Lec 2 CNS stimulants

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4th stage/ 1st course

- **CNS stimulants include:**

❖ **1. The psychomotor stimulants cause:**

➢ • Excitement and euphoria

➢ • Decrease feelings of fatigue

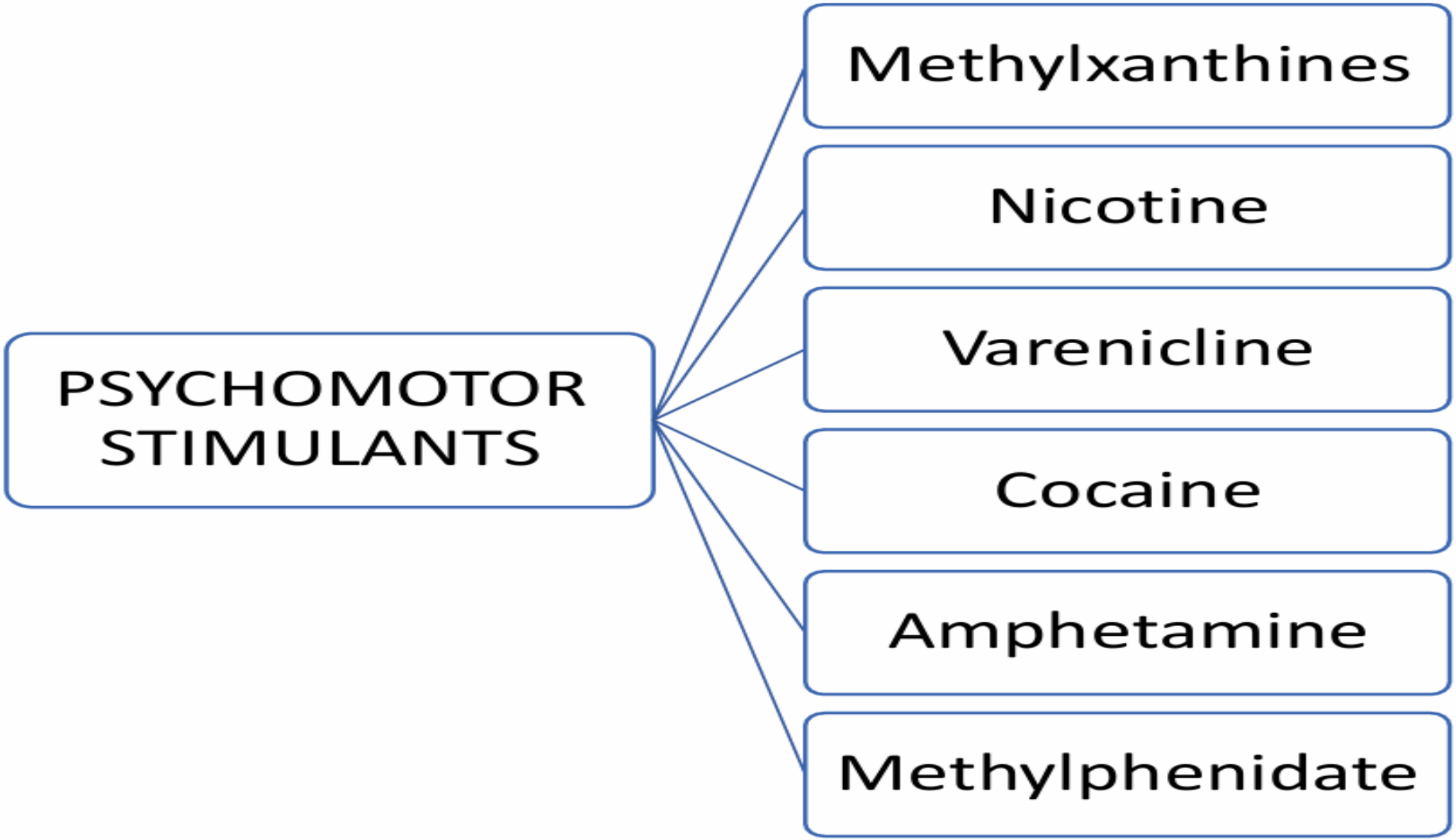
➢ • Increase motor activity

❖ **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

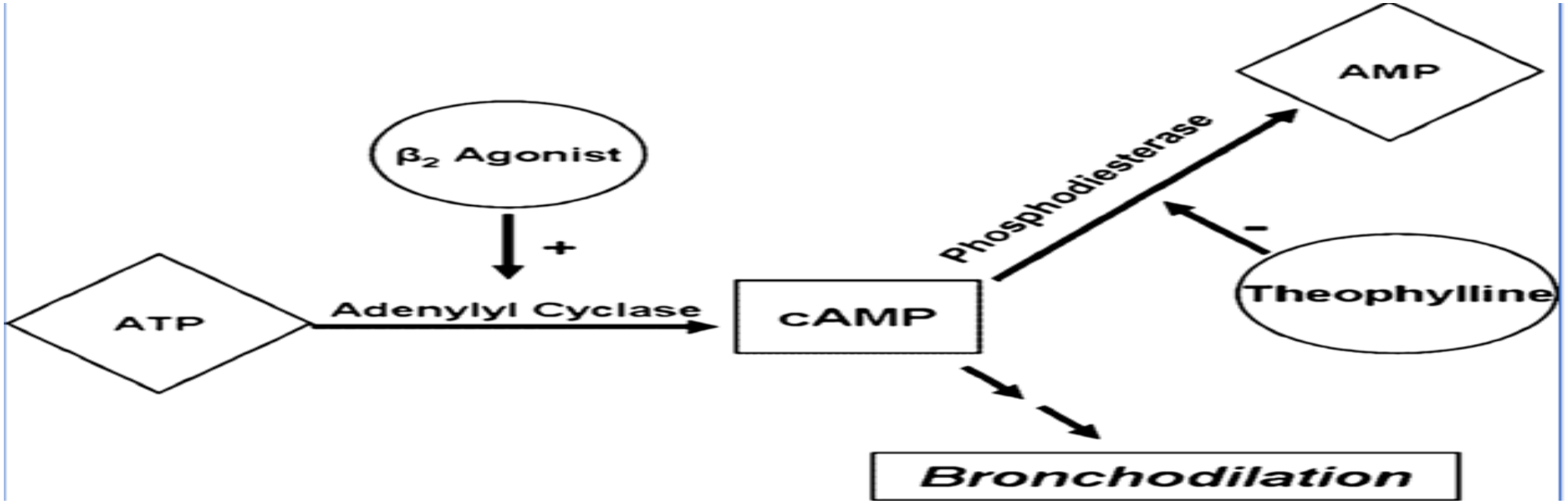
- They are a **purine-derived** group of pharmacologic agents.
- They are clinically used as broncho dilatory and stimulatory agents.
- **The methylxanthines include:**

➢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.**

- **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.

- **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 (cytochrome P450 pathway family 1 subfamily A2 member), and the metabolites are excreted in the **urine**.

- **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.

