CNS Stimulants

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- There are two groups of drugs that act primarily to stimulate the central nervous system (CNS).

- 1- psychomotor stimulants, **cause excitement and euphoria, decrease feelings of fatigue, and increase motor activity**.

- 2- The hallucinogens, or psychotomimetic drugs, **produce profound changes in thought patterns and mood, with little effect on the brainstem and spinal cord.**

PSYCHMOTOR STIMULANT	HALLUCINOGEN
Amphetamine Armodofinil Atomoxetine Caffeine Cocaine Dextroamphetamine Lisdexamfetamine MethylPhenidate Modofinil Nicotine Theobromine Theophylline Varenicline	1-Lysergic acid diethylamide 2- Phencyclidine 3- tetrahydrocannabinol

Psychomotor Stimulants

- **A. Methylxanthines**
- The methylxanthines include theophylline which is found in tea; theobromine, found in cocoa; and caffeine.

- Caffeine, the most widely consumed stimulant in the world, is found in highest concentration in coffee, but it is also present in tea, cola drinks, chocolate candy, and cocoa.

- **Mechanism of action**:
- Several mechanisms have been proposed for the actions of methylxanthines, including
- 1- Translocation of extracellular calcium
- 2- Increase in cAMP and cGMP caused by inhibition of phospho-di esterase
- 3- Blockade of adenosine receptors.
- The latter most likely accounts for the actions achieved by the usual consumption of caffeine-containing beverages.

- **Actions:**
  - **1- CNS:** The caffeine contained in one to two cups of coffee (100-200 mg) causes a decrease in fatigue and increased mental alertness as a result of stimulating the cortex and other areas of the brain.

Consumption of 1.5 g of caffeine (12 to 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; 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. Increased contractility can be harmful to patients with angina pectoris.

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

- **4- Gastric mucosa**: Because all methylxanthines stimulate secretion of hydrochloric acid from the gastric mucosa, individuals with peptic ulcers should avoid beverages containing methylxanthines.

- **Therapeutic uses**: Caffeine and its derivatives relax the smooth muscles of the bronchioles.

- **Pharmacokinetics:** The methylxanthines are
- 1- well absorbed orally
- 2- distributes throughout the body, including the brain
- 3- The drugs cross the placenta to the fetus
- 4- secreted into the mother's milk.
- 5- All the methylxanthines are metabolized in the liver, generally by the CYP1A2 pathway,
- 6- metabolites are excreted in the urine.

- **Adverse effects:**
- 1- Moderate doses of caffeine cause insomnia, anxiety, and agitation.
- 2- A high dosage is required for toxicity, which is manifested by emesis and convulsions.
- 3- The lethal dose is about 10 g of caffeine (about 100 cups of coffee), which induces cardiac arrhythmias;
- 4- death from caffeine is thus highly unlikely.
- 5- Lethargy, irritability, and headache occur in users who have routinely consumed more than 600 mg of caffeine per day (roughly six cups of coffee per day) and then suddenly stop.

- **B. Nicotine**
- Nicotine is the active ingredient in tobacco.
- Although this drug is not currently used therapeutically (except in smoking cessation therapy, **nicotine remains important, because it is second only to caffeine as the most widely used CNS stimulant and 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, as well as 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 at a number of sites in the CNS, which participate in the stimulant attributes of the drug.

- **Actions:**
  - 1- 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.
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- Nicotine is an appetite suppressant.

- **2- Peripheral effects:** The peripheral effects of nicotine are complex. Stimulation of sympathetic ganglia as well as the adrenal medulla increases blood pressure and heart rate.

- Thus, use of tobacco is particularly harmful in hypertensive patients

- Many patients with peripheral vascular disease experience an exacerbation of symptoms with smoking. For example, nicotine-induced vasoconstriction can decrease coronary blood flow, adversely affecting a patient with angina.

- Stimulation of parasympathetic ganglia also increases motor activity of the bowel.

- At higher doses, blood pressure falls, and activity ceases in both the gastrointestinal tract and bladder musculature as a result of a nicotine-induced block of parasympathetic ganglia

- **Pharmacokinetics:**
- 1- Absorption readily occurs via the oral mucosa, lungs, gastrointestinal mucosa, and skin.

- 2- Nicotine crosses the placental membrane and is secreted in the milk of lactating women.

- 3- By inhaling tobacco smoke, the average smoker takes in 1 to 2 mg of nicotine per cigarette (most cigarettes contain 6 to 8 mg of nicotine).

- 4- The acute lethal dose is 60 mg. More than 90 % of the nicotine inhaled in smoke is absorbed.

- 5- Clearance of nicotine involves metabolism in the lung and the liver and urinary excretion.

- 6- Tolerance to the toxic effects of nicotine develops rapidly, often within days after beginning usage.

- 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 on nicotine develops rapidly and can be severe.

