

What is new with ADHD  
medications?

تازه های درمان دارویی در درمان اختلال نقص تمرکز بیش فعالی

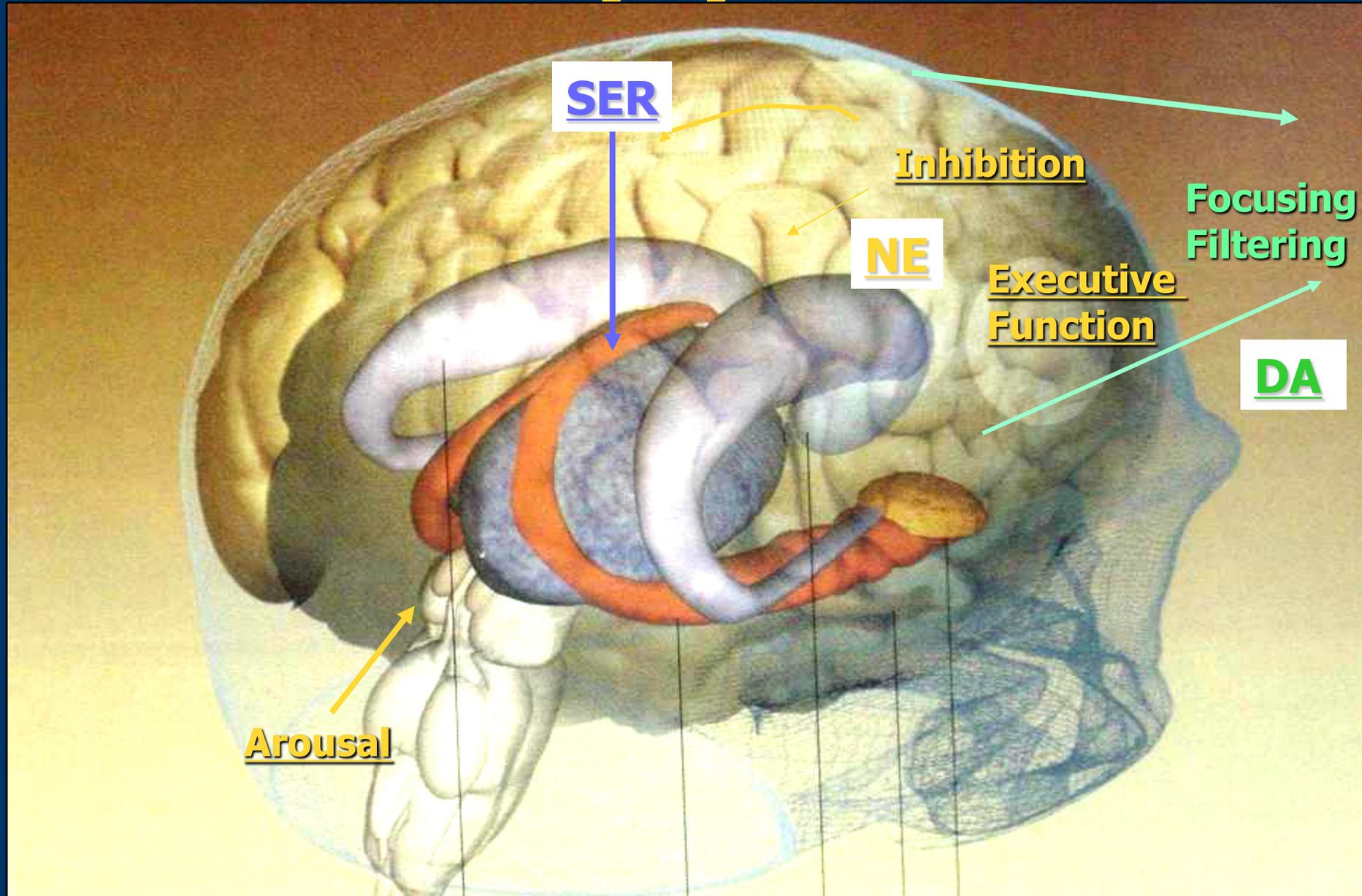
# prevalence

- 10-12 percent of children worldwide
- Increasing recognition of adult ADHD:
  - Could be due to undiagnosed ADHD in children cropping up in adulthood
  - The way we interact with the world (smart phone use, the combination email, text, real world interactions, multiple apps and streams of media and social media all coming at once trying to manage life) creates clouds of pulls on our attention

