Al-Mustaqbal University
College of Pharmacy
4th stage
Pharmacology II
Lecture: 2

CNS Stimulants

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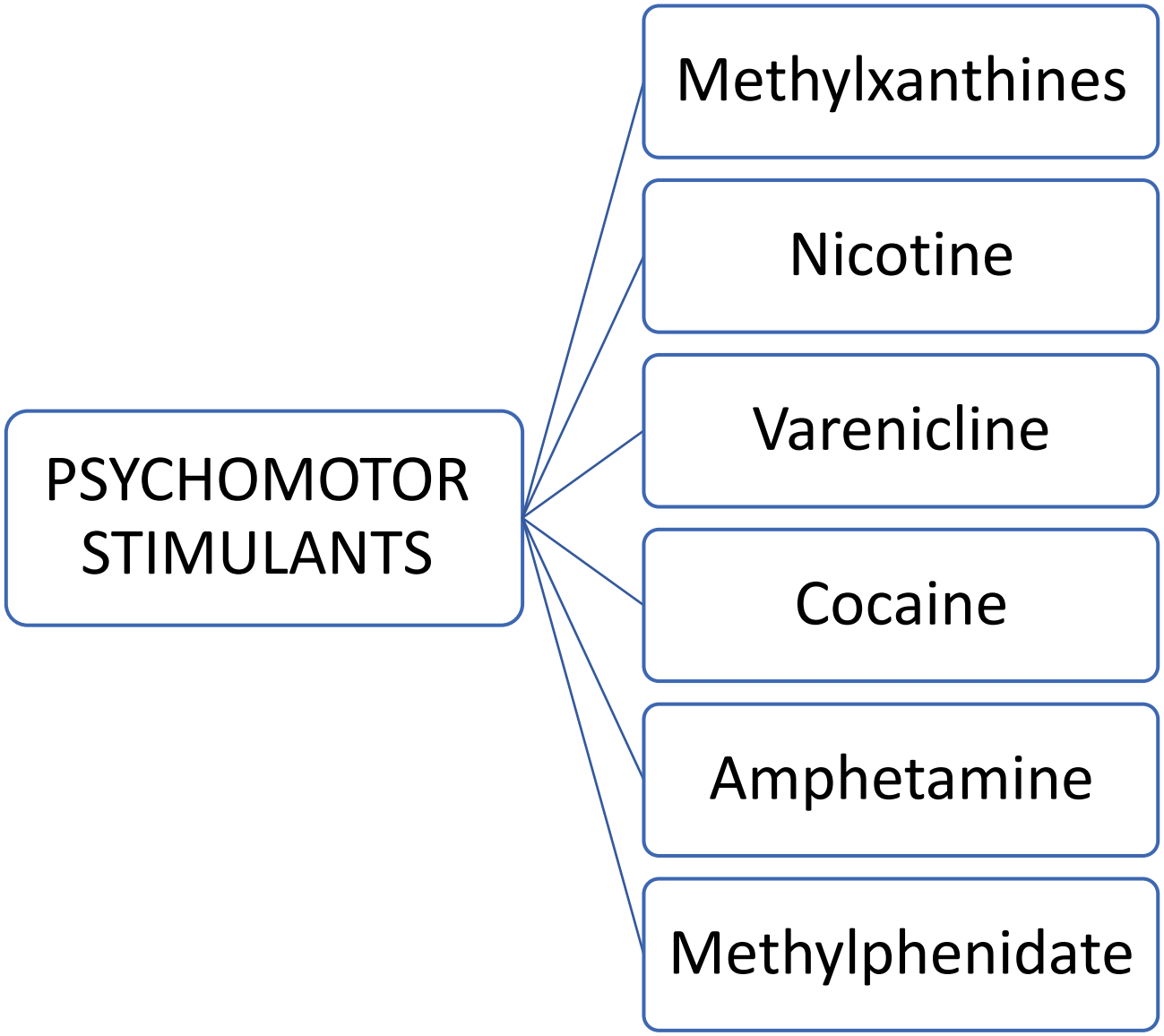
Overview

- **CNS stimulants include:**

1. The **psychomotor** stimulants cause:
   - Excitement and euphoria
   - Decrease feelings of fatigue
   - Increase motor activity
2. The **hallucinogens** produce
   - Changes in thought and mood

- CNS **stimulants** have diverse clinical uses and are important as drugs of **abuse**.