- Withdrawal is characterized by irritability, anxiety, restlessness, difficulty concentrating, headaches, and insomnia.

- Appetite is affected, and gastrointestinal pain often occurs.

- **The transdermal patch and chewing gum containing nicotine have been shown to reduce nicotine withdrawal symptoms and to help smokers stop smoking.**

- For example, the blood concentration of nicotine obtained from nicotine chewing gum is typically about one-half the peak level observed with smoking.

- **Bupropion, an antidepressant can reduce the desire for cigarettes.**

- **C. Varenicline**
- Varenicline is a partial agonist at β_2, α_4, neuronal nicotinic acetylcholine receptors in the CNS.

- Because it is only a partial agonist at these receptors, it produces less euphoric effects than those produced by nicotine itself (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 should be monitored for suicidal thoughts, dramatic nightmares and mood changes.

- **D. Cocaine**
- **Mechanism of action**:
- The primary mechanism of action underlying the central and peripheral effects of cocaine is
- **Blockade of reuptake of the monoamines (norepinephrine, serotonin, and dopamine) into the presynaptic terminals from which these neurotransmitters are released.**

- This blockade is caused by cocaine binding to the monoaminergic reuptake transporters and, thus, potentiates and prolongs the CNS and peripheral actions of these monoamines.

- In particular, the prolongation of dopaminergic effects in the brain's pleasure system (limbic system) produces the intense euphoria that cocaine initially causes.

- Chronic intake of cocaine depletes dopamine. This depletion triggers the vicious cycle of craving for cocaine that temporarily relieves severe depression

- **Actions:**
  - **CNS**: The behavioral effects of cocaine result from powerful stimulation of the cortex and brainstem.
  - 1- increases mental awareness
  - 2- produces a feeling of well-being
  - 3- euphoria similar to that caused by amphetamine.
  - Like amphetamine, cocaine
  - 1- produce hallucinations and delusions of paranoia or grandiosity.
  - 2- Cocaine increases motor activity, and at high doses, it causes tremors and convulsions, followed by respiratory and vasomotor depression.

- Peripherally, cocaine potentiates the action of norepinephrine, and it produces the flight syndrome characteristic of adrenergic stimulation.

- This is associated with tachycardia, hypertension, pupillary dilation, and peripheral vasoconstriction.

- **Hyperthermia**: Cocaine is unique among illegal drugs in that death can result not only as a function of dose but also from the drug's susceptibility to cause hyperthermia.

- Even a small dose of intranasal cocaine impairs sweating and cutaneous vasodilatation. Perception of thermal discomfort is also decreased.

- **Therapeutic uses**:

- 1- Cocaine has a local anesthetic action that represents the only current rationale for the therapeutic use of cocaine.

- 2- cocaine is applied topically as a local anesthetic during eye, ear, nose, and throat surgery.

- the local anesthetic action of cocaine is due to a block of voltage-activated sodium channels

- Cocaine has interaction with potassium channels may explain the ability of cocaine to cause cardiac arrhythmias.
  Cocaine is the only local anesthetic that causes vasoconstriction. This effect is responsible for the necrosis and perforation of the nasal septum seen in association with chronic inhalation of cocaine powder.]

- **Pharmacokinetics**: Cocaine is often self-administered by chewing, intranasal snorting, smoking, or intravenous (IV) injection.

- The peak effect occurs at 15 to 20 minutes after intranasal intake of cocaine powder, and the high disappears in 1 to 1.5 hours.

- Rapid but short-lived effects are achieved following IV injection of cocaine or by smoking the freebase form of the drug.

- Because the onset of action is most rapid, the potential for overdosage and dependence is greatest with IV injection and crack smoking.

- Cocaine is rapidly de-esterified and demethylated to benzoylecgonine, which is excreted in the urine.

- Detection of this substance in the urine identifies a user.

- **Adverse effects:**
  - **Anxiety**: The toxic response to acute cocaine ingestion can precipitate an anxiety reaction that includes hypertension, tachycardia, sweating, and paranoia.
  - Because of the irritability, many users take cocaine with alcohol.
  - A product of cocaine metabolites and ethanol is cocaethylene, which is also psychoactive and believed to contribute to cardiotoxicity.
  - **Depression**: Like all stimulant drugs, cocaine stimulation of the CNS is followed by a period of mental depression.
  - Addicts withdrawing from cocaine exhibit physical and emotional depression as well as agitation.

  The latter symptom can be treated with benzodiazepines or phenothiazines.

- **Toxic effects:** Cocaine can induce seizures as well as fatal cardiac arrhythmias.

- Use of IV diazepam and propranolol may be required to control cocaine-induced seizures and cardiac arrhythmias, respectively.

- The incidence of myocardial infarction in cocaine users is unrelated to dose, to duration of use, or to route of administration.

