ADHD Medications & How They Work

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Agenda

How the (ADHD) Brain Works (or doesn't)

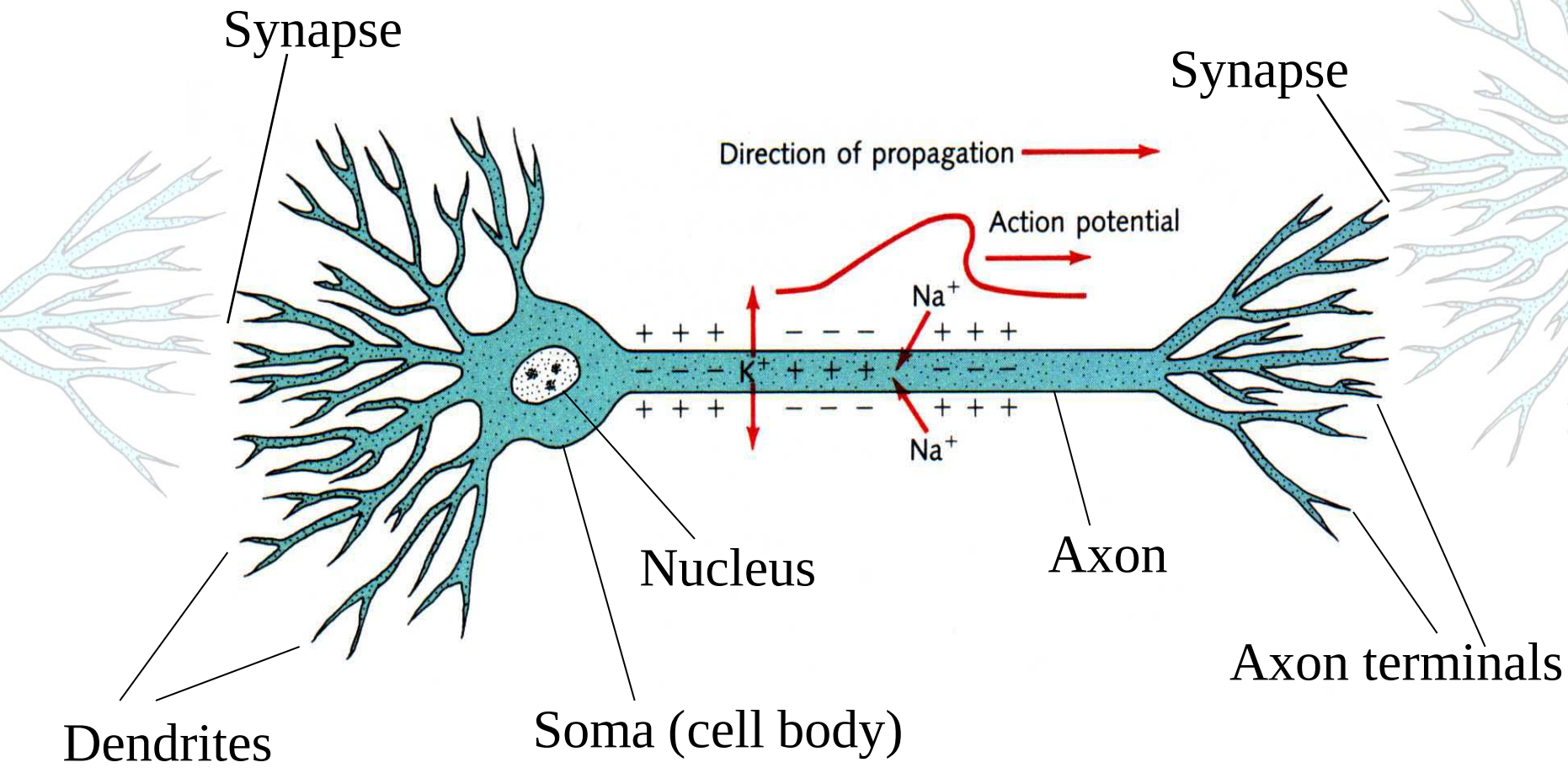
- Neurons and neurotransmitters
  - NE & DA: the major players in ADHD
- Channel vs. state functions