PSYCHOMOTOR STIMULANTS



Methylxanthines

- They are a **purine-derived** group of pharmacologic agents.
- They are clinically used as **bronchodilatory** and **stimulatory** agents.
- The methylxanthines include:

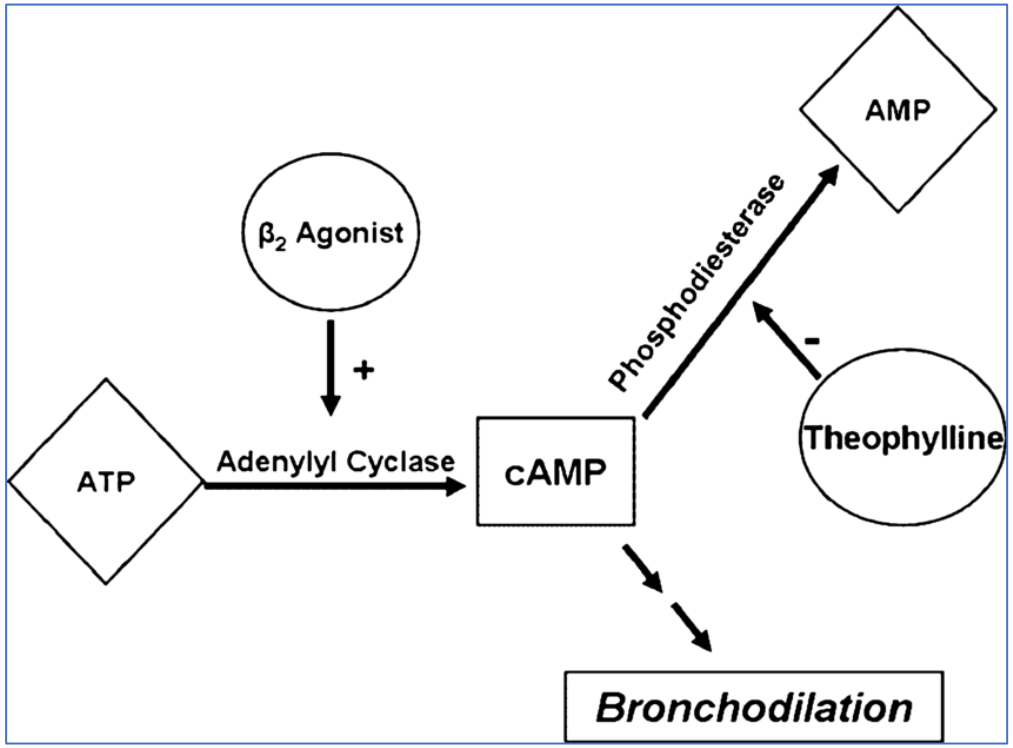
1. **Theophylline** which is found in **tea**
2. **Theobromine** found in **cocoa**
3. **Caffeine**, the most widely consumed stimulant in the world, is found in the highest concentration in certain **coffee** products, **tea**, **cola drinks**, **energy drinks**, **chocolate candy**, and **cocoa**.

Methylxanthines

Mechanisms of action:

1. **Translocation** of extracellular **calcium.**
2. **Increase** in cyclic AMP and cyclic GMP caused by **inhibition** of **phosphodiesterase (PDE inhibitors).**
3. **Blockade** of adenosine (CNS inhibitory Nt.) receptors.

- The **latter most** likely accounts for the actions achieved by the usual consumption of **caffeine-containing beverages**.



Methylxanthines

Actions:

1. CNS effects:

- The **caffeine** contained in **1-2 cups** of coffee (**100 -200 mg**) causes a **decrease in fatigue and increased mental alertness**.
- Consumption of **1.5 g** of caffeine (**12-15 cups** of coffee) produces **anxiety and tremors**.
- The **spinal cord** is stimulated only by **very high doses** (**2 -5 g**) of caffeine.
- **Tolerance** can rapidly develop to the **stimulating properties** of caffeine, and **withdrawal** consists of feelings of **fatigue and sedation**.

Methylxanthines

Actions:

2. Cardiovascular system:

- A high dose of caffeine has **positive inotropic** and **chronotropic effects** on the heart.
- In others, an accelerated **heart rate** can trigger **premature ventricular contractions.**

3. Diuretic action:

- Caffeine has a **mild diuretic** action that **increases the urinary output of sodium, chloride, and potassium**.

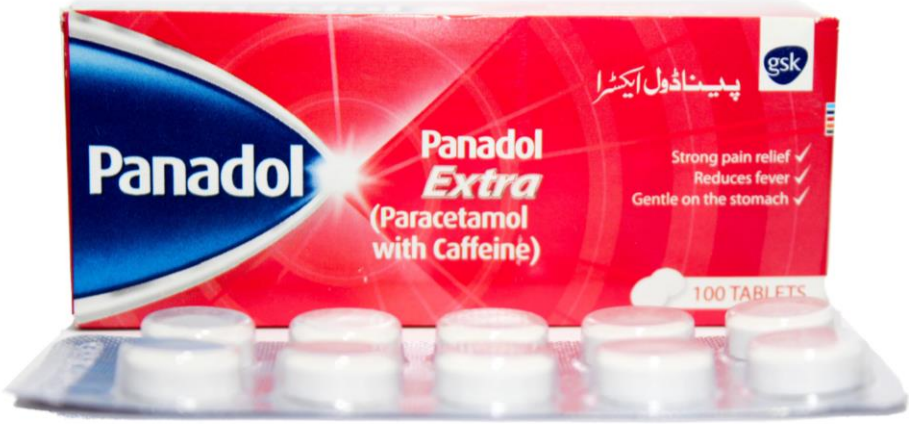
4. Gastric mucosa:

- Because methylxanthines **stimulate** the secretion of **gastric acid**, individuals with **peptic ulcers should avoid** foods and beverages containing methylxanthines.

