the Controlled Substance Act
- Multiple formulations now available
  - Dexedrine™ spansules & tablets – 100% D-isomer
  - Adderall™ – 25% L-isomer, 75% D-isomer
  - Vyvanse™ a prodrug stimulant (D-amp + Lysine)

Stimulant-Induced Side Effects

Anorexia, nausea, weight loss

- Administer stimulant with meals
- Use caloric-enhanced supplements
- Change preparation
- Consider adjunctive treatment

Stimulant-Induced Side Effects

Insomnia, nightmares

- Administer stimulants earlier in the day
- Change to short-acting preparations
- Discontinue p.m. doses
- Consider adjunctive treatments (e.g. clonidine, mirtazapine)

Stimulant-Induced Side Effects

Dizziness

- Reduce dose
- Monitor blood pressure
- Change to longer acting preparation

Rebound phenomena

- Overlap stimulant dosing
- Change to longer acting preparation
- Consider adjunctive or alternative treatment

Stimulant-Induced Side Effects

Irritability

- Assess timing of phenomena (peak or withdrawal?)
- Reduce dose or change to longer-acting preparation
- Evaluate co-morbidity (e.g. mood disorder)
- Consider adjunctive or alternative treatment

Mid-Lecture Questions

Health Risks of Stimulants

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

Cardiovascular

- Sudden death
  - Arrhythmias
  - Outflow obstruction
- Heart attack
- Stroke, focal brain damage
- Hypertension
- Elevated heart rate

Recent Concerns About Stimulants and Cardiac Disease

- Current FDA language stipulates that sudden death can occur at usual doses in patients with a pre-existing structural cardiac abnormality or other serious heart problem
- Careful history of heart related problems must be obtained and documented before starting stimulant medication

Recent Concerns About Stimulants and Cardiac Disease

- History of heart murmur, syncope, exercise intolerance, hypertension and/or cardiac insufficiency warrants further work up
- Stimulants can be safely prescribed for patients with hypertension provided there is adequate anti-hypertensive treatment

ADHD Drugs and Serious Cardiovascular Events in Children and Young Adults

William O. Cooper, M.D., M.P.H., Laurel A. Habel, Ph.D., et al, ***New England Journal of Medicine***, 11-1-11

Conducted a retrospective cohort study with automated data from four health plans (Tennessee Medicaid, Washington State Medicaid, Kaiser Permanente California, and OptumInsight Epidemiology), with 1,200,438 children and young adults between the ages of 2 and 24 years and 2,579,104 person-years of follow-up, including 373,667 person-years of current use of ADHD drugs.

Cohort members had 81 serious cardiovascular events (3.1 per 100,000 person-years). Current users of ADHD drugs were not at increased risk for serious cardiovascular events (adjusted hazard ratio, 0.75; 95% confidence interval [CI], 0.31 to 1.85). Risk was not increased for any of the individual end points, or for current users as compared with former users (adjusted hazard ratio, 0.70; 95% CI, 0.29 to1.72).

This large study showed no evidence that current use of an ADHD drug was associated with an increased risk of serious cardiovascular events

Psychiatric

- Psychosis (paranoia, delusions, hallucinations)
- Delirium (clouded consciousness, confusion)
- Mania, agitation, irritability, mood swings
- Anxiety, muscle tension, nervousness
- Insomnia
- Depression
- Decreased concentration
- Hyperactivity
- Hypersexuality

Amphetamine Intoxication

Clinically significant maladaptive behavioral or psychological changes that develop during, or shortly after, use of amphetamine or a related substance, including:

- Euphoria or affective blunting
- Changes in sociability
- Hypervigilance
- Interpersonal sensitivity
- Anxiety, tension or anger
- Stereotyped behaviors
- Impaired judgment
- Impaired social or occupational functioning

Amphetamine Withdrawal

- Cessation of (or reduction in) amphetamine (or a related substance) use that has been heavy and prolonged
- Dysphoric mood and two or more of the following physiological changes
  - Fatigue
  - Vivid, unpleasant dreams
  - Insomnia or hypersomnia
  - Increased appetite
  - Psychomotor retardation or agitation

Quiz Questions