How ADHD Medications Work

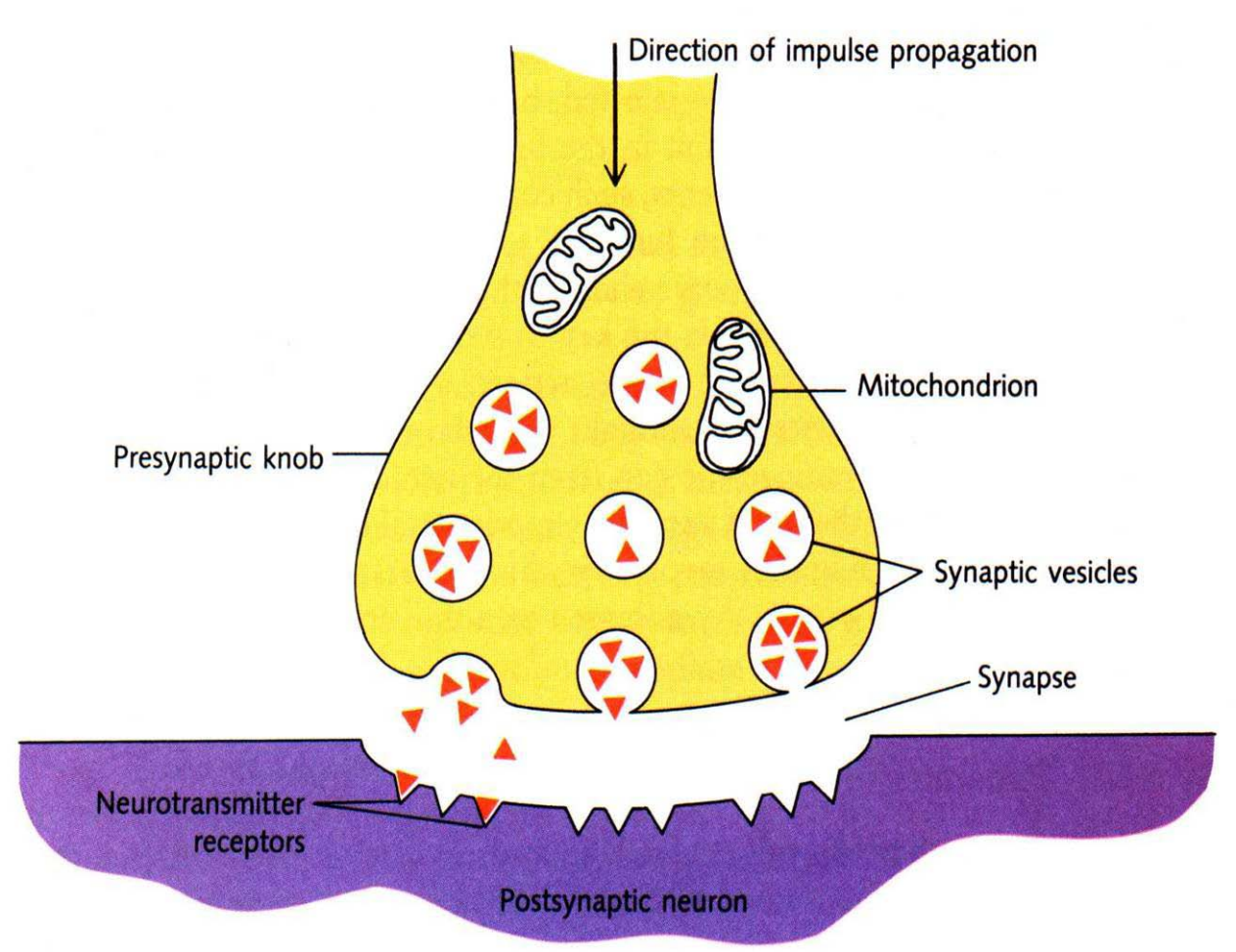
- Types of stimulants
  - Ritalin vs. amphetamines
- How stimulants affect NE & DA systems
  - Cortical vs. subcortical differences
- Other medications for ADHD
  - Strattera, Wellbutrin, Provigil, MAOI's, tricyclics, etc.

How the (ADHD) Brain Works (or doesn’t)

Neurons and Synapses



Neurons and Synapses



Classical Neurotransmitter Substances

- Dopamine (DA)
- Norepinephrine (NE)
- Epinephrine (E)

} Catecholamines

- Serotonin (5-HT)

Indolamine

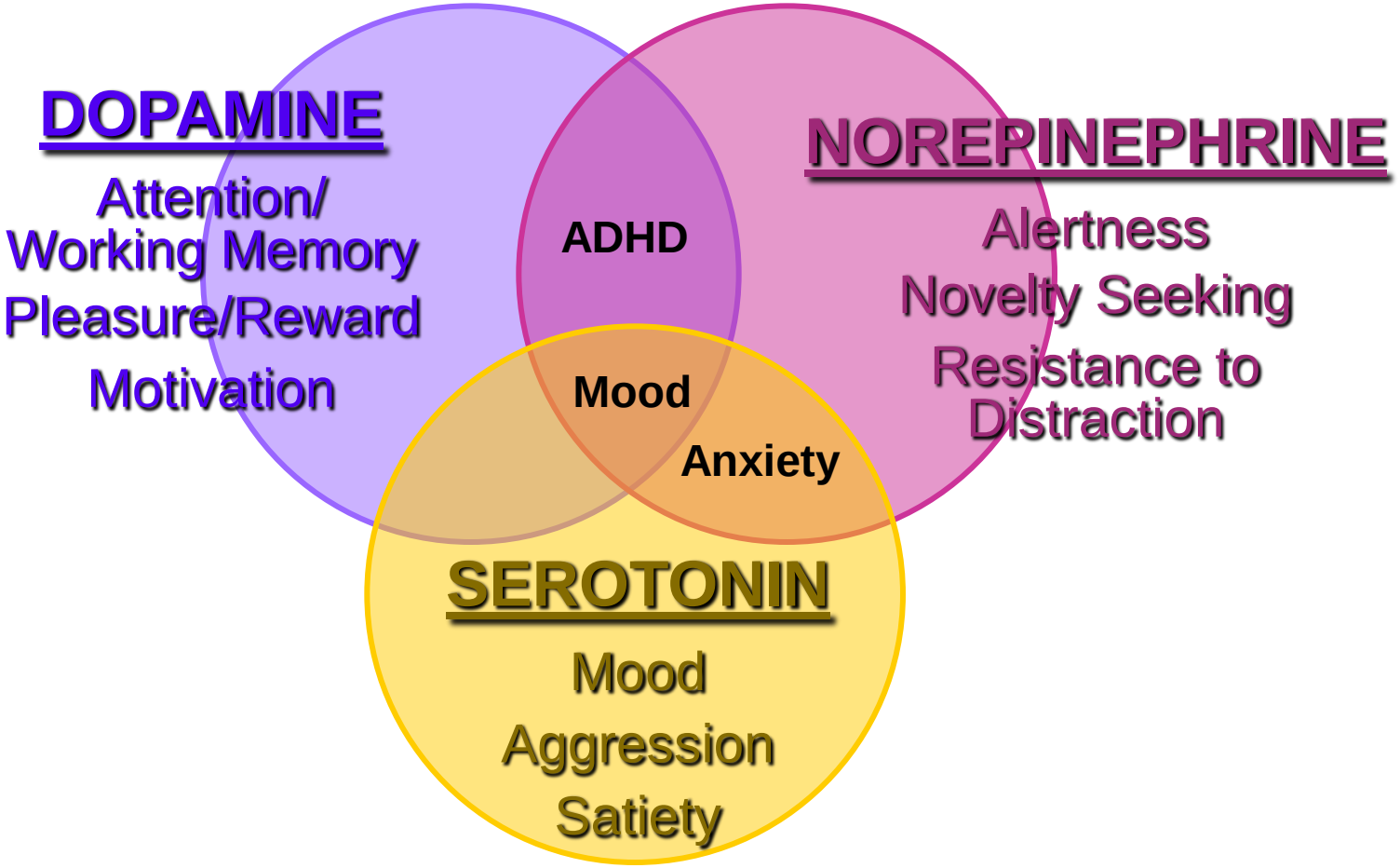
} Monoamines

- Glutamate
- GABA
- Glycine

} Amino Acids

- Acetylcholine (ACh)
- Histamine

Monoamine Neurotransmitters



Dopamine (DA)