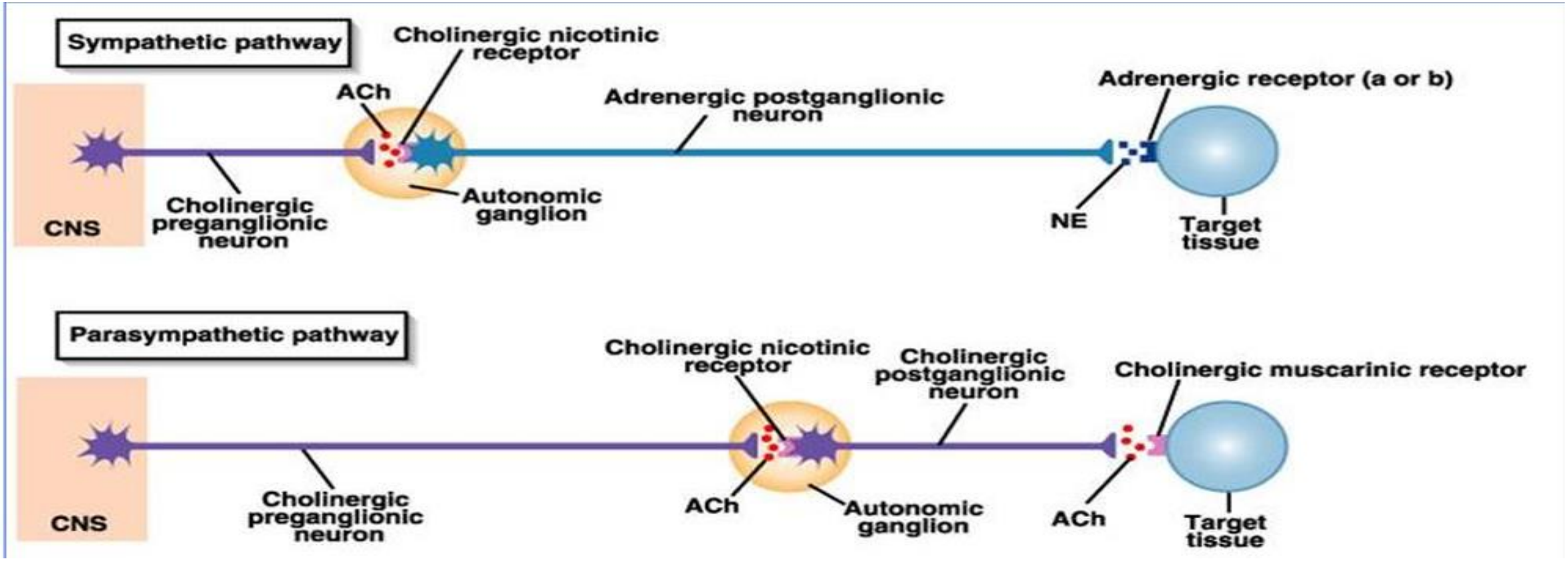
➢ • Lethargy, irritability, and headache occur in users who routinely consume more than 600 mg of caffeine per day (roughly 6 cups of coffee per day) and then **suddenly stop**.

❖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**.

- **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**



- **Pharmacokinetics:**

- It is **highly lipid soluble**, absorption readily occurs via the **oral GI mucosa**, **mucosa, lungs, 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**.

- **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**.

