

# Stimulants in ADHD

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# History of Stimulants

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- Amphetamines were the first stimulants to be synthesized.
- They were created in the late 19th century and were used by bavarian soldiers in the mid-1880s
- They were not widely used clinically until the 1930s when they were marketed as benzedrine inhalers for relief of nasal congestion.
- These drugs were used to treat sleepiness associated with narcolepsy.
- They have been classified as controlled drugs

# Stimulants

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- Sympathomimetics are effective in many ways
- The augmentation of antidepressant medications in specific treatment-resistant depressions.
- One formulation, Evekeo, has been approved by the fda as an adjunct in a regimen of weight reduction



# PHARMACOLOGIC ACTIONS

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- According to evidence-based guidelines, the most common recommended treatment options for ADHD include pharmacological and psychological interventions.
- Stimulant medication is generally recommended as first-line therapy for school-age children and adolescents with severe ADHD, along with implementation of behavioral interventions also recommended
- During the past decade, diagnosis rates for ADHD, medication prescription and use of complementary and alternative medical therapies by young people have risen substantially.

## Comparative efficacy and tolerability of medications for attention-deficit hyperactivity disorder in children, adolescents, and adults: a systematic review and network meta-analysis (2018)

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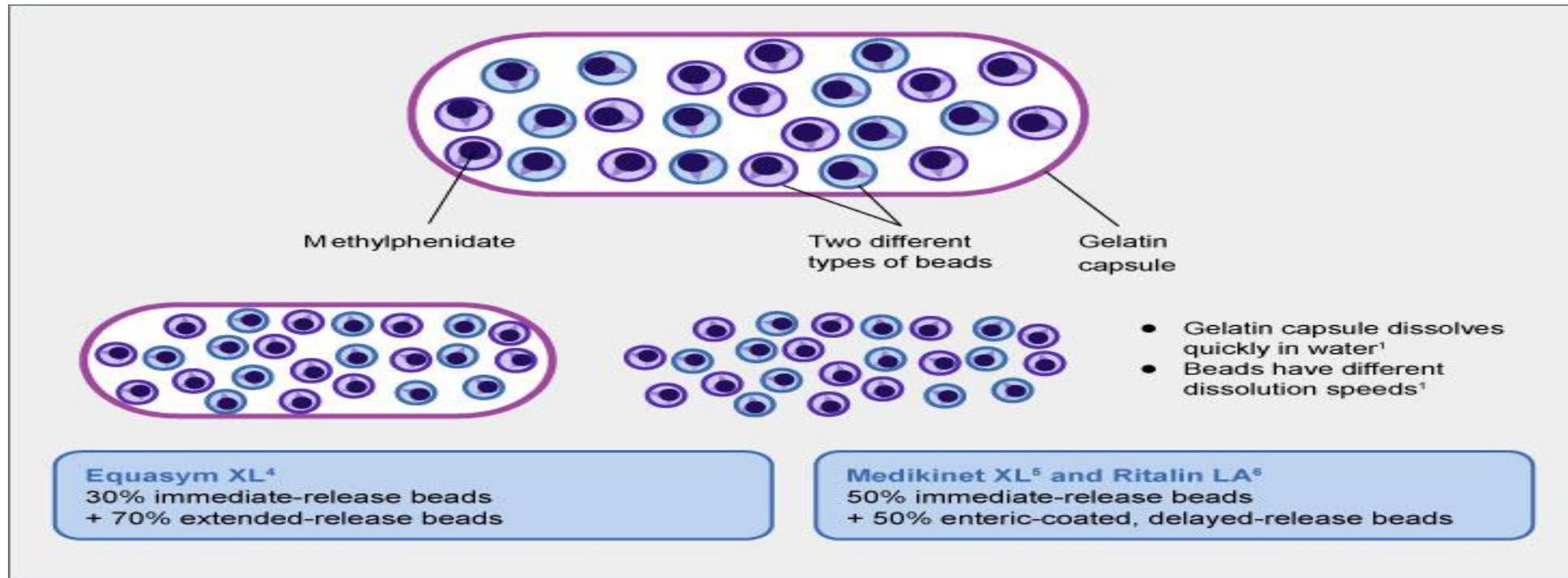
- 133 studies were retained for the network meta-analysis, 81 in children and adolescents, 51 in adults, and one including children, adolescents, and adults. In total, 14346 children and adolescents and 10296 adults were included
- With respect to ADHD core symptoms rated by clinicians in children and adolescents, all drugs were superior to placebo
- In adults, amphetamines, methylphenidate, bupropion, and atomoxetine were superior to placebo, but modafinil was not superior to placebo