- Coordination of movement
  - Motor readiness, “activation” of behavior
  - Motivated or exploratory behavior
- Reinforcement, reward, pleasure
  - Addictive behaviors
  - “Learning neurotransmitter”

Dopamine (DA)

- Attentional processes
  - Attentional set shifting
  - Sustained attention
- Working memory
  - Spatial working memory
    - Both storage and retrieval processes
  - Delayed response tasks

Norepinephrine (NE)

- Maintenance of levels of arousal and vigilance
- Attending to salient environmental stimuli that guide goal-oriented behavior
  - Novelty-seeking, orienting, focus, sustained attention
- Resistance to distraction
  - Increases signal-to-noise ratio

Catecholamines (DA & NE)

- Both participate in responses to external stimuli
  - NE regulates capacity for conscious registration of external stimuli
  - DA regulates capacity to respond to external stimuli

Catecholamines (DA & NE)

- Both are necessary to proper functioning of working memory
  - DA predominantly involved with maintaining information online
  - NE reduces disruptive effects of distracting stimuli

Catecholamines (DA & NE)

- Both respond to stimulant medications and mediate their effect on self-regulatory processes, including attention and impulse control

Serotonin (5-HT)

- Mood regulation
- Sleep, wakefulness
- Temperature regulation
- “Instinctive” behaviors
  - Feeding, aggression, sexual activity
- Inhibition of activity and behavior

Channel Functions and State Functions

- Most neural pathways that connect areas of the brain are reciprocal point-to-point channels
  - This is the basic anatomical substrate of specific “channel functions”
    - Used to represent specific content of information being transmitted
  - Damage to these channels leads to specific impairments
    - E.g., dyslexia, memory retrieval deficit

Channel Functions and State Functions

- Each brain area also receives widespread modulatory connections that arise from small groups of neurons

  These pathways:

  – Innervate the entire cerebral cortex

  – Employ small amines and GABA as transmitters

  – Determine the overall state of information processing rather than specific content (“state functions”)

    - Important in coordinating behavioral states related to arousal, attention, mood, and motivation

State Functions

- Six important state (modulatory) pathways:
  - Substantia nigra & ventral tegmental area → cerebral cortex (DA)
  - Locus coeruleus → cerebral cortex (NE)
  - Brainstem raphe nuclei → cerebral cortex (5-HT)
  - Basal forebrain → cerebral cortex (ACh, GABA)
  - Lateral & medial hypothalamus → cerebral cortex (Histamine)
  - Brainstem reticular formation → thalamus (ACh)

State Functions

- State pathways alter the tone, coloring, and interpretation of experience rather than its content
- Many areas of the cortex, especially components of the limbic system, also contain receptors for estrogen, testosterone, and other steroids
  - Changes in circulating levels of these hormones can similarly influence behavioral states

Separate Cognitive and Motor Symptom Clusters

- Research suggests that motor symptoms and cognitive symptoms of ADHD are mediated differently

  Two symptom clusters:

  – May present separately (DSM–IV subtypes)
  – Appear to be inherited separately
  – Have different response profiles to stimulant meds

Separate Cognitive and Motor Symptom Clusters

- Impairments of attention, working memory, and other cognitive functions likely to be mediated by dysfunction in prefrontal cortex
- Motor symptoms (hyperactivity and impulsivity) likely to result from dysfunction of subcortical brain areas

Separate Cognitive and Motor Symptom Clusters

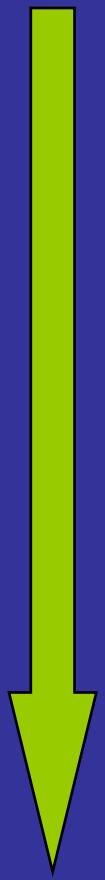
- Cognitive symptoms
  - Due to underarousal of prefrontal cortex, *under*activity of dopaminergic and noradrenergic neurons in this area
    - Also results in inability to effectively inhibit, modulate subcortical regions (limbic system)

Separate Cognitive and Motor Symptom Clusters

- Motor overactivity (hyperactivity and impulsivity)
  - Due to overreactivity in limbic system, *over*activity of dopaminergic neurons in these areas

How ADHD Medications Work

Medications for ADHD
All Affect NE and/or DA



Stimulants	methylphenidate HCl – Concerta, Ritalin amphetamine – Dexedrine, Adderall
NE Reuptake Inhibitor	atomoxetine (Strattera)
Antidepressants	bupropion (Wellbutrin) tricyclic antidepressants
Antihypertensives	clonidine guanfacine (Tenex)

Stimulant Medications
Methylphenidate HCl (MPH)

- Ritalin (immediate release)
- Methylin
- Metadate
- Generic MPH
- Focalin (isolated dextroisomer)

} *Short-Acting*

- Ritalin SR, LA
- Methylin ER
- Metadate ER, CD
- Focalin XR
- Concerta

} *Mid-Long Acting*

- Daytrana (transdermal patch)

Stimulant Medications
Amphetamine (AMP)