Methylxanthines

Therapeutic uses:

- **Caffeine** and its derivatives **relax** the smooth muscles of the **bronchioles**.
- **Previously** the mainstay of **asthma therapy**, **theophylline** has been largely **replaced** by other agents, such as β2 agonists and corticosteroids
- **Caffeine** is also used in **combination** with analgesics like **acetaminophen** and **aspirin** for the **management of headaches** in both prescription and over-the-counter products.



Methylxanthines

Pharmacokinetics:

- The methylxanthines are well absorbed **orally**.
- Caffeine **distributes** throughout the body, including the **brain**.
- These drugs **cross** the **placenta** to the fetus and are secreted into the **breast milk**.
- All **methylxanthines** are metabolized in the **liver**, generally by the CYP1A2 pathway, and the metabolites are excreted in the **urine**.

Methylxanthines

Adverse effects:

- **Moderate doses** of caffeine cause **insomnia, anxiety, and agitation**.
- **High dosage** results in toxicity, which is manifested by **emesis** and **convulsions**.
- **Lethal dose** is **10 g** of **caffeine** (about **100 cups** of coffee), which induces **cardiac arrhythmias**.
- **Lethargy, irritability, and headache** occur in users who **routinely** consume more than **600 mg** of caffeine per day (roughly **6 cups** of coffee per day) and then **suddenly stop**.

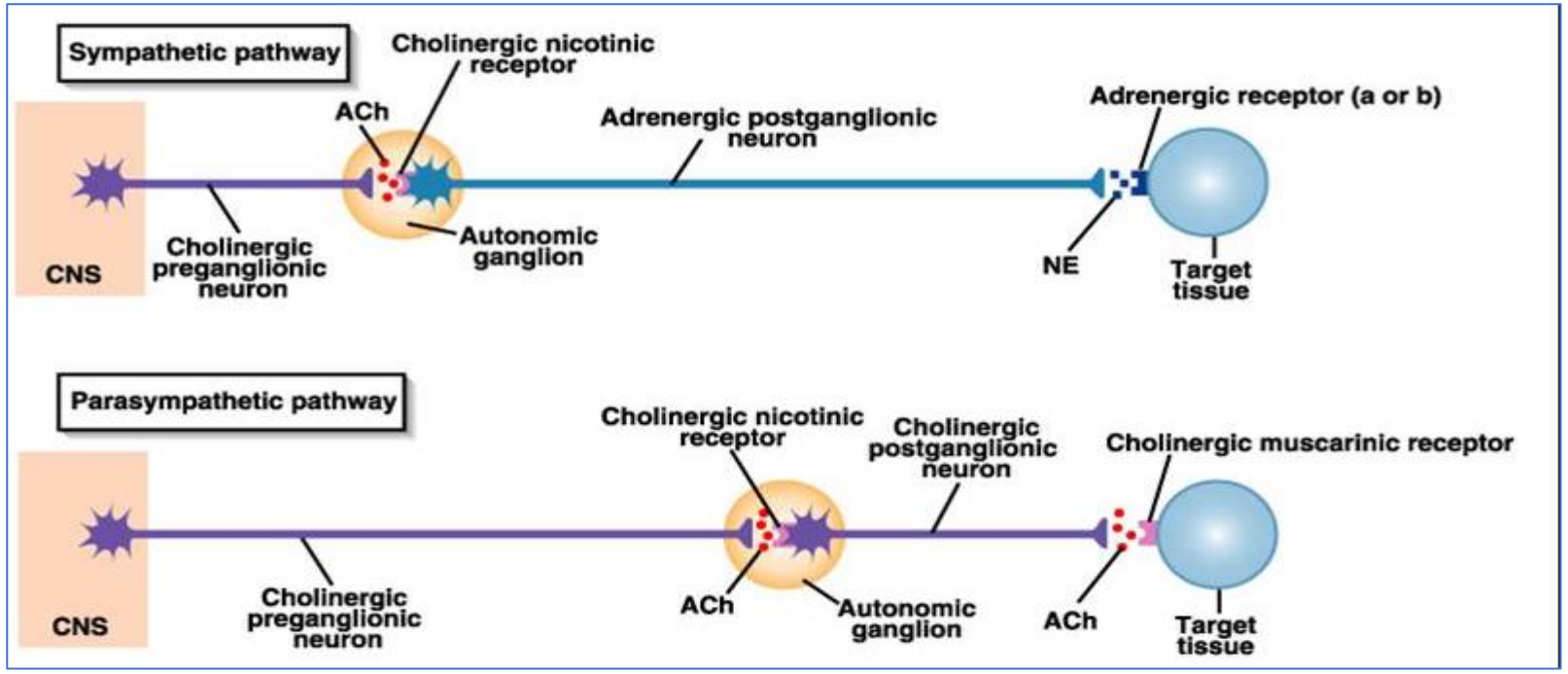
Nicotine

- Nicotine is the active ingredient in **tobacco**.
- It is **not** currently used **therapeutically** (except in **smoking cessation** therapy).
- It is **second** only to caffeine as the most widely used CNS **stimulant**, and it is **second** only to alcohol as the most **abused** drug.
- In combination with the tars and carbon monoxide found in cigarette smoke, nicotine represents a **serious risk factor** for lung and cardiovascular disease, various cancers, and other illnesses.
- **Dependency** on the drug is not easily overcome.