# PHARMACOLOGIC ACTIONS

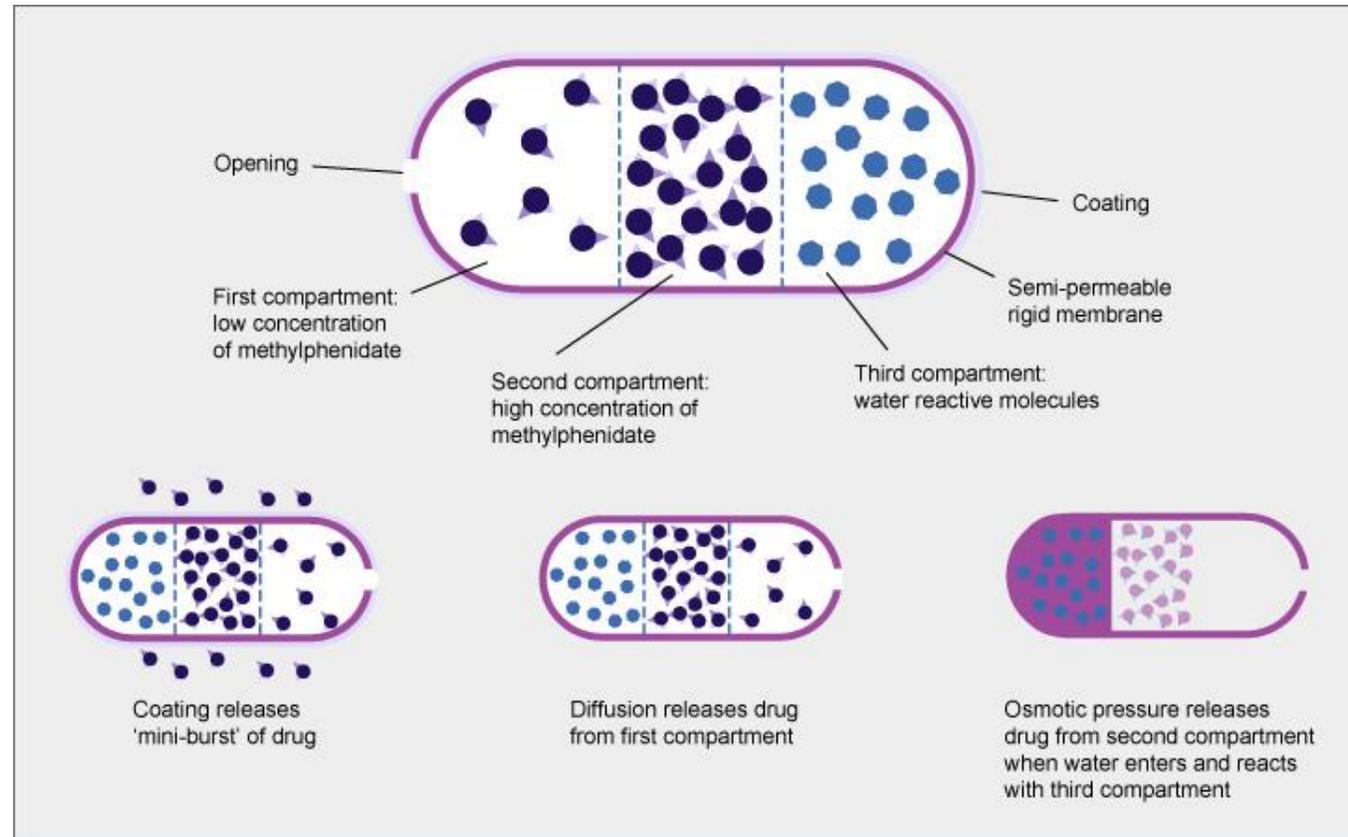
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- Immediate-release formulations: release their contents within minutes of ingestion
- The sustained-release formulation reaches peak plasma concentrations in 4 to 5 hours and doubles the effective half-life of methylphenidate.
- The extended-release formulation reaches peak plasma concentrations in 6 to 8 hours and is designed to be effective for 12 hours in once-daily dosing.