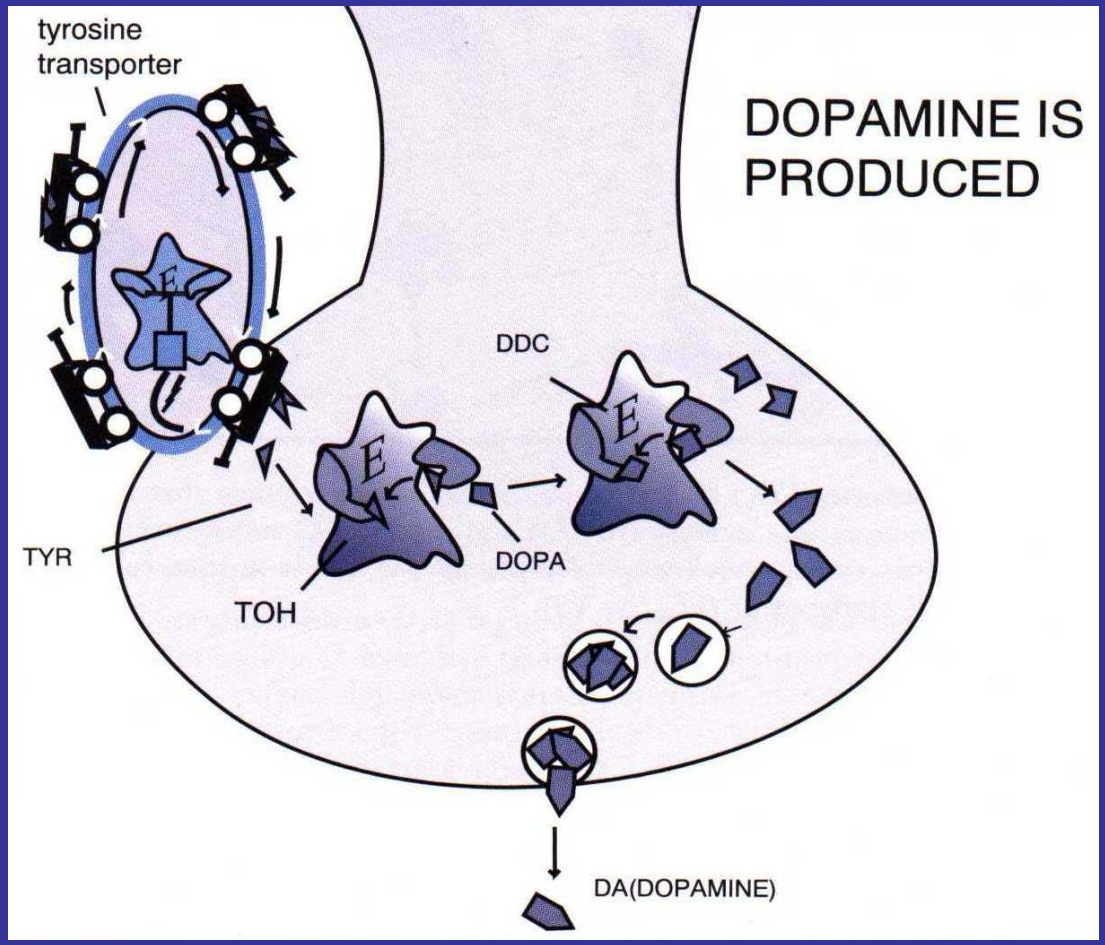
- Dexedrine, DextroStat, Dexedrine Spansule
  - dextroamphetamine sulfate
- Adderall, Adderall XR (mixed amphetamine salts)
  - dextroamphetamine sulfate
  - amphetamine sulfate
  - dextroamphetamine saccharate
  - amphetamine aspartate
- Desoxyn (?)
  - methamphetamine HCl
- Vyvanse (long-acting prodrug* stimulant)
  - lisdexamfetamine dimesylate

*Prodrug = a therapeutically inactive precursor of a drug converted to its active form by natural metabolic processes

