

CNS Stimulants

Psychomotor stimulants and hallucinogens are two groups of drugs that act primarily to stimulate the central nervous system (CNS).

1st Group:

Psychomotor stimulants:

Cause excitement and euphoria, decrease feelings of fatigue, and increase motor activity.

Drugs:

Amphetamine

Caffeine

Cocaine

Nicotine

Theophylline

Thiobromine

Hisdexamphetamine

Dextroamphetamine

Methylphenidate

Key: ACC NTT HDM

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- **1.5 grams of caffeine can make 12-15 cups of coffee. This is a very large dose and can cause tremors and anxiety.**
 - **Methylxanthines: Theophylline, Theobromine and Caffeine are Methylxanthines.**
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2nd Group

Hallucinogens:

The hallucinogens produce profound changes in thought patterns and mood, with little effect on the brainstem and spinal cord.

Drugs:

Hisergic Acid dimethyl amide (LSD)

Phencyclidine

Tetrahydrocannabinol (THC)

1. Psychomotor stimulants

A. Methylxanthines:

The methylxanthines include:

- Theophylline which is found in tea;
- Theobromine found in cocoa; and
- Caffeine

Mechanism of action:

Several mechanisms have been proposed for the actions of methylxanthines.

- 1) Ca^{+} is released from Sarcoplasmic reticulum in skeletal and cardiac muscles.
- 2) Methylxanthines also inhibit Phosphodiesterase enzyme.

We know that:

- ATP is converted to cAMP using enzyme *Adenylyl cyclase* and cAMP is further converted to 5-AMP using *Phosphodiesterase*.

Also, GTP is converted to cGMP which is further converted to 5-GMP by *Phosphodiesterase*.

Methylxanthine inhibit Phosphodiesterase which causes cAMP accumulation. It may result in Bronchodilation, cardiac stimulation, vasodilation etc.

- 3) Methylxanthine also causes the blockade of Adenosine receptor. We know that Adenosine is a local mediator in CVS and CNS and it contracts bronchial smooth muscles, dilate cerebral blood vessels, depress cardiac pace maker, decrease gastric secretions. So blocking Adenosine receptor means depressing all these actions.

Pharmacological Actions:

- Caffeine is found in tea leaves. Arabic coffee is most popular.
 - Thiobromine is in coca.
 - Theophylline is in tea leaves.
 - Choclates, Coffee and Tea leaves all have caffeine.
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CNS:

Caffeine: 150-250mg produces sensation of wellbeing and alertness. It decreases fatigue, thinking becomes clearer, improve performance, increase motor activity, caffeine is more effective in above effects than theophylline.

Caffeine in high dose causes nervousness, restlessness, panic, insomnia, delirium and convulsions. Consumption of 1.5 g of caffeine (12 to 15 cups of coffee) produces anxiety and tremors.

Theophylline: Theophylline is more dangerous than caffeine at higher dose. Theophylline has greater ability than caffeine to produce adverse drug reactions. Theophylline is more toxic. The high doses of theophylline cause more adverse effects than caffeine. It may cause gastric irritation, vomiting as they trigger CTZ, depress respiration, decrease vagal stimulation, arrhythmias may occur.

CVS:

It directly affects the heart (stimulation). There is a +ve Inotropic effect (increased force of contraction of heart) and +ve chronotropic effect (increase heart rate). There may be tachycardia, increased cardiac output, arrhythmia at higher doses, blood pressure can vary, vasomotor center, vasodilation, usually systolic b.p increases and diastolic b.p decreases. It enhances gastric secretion. Theophylline is more gastric irritant.

Kidney:

Mild diuretic effect as it inhibits tubular reabsorption of Sodium and Water.

Skeletal Muscles:

Increase contractile path of Skeletal muscles. At high dose increase release of calcium from Sarcoplasmic Reticulum by direct action. At low doses, caffeine twitch response of the nerve regulation is augmented.

Gastric mucosa:

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

Vascular Effect:

Renal blood flow increases so Glomerular Filtration Rate increases.

