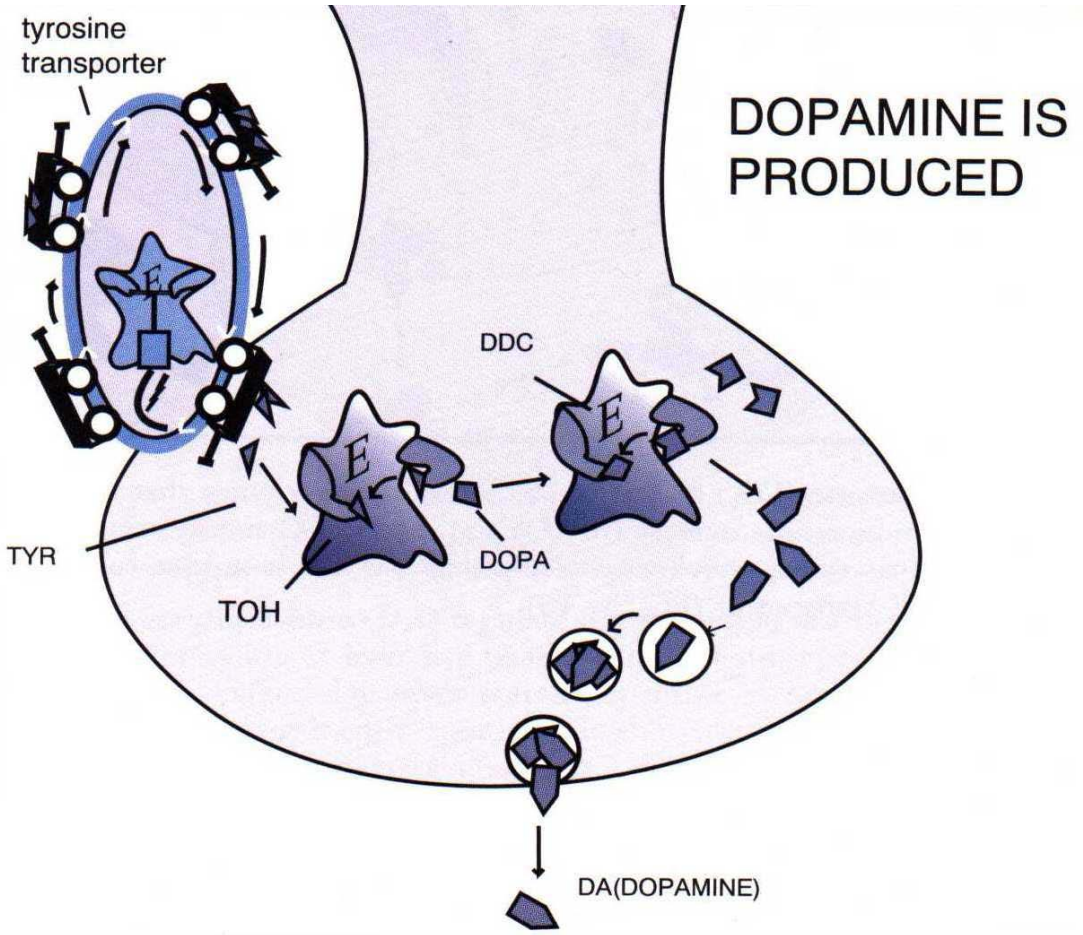
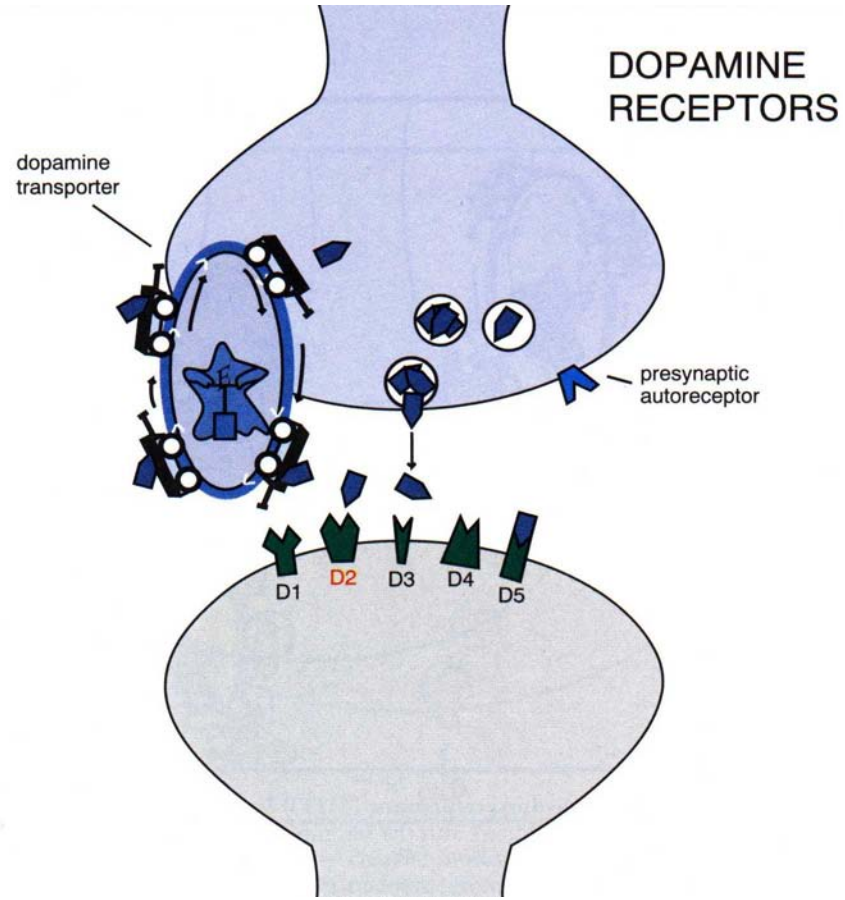
ADHD Meds, Part 2