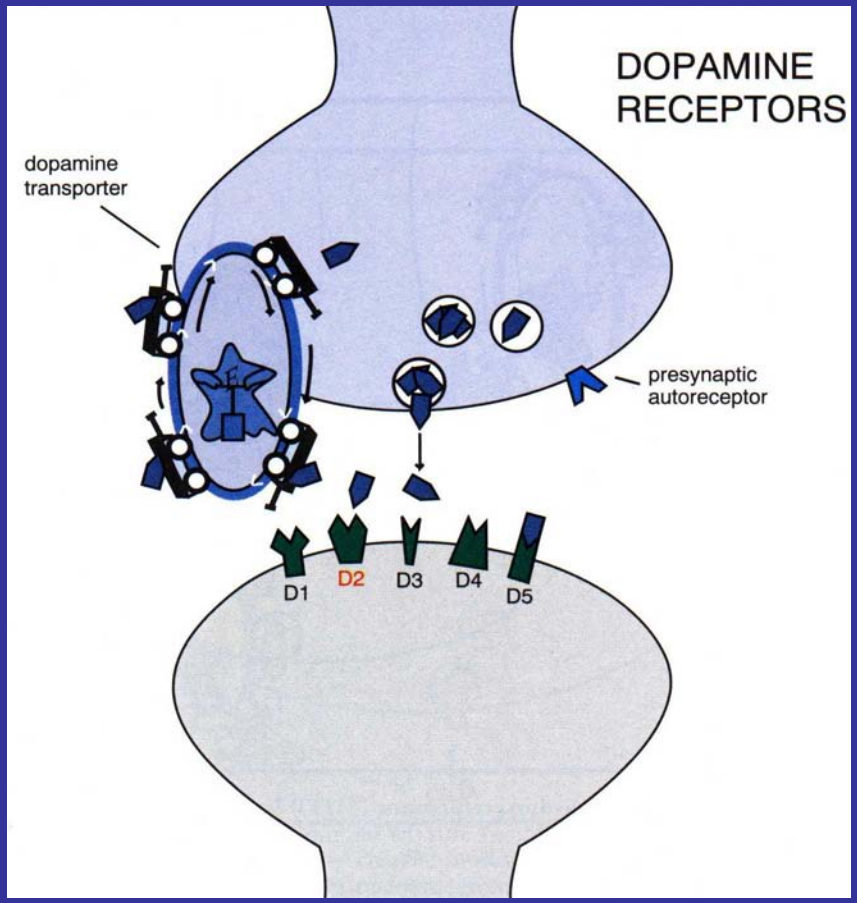
Non-stimulant Meds for ADHD

- NE reuptake inhibitors
  - Strattera (atomoxetine)
- NE & DA reuptake inhibitors
  - Wellbutrin (bupropion)
- Tricyclic antidepressants
  - Clomipramine, imipramine, desipramine
- Alpha agonists
  - Catapres (clonidine)
  - Tenex (guanfacine)

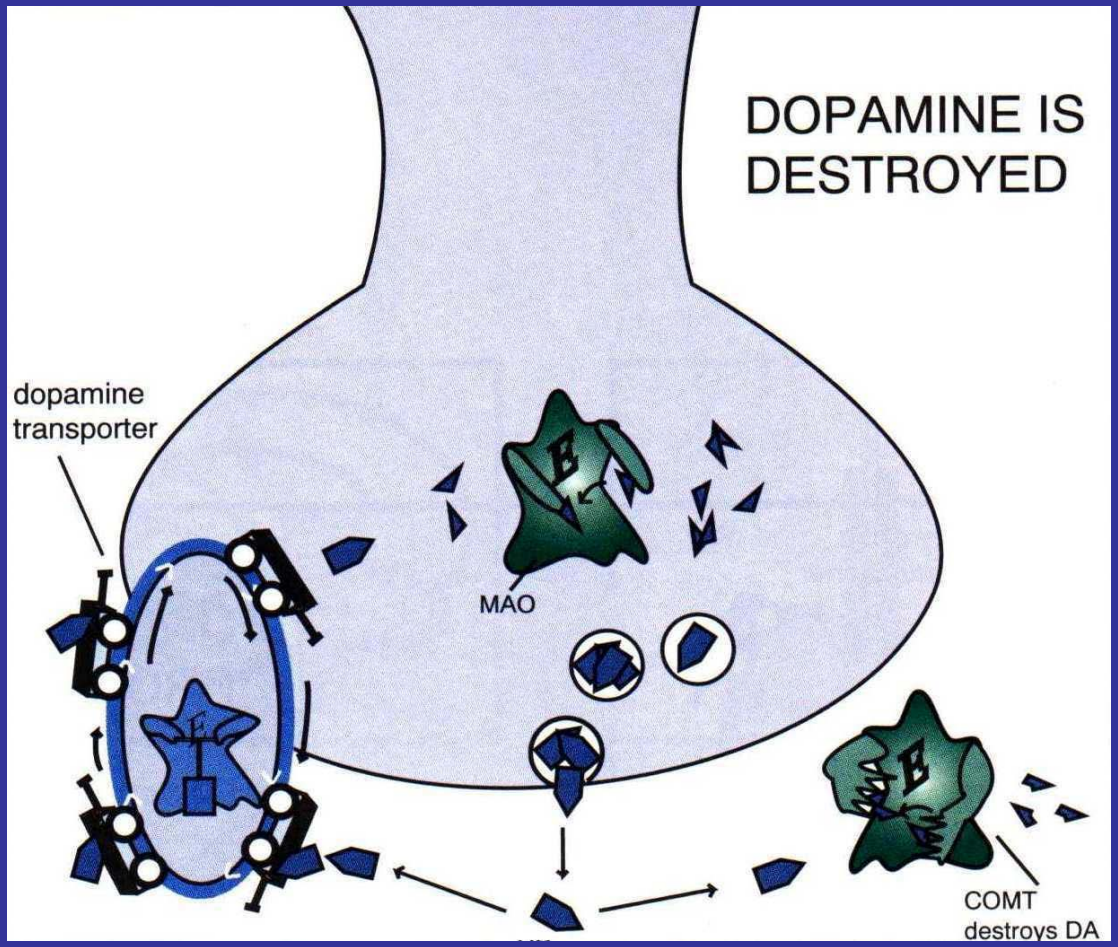
Dopamine Synthesis



Dopamine Receptors



Dopamine Metabolism



How MPH Works

In the Striatum

- Major effect is to block the normal process of DA reuptake into presynaptic terminal
  - Via inhibition of dopamine transporter (DAT)
- Inhibiting the DAT produces increased *tonic* levels of DA within synaptic space

How AMP Works

In the Striatum

- Major effect of AMP is to increase presynaptic DA release
- Unlike MPH, AMP also directly inhibits MAO
  - Inhibits breakdown of monoamines by MAO

How MPH and AMP Work
(Briefly)

- MPH
  - Blocks reuptake of dopamine more effectively than reuptake of norepinephrine
- AMP
  - Primarily causes release of dopamine and norepinephrine
- Cocaine
  - Blocks reuptake of all three monoamines (DA, NE, 5-HT)

All Meds are Not Created Equal

Stimulant Medications

Stimulant	Response rate
Methylphenidate	77%+
Adderall/Adderall XR	76%+
Dexedrine	74%+
Cylert (discontinued)	73%+
Trying all stimulants	**90%+**

Are MPH and AMP Interchangeable?