Nicotine

Mechanism of action:

- In **low doses**, nicotine causes **ganglionic stimulation** by depolarization.
- At **high doses**, nicotine causes **ganglionic blockade**.
- **Nicotine receptors** exist in the **CNS**, which participate in the **stimulant** effect.



Nicotine

Pharmacokinetics:

- It is **highly lipid soluble**, absorption readily occurs via the oral mucosa, lungs, GI mucosa, and skin.
- Nicotine crosses the **placental** membrane and is secreted in **breast milk**.
- By inhaling tobacco smoke, the average smoker takes in 1 to 2 mg of nicotine per cigarette and the acute **lethal** dose is **60 mg**.
- More than **90%** of the nicotine **inhaled** in smoke is **absorbed**.
- **Clearance** of nicotine involves **metabolism** in the **lung** and the **liver** and **urinary excretion**.
- **Tolerance** to the effects of nicotine develops **rapidly**, often within **days**.

Nicotine

Actions:

CNS:

- Nicotine is **highly lipid soluble** and readily crosses the blood-brain barrier.
- Cigarette smoking or administration of **low doses** of nicotine produces some degree of **euphoria** and **arousal**, as well as **relaxation**.
- It **improves** attention, learning, problem-solving, and reaction time.
- **High doses** of nicotine result in **central respiratory paralysis** and **severe hypotension** caused by medullary paralysis.
- Nicotine is also an **appetite suppressant**.

Nicotine

Actions:

Peripheral effects:

- Stimulation of the **sympathetic ganglia** as well as of the **adrenal medulla increases** blood pressure and heart rate.
- In addition, nicotine-induced **vasoconstriction ???** can decrease coronary blood flow, adversely affecting a patient with **angina**.
- Stimulation of the **parasympathetic** ganglia also increases **motor activity of the bowel**.

Nicotine

Adverse effects:

- The CNS effects of nicotine include **irritability and tremors**.
- Nicotine may also cause intestinal cramps, diarrhea, and increased heart rate and blood pressure.
- In addition, cigarette smoking **increases** the rate of **metabolism** for a number of drugs.

Nicotine

Withdrawal syndrome:

- Nicotine is an **addictive** substance, and **physical dependence** develops rapidly and **can** be **severe**.
- Withdrawal is **characterized** by

✓Irritability

✓Anxiety

✓Restlessness

✓Difficulty concentrating, headaches, and insomnia

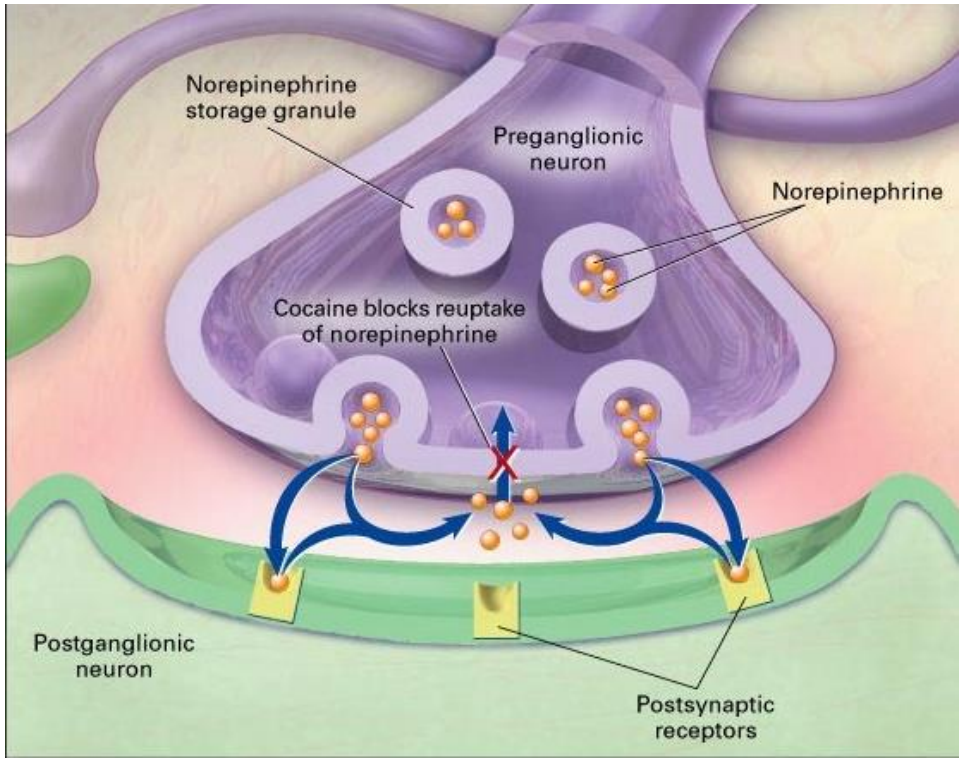
✓Appetite is affected, and GI upset often occurs

Varenicline

- Varenicline is a **partial agonist** at neuronal **nicotinic** acetylcholine receptors in the CNS.
- It produces **less euphoric effects** than nicotine (nicotine is a full agonist at these receptors).
- Thus, it is useful as an **adjunct** in the management of **smoking cessation** in patients with nicotine withdrawal symptoms.
- Additionally, varenicline tends to attenuate the **rewarding effects** of nicotine if a person relapses and uses tobacco.
- Patients taking varenicline should be monitored for **suicidal thoughts**, **vivid nightmares**, and **mood changes**.