# **Role of DA and NE in ADHD**

**Neurotransmitters in psychopathology  
and treatment**

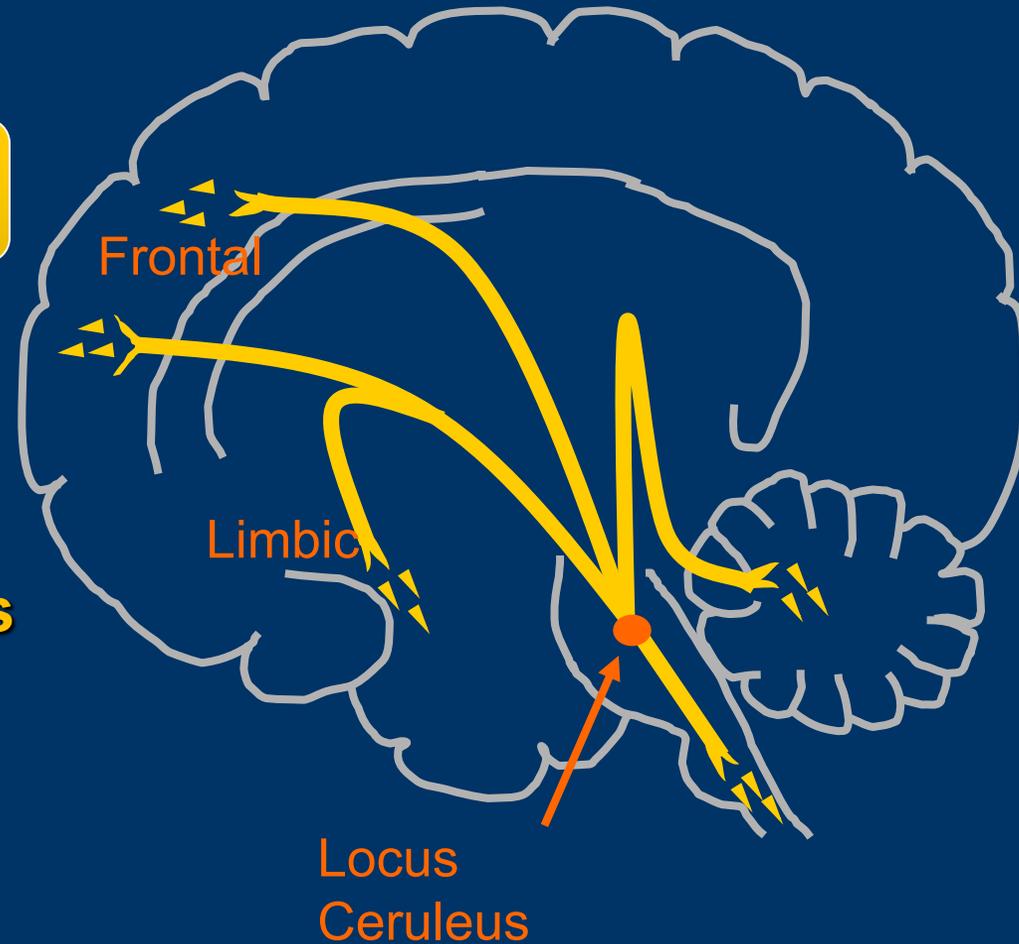
# Core Modulatory Systems

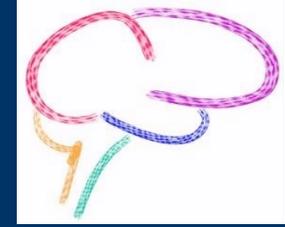


# Neurotransmission Relative to ADHD

## Norepinephrine

- Dampens noise
- Executive operations
- Increases inhibition





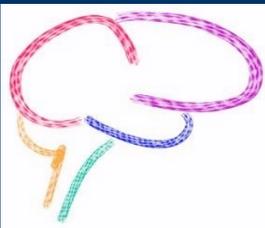
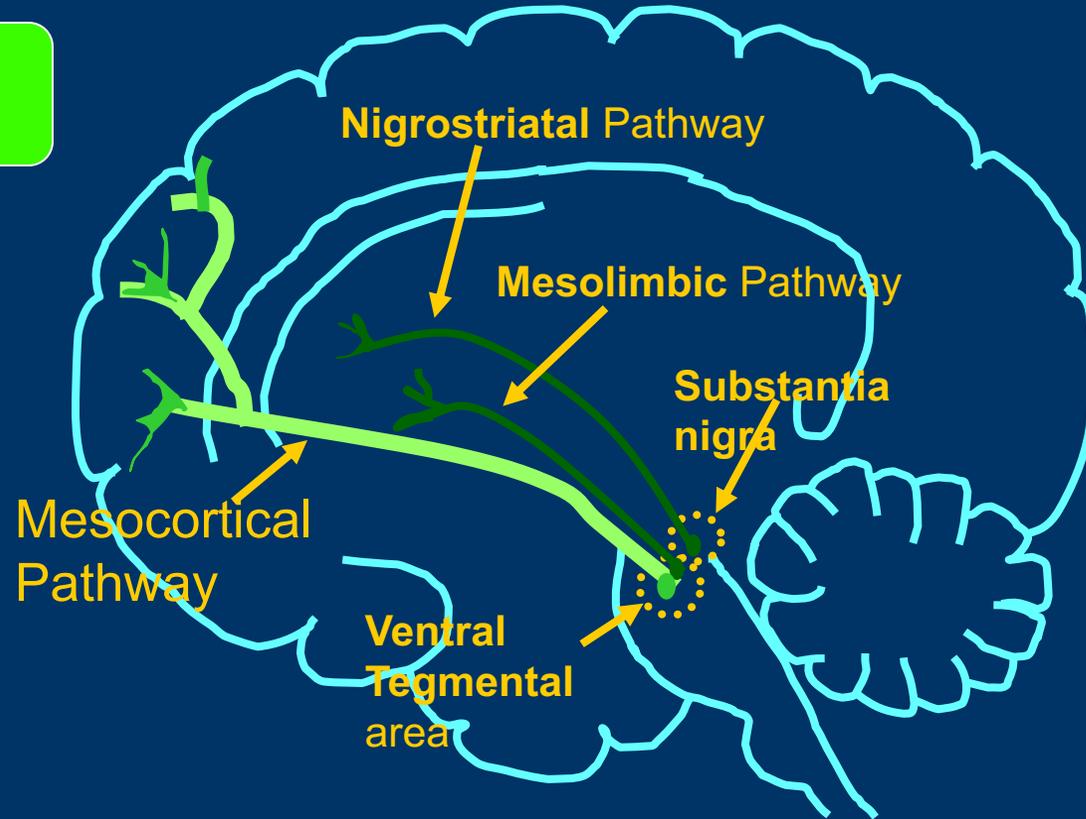
## Essential Roles of NE

- **Arousal**
  - Alerting & Energy
  - Acute Response
- **Executive Function**
  - Prioritization & Sequencing
  - Memory storage and retrieval
  - Meaning & Significance
- **Inhibition**
  - Cortical Sensory Down-regulation
  - Decreases Distractibility  
when paying attention to something else.

# Dopamine Neurotransmission Relative to ADHD

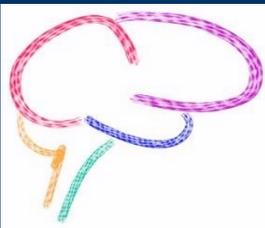
## Dopamine

- Enhances signal
- Improves attention
  - Focus
  - On-task behavior
  - On-task cognition