- Elia et al. (1991) reported that 25% of (N = 48) subjects in their ADHD study improved on only one of the two stimulants when both were tried

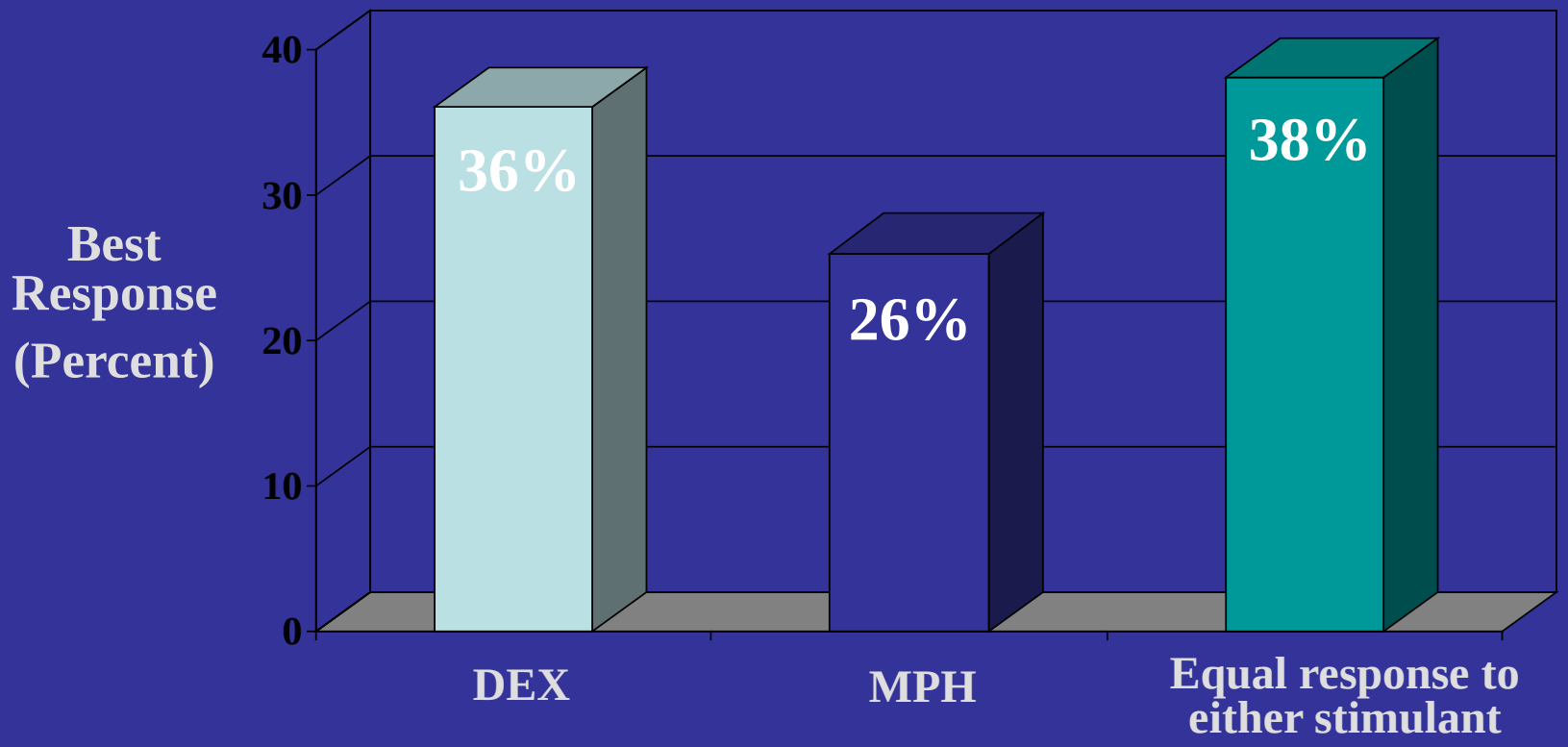
Are MPH and AMP Interchangeable?

- ADHD patient who responds poorly to one type of stimulant should try the other
  - 87% overall response rate if both are tried (Greenhill, 1996)
  - Some tendencies toward differing side effect profiles found (Arnold, 2000)
  - Clinical observations suggest AMP may be more arousing and activating, MPH more calming and focusing

Are MPH and AMP Interchangeable?

(Greenhill, 1996)

Meta-analysis of Within-subject Comparative Trials
Evaluating Response to Stimulant Medications



Are MPH and AMP Interchangeable?
(Greenhill, 1996)

- Implications of Greenhill study:
  - Patients with uncomplicated ADHD should receive trial of an alternate stimulant if they fail an initial stimulant trial
  - Those who are sub-optimal responders to a given stimulant may benefit significantly from a trial with alternative stimulant

