CNS STIMULANTS

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CNS stimulants

1. Psychomotor stimulants
cause: Excitement, Euphoria, Decrease feeling of fatigue and Increase motor activity
Ex. Methylxanthines (caffeine, theobromine, theophylline), nicotine, cocaine, amphetamine, atomoxetine, modafinil, methylphenidate.

2. Hallucinogens (psychotomimetic)
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

1. Theophylline (found in tea): long-acting, prescribed for night-time asthma
2. Theobromine: found in cocoa.
3. Caffeine: (short-acting) the most widely consumed
   - found in coffee (200 mg/cup),
   - carbonated soft drinks (60 mg/can),
   - cocoa and chocolate
Mechanism of action: include

several mechanism have been proposed
Mechanism of action of methylxanthine
1- It inhibits phosphodiesterase enz. $\rightarrow$ $\uparrow$ cAMP

2- Adenosine (A1, A2 and A3) receptors antagonist almost equally, which explains many of its cardiac effects
A2 receptors antagonist responsible for CNS stimulation & smooth muscles relaxation
**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 β-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.
- Used in smoking cessation therapy,
- Nicotine remains important, because:
  - it is 2nd only to caffeine as the most widely used CNS stimulant
  - and 2nd only to alcohol as the most abused drug.

**Actions of Nicotine:**

**Low dose:** ganglionic depolarization

**High dose:** ganglionic blockade
Actions of Nicotine

I. CNS:
1. Low dose: euphoria, arousal, relaxation, improves attention, learning, problem solving and reaction time.
2. High dose: CNS paralysis, severe hypotension (medullary paralysis)

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,
- 90% of nicotine inhaled in smoke is absorbed.
- Tolerance to toxic effects of nicotine develops rapidly.
Adverse effects:
- CNS; irritability and tremors
- Intestinal cramps, diarrhea
- $\uparrow$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 Nicotinic 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.
- SE: Nausea, change in taste, vomiting, abdominal pain, flatulence, and constipation.
- Serious side-effects, including suicidal behavior and depression
D. Cocaine (highly addictive drug)

**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.
Only clinical use as local anesthetics.
Action:

- Initially produces the intense euphoria by prolongation of dopaminergic effects in the brain’s pleasure system (limbic system) producing the “Rush”.
- This follows by dysphoria in few minutes as it is degraded by plasma estrases

- Chronic intake of cocaine depletes dopamine. This depletion triggers the vicious cycle of craving for cocaine.
Pharmacological effects:

a. CNS-behavioral effects result from powerful stimulation of cortex and brain stem.

- Cocaine acutely increases mental awareness and produces a feeling of wellbeing and euphoria similar to that produced by amphetamine.

- Like amphetamine, cocaine can 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.
Pharmacological effects:

b. Sympathetic NS: peripherally potentiate the action of NE → fight or flight

c. Hyperthermia:
- impair sweating & cutaneous vasodilation
- ↓ Perception of thermal discomfort

d. 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 treated by I.V diazepam
- Fatal cardiac arrhythmias treated by propranolol
E. Amphetamine

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

- dextroamphetamine is the major member of this class compounds.

- methamphetamine (speed) is a derivative of amphetamine that can be smoked and it is preferred by many abusers.

- Methylenedioxymethamphetamine (also known as MDMA, or Ecstasy) is a synthetic derivative of methamphetamine with both stimulant and hallucinogenic properties.
Mechanism of action:

Amphetamine, act by

- releasing intracellular stores of catecholamines.
- also inhibits MAO, high level catecholamines are readily released into synaptic spaces.
**Actions:**

**a. CNS:** the major behavioral effects of amphetamine result from a combination of its dopamine and NE release enhancing properties.

- Amphetamine stimulates the entire cerebrospinal axis, brainstem, and medulla.
- This leads to increase alertness, decrease fatigue, depressed appetite, and insomnia.

**b. Sympathetic Nervous System:** indirectly stimulating the receptors through NE release.
Adverse effects:
The amphetamines may cause addiction, dependence, tolerance, and drug seeking behavior.

a. CNS: insomnia, irritability, weakness, dizziness, tremor, hyperactive reflex, 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.

-Whereas long-term amphetamine is associated with psychic and physical dependence, tolerance to its effects may occur within few weeks.
Adverse effects:
The anorectic effect of amphetamine is due to its action in the lateral hypothalamic feeding center.

b. CVS: palpitations, cardiac arrhythmia, HTN, anginal pain, and circulatory collapse. Headache, chills, and excess sweating may also occur.

c. GIT: anorexia, nausea, vomiting, abdominal cramps, and diarrhea.

Overdoses are treated with chlorpromazine or haloperidol, with urine acidification to enhance excretion.

Contraindications: HTN, CV diseases, glaucoma, hyperthyroidism, patients with a history of drug abuse
F. Atomoxetine

- It is a NE reuptake inhibitor (should not be taken by individual on MAO inhibitors).