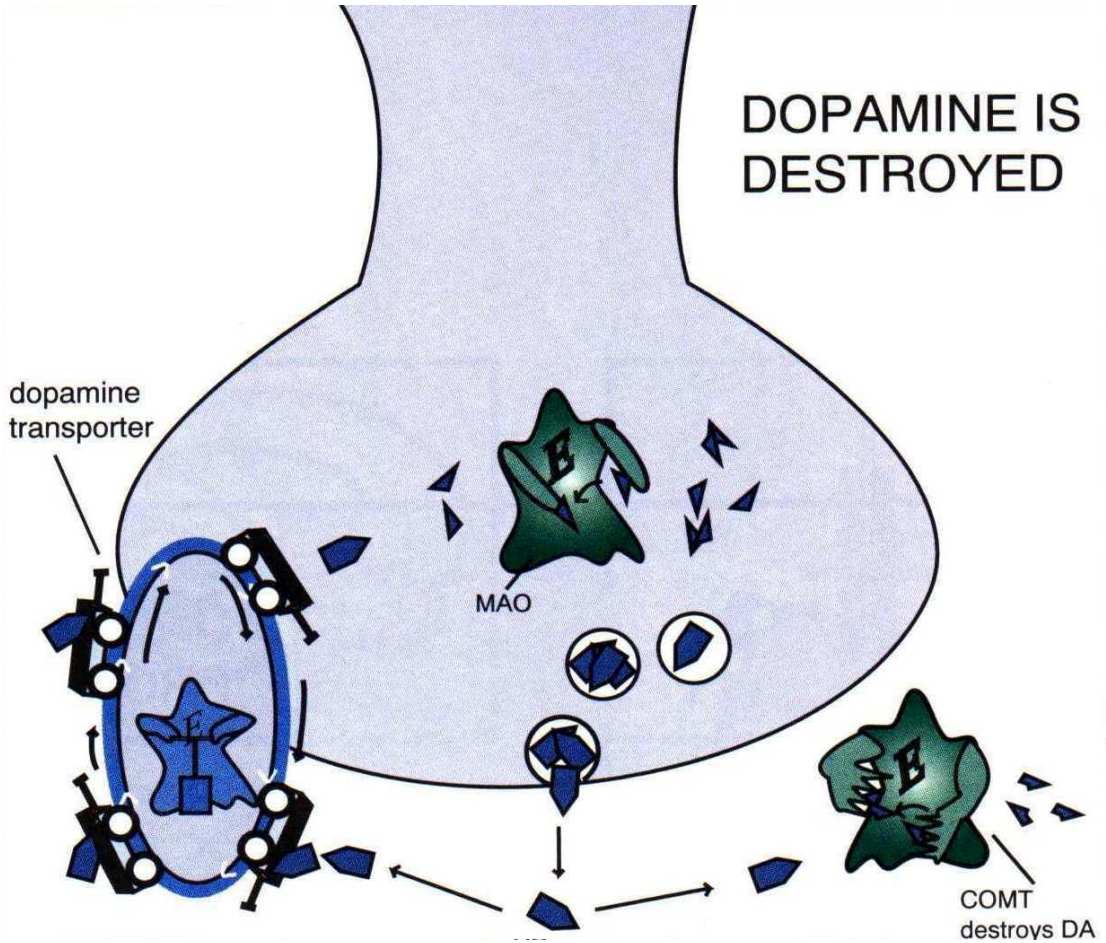
Dopamine Synthesis



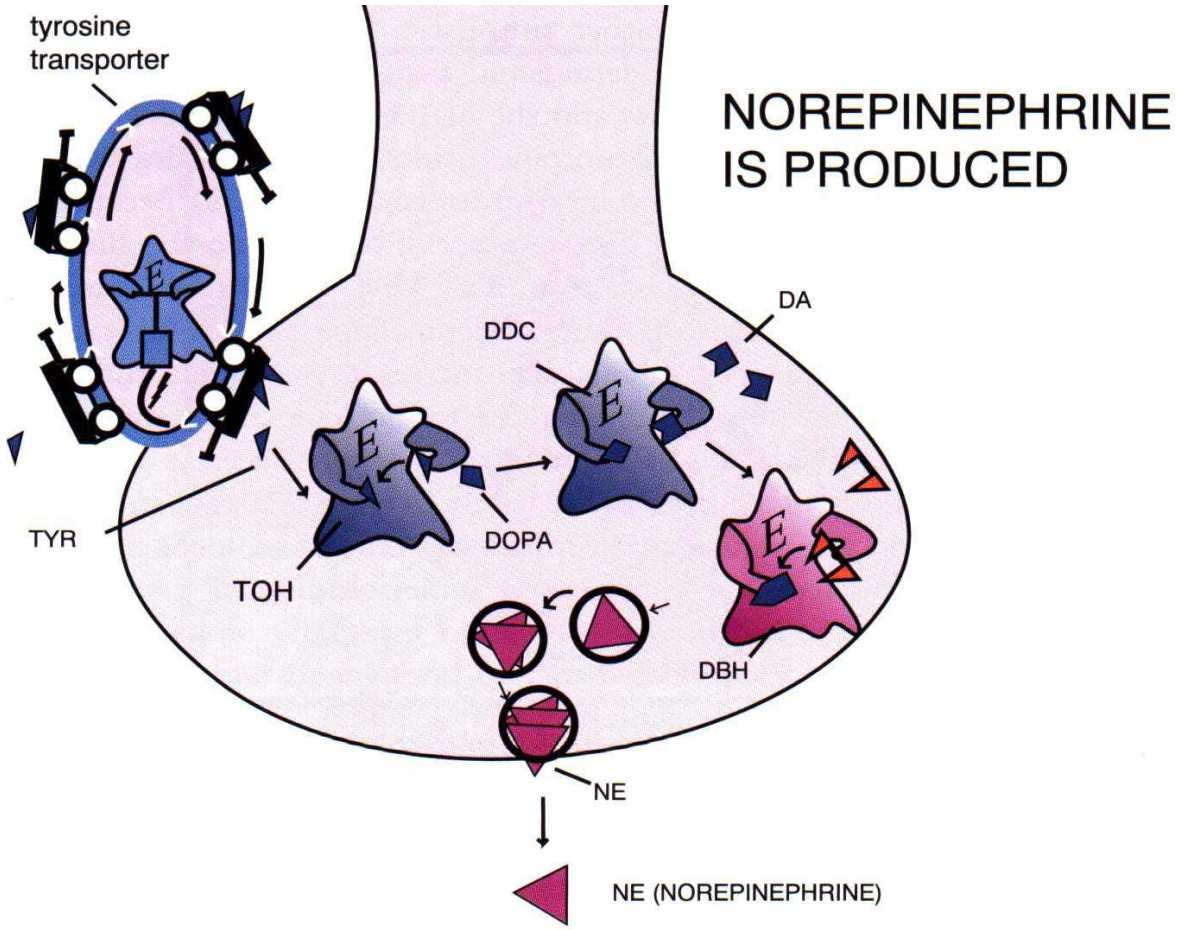
Dopamine Receptors



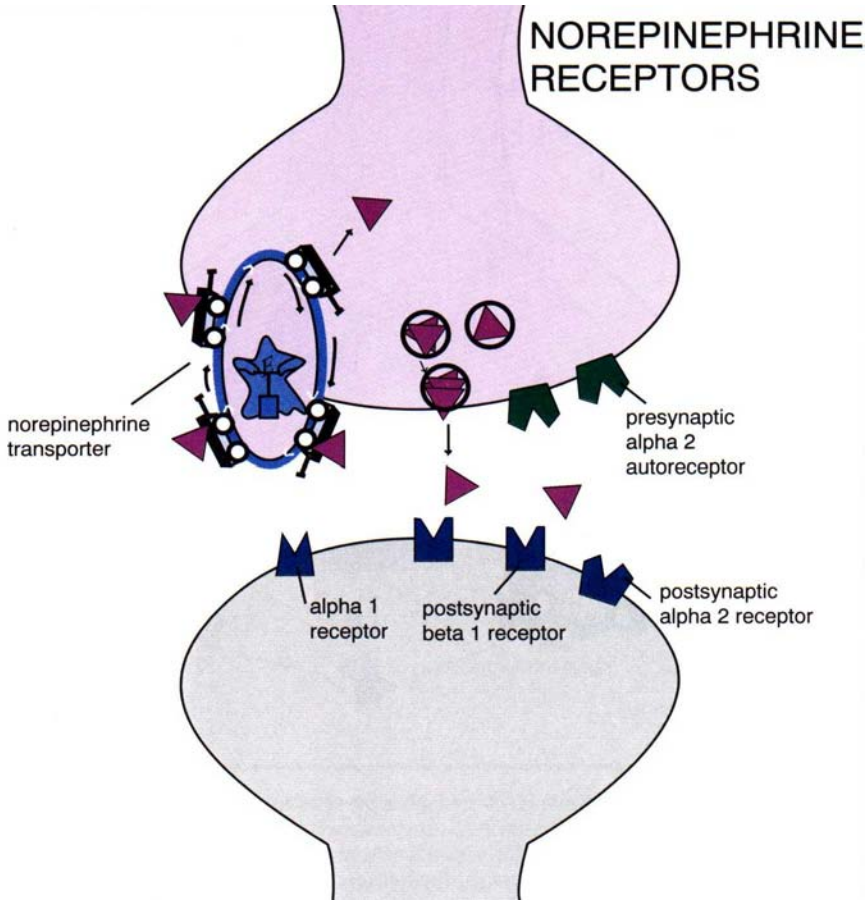
Dopamine Metabolism



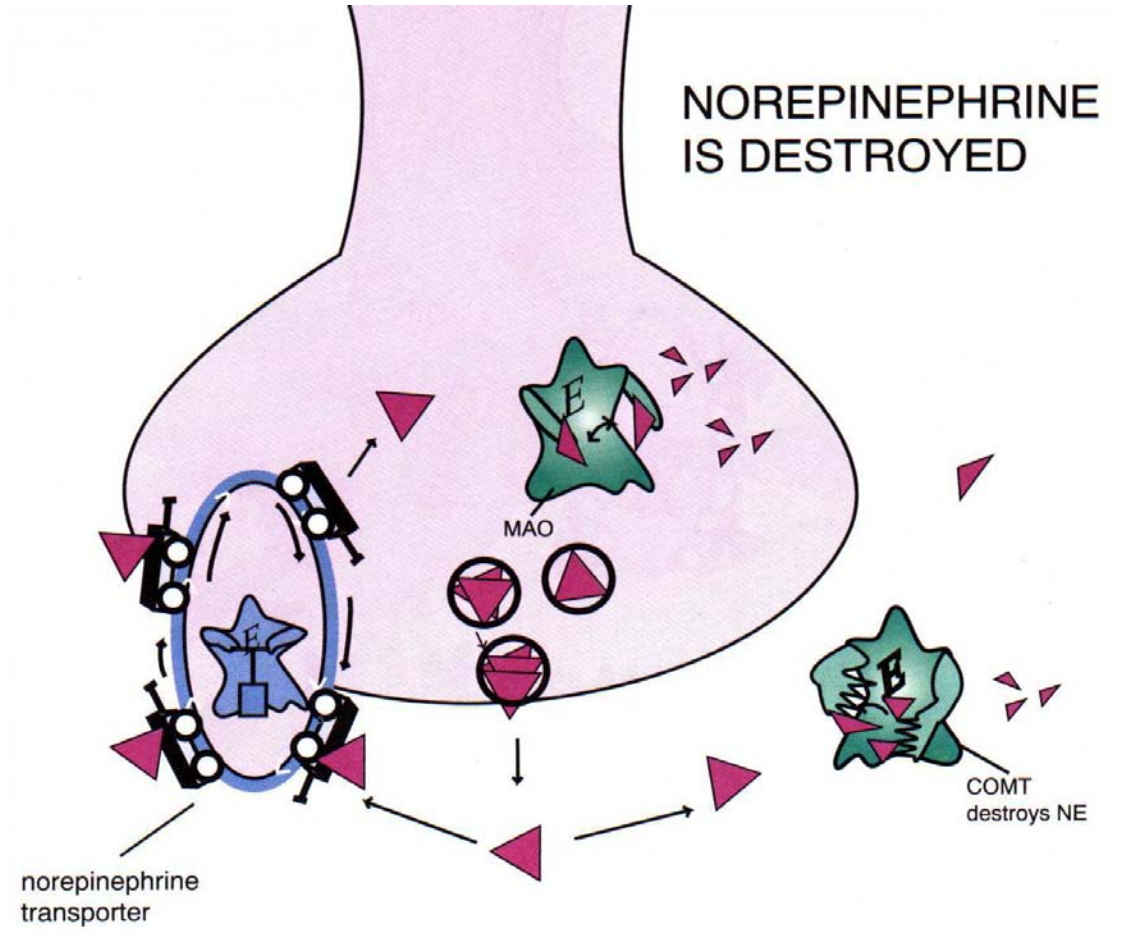
Norepinephrine Synthesis



Norepinephrine Receptors



Norepinephrine 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
- The increased tonic DA levels produced by MPH stimulate presynaptic autoreceptors, causing:
  - Reduced DA production
  - Inhibition of neuronal firing
  - Reduced subsequent *phasic* release of monoamine neurotransmitters

How AMP Works

In the Striatum

- Pharmacology of AMP considerably more complex than that of MPH
  - Effects of AMP cannot be fully explained by inhibition of monoamine reuptake (DAT inhibition) alone

How AMP Works

In the Striatum

- Major effect of AMP is to increase presynaptic DA release
  - To do so, it must first "hitch a ride" into the presynaptic DA terminal
    - Able to do so by mimicking DA (due to similarity in chemical structure)
- Unlike MPH, AMP also directly inhibits MAO
  - Inhibits breakdown of monoamines by MAO