Cocaine

- Cocaine is a widely available and highly **addictive drug**.
- Cocaine is classified as a **Schedule II drug** of controlled substances.
- The mechanism of action of cocaine is the **blockade of the reuptake of the monoamines** (norepinephrine, serotonin, and dopamine) into the presynaptic terminals.
- This **potentiates** and **prolongs** the **CNS** and **peripheral** actions of these monoamines.
- In particular, the **prolongation** of **dopaminergic** effects in the brain (limbic system) produces intense **euphoria**.
- **Chronic** intake of cocaine **depletes** dopamine triggering the vicious cycle of **craving** for cocaine which **temporarily** relieves severe **depression**.



Cocaine

Table I. Schedules of Controlled Substances within the CSA.[3,4]

Schedule	Definitions	Examples
Schedule I	No accepted medical use with a lack of accepted safety and high abuse potential; medications within this schedule may not be prescribed, dispensed, or administered for medical use	Heroin, peyote, ecstasy, lysergic acid diethylamide (LSD)
Schedule II	High abuse potential with severe psychological or physical dependence; however, these medications have an accepted medical use and may be prescribed, dispensed, or administered	Morphine, codeine, hydromorphone, methadone, oxycodone, fentanyl, methylphenidate, amphetamine, pentobarbital, combination products with < 15 mg of hydrocodone per dosage unit (eg, Vicodin)
Schedule III	Abuse potential less than Schedules I or II but more than Schedule IV medications; abuse may lead to moderate or low physical dependence or high psychological dependence	Products with < 90 mg of codeine per dosage unit (eg, Tylenol with codeine), dronabinol, anabolic steroids, ketamine
Schedule IV	Abuse potential less than Schedule III but more than Schedule V medications	Propoxyphene, various benzodiazepines, sibutramine
Schedule V	Medications with the least potential for abuse among the controlled substances	Robitussin AC, Phenergan with codeine, pregabalin

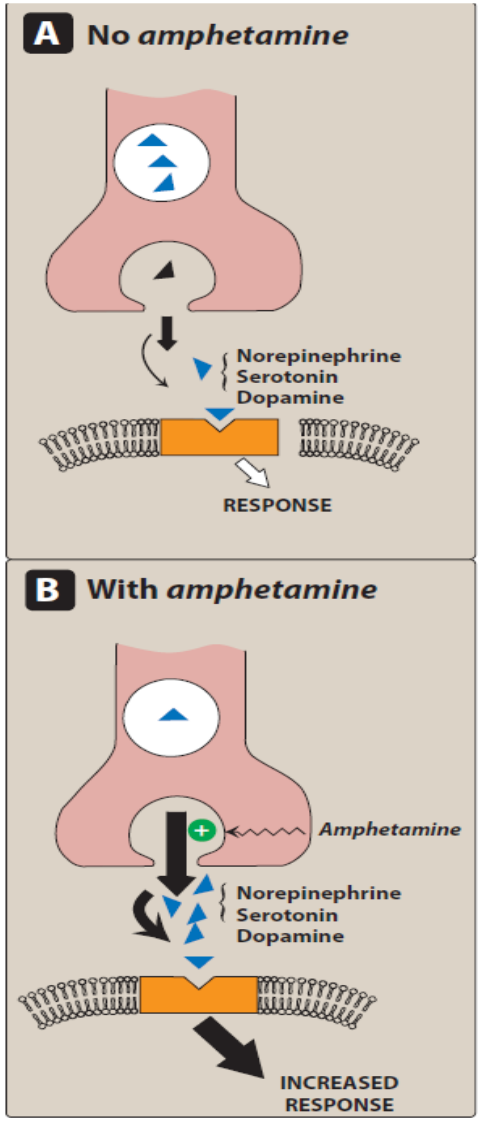
Amphetamine

- **Amphetamine** is a sympathetic amine that shows neurologic and clinical effects **similar** to **cocaine**.
- **Dextroamphetamine** is a **major** member of this class of compounds.
- **Methamphetamine** is a derivative of amphetamine available for prescription use.
- **3,4-Methylenedioxymethamphetamine** (also known as MDMA, or Ecstasy) is a synthetic derivative of methamphetamine with both **stimulant** and **hallucinogenic** properties.

Amphetamine

Mechanism of action:

- Amphetamine has an **indirect** effect via an **elevation** of the level of **catecholamines** in synaptic spaces by **releasing intracellular stores.**
- Also, it **inhibits MAO,** and it is a weak **reuptake inhibitor**.
- Despite different mechanisms of action, the **behavioral** effects of amphetamine and its derivatives are **similar** to those of **cocaine**.



