CNS Stimulants

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Central Nervous System (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

• Medically approved use is for the treatment of Attention deficit hyperactivity disorder (ADHD), narcolepsy, obesity & reversal of respiratory distress

• Drugs used to treat migraine headache

CNS stimulants can be divided into two distinct categories

1. Psychomotor stimulants: these agents increase motor activity and cause excitement, euphoria and relieve fatigue.

2. Psychomimetic drugs (hallucinogens) produce changes in thought patterns and mood.
Pathophysiology

• ADHD may be caused by dysregulation of the neurotransmitters viz. serotonin, nor-epinephrine (NE) & dopamine (DA).

• This occurs in children less than 7 years but may persist through the teenage years. More common in boys.

• Characterized by inattentiveness, inability to concentrate, restlessness, hyperactivity, inability to complete tasks & impulsivity.
General Signs & Symptoms of CNS Stimulation

- ↑ Heart rate
- ↑ Respiratory rate
- Instability
- Tremors
- Hair erection
- Convulsion
PSYCHOMOTOR STIMULANTS

Mechanism of action:

1- Block neurotransmitters reuptake: (Most reuptake inhibitors affect either NE or 5-HT(Serotonin): Cocaine, Tricyclic antidepressants (TCAs), Selective Serotonin reuptake inhibitors (SSRIs)

2- Promote neurotransmitters release: Amphetamine

3- Block Metabolism: MAO (monoamine oxidase) inhibitors: Phenelzine

4- Antagonize the effect of inhibitory neurotransmitter: Picrotoxin & Strychnine
Classifications

1. Psychomotor stimulants
   • Xanthine Derivatives: Caffeine
   • Nicotine
   • Cocaine
   • Amphetamine (Dexadrine)
   • Anorectic Agents: **Appetite suppressants** (Sanorex, Dextrim)
   • Analgetic: **Respiratory Stimulant** (Doxapram)
   • Stimulants for migraine
   • Stimulants for Attention Deficit Disorder
     - Methylphenidate (Ritalin)
     - Pemoline (Cylert)
Xanthenes Derivatives: Caffeine

- Weak CNS stimulant, diuretic and myocardial stimulant
- **Pharmacokinetics:** These xanthines are well absorbed orally and rapidly distributed throughout the body including the brain.

- **Pharmacological Actions**
  - **CNS:** 100-200 mg of caffeine (1-2 cups) results in a decrease in fatigue and increased alertness. 1.5gs (12-15 cups) produces anxiety & tremors. Tolerance rapidly develops to these effects and abstinence results in a withdrawal syndrome of fatigue & sedation.
  - **CV system:** + inotrope & chronotrope, this may cause symptoms of cardiac ischemia and arrhythmias.
  - **Renal:** it is a mild diuretic
  - **Gastric mucosa:** it stimulates the secretion of HCl.

- **Uses**
  - Reduces fatigue and increases sensory awareness (orally)
  - Treatment of mild to moderate respiratory depression
  - Pain relief associated with vascular headaches (migraines)
• **Common side effects**
  - Nervousness, insomnia, gastric irritation, anxiety and agitation.
  - Higher doses can cause emesis & convulsions.
  - The lethal dose of caffeine is 10.0 grams (100 cups of coffee), death is due to arrhythmias

• **Interactions**
  - May cause hypertensive reaction with MAOI
  - Increase in CNS stimulation caused by oral contraceptives
  - **Smoking** may increase elimination of caffeine
Nicotine

• The active ingredient in tobacco (most cigarettes contain 6-8 mg of nicotine), its therapeutic use is limited to smoking cessation. Nicotine has been identified as one of the most addictive drugs currently known.

• **Pharmacological Actions:**
  1. **CNS:** Nicotine rapidly crosses the Blood Brain Barrier (BBB); low doses produce improving attention, learning, problem solving and reaction time. At high doses nicotine produces medullary paralysis causing respiratory & cardiovascular failure.

  2. **Peripheral effects:**
     ✓ Stimulation of the sympathetic system result in increased blood pressure (vasoconstriction) and heart rate.
     ✓ Stimulation of the parasympathetic system increases intestinal motility.
     ✓ At high doses sympathetic & parasympathetic blockade result in hypotension and GI paralysis.
Pharmacokinetics:
Nicotine is **highly lipid soluble** so absorption occurs across any mucosa, 90% of inhaled nicotine is absorbed across the alveolar membrane. Clearance involves metabolism in the lung & liver ending with urinary excretion.

Adverse effects:
The CNS effects include irritability & tremors. It can cause intestinal cramps, diarrhea, hypertension & tachycardia.

Withdrawal syndrome:
Physical dependence develops rapidly and is profound. Withdrawal is characterized by irritability, anxiety, restlessness, difficulty concentrating, headaches & insomnia.
Cocaine

**Mechanism of action:** The primary central & peripheral action of cocaine is the blockade of reuptake of monoamines (NE, 5-HT & DA) into presynaptic terminals.

**Pharmacological Actions:**

1. **CNS:** cocaine produces an acute increase in awareness and euphoria, at higher doses it causes hallucinations, delusions and paranoia. Cocaine increases motor activity leading to tremors and convulsions followed by respiratory and vasomotor depression.