How MPH and AMP Work

In the Cortex

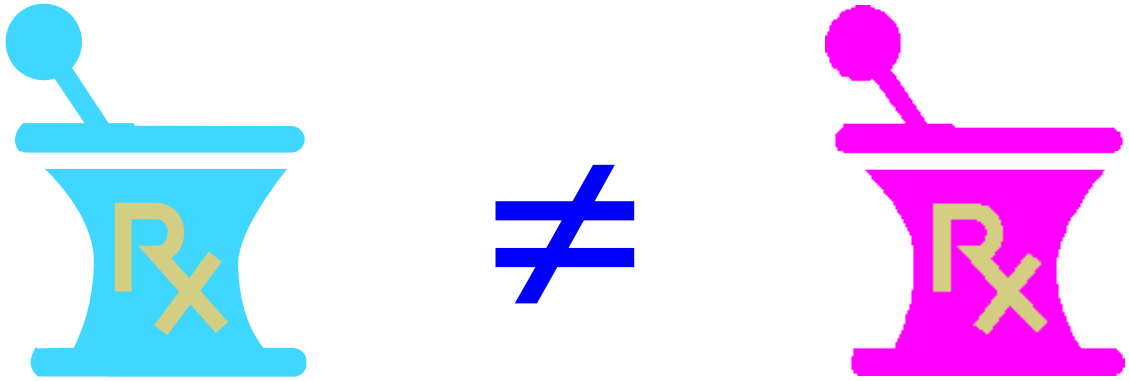
- In contrast to striatum, cortical (frontal) DA systems have considerably lower levels of DAT
- So drugs that selectively affect the DAT (e.g., MPH) have somewhat weaker ability to increase DA efflux in cortex than in striatum
  - Likely to account for differing clinical effects of MPH and AMP

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?

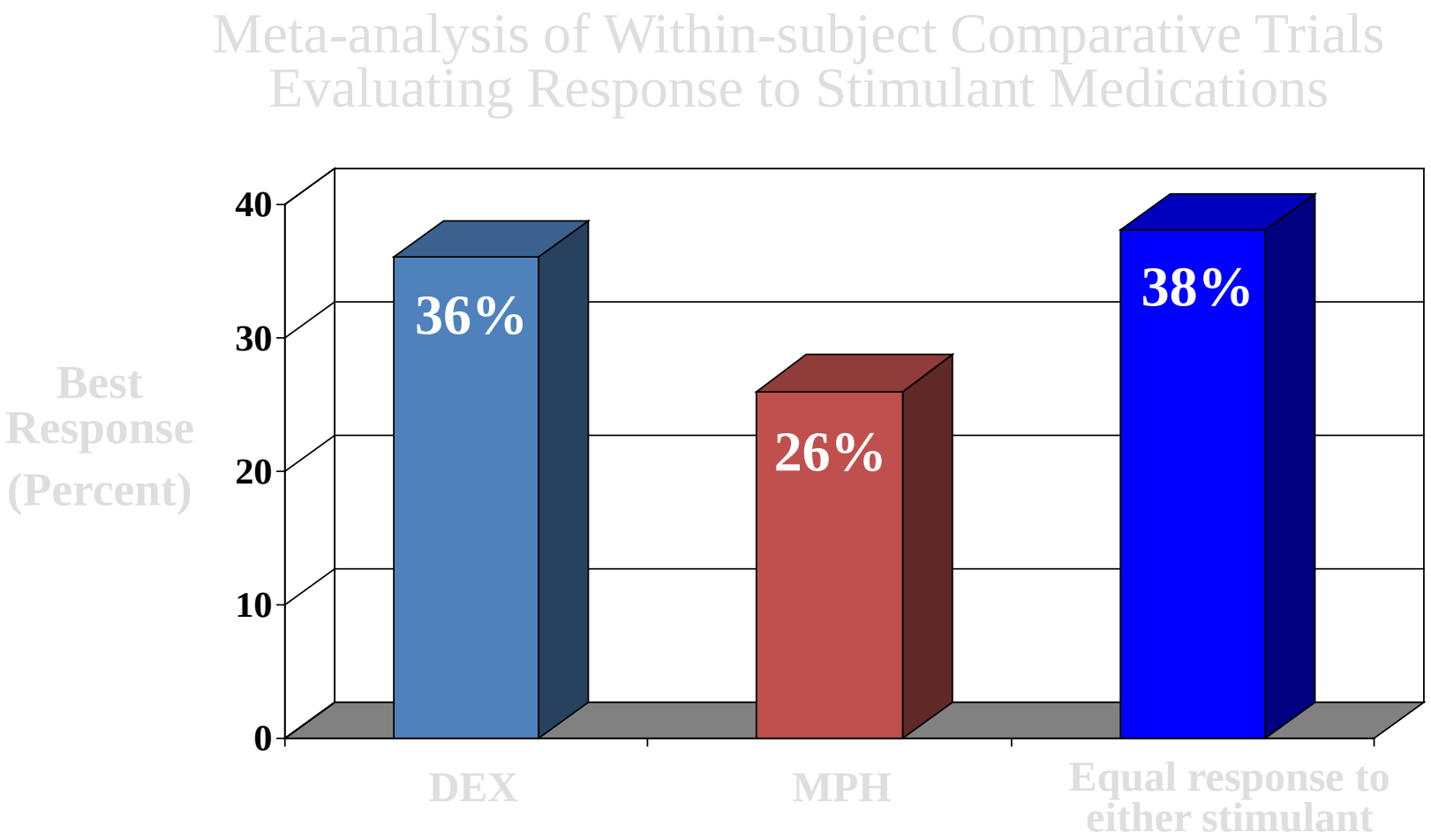
- Elia et al. (1991) reported that 25% of (N = 48) subjects in their ADHD study improved on only one of the two stimulants when both were tried

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)