Amphetamine

Actions:

- **CNS:**
- The **major behavioral effects** of amphetamine result from a **combination** of its dopamine and norepinephrine release-enhancing properties.
- Amphetamine increased alertness, decreased fatigue, depressed appetite, and insomnia.
- At **high doses**, psychosis and convulsions can ensue.

Sympathetic nervous system:

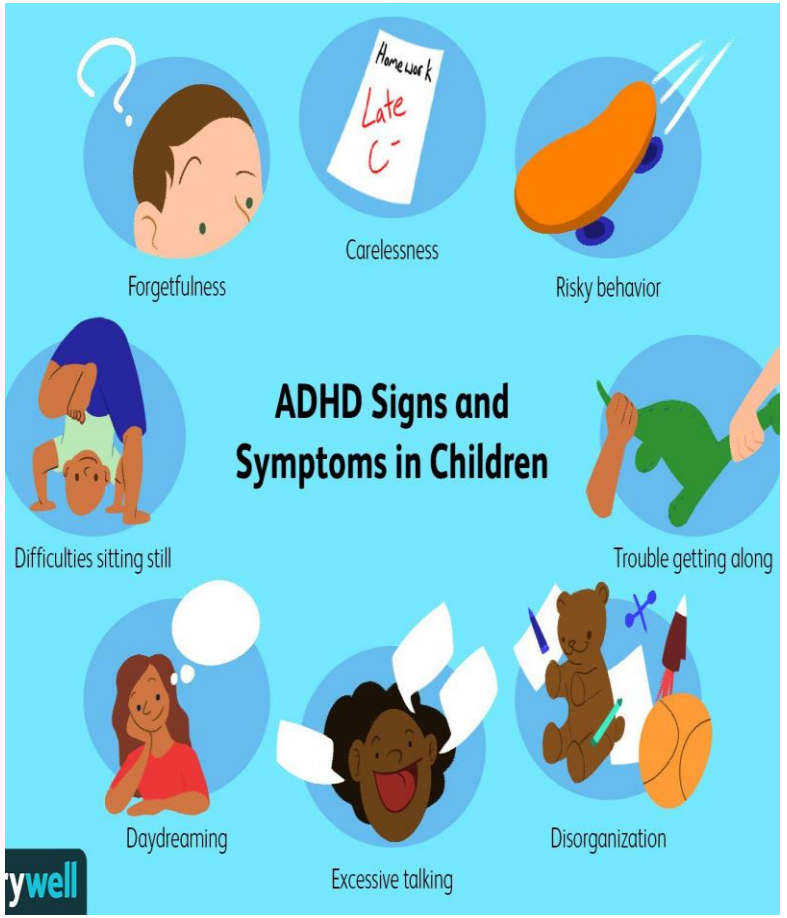
- In addition to its CNS action, amphetamine acts on the adrenergic system, **indirectly stimulating** the receptors through **norepinephrine release**.

Amphetamine

Therapeutic uses:

Attention deficit hyperactivity disorder (ADHD):

- Some young children are **hyperkinetic** and **lack** the ability to be involved in any one activity for **longer** than a **few minutes**.
- Dextroamphetamine, methamphetamine, and methylphenidate can help **improve** attention **span, alleviate** many of the **behavioral** problems associated with ADHD, and **reduce** hyperkinesia.
- **Lisdexamfetamine** is a **prodrug** that is converted to the active component **dextroamphetamine** after **GI** absorption and metabolism.



Amphetamine

Therapeutic uses:

Attention deficit hyperactivity disorder (ADHD):

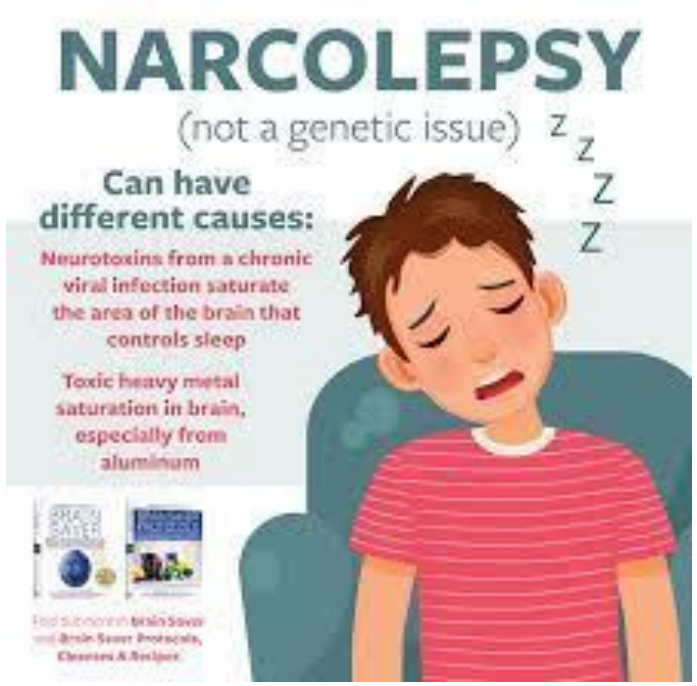
- **Atomoxetine** is a **non-stimulant** drug **approved** for ADHD in **children and adults**.
- **Unlike** methylphenidate, which blocks dopamine reuptake more than norepinephrine reuptake, atomoxetine is more **selective** for inhibition of **norepinephrine** reuptake.
- Therefore, it is **not** considered **habit-forming** and is **not** a **controlled substance**.