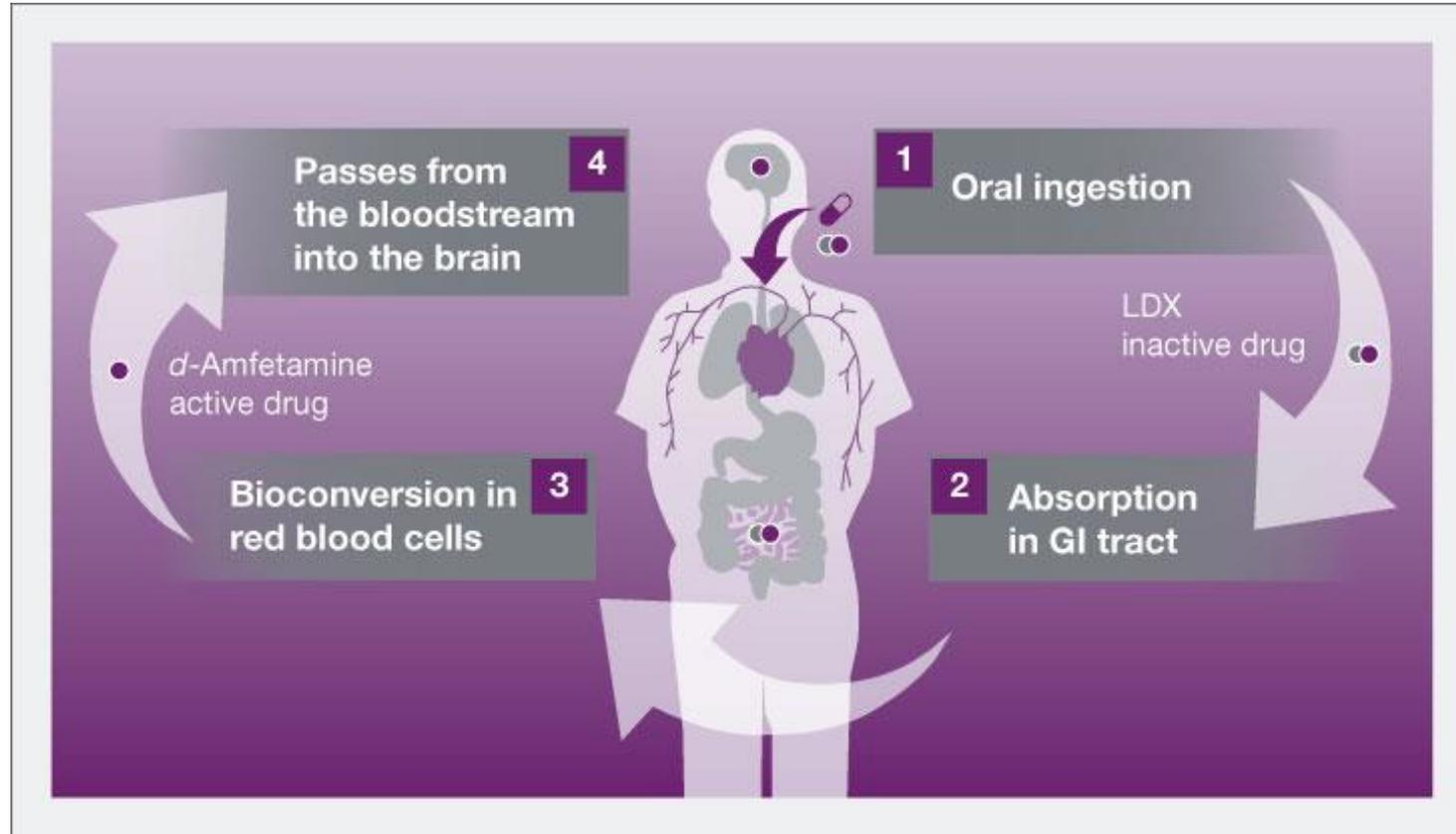
# Multiple bead system



# Osmotic-controlled release oral delivery system

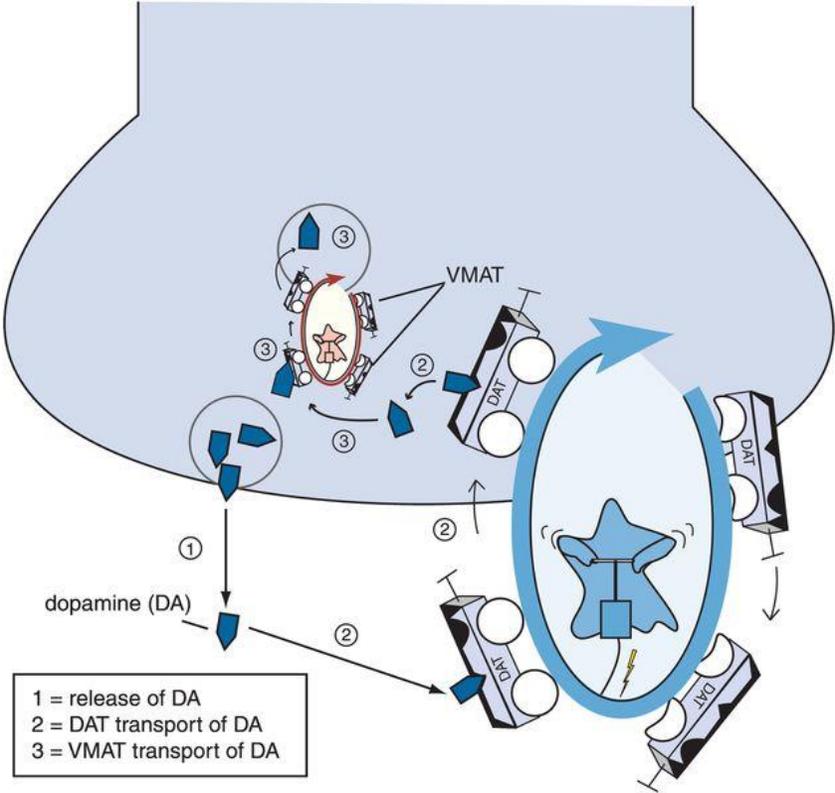


# Prodrug: Lisdexamfetamine dimesylate (LDX)

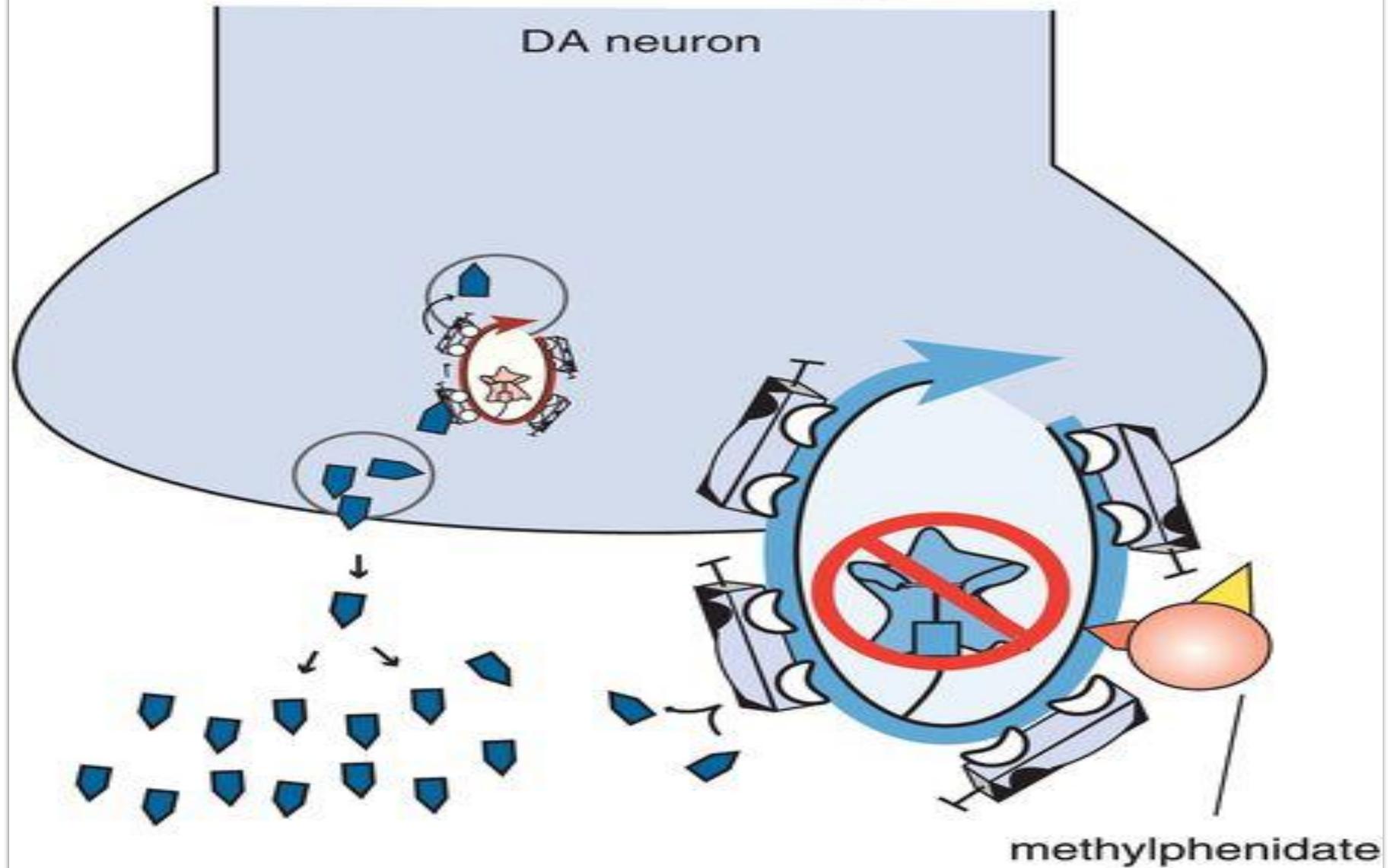


# How stimulants work?

Regulation of the Transport and Availability of Synaptic DA



## Mechanism of Action of Methylphenidate



# Amphetamine

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- Unlike methylphenidate and antidepressants, amphetamine is a competitive inhibitor and pseudosubstrate for NET and DAT
- Binding at the same site that the monoamines bind to the transporter, thus inhibiting NE and DA reuptake
- At the doses of amphetamine used for the treatment of ADHD, the clinical differences in the actions of amphetamine versus methylphenidate can be relatively small.
- These pharmacologic actions of high-dose amphetamine are not linked to any therapeutic action in ADHD but to reinforcement, reward, euphoria, and continuing abuse.