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
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- AMP
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- Cocaine
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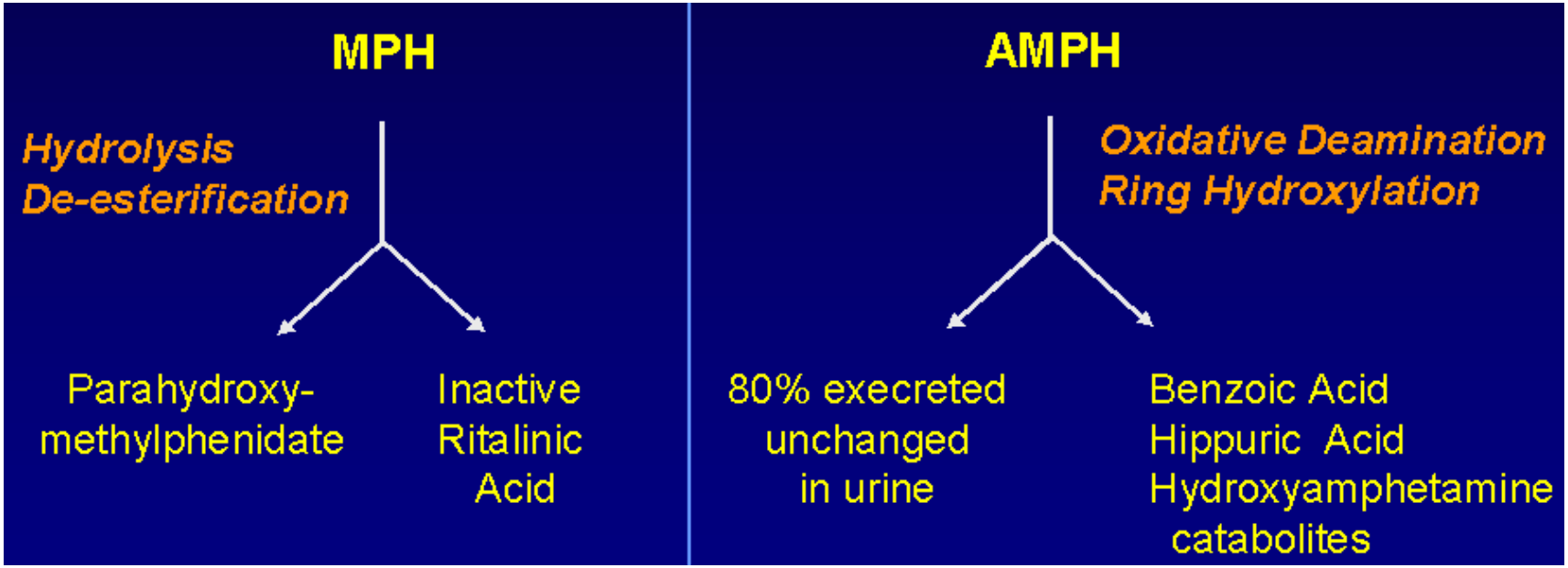
Important Differences between MPH and AMP

- 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)

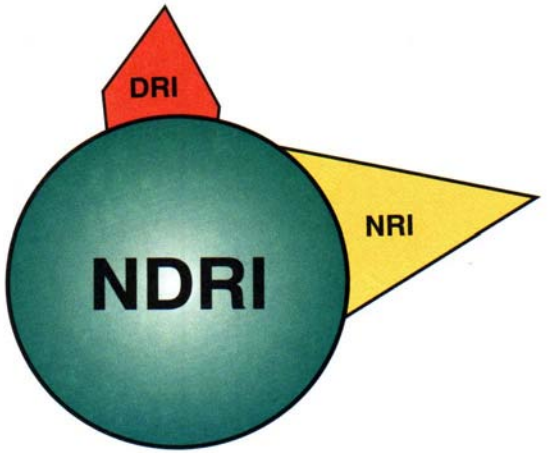
- Reduces ADHD, ODD, aggression, depression
- Increases in school productivity and social behavior
- Improved self-esteem and parent-child relations
- Improved enuresis and “morning after dose” behavior
- Less insomnia than MPH (7% vs. 30 – 50%)
  - Faster time to sleep onset
- Can be combined with stimulant

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)



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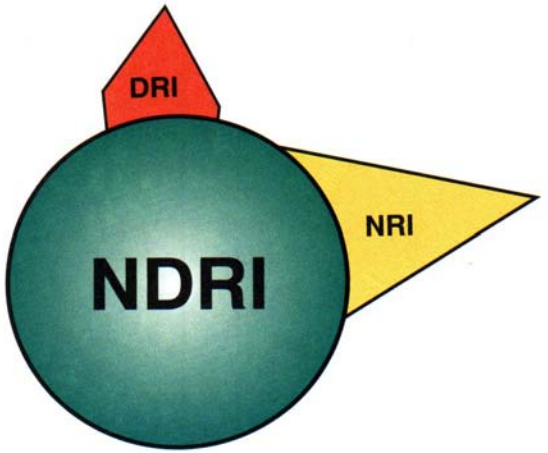