Therapeutic Uses:

- In bronchial asthma
- Chronic Obstructive Pulmonary Disease
- Apnea/Dyspnea (in less oxygen level)

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. There is 50%

PHARMACOLOGY

protein binding. All methylxanthines are metabolized in the liver by oxidation/demethylation and the metabolites are excreted in the urine. 10% is excreted unchanged.

Adverse Effects:

- Insomnia
- Anxiety
- Agitation

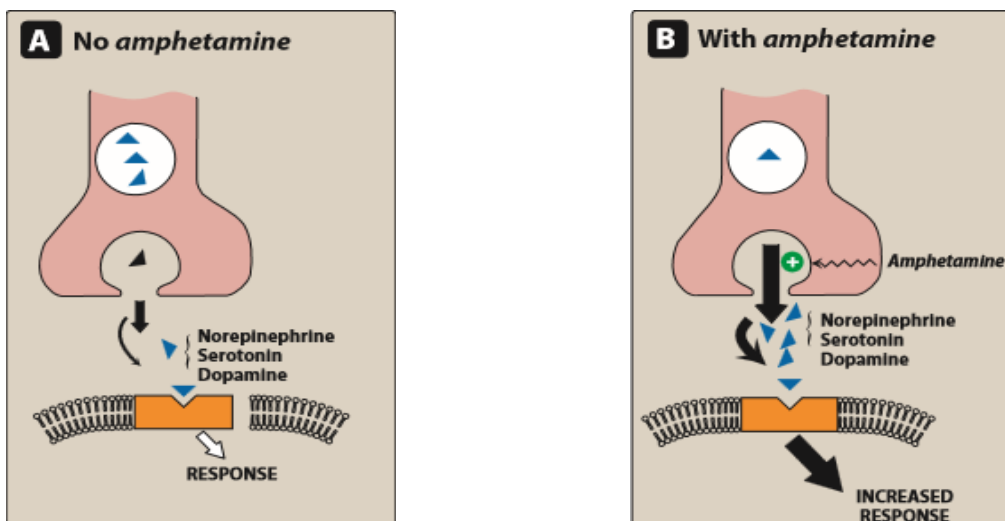
B. Amphetamine

Amphetamine is a sympathetic amine that shows neurologic and clinical effects quite similar to those of cocaine.

It stimulates alpha and beta adrenoreceptor, increase the level of catecholamine neurotransmitters, amphetamine also inhibits monoamine oxidase (MAO) such as dopamine, serotonin and nor-epinephrine.

Mechanism of action:

- The effects of amphetamine on the CNS and peripheral nervous system are indirect.
- Effect depends upon an elevation of the level of catecholamine neurotransmitters in synaptic spaces.
- Achieves this effect by releasing intracellular stores of catecholamines and by inhibiting monoamine oxidase (MAO) enzyme.
- High levels of catecholamines are readily released into synaptic spaces.
- Despite different mechanisms of action, the behavioral effects of amphetamine and its derivatives are similar to those of cocaine.



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Actions:

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- Increase motor activity
 - Euphoria
 - Anorexia
 - Excitement
 - Prolonged use may cause stereotype effects
 - Psychotic behavior
 - May show dopaminergic and nor-epinephrine effects.

Dopaminergic effects: emotions, reward system and motor control

Nor-epinephrine effects: cardiovascular regulation, wakefulness and mood

Serotonin effects: feeding behavior, control of body temperature, modulation of sensory pathways (e.g. nociceptors), mood, wakefulness.

Amphetamine Effects:

- Dopaminergic stimulatory effect remains for hours followed by anxiety and depression.
- Tolerance may develop regarding its stimulant effects.
- Mostly used in treating Narcolepsy (uncontrollable bouts of sleepiness during the day) and hyperkinetic children.
- Used as appetite control, appetite suppressants (long term use). Its prolonged use may cause pulmonary suppression, Amphetamine psychosis and schizophrenia.
- Amphetamine stimulates the entire cerebrospinal axis, cortex, brainstem, and medulla causing decrease in alertness, decrease in appetite, increase in insomnia and increase in fatigue.