# “Slow-release versus fast-release stimulants and the mysterious DAT

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- Rapid and high degrees of DAT occupancy by stimulants may cause euphoria and lead to abuse
- Slow onset and lower degrees of DAT occupancy may be consistent with antidepressant actions and improvement in attention in ADHD.
- A completely different set of responses if occupancy by that same stimulant of that very same DAT target ramps up slowly, has incomplete target saturation, and lasts a long time (resulting in therapeutic actions in ADHD and depression without “highs” or abuse)

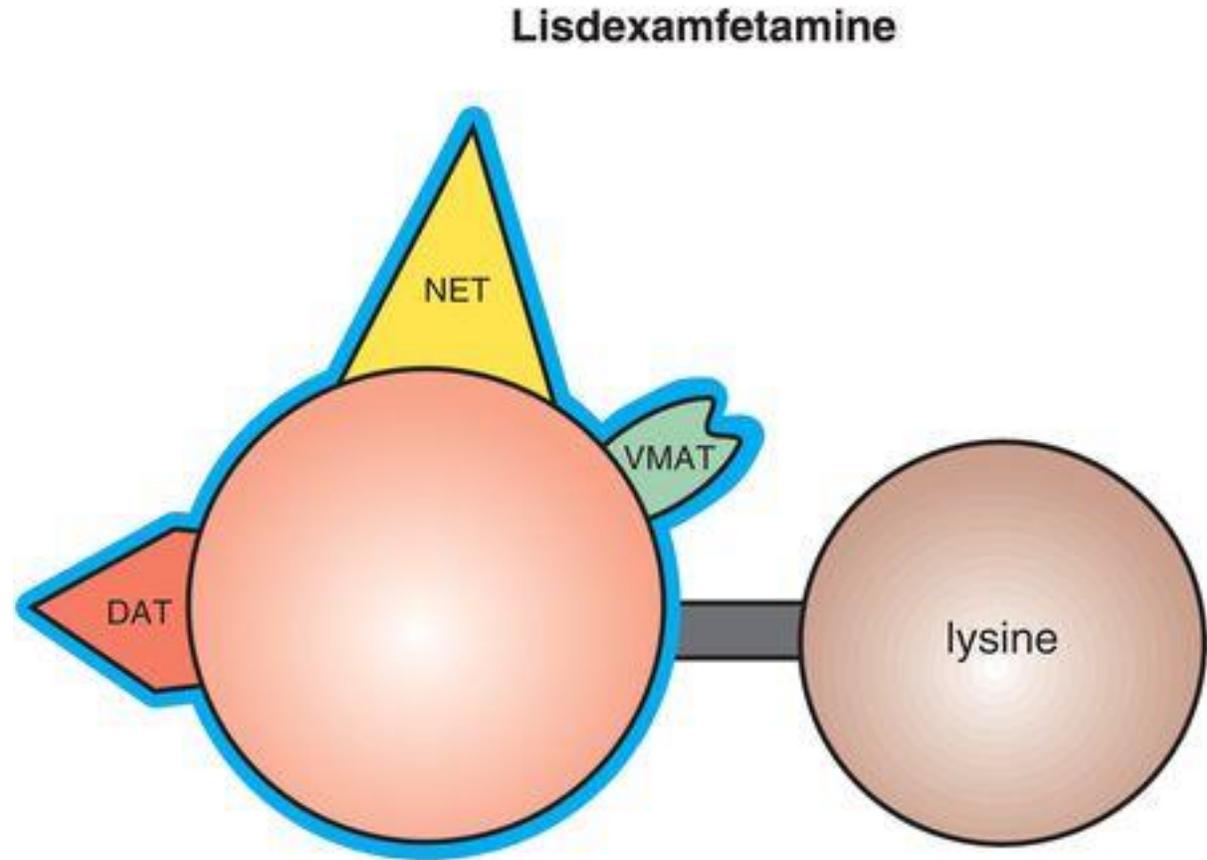
# Slow release preparations

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- When using stimulants to treat a patient it may be preferable to obtain a slow-rising, constant, steady-state level of the drug
- Under those circumstances the firing pattern of DA will be tonic, regular, and not at the mercy of fluctuating levels of DA.
- Some pulsatile firing is fine, especially when involved in reinforcing learning and salience

# Lisdexamfetamine.

- The prodrug of d-amphetamine, linked to the amino acid lysine.
- It is only centrally active as d-amphetamine once it has been cleaved in the stomach into the active compounds d-amphetamine plus free l-lysine.



# Lisdexamfetamine dimesylate

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- This results in the gradual release of dextroamphetamine into the bloodstream.
- Apart from having an extended duration of action, this type of formulation reduces its abuse potential.
- Lisdexamfetamine is indicated for the treatment of ADHD in children 6 to 12 years and in adults as an integral part of a total treatment program that may include other measures.

# Concerta (Sandoz Methylphenidate)

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- An extended-release formulation
- Has an immediate-release portion of 22% of the total drug load in a water soluble outer coating
- An extended-release core that delivers 78% of the MPH dose.
- The extended-release core is an osmotic controlled-release oral delivery system (OROS) which is surrounded by the IR overcoat
- Sandoz has developed a generic osmotic-controlled release (OCR) methylphenidate formulation (Sandoz MPH OCR) to be bioequivalent to Concerta.

# The Concerta

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- ❖ The Concerta formulation delivers a biphasic plasma concentration curve for MPH with two phases of drug release.
- ❖ The first phase is determined by the immediate-release dose fraction, which provides a therapeutic drug level shortly after administration and is thought to prevent the development of acute tolerance to MPH.
- ❖ The second phase provides the dose of MPH required to maintain an effective therapeutic level for a prolonged period.