Important Differences between MPH and AMP

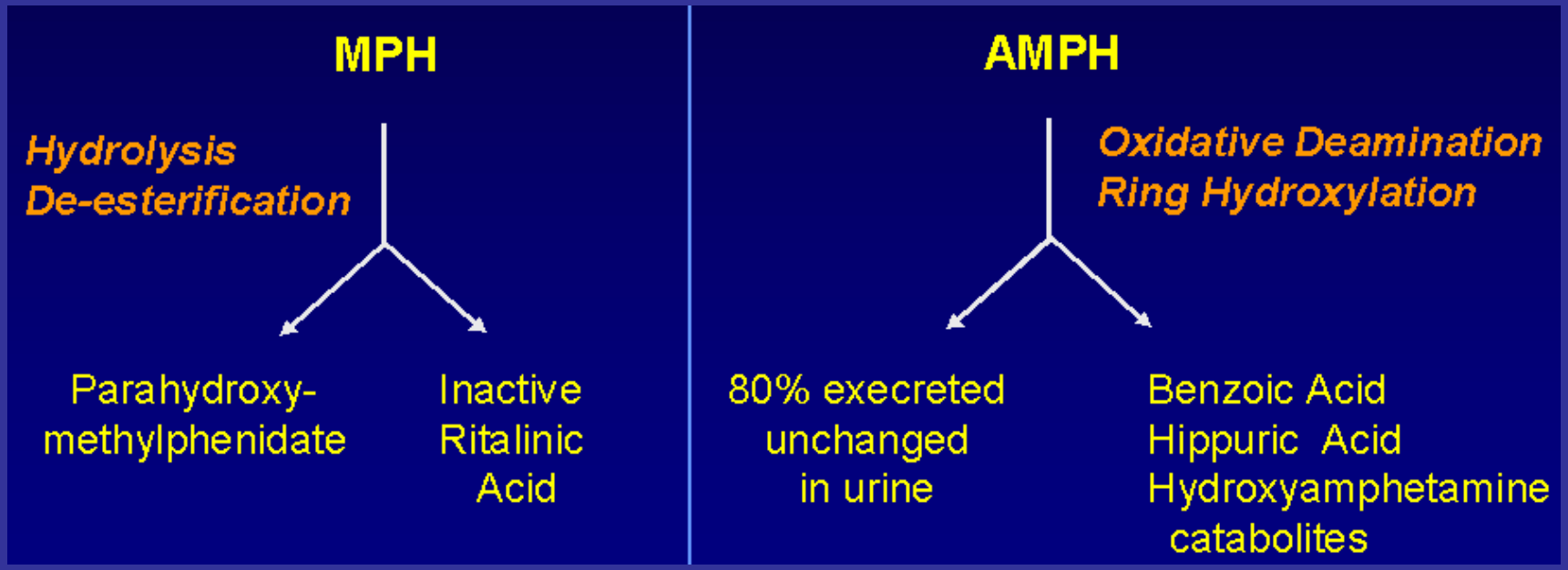
- MPH
  - Blocks reuptake of dopamine more effectively than reuptake of norepinephrine
- AMP
  - Primarily causes release of dopamine and norepinephrine
- Cocaine
  - Blocks reuptake of all three monoamines (DA, NE, 5-HT)

Important Differences between MPH and AMP

- Mechanisms of action at cellular level:
  - MPH only inhibits reuptake of DA and NE
    - A “pure uptake inhibitor”
  - *d*-AMP inhibits reuptake of catecholamines and also facilitates their release
- Duration of effect:
  - AMP ≈ 4 - 6 hrs.
  - MPH ≈ 2 - 3 hrs.
    - Excreted at much faster rate than *d*-AMP

Important Differences between MPH and AMP

- Because of differences in metabolism from AMP, MPH does not show up on routine drug testing



Important Differences between MPH and AMP

- Differences in development of tolerance:
  - Tachyphylaxis appears to occur only with MPH
    - Tachyphylaxis = Loss of drug effect within the first few doses on the same day
    - May explain ineffectiveness of SR formulations with “flat” serum profile
    - Can be offset via “ascending” profile, like that delivered by Concerta

Differential Response of Symptom Clusters to Stimulant Medication

Cognitive dysfunction

- Effects last 2 – 3 hours
- Higher doses needed to improve vigilance*
- Smaller effect sizes (0.6 – 0.8) in studies of cognitive changes

Motor overreactivity

- Effects last 7 – 8 hours
- Lower (subclinical) doses can reduce activity level
- Larger effect sizes (0.8 – 1.0) in studies of behavioral changes

*Smaller doses needed to optimize simpler, "automatic" functions like target detection; larger doses required to optimize higher-order cognitive functions such as learning

Strattera (Atomoxetine)

- Not a controlled substance
  - Originally developed and tested (1980's) as an antidepressant
- Overall 75% positive response rate
- Equal efficacy with MPH
  - Though effect sizes somewhat smaller
    - .6 – .8 (Strattera) vs. .7 – 1.0 (MPH)
  - Fewer side effects (insomnia, next morning behavior)

Strattera (Atomoxetine)

- A specific norepinephrine reuptake inhibitor
  - High affinity for NE system
  - Low affinity for other neurotransmitter systems
  - Thought to enhance signal processing by increasing cortical NE levels

Strattera (Atomoxetine)

- Less effect on dopaminergic system
  - Does not increase DA levels in:
    - Nucleus accumbens (substance abuse)
    - Striatum (tics)
  - But is associated with downstream increase of DA levels in prefrontal cortex
    - Working memory
    - Response rehearsal
    - Level of impulsivity

Strattera (Atomoxetine)

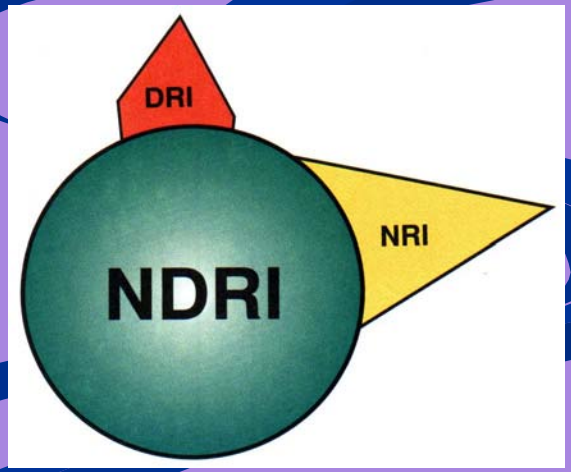
- Reduces ADHD, ODD, aggression, depression
- Increases in school productivity and social behavior
- Improved self-esteem and parent-child relations
- Improved enuresis and "morning after dose" behavior
- Less insomnia than MPH (7% vs. 30 – 50%)
  - Faster time to sleep onset
- Can be combined with stimulant