Amphetamine

Therapeutic uses:

Narcolepsy:

- Narcolepsy is a relatively **rare** sleep disorder that is characterized by **uncontrollable bouts** of sleepiness during the **day**.
- It is sometimes accompanied by **catalepsy**, a **loss in muscle control, and even paralysis** brought on by **strong emotions** such as laughter.
- The sleepiness can be treated with drugs, such as mixed **amphetamine** salts or **methylphenidate**.

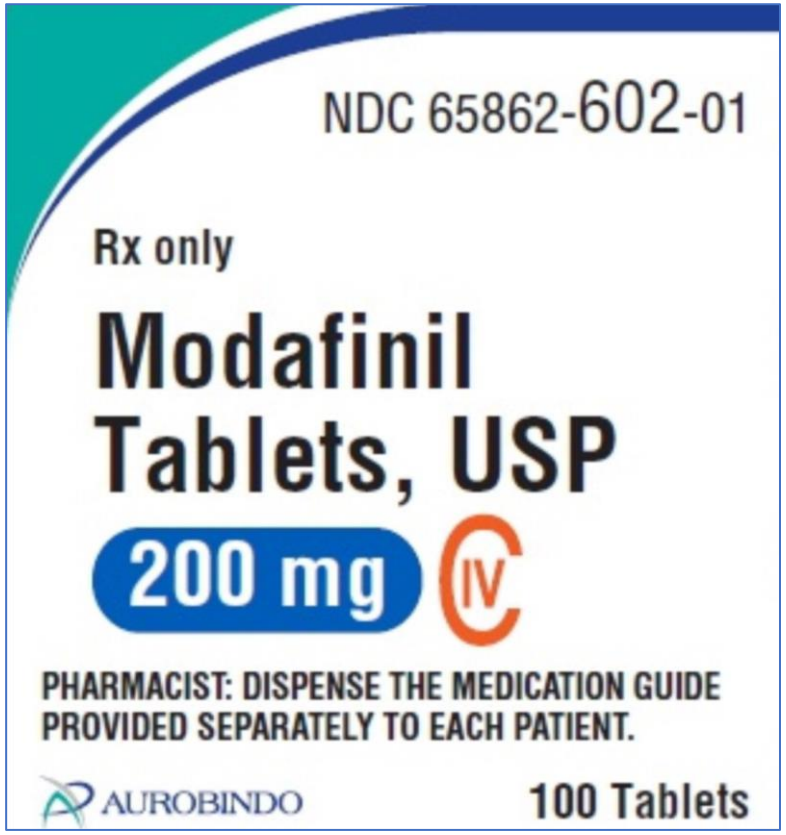


Amphetamine

Therapeutic uses:

Narcolepsy:

- **Modafinil** and its R-enantiomer derivative, **Armodafinil**, are considered **first-line** agents for the treatment of **narcolepsy**.
- Modafinil is effective **orally**, it is well distributed throughout the body and undergoes extensive **hepatic** metabolism, and the metabolites are excreted in the **urine**.
- Headaches, nausea, and nervousness are the primary adverse effects, they may have some potential for **abuse and physical dependence**.



Amphetamine

Therapeutic uses:

Appetite suppression:

- **Phentermine** and **diethylpropion** are sympathomimetic amines that are **related structurally to amphetamine**.
- These agents are used for their **appetite-suppressant** effects in the **management of obesity**.

Amphetamine

Pharmacokinetics:

- **Amphetamine** is completely **absorbed** from the GI tract, **metabolized** by the liver, and **excreted** in the urine.
- Note: Administration of **urinary alkalinizing agents** such as sodium bicarbonate will **increase** the nonionized species of the drug and enhance the **reabsorption** of **dextroamphetamine** from the renal tubules into the bloodstream.
- Amphetamine **abusers** often administer the drugs by **IV** injection and/or by **smoking**.
- The **euphoria** caused by amphetamine lasts 4 to 6 hours, or four- to eightfold longer than the effects of **cocaine**.

Amphetamine

Adverse effects:

CNS effects:

- Adverse effects of amphetamine usage include insomnia, irritability, weakness, dizziness, tremor, and hyperactive reflexes.
- Amphetamine can also cause confusion, delirium, panic states, and suicidal tendencies, especially in mentally ill patients.
- **Chronic** amphetamine use produces a state of "**amphetamine psychosis**" that resembles the **psychotic** episodes associated with **schizophrenia**.

Amphetamine

Adverse effects:

Cardiovascular effects:

- Amphetamine causes palpitations, cardiac arrhythmias, hypertension, anginal pain, and circulatory collapse.

GI system effects:

- Amphetamine acts on the GI system, causing anorexia, nausea, vomiting, abdominal cramps, and diarrhea.

