**CNS Stimulants**

* Molecular Basis of CNS Stimulation: Imbalance between inhibitory and excitatory Processes. This hyper-excitability of neurons results from: potentiating of excitatory neurotransmission(e.g. amphetamine) or antagonism of inhibitory transmission (e.g. Strychnine) , presynaptic control of neurotransmitter release (e.g. picrotoxin)

**Classification of CNS Stimulants**

* + Analeptic Stimulants ( Respiratory Stimulants ,Convulsants )
* Psychomotor Stimulant
* Analeptic Stimulants

**Doxapram:**  used to counteract postanesthetic respiratory depression and for acute hypercapnia in chronic pulmonary disease. Doxapram is a respiratory stimulant, it stimulates chemoreceptors in the carotid bodies of the carotid arteries, which in turn, stimulates the respiratory centre in the brain stem. Doxapram is used in intensive care settings to stimulate the respiratory rate in patients with respiratory failure. It may be useful for treating respiratory depression in patients who have taken excessive doses of drugs such as buprenorphine which may fail to respond adequately to treatment with naloxone.

 **Nikithamide** It is especially useful for mountain climbers to increase endurance at high altitudes.

**Pentylenetetrazole**: has the opposite effect when it binds to the GABA-A receptor Pentylenetetrazol has been used experimentally to study seizure phenomena and to identify pharmaceuticals that may control seizure susceptibility. It is also a prototypical anxiogenic drug and, has been extensively utilized in animal models of anxiety. Pentylenetetrazol produces a reliable discriminative stimulus which is largely mediated by the GABAA receptor.

Recently, it used for treatment of Down syndrome, restoring the declarative memory deficits associated with the mouse model of human Down Syndrome.

* Used clinically as a tool for screening latent epileptics and experimentally to screen compounds for anti-epileptic activity.

**Picrotoxin**: also known as **cocculin**, is a poisonous crystalline plant compound . It acts as a non-competitive channel blocker for the GABAA receptor chloride channels, used to counter barbiturate poisoning

* **Strychnine**: is a neurotoxin which acts as an antagonist of glycine and acetylcholine receptors. It primarily affects the motor nerves in the spinal cord which control muscle contraction, lead to excitement, euphoria, decrease feelings of fatigue, and increase motor activity.

**PSYCHOMOTOR STIMULANTS**

**Methylxanthines**

The methylxanthines include theophylline, which is found in tea; theobromine, found in cocoa; and caffeine, it is also present in tea, cola drinks, chocolate candy, and cocoa.

**1. Mechanism of action:** increase in cyclic adenosine monophosphate and cyclic guanosine monophosphate caused by inhibition of phosphodiesterase, and blockade of adenosine receptors.

**2. Actions:**

**a. CNS:** 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 produces anxiety and tremors. Tolerance can rapidly develop to the stimulating properties of caffeine, and withdrawal consists of feelings of fatigue and sedation.

**b. Cardiovascular system:** positive inotropic and chronotropic effects on the heart.

**c. Diuretic action:** mild diuretic action that increases urinary output of sodium, chloride, and potassium.

**d. Gastric mucosa:** stimulate secretion of hydrochloric acid from the gastric mucosa.

**3. Therapeutic uses:** asthma and chronic bronchitis.

**4. 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 mother’s milk. All the methylxanthines are metabolized in the liver, generally by the CYP1A2 pathway, and the metabolites are then excreted in the urine.

**5. Adverse effects:** Moderate doses of caffeine cause insomnia, anxiety, and agitation. A high dosage cause emesis and convulsions.

**Nicotine**: is as used CNS stimulant .

**1. 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:**

**a. CNS:** Nicotine is highly lipid soluble and readily crosses the blood brain barrier produces euphoria, arousal and 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.

**b. 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 decreased 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 (GI) tract and bladder musculature because of a nicotine-induced block of parasympathetic ganglia.