Other Medications for ADHD

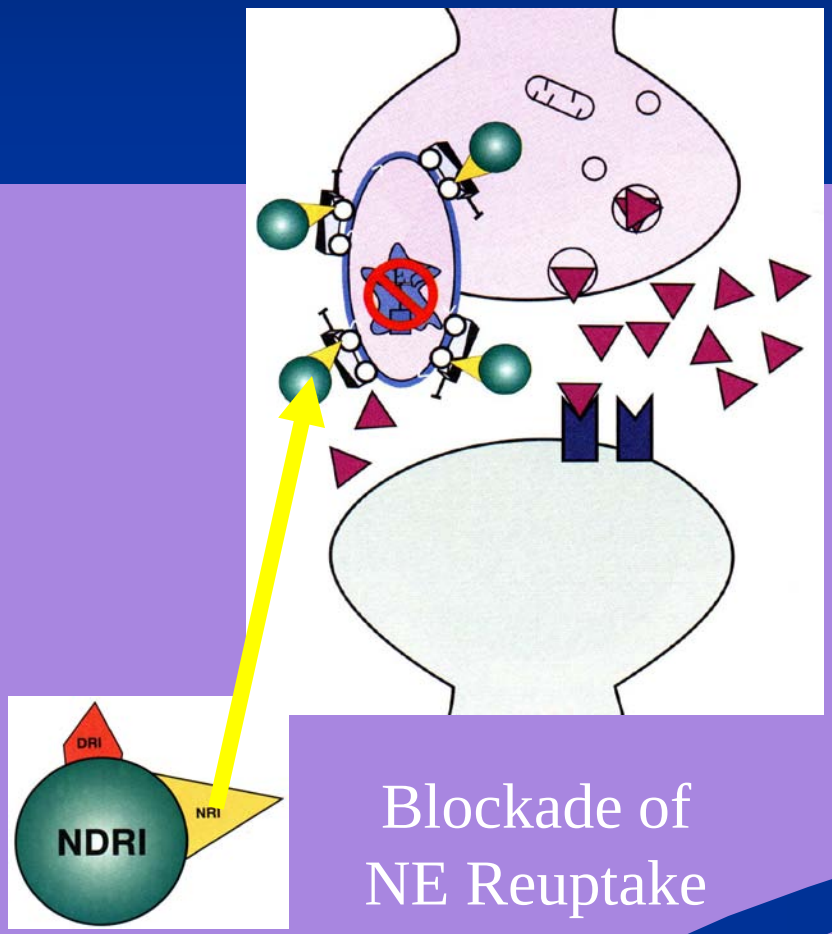
- modafinil (Provigil)
  - Approved for treatment of narcolepsy
    - Studies failed to support effectiveness with ADHD in adults
    - Child ADHD studies in progress
  - Works selectively in anterior hypothalamus to promote wakefulness
    - vs. widespread CNS effects of stimulants

Norepinephrine-Dopamine Reuptake Inhibitors (NDRI's)

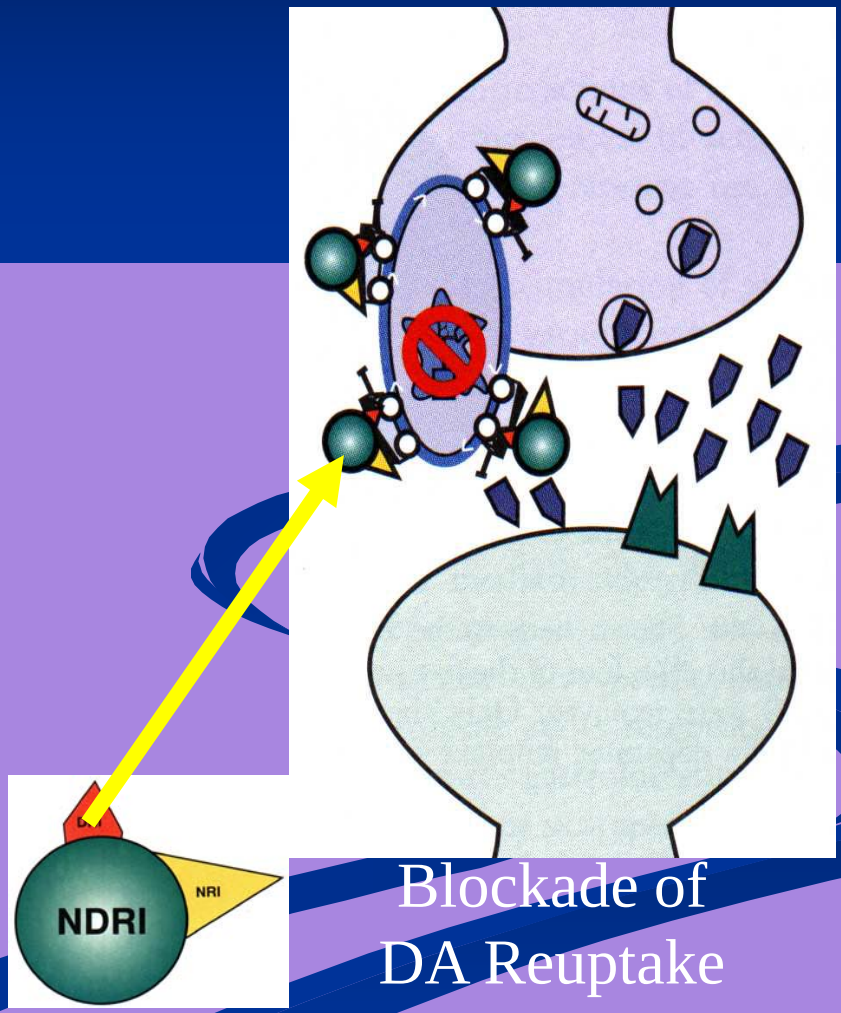
- bupropion (Wellbutrin SR)
  - Has only weak reuptake properties for DA and NE
    - But metabolized to an active metabolite which is a more powerful blocker of NE and DA reuptake than bupropion itself
    - More of a "pro-drug" (precursor)



Norepinephrine-Dopamine Reuptake Inhibitors (NDRI's)



Blockade of NE Reuptake



Blockade of DA Reuptake

NDRI's - bupropion

- Generally activating or even stimulating
- Does not appear to have troublesome sexual side effects associated with SSRI's
  - Probably due to lack of significant serotonergic component in mechanism of action
- Also useful in decreasing craving associated with smoking cessation