Therapeutic uses:

Factors that limit the therapeutic usefulness of amphetamine include psychological and physiologic dependence similar to those with cocaine and, with chronic use, the development of tolerance to the euphoric and anorectic effects.

- **Narcolepsy** (rare sleep disorder that is characterized by uncontrollable bouts of sleepiness during the day)
- **Nocturnal enuresis** (night time involuntary urination while asleep after the age at which bladder control usually occurs)
- **Attention deficit hyperactivity disorder (ADHD)**
- **Appetite suppressant:** These agents are used for their appetite suppressant effects in the management of obesity.
- Mydriatic
- Nasal decongestant (not now)

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Pharmacokinetics:

Absorption: through GIT

Metabolism: through liver

Excretion: by urine

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.

Adverse effects:

CNS effects: <ul style="list-style-type: none">• Insomnia, irritability, weakness, dizziness, tremor, and hyperactive reflexes.• Amphetamine can also cause confusion, delirium, panic states, and suicidal tendencies, especially in mentally ill patients.• Long-term amphetamine use is associated with psychic and physical dependence, tolerance to its effects may occur within a few weeks.• Over dosage can be treated by alpha blockers and at time beta blockers e.g. haloperidol, chlorpromazine.	Cardiovascular effects: <ul style="list-style-type: none">• Palpitations, cardiac arrhythmias, hypertension, anginal pain, and circulatory collapse.• Headache chills, and excessive sweating may also occur.
GIT effects: <ul style="list-style-type: none">• Amphetamine acts on the GI system, causing anorexia, nausea, vomiting, abdominal cramps, and diarrhea.	Eye: <ul style="list-style-type: none">• Mydriasis

Contraindications:

- Patients with hypertension,
- Cardiovascular disease,
- Insomnia
- Hyperthyroidism,
- Glaucoma,
- Or a history of drug abuse or those taking MAO inhibitors should not be treated with amphetamine.

Therapeutic Dose:

5-10 mg by IV or IM administration.

C. Cocaine:

Cocaine is a widely available and highly addictive drug.

In severe conditions, dopamine is exhausted and there is no more accumulation of dopamine so addicted person take it more and more for dopamine accumulation.

Mechanism of Action:

- Similar to Amphetamine
- Primary mechanism of action underlying the effects of cocaine is blockade of reuptake of the monoamines (norepinephrine, serotonin, and dopamine) into the presynaptic terminals.
- This potentiates and prolongs the CNS and peripheral actions of these monoamines.

Actions:

- Gives more dopaminergic effect, inhibit dopamine reuptake
- Increase brain's pleasure system (limbic system)
- Produce intense euphoria initially
- Chronic use may lead to depletion in dopamine and dopamine receptor gets empty. So to go back to pleasure state patient starts craving (physical and psychological dependence occurs) which may lead to withdrawal symptoms.

Therapeutic Uses:

- Ocular anesthetic
- If injected, cause tissue necrosis
- Marked effect on mood and behavior
- Induce sense of well being
- Delay state of tension
- Psychological and physiological dependence
- Tolerance develops
- Stimulate vagal center → bradycardia
- Stimulate vasomotor center → B.P

Over dosage:

Arrhythmia, Respiratory depression, Seizure, Vasoconstriction, Hypertension.

Test:

Urine test (for presence of cocaine).

Cocaine converted to benzyl-cocaine is easily detected in urine.

Nicotine:

Lethal dose = 60 mg

Normal cigarette: 1-2 mg

2. Hallucinogens

The individual under the influence of these drugs is incapable of normal decision making because the drug interferes with rational thought.