Contraindications:

- Patients with hypertension, cardiovascular disease, hyperthyroidism, glaucoma.
- History of drug abuse or those taking MAO inhibitors.

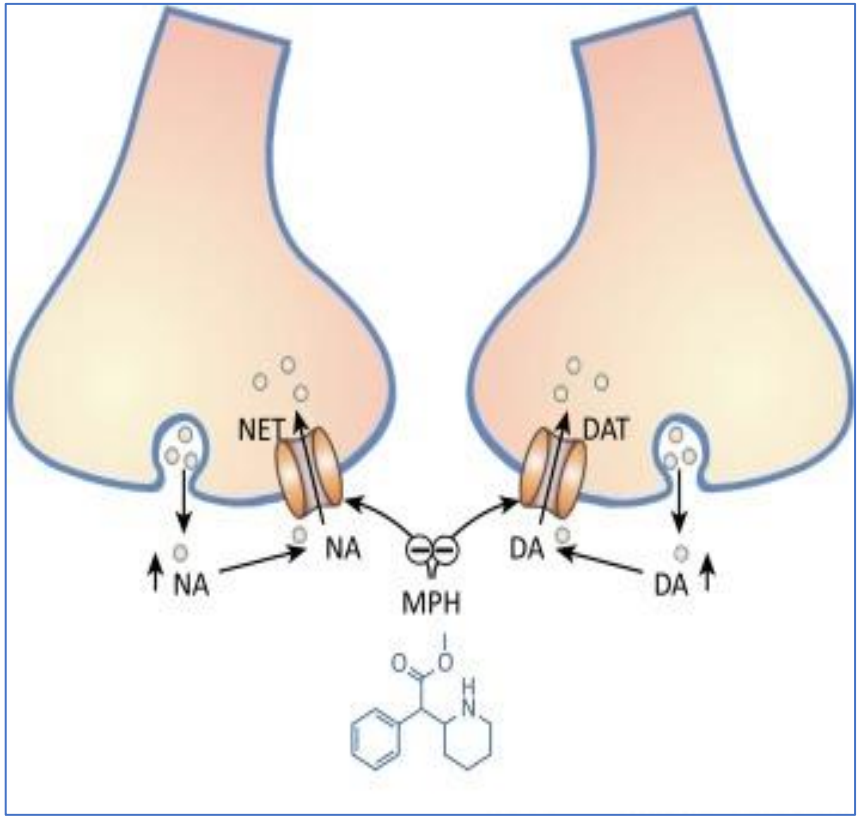
Methylphenidate

- Methylphenidate has **CNS-stimulant** properties similar to those of amphetamine and may also lead to **abuse**, although its **addictive** potential is controversial.
- It is a **Schedule II** drug.
- Methylphenidate is presently one of the most prescribed medications in **children**.
- It is estimated that **4 to 6 million** children in the United States take methylphenidate daily for **ADHD**.
- Its active isomer, **dexmethylphenidate**, is also a **Schedule II** drug used for the treatment of **ADHD**.

Methylphenidate

Mechanism of action:

- Children with ADHD may produce **weak dopamine signals**, which suggests that **once-interesting** activities provide **fewer rewards** to these children.
- Methylphenidate is a dopamine and norepinephrine **transport inhibitor** and may act by increasing both dopamine and norepinephrine in the synaptic space.
- Methylphenidate may have **less potential for abuse** than cocaine, **because** it enters the brain much **more slowly** than cocaine and, thus, does not increase dopamine levels as **rapidly**.



Methylphenidate

Therapeutic uses:

- Methylphenidate has been used for the treatment of **ADHD**.
- Methylphenidate is also effective in the treatment of **narcolepsy**.
- Unlike, methylphenidate, **dexmethylphenidate** is **not** indicated in the treatment of **narcolepsy**.

Pharmacokinetics:

- Both methylphenidate and dexmethylphenidate are **readily absorbed** after **oral** administration.
- Methylphenidate is available in **extended-release** oral formulations and as a **transdermal patch** for once-daily application.
- The de-esterified product, **ritalinic acid**, is excreted in urine.

Methylphenidate

Adverse effects:

- **GI adverse** effects are the most common and include abdominal pain and nausea.
- Other reactions include anorexia, insomnia, nervousness, and fever.
- In **seizure** patients, methylphenidate may **increase** seizure **frequency**, especially if the patient is taking **antidepressants**.
- It is **contraindicated** in patients with glaucoma.
- Methylphenidate can **inhibit the metabolism** of warfarin, phenytoin, phenobarbital, primidone, and tricyclic antidepressants.

HALLUCINOGENS

- A few agents have, as their primary action, the ability to induce **altered** perceptual states reminiscent of dreams.
- Many of these altered states are accompanied by **visions of bright**, **colorful changes** in the environment and by the **plasticity** of constantly changing shapes and colors.
- The individual under the influence of these agents is **incapable** of **normal decision-making** because the drug interferes with **rational thought**.
- These compounds are known as **hallucinogens**, and **lysergic acid diethylamide** (LSD) and **tetrahydrocannabinol** (from marijuana) are examples of agents in this class.

THANK YOU FOR YOUR ATTENTION