CNS stimulants

CNS stimulants are drugs which increase the muscular (motor) and the mental (sensory) activities .Their effects vary from the increase in the alertness and wakefulness (as with caffeine) to the production of convulsion (as with strychnine) or death due to over stimulation. CNS stimulants are the psychoactive drugs that induce temporary improvement in either mental or physical function or both. CNS stimulants have few clinical uses and are important as drugs of abuse.

Factors that limit the therapeutic usefulness include:

1. Dependence: Psychological and physiological.
2. Tolerance to the euphoric and anorectic effects

Behavioral Manifestations of CNS Stimulation :

Mild elevation in alertness, decrease in drowsiness and lessening of fatigue (Analeptic effect), increased nervousness and anxiety - convulsions.

There are two types of CNS stimulants:

1. Psychomotor stimulants: cause excitement, euphoria, Decrease feeling of fatigue & Increase motor activity Ex., Methylxanthines (caffeine, theobromine, theophylline), nicotine, cocaine, amphetamine, atomoxetine, modafinil, methylphenidate.
2. Hallucinogens or Psychomimetic drugs: Affect thought, perception, and mood.

Ex. Lysergic acid diethylamide (LSD), Phencyclidine (PCP), Tetrahydrocannabinol (THC), Rimonabant.

Therapeutic Indications and Contraindications for CNS Stimulants:

Obesity (anorectic agents).

Attention Deficit Hyperactivity Disorder (ADHD); lack the ability to be involved in any one activity for longer than a few minutes.

Narcolepsy: It 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, or even paralysis brought on by strong emotion, such as laughter.

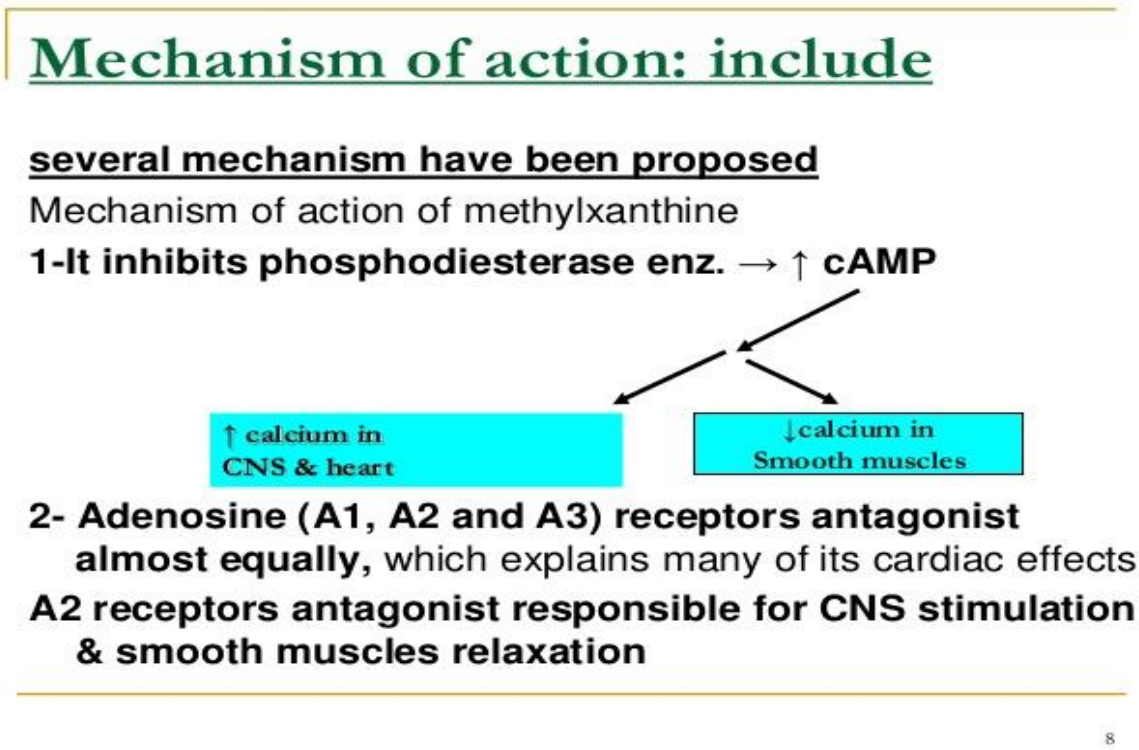
Contraindications: patients with anorexia, insomnia, asthenia, psychopathic personality, a history of homicidal or suicidal tendencies.