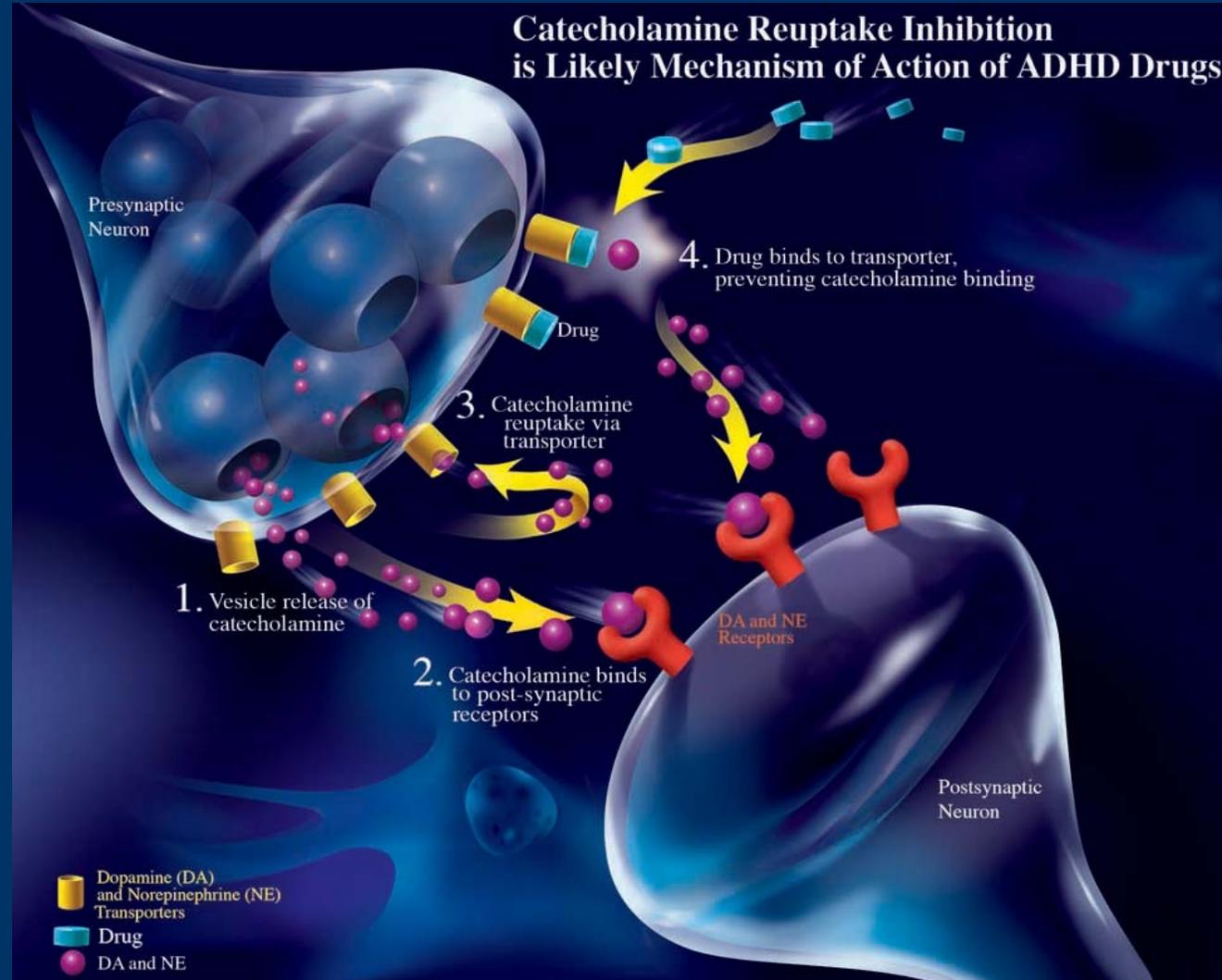


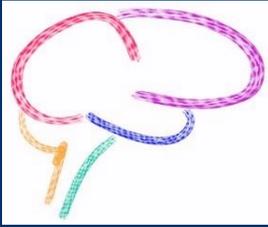
# Dopamine

- Role in ADHD
  - *Focusing of Attention*
  - *Activation of Executive Function*
  - *Decrease Distractibility*
    - Dopamine typically *inhibitory* tonically (PFC)
  - *Reward & Pleasure → Meaning & Purpose*



# Catecholamine Reuptake Inhibition is Likely Mechanism of Action of ADHD Drugs





## Executive Function in ADHD

Linking Goals → Strategies → Actions

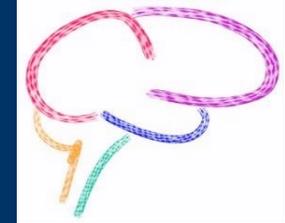


**Creativity**  
**Productivity**  
**Identity**

# Executive Function Scale – Prerequisites & Ingredients - R. Hunt, MD<sup>©</sup>

1. **Energy** – has energy to do tasks, activities
2. **Motivation** – by sense of purpose, tries hard
3. **Initiation** – gets started on tasks without nagging
4. **Organized** – creates a plan for getting tasks done
5. **Sets Priorities** – for important tasks & chores
6. **Autonomy** – does tasks, chores, homework  
without nagging, frequent reminders
7. **Execution** – follows plan, priorities; Does first things first.
8. **Frustration** – handles difficulties, frustrations,  
does not give up easily, returns to task
9. **Completion** – gets important things done; Feels Pride, Satisfied
10. **Efficient** – gets a lot accomplished for time spent

# Attention & Executive Function



External

## Attention

Focusing  
Selecting  
Sustaining

Internal

## Executive Function

Priority setting  
Problem-Solving  
Reasoning

Attention: The Gateway to Executive Function.  
AMPH Enhances EF

# Attention in Cognition



## Stimulus

### Characteristics

#### External

- Movement
- Clarity / Color
- MultiSensory
- Distraction

#### Internal

- Thoughts
- Plans
- Feelings

## Emotional

### Characteristics

- Interest
- Mood
- Frustration

## Processing

### Characteristics

- Energy
- Focusing
- Inhibiting
- Interpreting
- Linking
- Storing

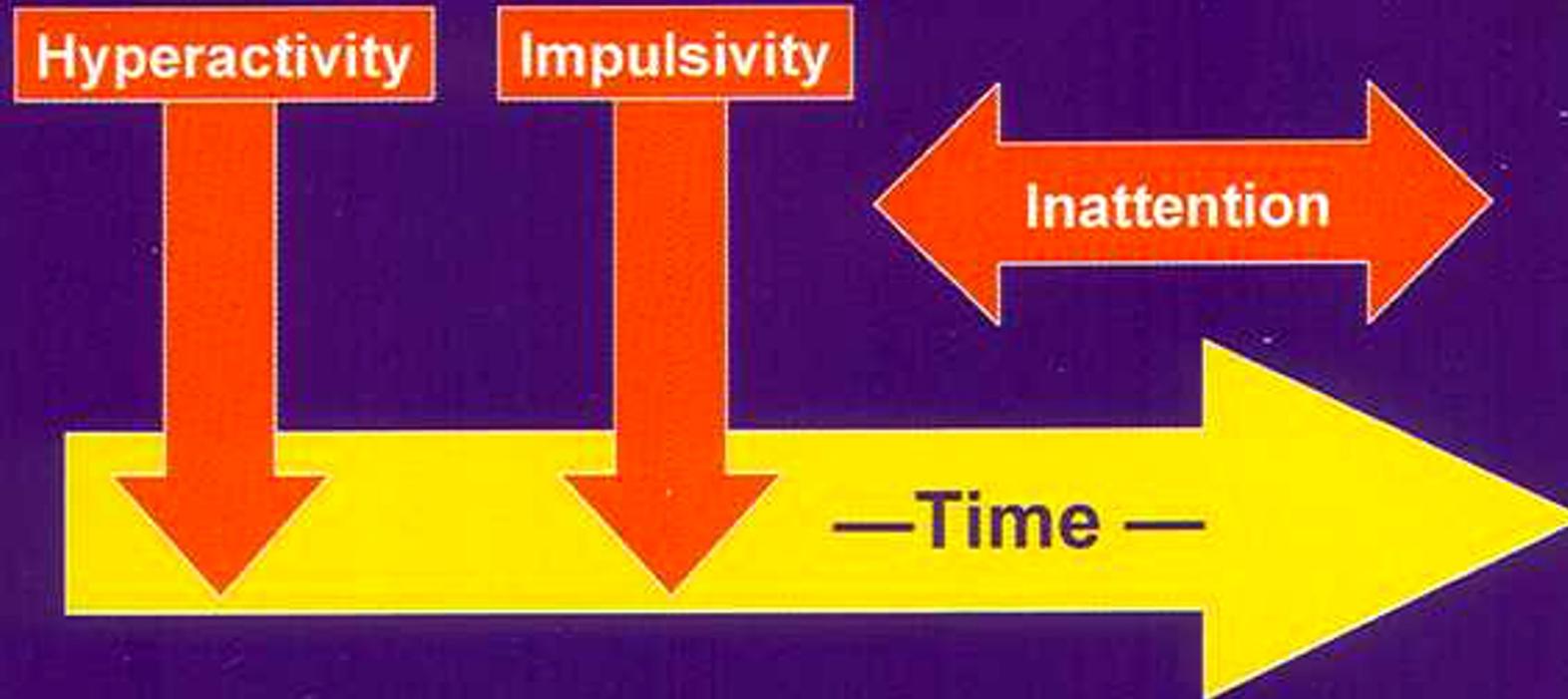
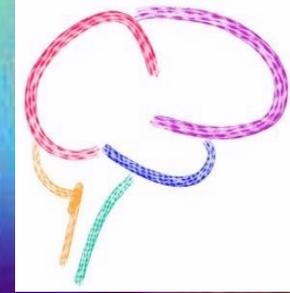
Generation of Attention