❖ **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.**

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

➢Irritability

➢Anxiety

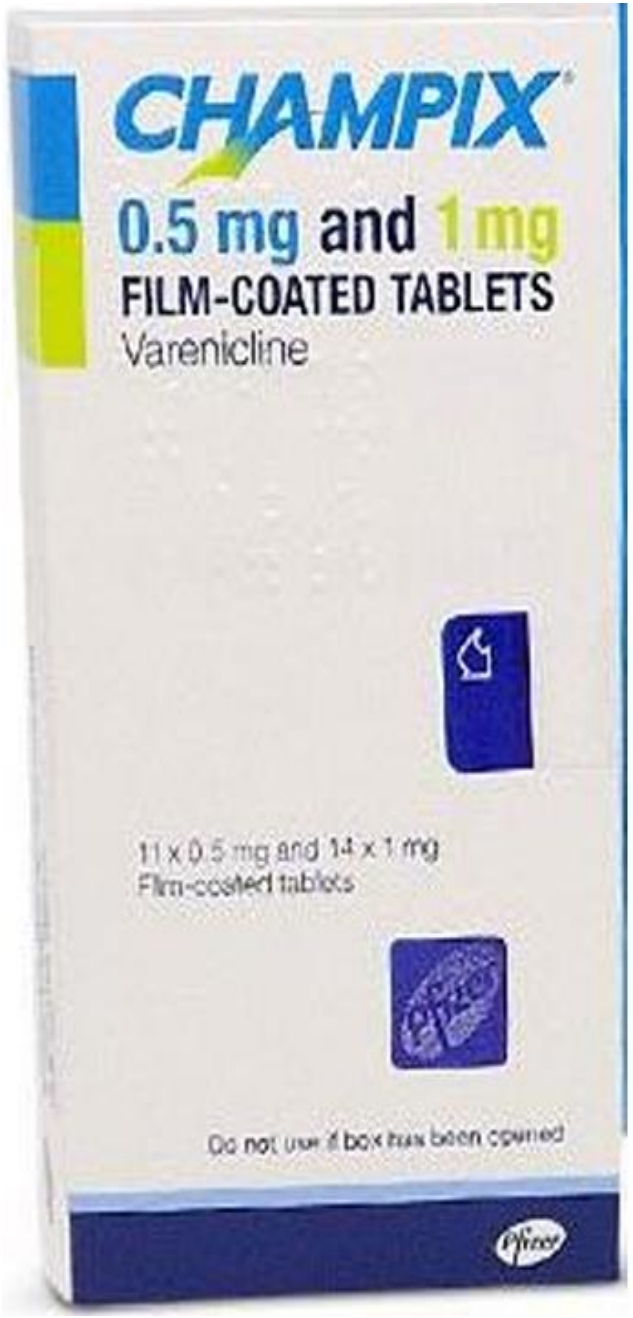
➢Restlessness

➢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**.