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

- Dextroamphetamine is the major member of this class of compounds.
- Methamphetamine is a derivative of amphetamine that can be smoked, and it is preferred by many abusers.

- **Mechanism of action:** As with cocaine, the effects of amphetamine on the CNS and peripheral nervous system are indirect; that is, both depend upon an elevation of the level of catecholamine neurotransmitters in synaptic spaces.

- Amphetamine, however, achieves this effect by releasing intracellular stores of catecholamines.

- Because amphetamine also inhibits monoamine oxidase (MAO), high levels of catecholamines are readily released into synaptic spaces.

- **Actions:**
  - **1- CNS**: The major behavioral effects of amphetamine result from a combination of its dopamine and norepinephrine release-enhancing properties.
  - Amphetamine stimulates the entire cerebrospinal axis, cortex, brainstem, and medulla. This leads to increased
  - 1- alertness
  - 2- decreased fatigue
  - 3- depressed appetite and insomnia.
  - These CNS stimulant effects of amphetamine and its derivatives have led to their use in therapy for hyperactivity in children, narcolepsy, and for appetite control.
  - At high doses, psychosis and convulsions can result.

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

- **Therapeutic uses:** Factors that limit the therapeutic usefulness of amphetamine include **psychological and physiological dependence similar to those with cocaine and the development of tolerance to the euphoric and anorectic effects with chronic use.**

- **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 and the amphetamine derivative methylphenidate are able to improve attention and to alleviate many of the behavioral problems associated with this syndrome, and to reduce the hyperkinesia that such children demonstrate.

- Lisdexamfetamine is a prodrug that is converted to the active component dextroamphetamine after gastrointestinal absorption and metabolism.

- The drug prolongs the patient's span of attention allowing better function in a school atmosphere.
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- Atomoxetine is a nonstimulant drug approved for ADHD in children and adults.

- It should not be taken by individuals on MAO inhibitors, and it is not recommended for patients with narrow-angle glaucoma.]

- Unlike methylphenidate which blocks dopamine reuptake, **atomoxetine is a norepinephrine reuptake inhibitor.**

- It is not habit forming and is not a controlled substance

- **Narcolepsy**:
- Narcolepsy is a relatively rare sleep disorder that is characterized by uncontrollable bouts of sleepiness during the day.

- It is sometimes accompanied by
- 1- catalepsy
- 2- a loss in muscle control
- 3- paralysis brought on by strong emotions, such as laughter.

- However, it is the sleepiness for which the patient is usually treated with drugs such as amphetamine or methylphenidate.

- **Recently, a newer drug, modafinil, and its R-enantiomer derivative, armodafinil, have become available to treat narcolepsy.**

- Modafinil produces fewer psychoactive and euphoric effects as well as, alterations in mood, perception, thinking, and feelings typical of other CNS stimulants. It does promote wakefulness.

- The mechanism of action remains unclear but may involve the adrenergic and dopaminergic systems, although it has been shown to differ from that of amphetamine.

- Modafinil is effective orally. It is well distributed throughout the body and undergoes extensive hepatic metabolism. The metabolites are excreted in the urine.

- Headaches, nausea, and rhinitis are the primary adverse effects. There is some evidence to indicate the potential for abuse and physical dependence with modafinil.

- **Pharmacokinetics**: Amphetamine is completely absorbed from the gastrointestinal tract, metabolized by the liver, and excreted in the urine.

- Amphetamine abusers often administer the drugs by IV injection and 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:** The amphetamines may cause addiction, leading to dependence, tolerance, and drug-seeking behavior. In addition, they have the following undesirable effects.
  - **Central effects:** Undesirable side 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.

- 3,4-Methylenedioxymethamphetamine (also known as MDMA, or Ecstasy) is a synthetic derivative of methamphetamine with both stimulant and hallucinogenic properties

- **Cardiovascular effects**: In addition to its CNS effects, amphetamine causes palpitations, cardiac arrhythmias, hypertension, anginal pain, and circulatory collapse.

- Headache chills, and excessive sweating may also occur.

- Gastrointestinal system effects: Amphetamine acts on the gastrointestinal system, causing anorexia, nausea, vomiting, abdominal cramps, and diarrhea.

- Administration of sodium bicarbonate will increase the reabsorption of dextroamphetamine from the renal tubules into the bloodstream.
- Contraindications: Patients with hypertension, cardiovascular disease, hyperthyroidism, or glaucoma

- **F. Methylphenidate**

- Methylphenidate has CNS stimulant properties similar to those of amphetamine and may also lead to abuse, although it's addictive potential is controversial.

- It is a Schedule II drug. It is presently one of the most prescribed medications in children.

- The pharmacologically active isomer, dexmethylphenidate, has been approved in the United States for the treatment of ADHD.

- **Mechanism of action:** Children with ADHD may produce weak dopamine signals, which suggests that usually interesting activities provide fewer rewards to these children.