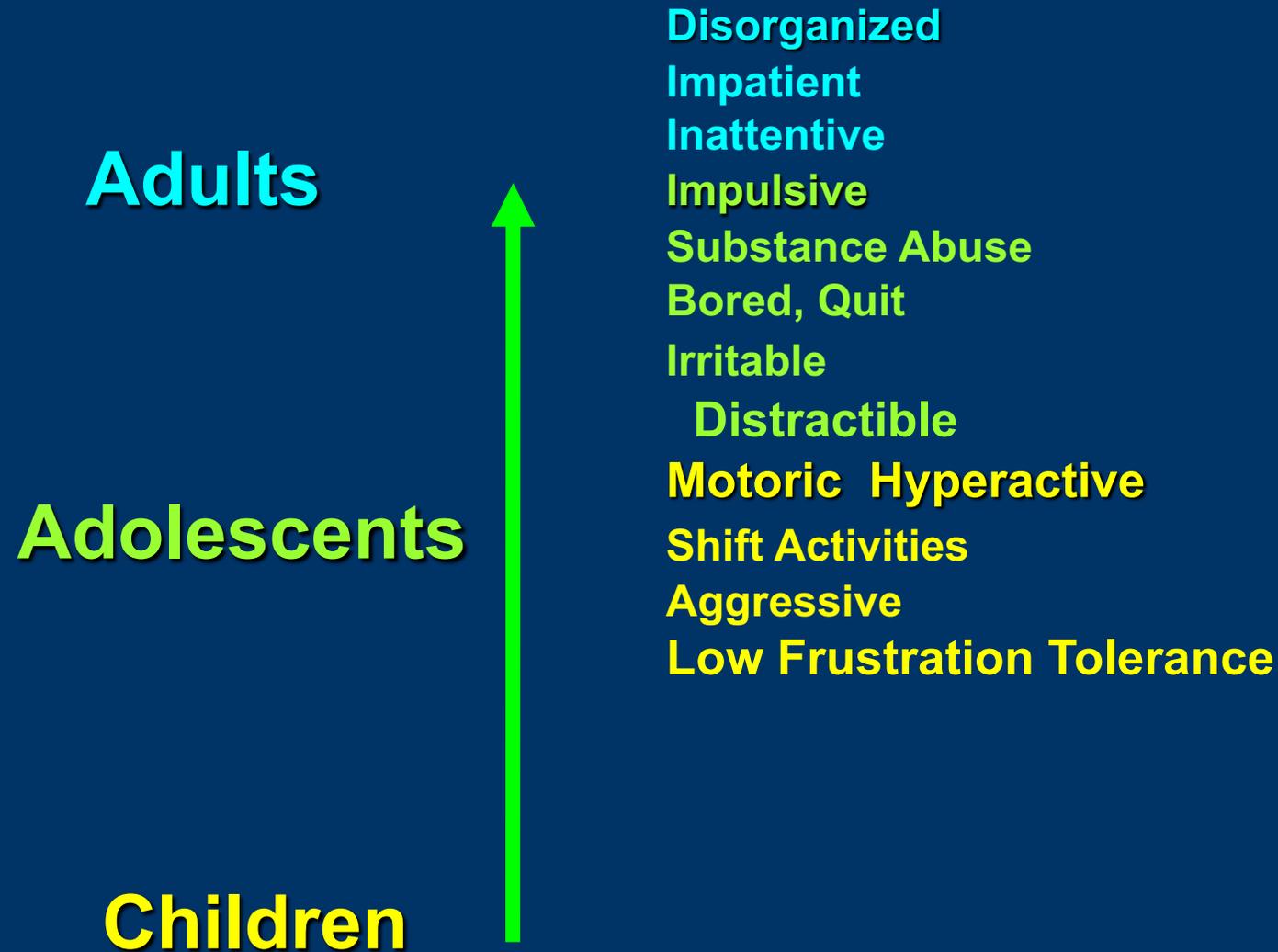
Inhibition & Selection

# Course

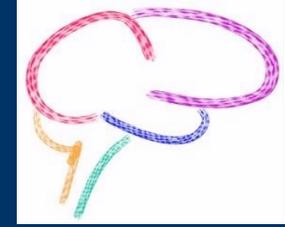
## ADHD Course of the Disorder



# ADHD: Developmental Issues



# Contrasting Effects on Attention



**RITALIN**



**Both**

- Attention
- Organization
- Behavior

**ADDERALL**

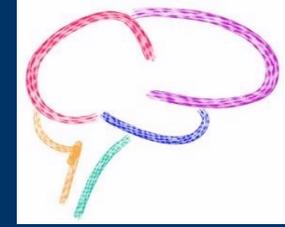


- More Inhibiting
- Less Affect, Fixed
- Less (-) Social

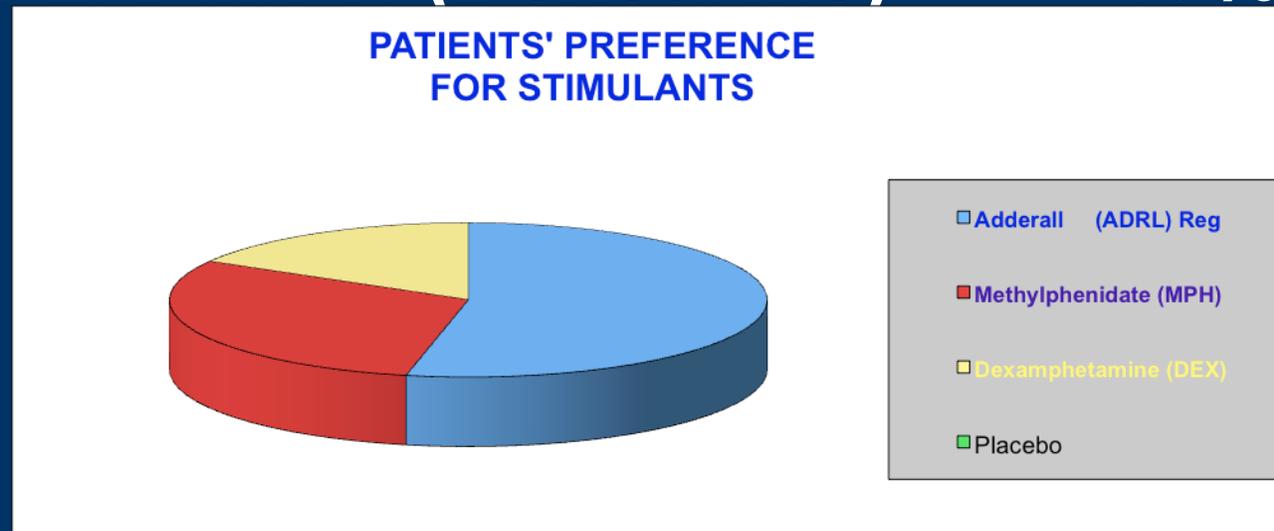
- More Activating
- More Affect; Flexible
- More + Social

# RESULTS:

## PREFERENCE for STIMULANTS



- Overall patient preference favored
  - AMPH (Adderall) = 55 %
- About equivalent number preferred
  - MPH (Ritalin) = 22%
  - DEXAMPH (Dexedrine) = 19%



# Clinical Differences MPH vs AMPH

## *Methylphenidate*

- Activation – Energy
  - Less
- Task Flexibility
  - Less → one thing
- Neurotransmitters
  - DA >> NE

## *Amphetamine*

- Activation – Energy
  - Greater
- Task Flexibility
  - Greater → multitask
- Neurotransmitters
  - DA > NE >> Ser.