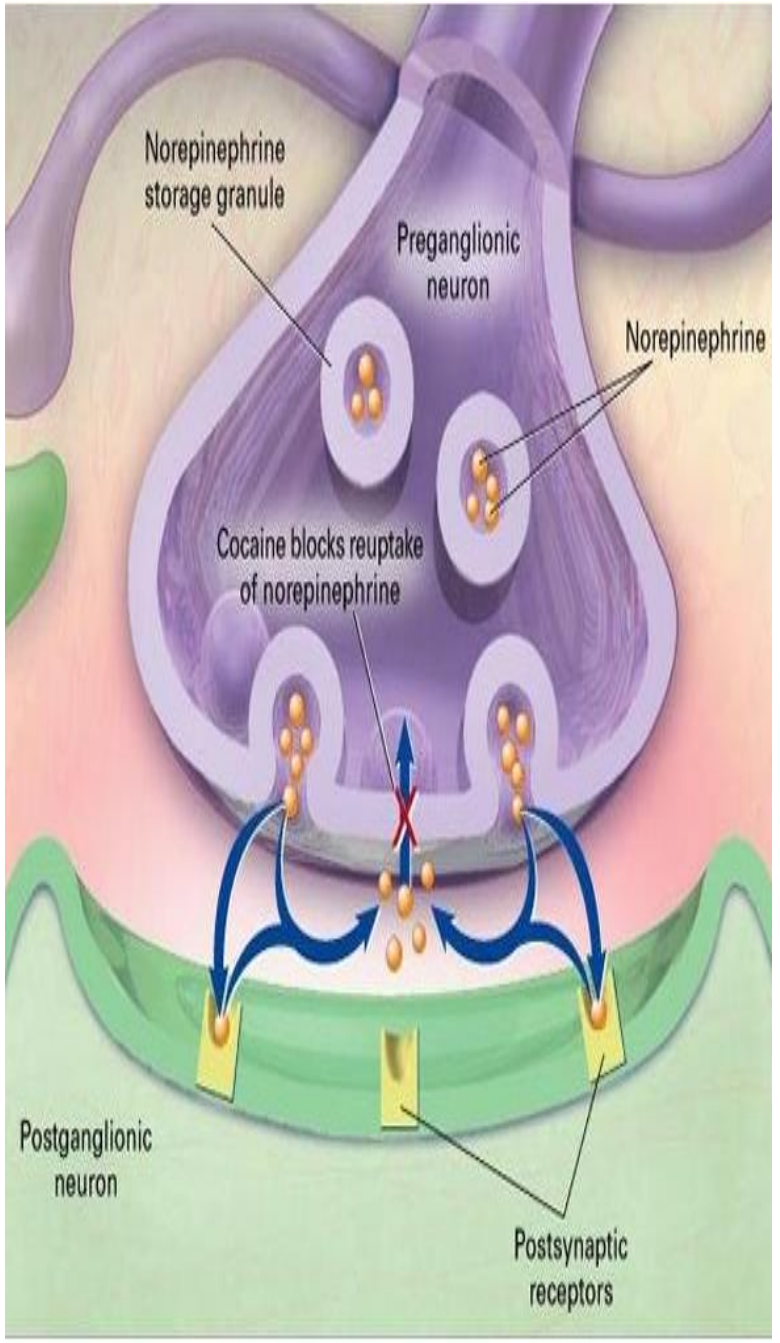


Table I. Schedules of Controlled Substances within the CSA.[3,4] **(Controlled Substances Act)**

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-Methylene dioxy meth amphetamine** (also known as MDMA, or Ecstasy) is a synthetic derivative of methamphetamine with both **stimulant and hallucinogenic properties.**

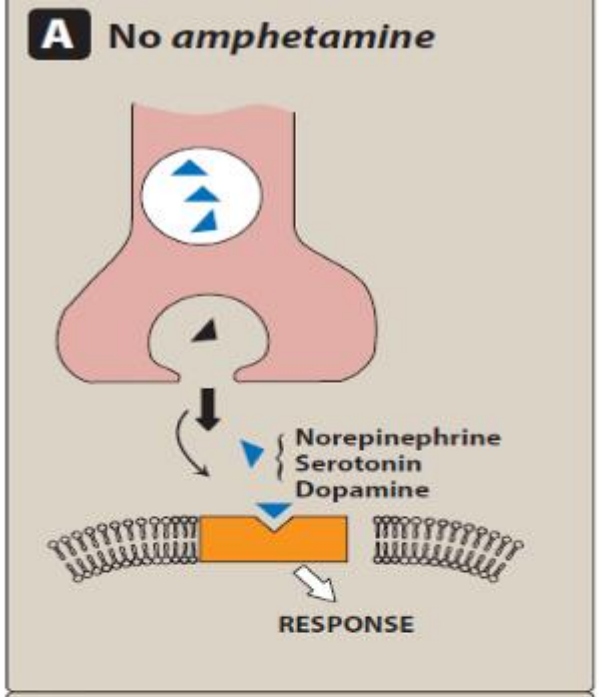
- **Mechanism of action:**
- • Amphetamine has an **indirect effect** via an elevation of the level of **catecholamines** in synaptic spaces by releasing intracellular stores.
- • Also, it **inhibits MAO,** and it is a weak **reuptake inhibitor**.
- • Despite different mechanisms of action, the behavioral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

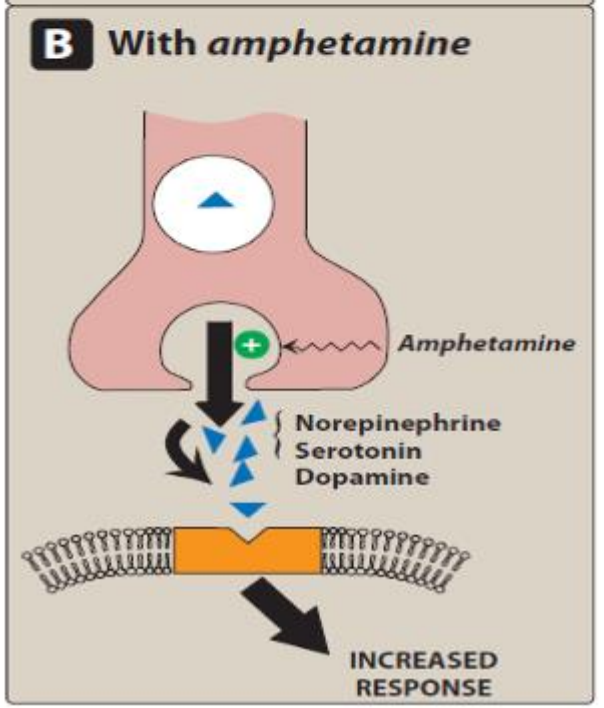
1. • **CNS:**

➢• The major behavioral effects of amphetamine result from a combination of its **dopamine and norepinephrine**

➢• Amphetamine increased **release-enhancing properties. alertness, decreased insomnia** .