**3. Pharmacokinetics:** Because nicotine 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 the milk of lactating women. The acute lethal dose is 60 mg. More than 90 percent 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 toxic effects of nicotine develops rapidly,

**4. 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.

**5. 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. The transdermal patch and chewing gum containing nicotine have been shown to reduce nicotine withdrawal symptoms. 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 craving for cigarettes.

**Varenicline:** is a partial agonist at neuronal nicotinic acetylcholine receptors in the CNS, it produces less euphoric effects than those produced by nicotine itself . 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, vivid nightmares, and mood changes.

**Cocaine**

**1. Mechanism of action:** The primary mechanism of action is blockade of reuptake of the monoamines (norepinephrine, serotonin, and dopamine) into the presynaptic terminals. This blockade is caused by cocaine binding to the monoaminergic reuptake transporters, 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.

**2. Actions:**

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

**b. Sympathetic nervous system:** Peripherally, cocaine potentiates the action of norepinephrine, and it produces the “fight-or flight” syndrome characteristic of adrenergic stimulation. This is associated with tachycardia, hypertension, papillary dilation, and peripheral vasoconstriction. Perception of thermal is also decreased.

**3. Therapeutic uses:** local anesthetic only.

 **Pharmacokinetics:** Cocaine is often self-administered by chewing, intranasal snorting, smoking, or intravenous (IV) injection. Rapid but short-lived effects are achieved following IV injection of cocaine or by smoking the freebase form of the drug (“crack”). Because the onset of action is most rapid, the potential for over dosage and dependence is greatest with IV injection and crack smoking.

**5. Adverse effects:**

**a. Anxiety:** anxiety reaction that includes hypertension, tachycardia, sweating, and paranoia. A product of cocaine metabolites and ethanol is cocaethylene, which is also psychoactive and believed to contribute to cardiotoxicity.

**b. Depression:** cocaine stimulation of the CNS is followed by a period of mental depression.

**c. Toxic effects:** seizures as well as fatal cardiac arrhythmias.

**Amphetamine**: is a sympathetic amine that shows neurologic and clinical effects quite similar to those of cocaine. Dextroamphetamine is the major member of this class of compounds.

**1. Mechanism of action:** by releasing intracellular stores of catecholamines and inhibits monoamine oxidase (MAO).

**2. Actions:**

**a. CNS:** Amphetamine stimulates the entire cerebrospinal axis, cortex, brainstem, and medulla. This leads to increased alertness, decreased fatigue, depressed appetite, and insomnia.

**b. Sympathetic nervous system:** indirectly stimulating the receptors through norepinephrine release.

**3. Therapeutic uses:**

 **a. 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

 **b. Narcolepsy:**  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. Usually treated with drugs, such as amphetamine or methylphenidate. Recently, **modafinil** produces fewer psychoactive and euphoric effects as well as fewer alterations in mood, perception, thinking, and feelings typical of other CNS stimulants. It does promote wakefulness. The mechanism of action involves the adrenergic and dopaminergic systems, although it has been shown to differ from that of amphetamine. Modafinil is effective orally.

**4. Pharmacokinetics:** Amphetamine is completely absorbed from the GI tract, metabolized by the liver, and excreted in the urine. [Note: Administration of urinary alkalinizing agents will increase the nonionized species of the drug and decrease its excretion.]. The euphoria caused by amphetamine lasts 4 to 6 hours eightfold longer than the effects of cocaine.

**5. Adverse effects:**  addiction, dependence, tolerance, and drug-seeking behavior.

**a. CNS effects:**  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. Overdoses of amphetamine are treated with chlorpromazine or haloperidol, which relieve the CNS symptoms as well as the hypertension because of their α-blocking effects. The anorectic effect of amphetamine is due to its action on hypothalamic feeding center.

**b. Cardiovascular effects:** palpitations, cardiac arrhythmias, hypertension, angina pain, and circulatory collapse. Because of its cardiovascular effects, amphetamine should not be given to patients with cardiovascular disease and those receiving MAO inhibitors.

**c. GI system effects:**  anorexia, nausea, vomiting, abdominal cramps, and diarrhea. Administration of sodium bicarbonate will increase the reabsorption of dextroamphetamine from the renal tubules into the bloodstream.