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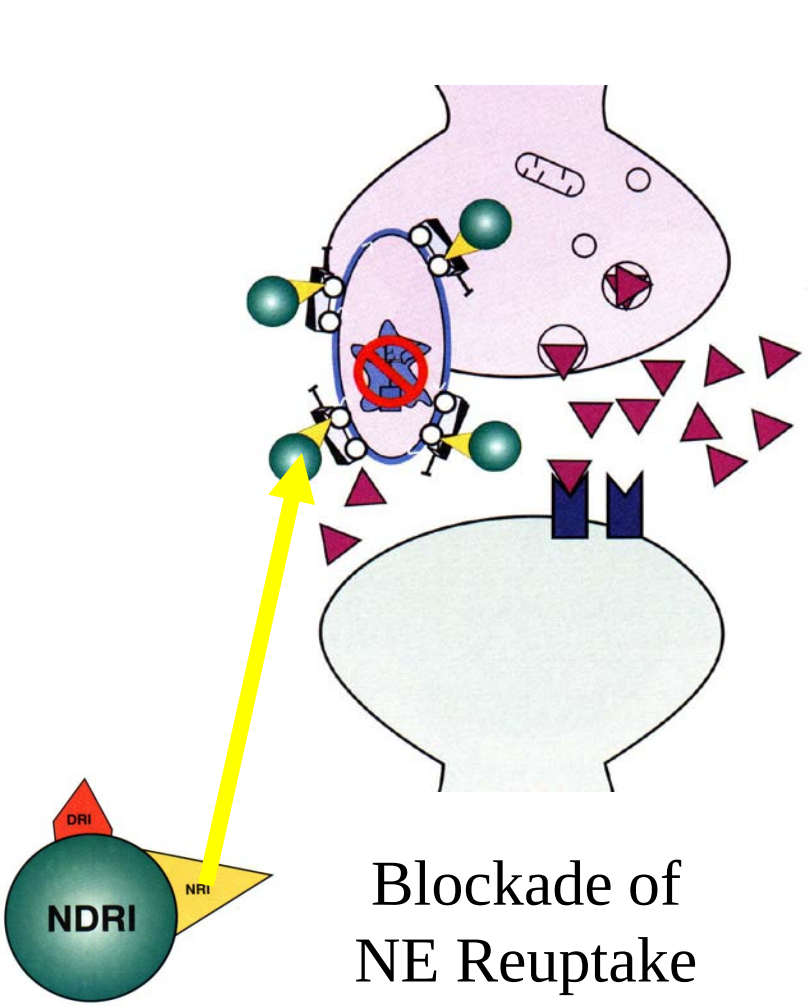
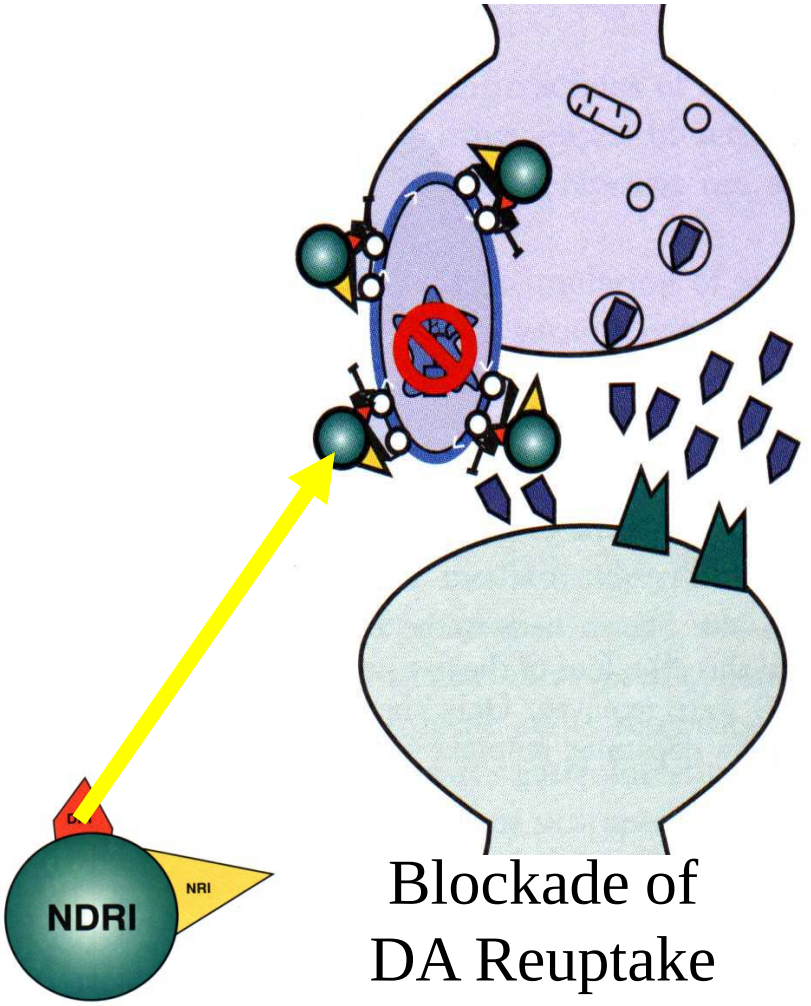
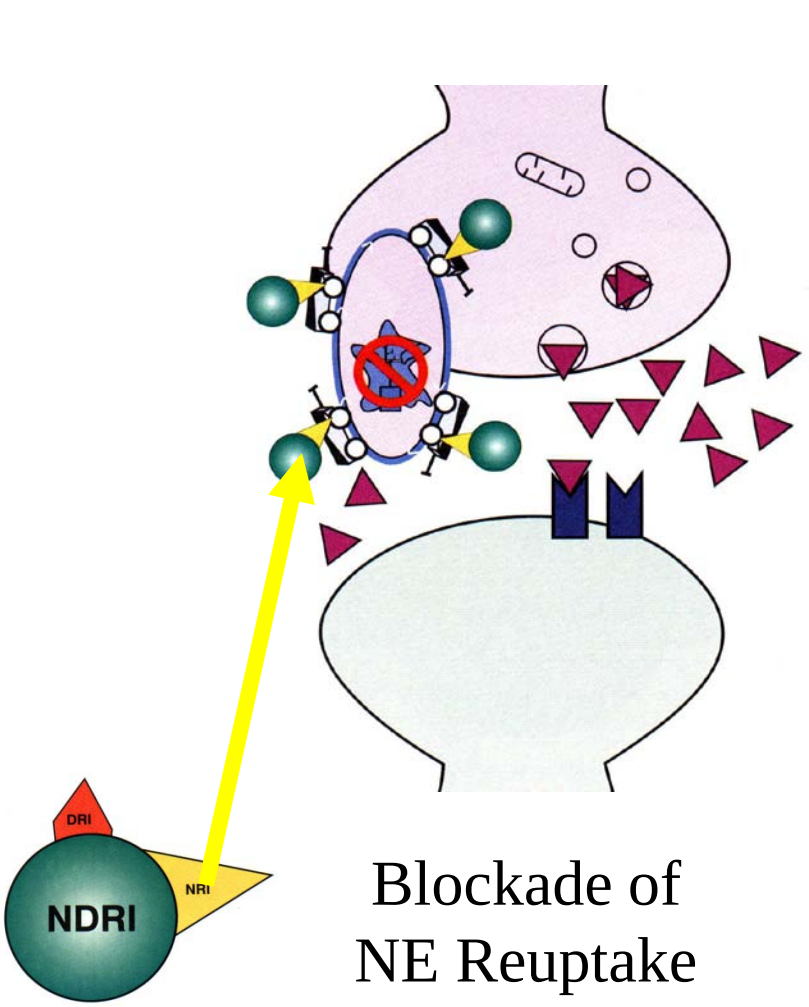