# Task Differentiation

Single Tasking – *MPH*  
*Ritalin*



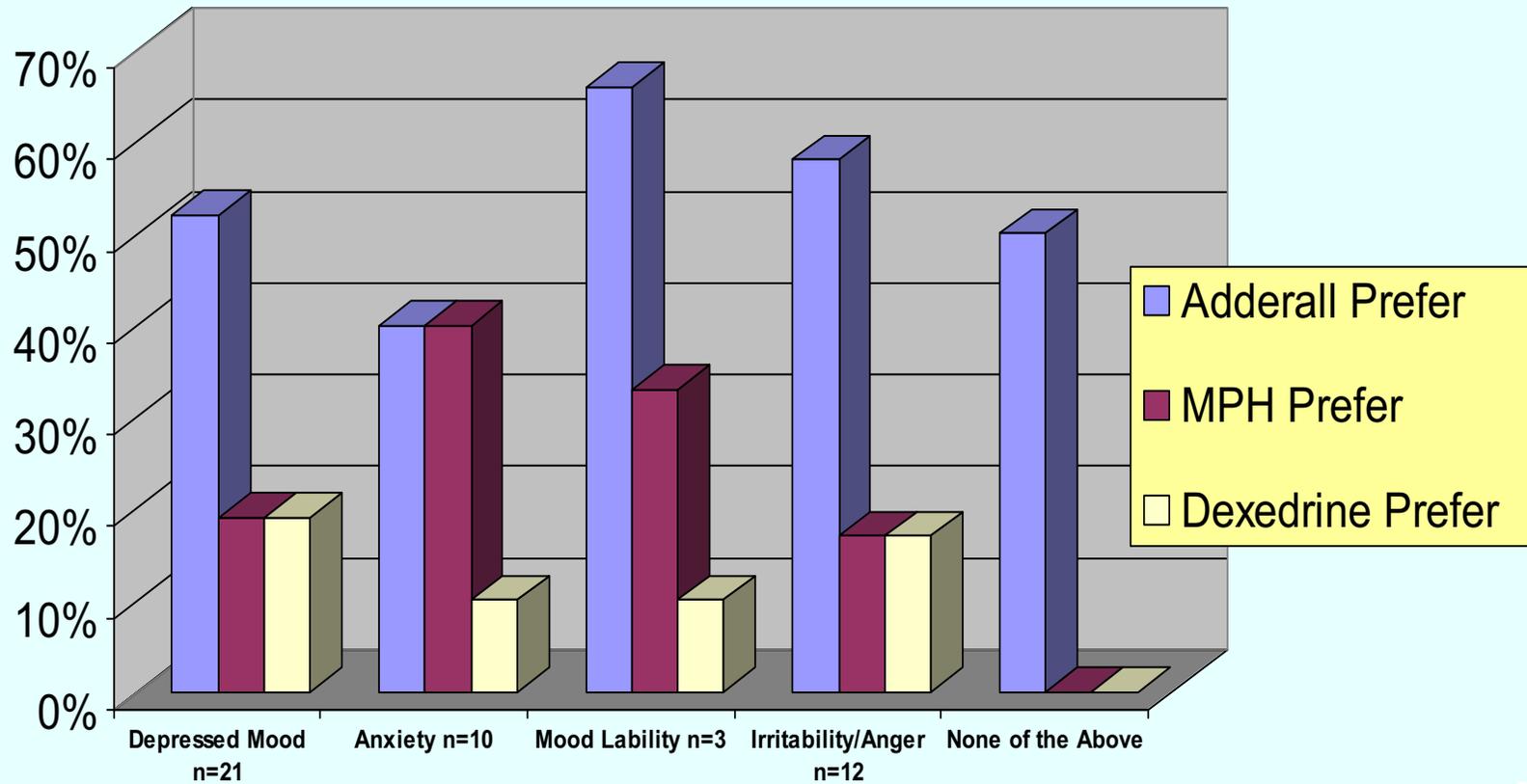
Multitasking – *AMPH*  
*Adderall*



# Personality Characteristics

## PERSONALITY CHARACTERISTICS & STIMULANT MEDICATION PREFERENCES

in 30 Adults with ADD



# Clinical Preference for MAS (Adderall XR) vs MPH (Concerta)

## 1. Increased Cognitive Flexibility

- Less perseveration
- Greater Creativity – Flexible Problem-Solving

## 2. Enhanced Energy

- More alert, Engaged
- Greater Perseverance

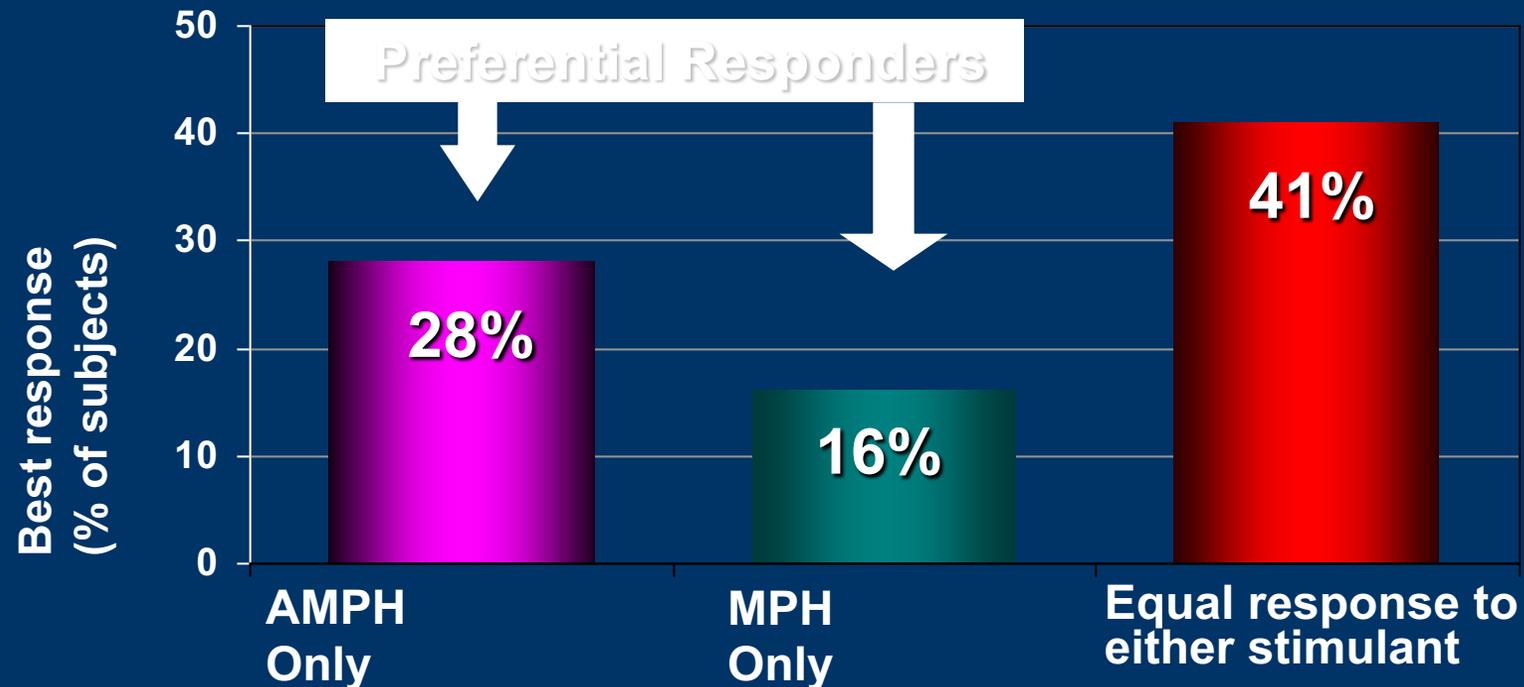
## 3. Social Interaction

- Enhanced Involvement
- Better Social Processing
- More interactive / Engaged



# No Single Stimulant is Best

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



Arnold et al. *J Attention Dis.* 2000;3:200.