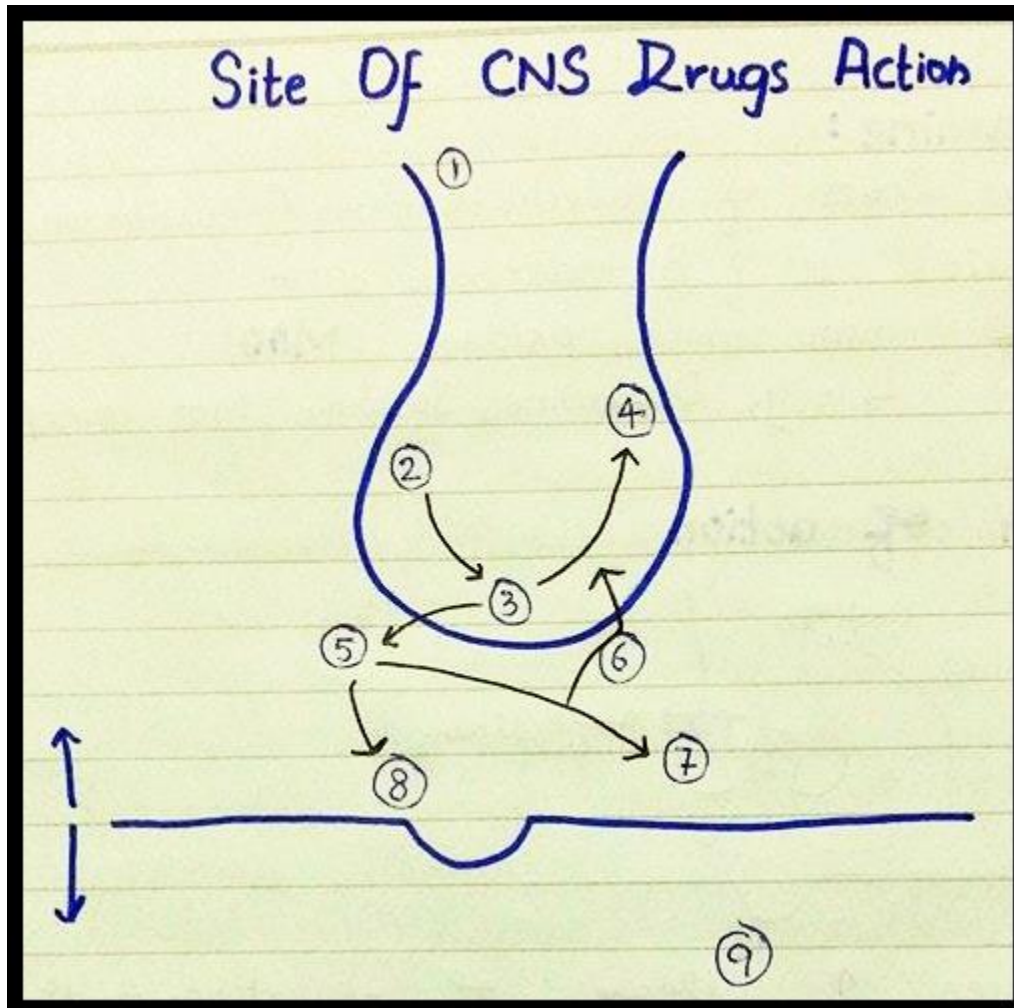
These compounds are known as hallucinogens, and lysergic acid diethylamide (LSD) and tetrahydrocannabinol (from marijuana) are examples of agents in this class.

Also include hard Drugs like Heroine and also charas, gaanja, afheem (in local language) etc.

Properties of Hallucinogens:

- 1) Dream like state
- 2) Loss of contact with reality
- 3) Field of vision may appear to be sway and object distorted like image in curved mirror
- 4) Face may appear ugly
- 5) On closing eyes, an unchanged series of colorful, very realistic and fantastic images appears to surge (sudden and powerful increase)
- 6) Time sense is altered
- 7) Music appears tangible
- 8) Impaired ability to concentrate
- 9) One can read but does not know what he/she is reading
- 10) Feel relaxed and surprisingly happy
- 11) Weeping

General Mechanism: Site of CNS Drugs Action



- 1) Action potential in pre-synaptic fiber
- 2) Synthesis of neurotransmitter
- 3) Storage
- 4) Metabolism of neurotransmitter within the nerve ending
- 5) Release of neurotransmitter
- 6) The uptake
- 7) Extracellular deposition of neurotransmitter
- 8) The post synaptic receptor (that follow receptor activation)
- 9) The post synaptic effect (that follow receptor activation)