- Approved for ADHD (significant problems of attention, hyperactivity, or acting impulsively) in children and adults.

- SE: Nausea, Xerostomia (dry mouth), appetite loss, Insomnia, Irritability, hypertension and Hostility.

- It is not habit forming and is not a controlled substance.
G. Methylphenidate

- It has CNS stimulant properties similar to those of amphetamine and may also lead to abuse.

- Methylphenidate is a more potent dopamine transport inhibitor than cocaine, thus making more dopamine available.

- It has less potential for abuse than cocaine, because it enters the brain much more slowly than cocaine and does not increase dopamine levels as rapidly.
Therapeutic uses:

- Methylphenidate and its active isomer, (Dexmethylphenidate), have 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.
Adverse reactions:

- GIT effects are the most common; abdominal pain and nausea.

- Other reactions include anorexia, insomnia, nervousness, and fever.

- In seizure patients, methylphenidate seems to increase the seizure frequency, especially if the patient is taking antidepressants.

- Methylphenidate is contraindicated in patients with glaucoma.
Narcolepsy: (day time sleepiness)

- Amphetamine, methylphenidate.

- Recently, a new drug, modafinil (wakefulness-promoting agent) 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.
H. Picrotoxin (cocculin)

- Is a poisonous crystalline plant compound.
- It acts as a non-competitive channel blocker for the GABAA receptor chloride channels.
- Infusion of picrotoxin has stimulant and convulsant effects.
- Used to counter barbiturate poisoning, that can occur during general anesthesia or during a large intake outside of the hospital.
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 (LSD)

- Multiple sites in the CNS are affected by (LSD) and shows serotonin (5-HT) agonist.

- It produces hallucinations with a dreamlike state (LSD trip).

- Activation of the sympathetic nervous system occurs, which causes pupillary dilation, increased BP, piloerection, and increased body temperature.

- Uses: treatment of alcoholism, pain and cluster headache relief, end-of-life anxiety, for spiritual purposes, and to enhance creativity.
Adverse effects:

- Include hyperreflexia, nausea, and muscular weakness.

- High doses may produce long-lasting psychotic changes in susceptible individuals.

- Temporarily impair the ability to make sensible judgments and understand common dangers, temporary confusion, difficulty with abstract thinking, or signs of impaired memory and attention span, thus making the user more susceptible to accidents and personal injury.
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.

- Affect short-term memory and mental activity, decreases muscle strength and impairs highly skilled motor activity, such as that required to drive a car.

- SE: appetite stimulation, xerostomia, visual hallucinations, delusions, and enhancement of sensory activity.
Mechanism of action:

- THC receptors, designated CB1 receptors, have been found on inhibitory presynaptic nerve terminals. CB1 is coupled to a G protein.

- Interestingly, endocannabinoids have been identified in the CNS.

- These compounds, which bind to the CB1 receptors, are membrane-derived and are synthesized on demand, and they may act as local neuromodulators.

- The action of THC is believed to be mediated through the CB1 receptors but is still under investigation.
Pharmacokinetics:

- The effects of THC appear immediately after the drug is smoked, but maximum effects take about 20 minutes. By 3 hours, the effects largely disappear.

- Dronabinol is administered orally and has a peak effect in 2 to 4 hours. Its psychoactive effects can last up to 6 hours, but its appetite-stimulant effects may persist for 24 hours.

- It is highly lipid soluble and has a large volume of distribution.

- THC itself is extensively metabolized by the mixed-function oxidases.

- Elimination: is largely through the biliary route.
Therapeutic uses of Dronabinol

- As an appetite stimulant for patients with acquired immunodeficiency syndrome who are losing weight.
- 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.

- At high doses, a toxic psychosis develops. Tolerance and mild physical dependence occur with continued, frequent use of the drug.
C. Rimonabant:

Cannabinoid receptor 1 (CB1) antagonist

- is an anorectic antiobesity drug that use to treat obesity (decrease appetite and body weight in humans).

- induces psychiatric disturbances, such as anxiety and depression, during clinical trials.
D. Phencyclidine:

- Phencyclidine (also known as PCP, or “angel dust”).
- Inhibits the reuptake of dopamine, 5-HT, and NE.
- The major action of phencyclidine is to block the ion channel regulated by the NMDA subtype of glutamate receptor.
- Recreational dissociative drug produces analgesia and anesthesia, can be ingested, smoked, inhaled or injected.
- Phencyclidine causes anticholinergic activity with severe changes in body image, loss of ego boundaries, paranoia, depersonalization. Hallucinations, euphoria, and suicidal impulses also reported.
Q: A very agitated young male was brought to the emergency room by the police. Psychiatric examination revealed that he had snorted cocaine several times in the past few days, the last time being 10 hours previously. He was given a drug which seated him and fell asleep. The drug very likely used to counter this patient’s apparent cocaine withdrawal was:

A: Phenobarbital  B: Lorazepam
C: Cocaine  D: Salbutamol
E: Adrenaline