1. Psychomotor stimulants:

A. methylxanthines: Xanthine is a purine base found in most human body tissues and fluids and in other organism and it is also Bronchodilators.

Theophylline (found in tea): long-acting, prescribed for night-time asthma

Theobromine: found in cocoa .Caffeine: (short-acting) the most widely consumed.



Actions:

a. CNS:

- ❑ decrease in fatigue, increased alertness: 100-200 mg caffeine in 1 or 2 cups of coffees
- ❑ Anxiety & tremors- 1.5 g of caffeine: 12-15 cups of coffee
- ❑ Spinal cord stimulation: 2-5 g (very high dose)

Tolerance can rapidly develop

Withdrawal symptoms: feeling of fatigue & sedation.

b. CVS; at high dose of caffeine +ve inotropic and chronotropic effects on the heart, ↑COP

c. Diuretic action: mild ↑ urinary output of Na+, Cl^- and K^+

d. Gastric mucosa: all methylxanthines stimulate secretion of HCl

e. Respiratory smooth muscle: bronchodilator, Rx asthma replaced by β2-agonists, corticosteroids.

Pharmacokinetics

The methylxanthines are well absorbed orally. Caffeine distributes throughout the body, including the brain. The drugs cross the placenta to the fetus and is secreted into the mother's milk. All are metabolized in the liver, generally by the CYP1A2 pathway; the metabolites are then excreted in the urine.

Adverse effects

- ■ Moderate doses: insomnia, anxiety, agitation
- ■ High doses: emesis, convulsion
- ■ Lethal dose (10 gm of caffeine): cardiac arrhythmia
- ■ Suddenly stop: lethargy, irritability, headache

B. Nicotine:

Nicotine is the active ingredient in tobacco. It used therapeutically only 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.

Actions of Nicotine:

Low dose: ganglionic depolarization

High dose: ganglionic blockade

Actions:

I. CNS: *Nicotine* is highly lipid soluble and readily crosses the

Blood–brain barrier.

1. Low dose: euphoria, arousal, relaxation, improves attention, learning, problem solving and reaction time.
2. High dose: central respiratory paralysis.

Nicotine also an appetite suppressant.

II. Peripheral effects:

- Stimulation of sympathetic ganglia and adrenal medulla→↑ BP and HR (harmful in HTN patients)
- Stimulation of parasympathetic ganglia→↑ motor activity of the bowel
- At higher doses, BP falls & activating ceases in both GIT and bladder

Pharmacokinetics:

Highly lipid soluble absorbed everywhere (oral mucosa, lung, GIT, skin).Crosses the placental membrane, secreted with milk. Most cigarettes contain 6-8 mg of nicotine, by inhaling tobacco smoke; the average smoker takes in 1 to 2 mg of nicotine per cigarette. The acute lethal dose is 60 mg, it absorbed through skin (toxic).

Adverse effects: CNS; irritability and tremors

- Intestinal cramps, diarrhea, lung cancer.
- ↑HR & BP

Withdrawal syndrome: nicotine is addictive substance,

- Physical dependence on nicotine develops rapidly and can be severe.
- Bupropion: can reduce the craving for cigarettes
- Transdermal patch and chewing gum containing nicotine

C. Varenicline: partial agonist at Nn receptor in CNS. It produces less euphoric effects than those produced by nicotine itself (nicotine is full agonist at these receptors). Thus, it is useful as an adjunct in the management of smoking cessation in patients with nicotine withdrawal symptom.