AMPH=amphetamine.  
MPH=methylphenidate.



# Medication Management

## Do Your Own Clinical Trial

### Optimize Treatment Response

#### — Find the Best *Medication*

- Preferential Responder - AMPH / MPH
- *Personality* Factors
- *Developmental* Factors

#### — Find the Best *Dose*

- *Duration* of Action
- *Task* Performance

#### — Find the Best *Response*

- *Behavioral* Control
- *Social* Functioning
- *Creativity & Organization*

What are the mode of action of  
pharmacological treatments for  
ADHD

# Hypothesized mode of action of pharmacological treatments for ADHD

## Stimulants



### Methylphenidate

Targets the DAT and the NET, inhibiting DA and NA reuptake, thereby increasing DA and NA levels in the synaptic cleft<sup>24-31</sup>



### Amphetamine

Targets the DAT and the NET, inhibiting DA and NA reuptake, thereby increasing DA and NA levels in the synaptic cleft<sup>24,25,32-34</sup>  
Also binds VMAT2, promoting the release of DA into the synapse<sup>35-37</sup>

## Non-stimulants



### Atomoxetine

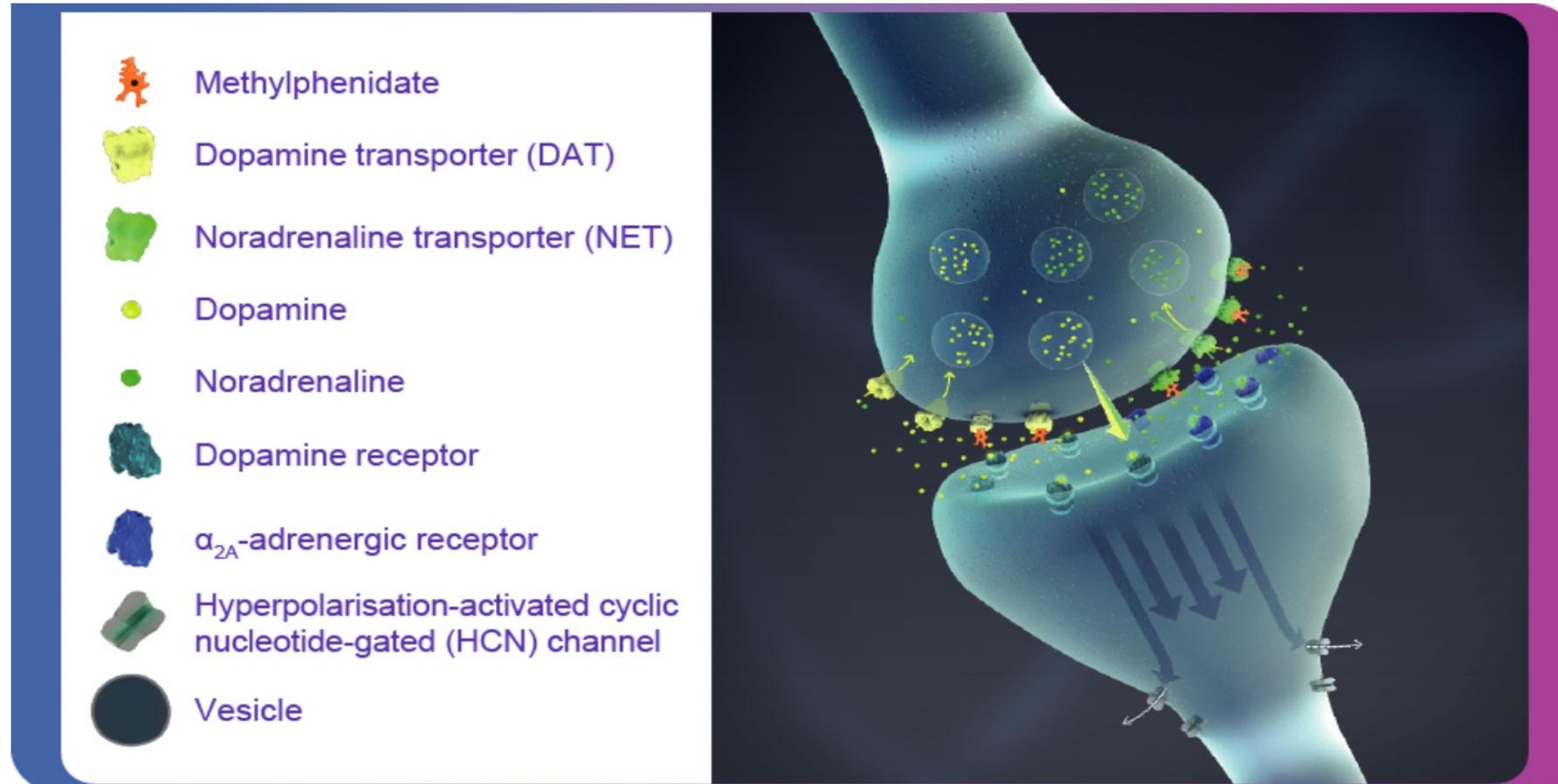
Targets the NET, inhibiting the reuptake of NA, therefore increasing NA levels in the synaptic cleft<sup>38,39</sup>



### Guanfacine

Binds to postsynaptic  $\alpha_2A$ -adrenergic receptors, mimicking NA<sup>40</sup>