# THERAPEUTIC INDICATIONS

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# THERAPEUTIC INDICATIONS

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## ADHD

- Sympathomimetics are the first-line drugs for treatment of ADHD in children and are effective about 75% of the time.
- Methylphenidate and Dextroamphetamine are equally effective and work within 15 to 30 minutes
- permit improved social interactions with teachers, family, other adults, and peers

# ADHD

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- Sympathomimetic drugs decrease hyperactivity, increase attentiveness, and reduce impulsivity
- They may also reduce comorbid oppositional behaviors associated with ADHD.
- Many persons take these drugs throughout their schooling and beyond.
- In responsive persons, use of a sympathomimetic may be a critical determinant of scholastic success

# ADHD

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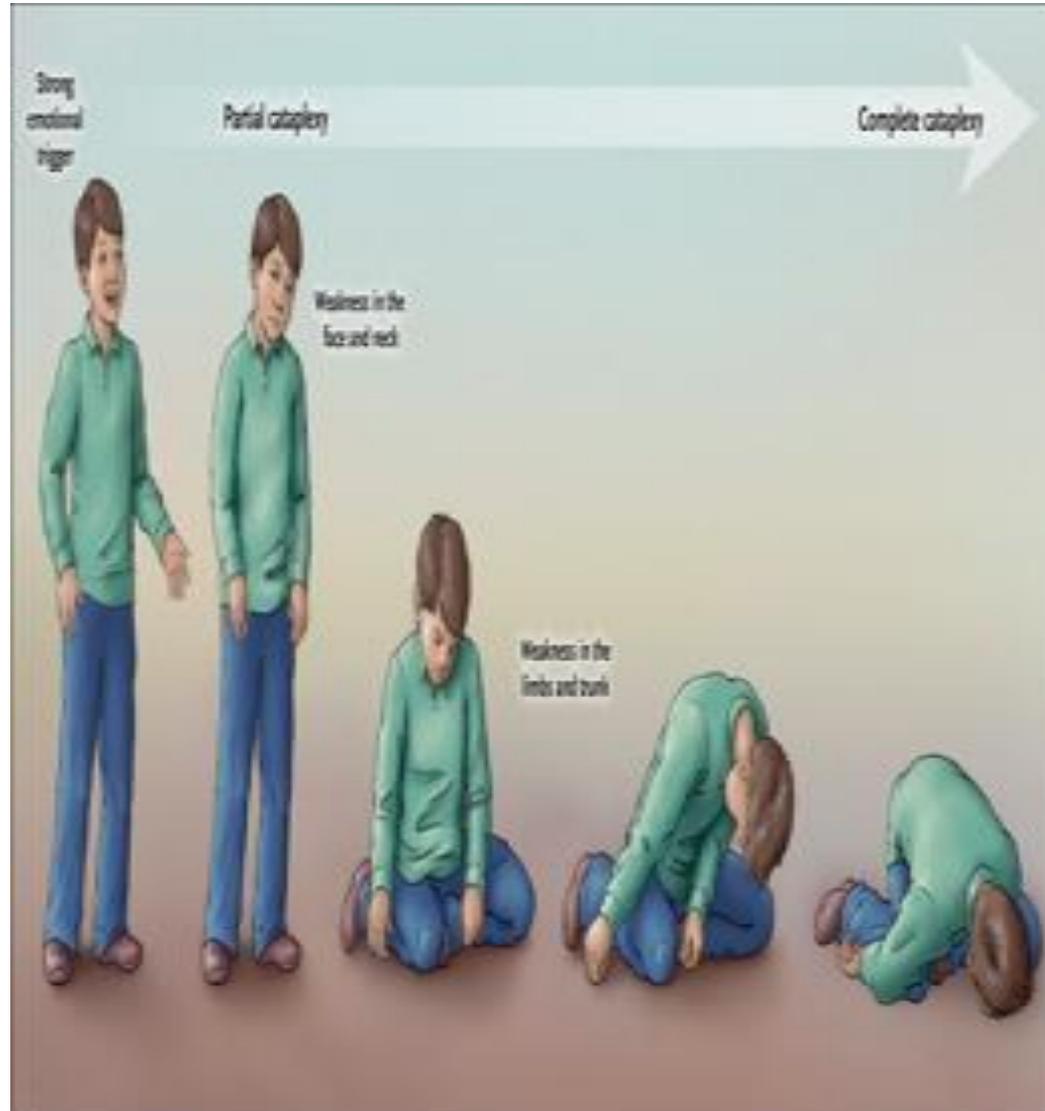
- Methylphenidate is the most commonly used initial agent, at a dosage of 5 to 10 mg every 3 to 4 hours.
- Dosages may be increased to a maximum of 20 mg four times daily or 1 mg/kg a day.
- Use of the 20-mg sustained-release formulation to achieve 6 hours of benefit and eliminate the need for dosing at school is supported by many experts
- Although other authorities believe it is less effective than the immediate-release formulation of psychiatric drug treatment