D. Cocaine (highly addictive drug):

1. Mechanism of action: blockade of reuptake of the monoamines (NE, serotonin and dopamine) thus, potentiates and prolongs the CNS and peripheral actions of these monoamines. Initially produces the intense euphoria by prolongation of dopaminergic effects in the brain's pleasure system (limbic system). Chronic intake of cocaine depletes dopamine. This depletion triggers the vicious cycle of craving for cocaine that temporarily relieves severe depression.

2. Actions:

a. CNS-behavioral effects result from powerful stimulation of cortex and brain stem. Cocaine acutely increase mental awareness and produces a feeling of wellbeing and euphoria similar to that produced by amphetamine.

b. Hyperthermia: impair sweating & cutaneous vasodilation, ↓Perception of thermal discomfort.

c. local anesthetic action: blockade of voltage-activated Na^+ channel.

- Cocaine is the only LA that causes vasoconstriction, chronic inhalation of cocaine powder → necrosis and perforation of the nasal septum
- Cocaine is often self-administered by chewing, intranasal snorting, smoking, or intravenous (IV) injection.

Adverse effects: 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 cause 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:

- Seizures RX I.V diazepam
- Fatal cardiac arrhythmias. propranolol

<u>E. Amphetamine</u>:

- Is a non-catecholamine, (shows neurologic and clinical effects quite similar to those of cocaine),

<u>Narcolepsy:</u> treated by Amphetamine, methylphenidate.

- Recently, a new drug, modafinil and its R-enantiomer derivative, armodafinil, have become first line treatment for narcolepsy.

3. <u>Adverse effects:</u>

The amphetamines may cause addiction, dependence, tolerance, and drug seeking behavior. Insomnia, irritability, weakness, dizziness, tremor, hyperactive reflex, confusion, delirium, panic states, and suicidal tendencies, especially in mentally ill patients. Overdoses are

treated with chlorpromazine or haloperidol, which relieve the CNS symptoms as well as the HTN because of their α–blocking effects.

Contraindications: HTN, CV diseases, Hyperthyroidism, Glaucoma, Patients with a history of drug abuse

Atomoxetine: approved for ADHD in children and adults. It is a NE reuptake inhibitor (should not be taken by individual on MAOI).It is not habit forming and is not a controlled substance.

Methylphenidate (Ritalin) ®: It has CNS stimulant properties similar to those of amphetamine and may also lead to abuse, although its addictive potential is controversial.

Therapeutic uses: Methylphenidate has been used for several decades in the treatment of ADHD in children aged 6 to 16. It is also effective in the treatment of narcolepsy. Unlike methylphenidate, dexmethylphenidate is not indicated in the treatment of narcolepsy.

Adverse reactions: GIT effects are the most common; abdominal pain and nausea.

In seizure patients, methylphenidate seems to increase the seizure frequency, especially if the patient is taking antidepressants. Methylphenidate is contraindicated in patients with glaucoma.

II. Hallucinogens (psychotomimetic): A few drugs have the ability to induce altered perceptual states reminiscent of dreams, are accompanied by bright, colourful changes in the environment and by a plasticity of constantly changing shapes and colour.

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

A. Lysergic acid diethylamide: The drug shows serotonin (5-HT) agonist activity at presynaptic 5-HT1 receptors in the midbrain, and also stimulates 5-HT_2 receptors. Activation of the sympathetic nervous system occurs, which causes pupillary dilation, increased BP, piloerection, and increased body temperature.

Adverse effects: include hyperreflexia, nausea, and muscular weakness

Haloperidol and other neuroleptics can block the hallucinatory action of LSD and quickly abort the syndrome.

B. Tetrahydrocannabinol (THC): The main psychoactive alkaloid contained in marijuana is tetrahydrocannabinol (THC), which is available as dronabinol. THC can produce euphoria, followed by drowsiness and relaxation. THC receptors, designated CB1 receptors, have been found on inhibitory presynaptic nerve terminals. CB1 is coupled to a G protein.

1. Therapeutic uses of Dronabinol: as an appetite stimulant for patients with acquired immunodeficiency syndrome who are losing weight.
2. It is also sometimes given for the severe emesis caused by some cancer chemotherapeutic agents.

Adverse effects: include increased heart rate, decreased blood pressure, and reddening of the conjunctiva.