# Hypothesized mode of action of methylphenidate



# Hypothesized mode of action of pharmacological treatments for ADHD

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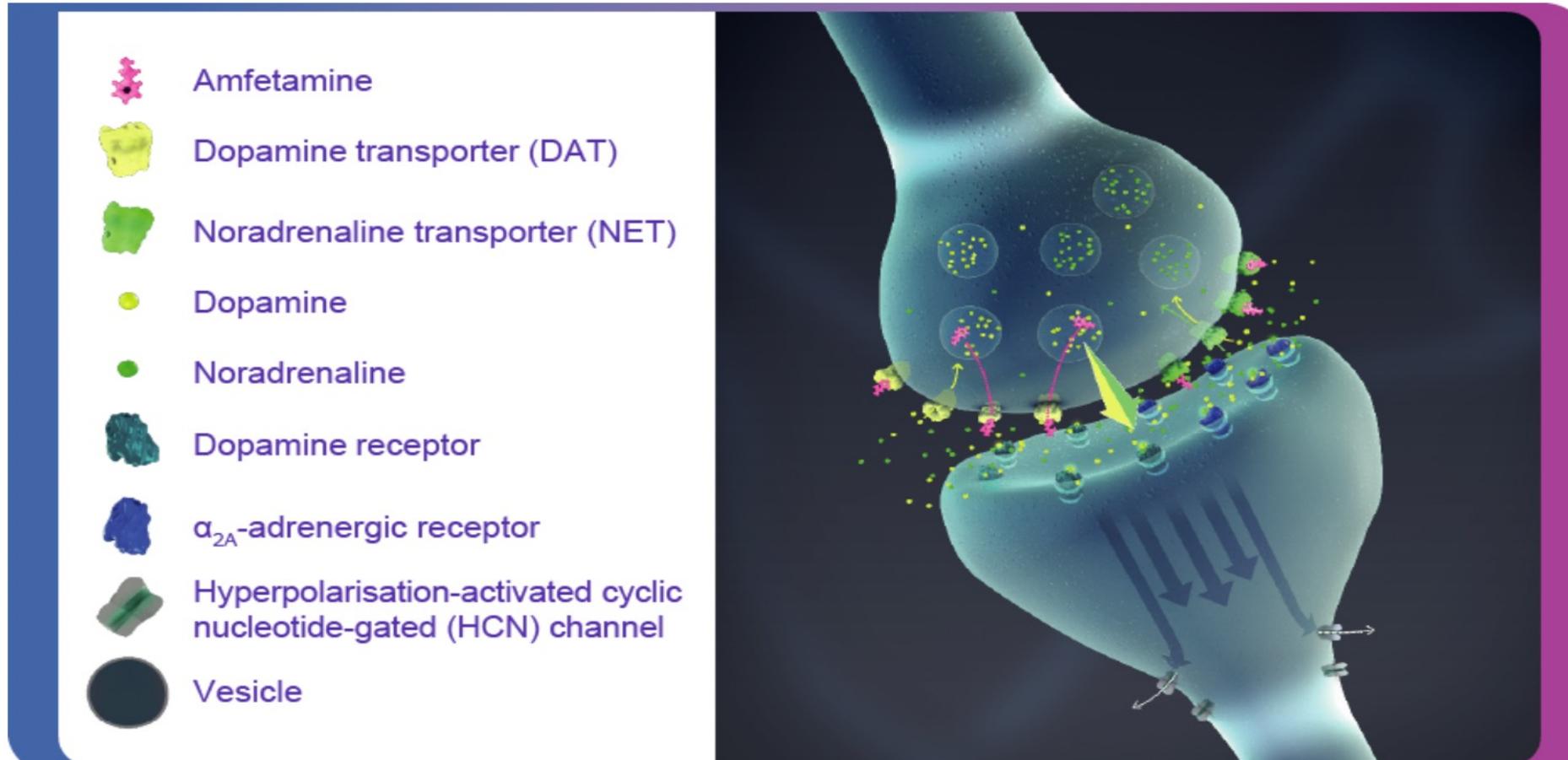
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# Hypothesized mode of action of amphetamine



# Hypothesized mode of action of pharmacological treatments for ADHD

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## Non-stimulants



### Atomoxetine

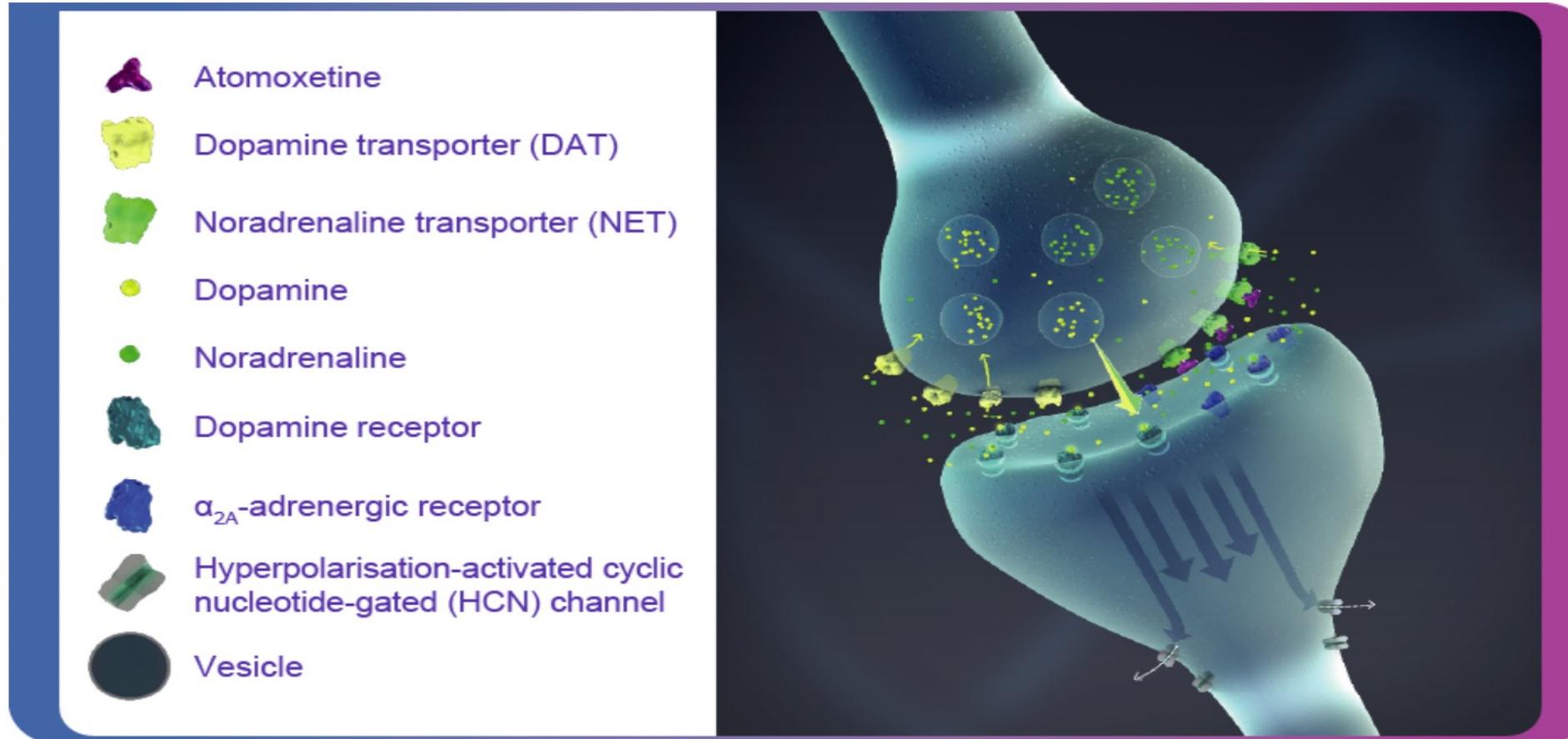
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# Hypothesized mode of action of atomoxetine