Blockade of NE Reuptake

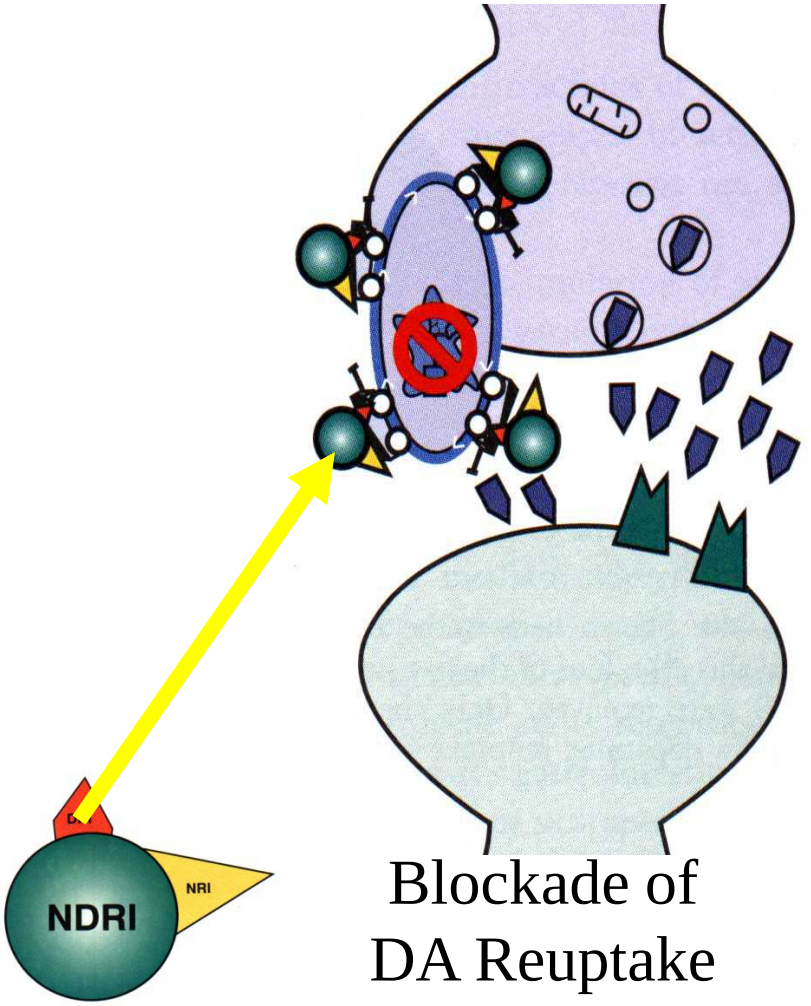


Blockade of DA Reuptake

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