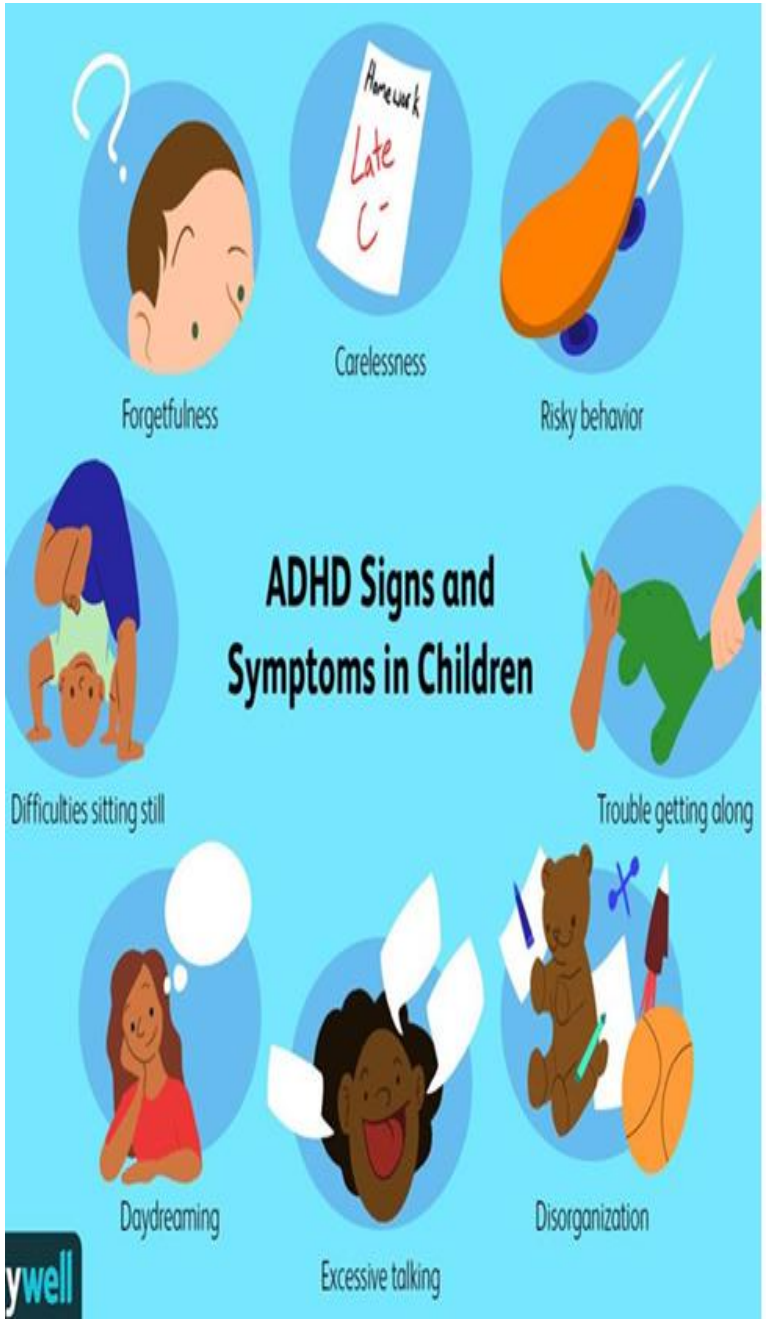
➢• At high doses, **psychosis and convulsions fatigue, depressed** can ensue.





2- Sympathetic nervous system

- In addition to its CNS action, amphetamine acts on the **adrenergic system**, indirectly stimulating the receptors through **norepinephrine** release.
- **Therapeutic uses:**
- **1- 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.



- • **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.

- **2- 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.
- **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.