# Hypothesized mode of action of pharmacological treatments for ADHD

## Stimulants



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## Non-stimulants



### Atomoxetine

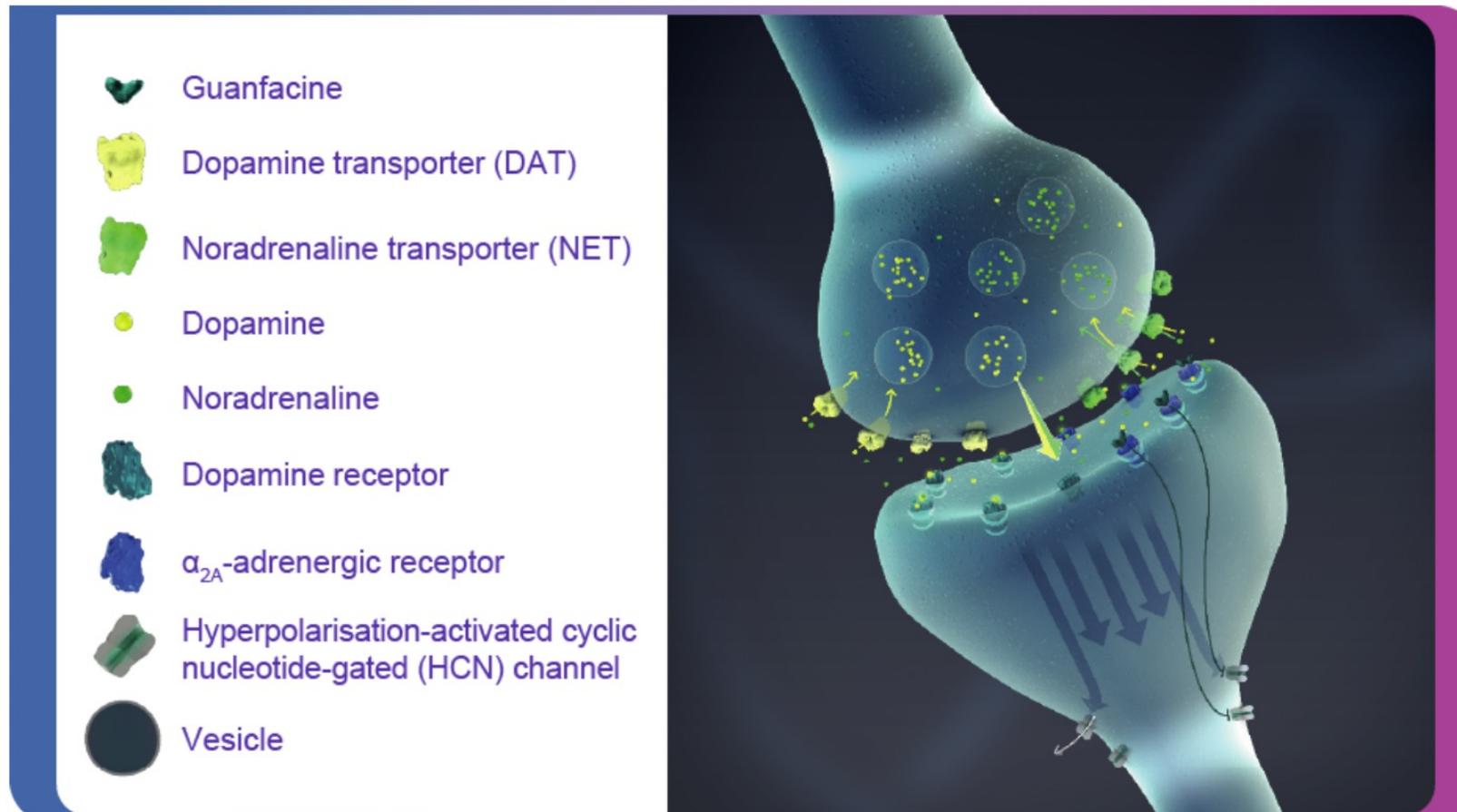
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# Hypothesized mode of action of guanfacine



How does the mechanism of delivery differ between pharmacological therapies for ADHD?

- **Immediate-release** tablets or capsules are the most widely used drug-delivery systems.
- They are designed to undergo disintegration in the stomach into smaller granules and subsequent dissolution in the fluids of the gastrointestinal tract.
- **Extended-release** formulations are designed to produce slow, uniform absorption of the drug.

- **Multiple bead system** consists of a water-soluble gelatin capsule that dissolves quickly once swallowed, releasing drug-containing beads of two different dissolution rates.
- Multiple bead formulations release a steady level of drug into the bloodstream, allowing for once-daily dosing.
- Once-daily dosing has practical advantages, particularly in young individuals, and the potential for stimulant abuse may be lower for extended-release formulations compared with immediate-release formulations.

- **Osmotic-controlled release oral delivery system** is designed to provide a longer duration of effect than the multiple bead system.
- For example, methylphenidate is available in this formulation.
- The outer layer of the capsule is coated with methylphenidate, which quickly releases once the pill is ingested.

- The inner layers are set up along an osmotic gradient; the first compartment, with a small amount of the drug, releases via simple diffusion, but the second compartment, with a higher amount of the drug, releases as a result of the osmotic pressure created when water reacts with the third compartment.

- **Prodrugs** are pharmacologically inactive molecules that are converted into one or more active metabolites through a natural metabolic process.
- Prodrugs are designed to enhance the attributes of the active drug, such as enhanced solubility, increased or enhanced absorption and distribution and prolonged systemic availability.

- Lisdexamfetamine dimesylate is a prodrug where lysine is covalently linked to amphetamine and the drug only becomes active after lysine is cleaved by enzymes in the bloodstream.
- The lisdexamfetamine prodrug becomes active only after it has been absorbed by the intestinal tract and has been converted to dextroamphetamine and *l*-lysine.

New medications

# Azstarys

Serdexmethylphenidate/dexmethylphenidate

- **Dexmethylphenidate:** Catecholamine reuptake inhibitor
- **Serdexmethylphenidate:** Prodrug of dexmethylphenidate
- Significant ADHD Symptom Improvement with 30-Minute Onset and **13-Hour** Duration of Efficacy Delivered by Once-Daily Corium Product

# Qelbree

viloxazine extended-release capsules

- noradrenergic medication
- Comes in capsule form; parents can break open the capsules and sprinkle the contents of a Qelbree capsule into a teaspoonful of applesauce.
- Quick onset
- Extended-release formulation

New horizon in treatment

# EndeavorRx

New trends in ADHD treatment

- EndeavorRx is an **ADHD treatment for kids aged 8-12**.
- It's delivered through an immersive **video game** experience on mobile devices
- However, It is not intended as a stand-alone therapeutic, nor is it a substitute for medication.

How can clinicians improve adherence to pharmacological therapies for ADHD?

*Psychoeducation and an individual's acceptance of their ADHD may help adherence to pharmacotherapy, particularly in adolescents*

- The decision regarding which medication is used to treat ADHD may depend on a range of factors, including:
  - presence of psychiatric [comorbidities](#);
  - undesirable effects of the medication;
  - individual compliance needs; potential for drug diversion;
  - and the personal preference of the individual and their family or carers.

- **Adherence to pharmacological therapy for ADHD can be suboptimal, which may negatively affect treatment outcomes.**
- For example, individuals with ADHD and their families may think that a pharmacotherapy has less than optimal effectiveness and is associated with intolerable adverse effects, which may contribute to poor adherence.

- [Psychoeducation](#) and an individual's acceptance of their ADHD may help adherence to pharmacotherapy, particularly in adolescents.
- In support of this, adolescents' perceptions of the degree of stigma associated with ADHD have been reported to affect receptiveness to treatment.

- Multiple daily doses of medication, including dosing during school hours, could also be considered a source of embarrassment for some students with ADHD.
- Moreover, ADHD-related forgetfulness may cause difficulty in adhering to a treatment plan that requires multiple daily doses; therefore, for some individuals once-daily dosing may be more helpful.

- It is recommended that clinicians ensure that individuals with ADHD are fully informed of the balance of risks and benefits of any treatment for ADHD, and check that problems with adherence are not due to misconceptions.
- Encourage people with ADHD to be responsible for their own health, including taking their medication as needed.

- Provide the individual with clear instructions about how to take their medication in picture or written format. This information may include dose, duration, adverse effects and dosage schedule.
- Advise the individual to use visual reminders to take their medication regularly (e.g. alarms, apps, clocks, pill dispensers or notes on calendars or fridges).

- Suggest that the individual takes their medication as part of their daily routine (e.g. before meals or after brushing their teeth).
- Encourage the individual with ADHD and their family or carers to attend peer support groups and encourage parents or carers to oversee ADHD medication for children and adolescents.