# ADHD

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- Dextroamphetamine is about twice as potent as methylphenidate on a per milligram basis
- Provides 6 to 8 hours of benefit.
- Some 70% of nonresponders to one sympathomimetic may benefit from another

# Narcolepsy and Hypersomnolence



# Narcolepsy

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- Sympathomimetics reduce narcoleptic sleep attacks and improve wakefulness in other types of hypersomnolent states.
- Modafinil is approved as an antisomnolence agent for treatment of narcolepsy, for people who cannot adjust to night shift work, and for those who do not sleep well because of obstructive sleep apnea.
- Sympathomimetics are also used to maintain wakefulness and accuracy of motor performance in persons subject to sleep deprivation
- Persons with narcolepsy, unlike persons with ADHD, may develop tolerance for the therapeutic effects of the sympathomimetics

# Depressive disorders



# Depression

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- ✓ Used for treatment-resistant depressive disorders, usually as augmentation of standard antidepressant drug therapy.
- ✓ Possible indications for use of sympathomimetics as monotherapy include:
  - ✓ Depression in elderly persons
  - ✓ Who are at increased risk for adverse effects from standard antidepressant drugs
  - ✓ Depression in medically ill persons
  - ✓ Clinical situations in which a rapid response is important but for which electroconvulsive therapy is contraindicated.
  - ✓ Abulia and anergia may also benefit

# Depression

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- Dextroamphetamine may be useful in differentiating pseudodementia of depression from dementia.
- A depressed person generally responds to a 5-mg dose with increased alertness and improved cognition.
- Sympathomimetics provide only short-term benefit (2 to 4 weeks) for depression because most persons rapidly develop tolerance for the antidepressant effects of the drugs

# Encephalopathy Caused by Brain Injury



# Brain injury

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- Increase alertness, cognition, motivation, and motor performance in persons with neurologic deficits caused by strokes, trauma, tumors, or chronic infections.
- Treatment with sympathomimetics may permit earlier and more robust participation in rehabilitative programs.
- Poststroke lethargy and apathy may respond to long-term use of sympathomimetics.

# Obesity



# Obesity

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- Anorexia-inducing effects
- Because tolerance develops for the anorectic effects and because of the drugs' high abuse potential, their use for this indication is limited

# Fatigue



# Fatigue

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- Between 70% and 90% of individuals with multiple sclerosis experience fatigue.
- Modafinil, amphetamines, methylphenidate, are sometimes effective in combating this symptom.
- Other causes of fatigue such as chronic fatigue syndrome respond to stimulants in many cases.

# PRECAUTIONS AND ADVERSE REACTIONS

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# Adverse reactions

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## ANOREXIA, NAUSEA, WEIGHT LOSS:

- tolerance usually develops for this effect
- Administer stimulant with meals.
- Use caloric-enhanced supplements.
- Discourage forcing meals

## INSOMNIA, NIGHTMARES

- Administer stimulants earlier in day
- Change to short-acting preparations.
- Discontinue afternoon or evening dosing.
- Consider adjunctive treatment (e.g., antihistamines, clonidine, antidepressants).

# Adverse reactions

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## DIZZINESS

- Monitor BP.
- Encourage fluid intake.
- Change to long-acting form

## REBOUND PHENOMENA

- Overlap stimulant dosing.
- Change to long-acting preparation or combine long- and short-acting preparations.
- Consider adjunctive or alternative treatment (E.G., clonidine).

# Adverse reactions

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## IRRITABILITY

- Assess timing of phenomena (during peak or withdrawal phase).
- Evaluate comorbid symptoms.
- Reduce dose.
- Consider adjunctive or alternative treatment (e.g., lithium, antidepressants, anticonvulsants).

## DYSPHORIA, MOODINESS, AGITATION

- Consider comorbid diagnosis (e.g., mood disorder).
- Reduce dosage or change to long-acting preparation.
- Consider adjunctive or alternative treatment (e.g., lithium, anticonvulsants, antidepressants).

Refer for a cardiology opinion before starting medication if any of the following apply  
[NICE]

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- The drugs can also cause increases in heart rate and blood pressure (BP) and palpitations
- Refer when: history of congenital heart disease or previous cardiac surgery
- history of sudden death in a first-degree relative under 40 years suggesting a cardiac disease
- shortness of breath on exertion compared with peers
- fainting on exertion or in response to fright or noise

## Refer for a cardiology opinion before starting medication if any of the following apply [NICE]

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- Palpitations that are rapid, regular and start and stop suddenly
- Chest pain suggesting cardiac origin
- Signs of heart failure
- A murmur heard on cardiac examination
- Refer to a pediatric hypertension specialist before starting medication for ADHD if blood pressure is consistently above the 95th centile for age and height
- Note: (amphetamines significantly increased diastolic blood pressure in children and adolescents, but not in adults)

# Adverse reactions

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■ Sympathomimetics may exacerbate:

■ glaucoma

■ hypertension

■ cardiovascular disorders

■ hyperthyroidism

■ anxiety disorders

■ psychotic disorders

■ seizure disorders

■ High dosages of sympathomimetics can cause:

■ dry mouth

■ pupillary dilation

■ bruxism

■ formication

■ restlessness

■ emotional lability

■ occasionally seizures

# Adverse reactions

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- The possible induction of movement disorders, such as tics, tourette's disorder-like symptoms, and dyskinesias
- All of which are often self-limited over 7 to 10 days.
- A correlation between the dose of the medication and the severity of the disorder must be firmly established before adjustments are made in the medication dosage.
- In severe cases, augmentation with risperidone (risperdal), clonidine (catapres), or guanfacine (Tenex) is necessary

# Adverse reactions

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- Methylphenidate may worsen tics in one-third of persons; these persons fall into two groups:
- Those whose methylphenidate-induced tics resolve immediately upon metabolism of the dosage
- A smaller group in whom methylphenidate appears to trigger tics that persist for several months but eventually resolve spontaneously
- If tics are present, many experts will not prescribe sympathomimetics but will instead choose clonidine or antidepressants.
- However, recent data indicate that sympathomimetics may cause only a mild increase in motor tics and may actually suppress vocal tics

# Stunted growth

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- There are 3 main mechanisms that can affect height growth in children receiving stimulant medications.
- 1- suppression of appetite is described among children
- 2- A second proposed mechanism is associated with the dopaminergic effect of stimulants.
- Dopamine might suppress growth hormone secretion and directly affect height development in children.
- 3- some studies suggest that stimulants might slow down the growth of cartilage tissue, affecting growth of bones

A Randomized  
Controlled Trial of  
Interventions for  
Growth Suppression in  
Children With  
Attention-Deficit/  
Hyperactivity Disorder  
Treated With Central  
Nervous System  
Stimulants (dec.2020)

- Drug holidays, caloric supplementation, and increased monitoring all led to increased weight velocity in children taking CNS stimulants, but none led to increased height velocity.

# Adverse reactions

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- Short-term use of the sympathomimetics induces a euphoric feeling
- Tolerance develops for both the euphoric feeling and the sympathomimetic activity

# Raynaud's Phenomenon

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- The painful disorder most commonly affects the fingers
- Cold air triggers spasms in the small blood vessels of the extremities.
- The spasms temporarily cut off blood flow.
- The skin may first turn white before it turns blue for a short time. As the blood flow returns, the affected areas may turn red.
- Patients may experience throbbing, tingling, burning or numbness.
- In rare cases, tissue deprived of blood flow for long periods of time may develop gangrene

# Prolonged Erections

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- Prolonged and painful erections with methylphenidate-containing products.
- It happens when blood becomes trapped in the penis.
- The condition doesn't generally develop immediately.
- It occurs after "some time on the drug" or when dosage is increased.
- It may also occur when a person stops using the drug or takes a brief break from it.
- In 2013, the FDA warned priapism can occur with methylphenidate ADHD medications. The agency reviewed adverse event reports submitted between 1997 and 2012 and found 15 patients who developed the condition from a methylphenidate drug.
- Two of the patients needed surgery. Four of the cases occurred when patients stopped taking the drug.

# Adverse reactions

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- The most limiting adverse effect of sympathomimetics is their association with psychological and physical dependence.
- At the doses used for treatment of ADHD, development of psychological dependence virtually never occurs.
- A larger concern is the presence of adolescent or adult cohabitants who might confiscate the supply of sympathomimetics for abuse or sale.

# USE IN PREGNANCY AND LACTATION

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- There might be a small increase in the risk of cardiac malformations associated with intrauterine exposure to methylphenidate.
- No association has observed between amphetamines and any congenital or cardiac malformations.
- Both Dextroamphetamine and methylphenidate pass into the breast milk.

# Administration

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- ❖ Amphetamines are listed as schedule II drugs by the drug enforcement agency.
- ❖ Pretreatment evaluation should include:
  - ❖ An evaluation of the person's cardiac function,
  - ❖ Liver function and renal function should be assessed, and dosages of sympathomimetics should be reduced for persons with impaired metabolism

# Overdoses

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- Overdosages of sympathomimetics result in:
  - Hypertension, tachycardia, hyperthermia, toxic psychosis, delirium, hyperpyrexia, convulsions, coma, chest pain, arrhythmia, heart block, hyper- or hypotension, shock, and nausea.
- Toxic effects of amphetamines can be seen at 30 mg
- Idiosyncratic toxicity can occur at doses as low as 2 mg
- Conversely, survival has been reported up to 500 mg.

# Nice guideline:

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- Methylphenidate is recommended as the first choice in children and adolescents
- Methylphenidate or lisdexamfetamine as first choice in adults.
- Additionally, although nice recommend atomoxetine or guanfacine as a possible third-line choice in children, our results suggest that, despite comparable efficacy on adhd core symptoms rated by parents,
- Atomoxetine was equal to placebo in terms of tolerability, whereas guanfacine was worse



Have  
a  
beautiful  
day