- **3- 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.**

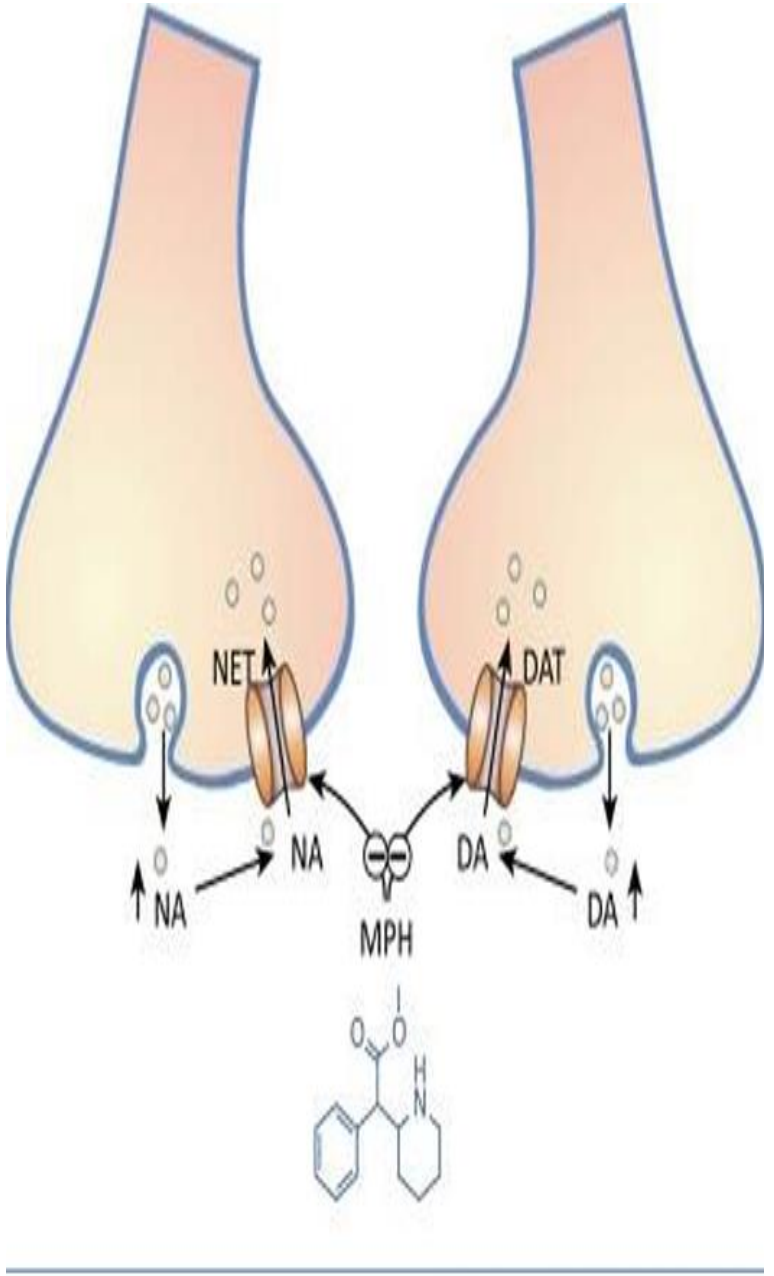
- **Pharmacokinetics:**
- • **Amphetamine** is completely absorbed from the GI tract, metabolized by the liver, and excreted in the urine.
- • **Note:** Administration of urinary alkalinizing agents such as sodium bicarbonate will increase the nonionized species of the drug and enhance the reabsorption 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 eight fold longer than the effects of cocaine

- **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 **schizophrenia**.
- Cardiovascular effects:
- • Amphetamine causes **palpitations, cardiac arrhythmias, hypertension, anginal pain, and circulatory collapse**.
- GI system effects:
- • Amphetamine acts on the GI system, causing **anorexia, abdominal cramps, and diarrhea.**
- **Contraindications:** • Patients with hypertension, nausea, vomiting, 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.

- **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.



- **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.

- **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.**