**d. Contraindications:** hypertension, cardiovascular disease, hyperthyroidism, or glaucoma and history of drug abuse, taking MAO inhibitors.

**F. Methylphenidate** has CNS-stimulant properties similar to those of amphetamine.

**1. Mechanism of action:** Methylphenidate is a dopamine transport inhibitor.

**2. Therapeutic uses:** ADHD in children ages 6 to 16 years, narcolepsy.

**3. Pharmacokinetics:** Both methylphenidate and dexmethylphenidate are readily absorbed upon oral administration. Methylphenidate is available in extended release capsules and as a transdermal patch.

**4. Adverse reactions:** insomnia, nervousness, and fever.

**HALLUCINOGENS**: drugs have the ability to induce altered perceptual states reminiscent of dreams.

**A. Lysergic acid diethylamide**: The drug shows serotonin (5-HT) agonist activity at presynaptic 5-HT1 receptors in the midbrain, and it stimulates 5-HT2 receptors. Activation of the sympathetic nervous system occurs, which causes papillary dilation, increased blood pressure, piloerection, and increased body temperature. Taken orally, low doses of LSD can induce hallucinations with brilliant colors. **Adverse effects:** include hyperreflexia, nausea, and muscular weakness. High doses may produce long-lasting psychotic changes in susceptible individuals. Haloperidol and other neuroleptics can block the hallucinatory action of LSD .

**B. Tetrahydrocannabinol:** (dronabinol ) This product is prescribed to treat emesis and to stimulate the appetite, produce euphoria, followed by drowsiness and relaxation. Its wide range of effects includes appetite stimulation, xerostomia, visual hallucinations, delusions, and enhancement of sensory activity. Dronabinol is indicated as an appetite stimulant for patients with acquired immunodeficiency syndrome who are losing weight. The CB1-receptor antagonist, rimonabant , is effective in the treatment of obesity .

**C. Phencyclidine** “angel dust” inhibits the reuptake of dopamine, 5-HT, and norepinephrine. Phencyclidine has anticholinergic activity but, surprisingly, produces hypersalivation. Phencyclidine, an analog of ketamine, causes dissociative anesthesia (insensitivity to pain without loss of consciousness) and analgesia. Increased sensitivity to external stimuli results and the CNS actions may persist for a week.

**Indications of CNS stimulants:**

 To counteract lethargy and fatigue, Narcolepsy, Obesity, ADHD and [Resistant depression](http://en.wikipedia.org/wiki/Treatment-resistant_depression).

**Orexin**: also called hypocretin, is a [neurotransmitter](http://en.wikipedia.org/wiki/Neurotransmitter) that regulates [arousal](http://en.wikipedia.org/wiki/Arousal), [wakefulness](http://en.wikipedia.org/wiki/Wakefulness), and [appetite](http://en.wikipedia.org/wiki/Appetite).  The brain contains very few cells that produce orexin; in a human brain, about 10,000 to 20,000 [neurons](http://en.wikipedia.org/wiki/Neurons) in the [hypothalamus](http://en.wikipedia.org/wiki/Hypothalamus). There are two types of orexin: [orexin-A](http://en.wikipedia.org/wiki/Orexin-A%22%20%5Co%20%22Orexin-A) and B. They are excitatory [neuropeptide](http://en.wikipedia.org/wiki/Neuropeptide%22%20%5Co%20%22Neuropeptide) [hormones](http://en.wikipedia.org/wiki/Hormones)  via the [dopamine](http://en.wikipedia.org/wiki/Dopamine), [norepinephrine](http://en.wikipedia.org/wiki/Norepinephrine%22%20%5Co%20%22Norepinephrine), [histamine](http://en.wikipedia.org/wiki/Histamine) and acetylcholine systems. Orexin blocker, **[suvorexant](http://en.wikipedia.org/wiki/Suvorexant%22%20%5Co%20%22Suvorexant),** fell asleep faster and slept an hour longer used for insomnia and [alcoholism](http://en.wikipedia.org/wiki/Alcoholism).