2. **Sympathetic nervous system:** Cocaine potentiates the action of NE producing a “fight or flight” syndrome associated with sympathetic hyper-stimulation.

3. **Hyperthermia:** through hypothalamic mechanisms even a small dose of cocaine impairs thermoregulation, the mortality rate of cocaine overdoses increase during warm weather.
**Pharmacokinetics:** Nasal insufflations results in peak levels after 15-20 minutes. IV or inhalation peak effect occurs within seconds.

**Therapeutic uses:** Cocaine is one of the most effective local anesthetics when applied topically, it is used in ophthalmologic surgery due to its anesthetic effect in addition to the intense local vasoconstriction that reduces operative bleeding (this is the mechanism for necrosis and perforation of the nasal septum associated with cocaine insufflations).

**Adverse effects**
1. Anxiety
2. Depression
3. Cerebro-vascular disease: Cocaine can induce fatal arrhythmias and overt myocardial ischemia even in those with a normal cardiovascular system. Seizures, stroke and intracranial hemorrhage are also seen.
**Amphetamine: a non-catecholamine sympathetic amine**

- **Mechanism of action:** Like cocaine, amphetamine effects on the central & peripheral nervous system involve elevated levels of neurotransmitters in the synaptic space. Amphetamine achieves this effect by promoting the release of intracellular stores of these catecholamines (NE & Dopa) and the inhibition of monoamine oxidase.
• **Pharmacokinetics:** Amphetamine is completely absorbed from the GI tract, metabolized in the liver and excreted in the urine. The duration of action is 4-6 hours (much longer than cocaine).

• **Pharmacological Actions:** The major behavioral effects of amphetamine are due to the release of dopamine (vs. NE), resulting in increased alertness, insomnia, decreased appetite and decreased fatigue. In the sympathetic nervous system, amphetamine prolongs the action of NE in the adrenergic system.

• **Therapeutic uses:** uses are limited due to the physical and psychological dependence which can develop and the tolerance to the euphoric and anorectic effects; there is less tolerance to the convulsive effects.

  • **Attention deficit hyperactivity disorder (ADHD):** Dextroamphetamine and methylphenenidate (Ritalin)
  • **Narcolepsy**
Adverse effects: Amphetamine causes addiction

1. **Central effects**: These include insomnia, irritability, weakness, tremor, confusion, delirium, panic states and suicidal tendencies. Chronic use produces symptoms similar to an acute schizophrenic episode (amphetamine psychosis). Treatment with anti-psychotic agents can greatly reduce these symptoms.

2. **Cardiovascular effects**: Tachyarrhythmias, hypertension, acute coronary ischemia.

3. **GI effects**: Nausea, vomiting, abdominal cramps and diarrhea.
Anorectic Agents

- Primarily indicated for obesity in conjunction with a carefully supervised program of diet and exercise

- Psychological & Physical Dependence: The use of amphetamines as appetite suppressants for obesity is discouraged because of tolerance, dependence & abuse.

- **Side effects:** nervousness, irritability, insomnia, palpitations, restlessness, hypertension

- Fenfluramine, Phentermine, Phenylpropranololamine (Dexatrim)
- Benzphetamine (Didrex)
- Dextroamphetamine (Dexedrine)
Respiratory Stimulant (Analeptics)

- Doxapram HCl (Dopram),
- Methylxanthines – caffeine, theophylline
- CNS & respiratory stimulant used to treat respiratory depression caused by drug overdose, pre- & post-anesthetic respiratory depression & chronic obstructive pulmonary disease (COPD)
- Primary use is to stimulate respiration like in newborns with respiratory distress
- Act on respiratory center in the brain stem as well as on peripheral carotid chemoreceptors to increase the depth and rate of respiration
- **Side Effect**: nervousness, restlessness, tremors, palpitations, insomnia, diuresis, GI irritation, also stimulate other centers causing CVS stimulation, vomiting, Narrow safety margin
MIGRAINE HEADACHES

• Unilateral throbbing headache accompanied by nausea, vomiting & photophobia
• Caused by inflammation & dilatation of the cerebral blood vessels. Etiology is unknown but some suggest a decrease in the neurotransmitter serotonin (vasoconstrictor)

Treatment
• Analgesics – opioid, NSAIDs
• Ergot Alkaloids – nonspecific serotonin agonist. E.g. Ergotamine tartrate
• Triptans – selective 5HT₁ receptor agonists. E.g. Sumatriptan
Stimulants for Attention Deficit Disorder

- Methylphenidate (Ritaline), Pemoline (Cylert)
- CNS stimulant similar to amphetamine, but having a more marked effect on mental rather than physical or motor activities at normal doses
- Potential for habituation and psychological addiction
- Side effects: Nervousness, insomnia

Children: anorexia, mild weight loss, tachycardia
Non-Amphetamine Behavioral Stimulants:

**Sibutramine (Meridia)**
- Serotonin and norepinephrine reuptake inhibitor
- Causes significant increases in heart rate and blood pressure, limiting its use

**Methylphenidate (Ritalin)**
- Used in treatment of ADHD to calm hyperactivity and improve attention (prescribed in 90% of cases)
- Half-life $\approx 2-4$ hours
- Increases synaptic conc. of DA by blocking the presynaptic DA transporter (like cocaine) and increases the release of DA (like amphetamine)
Non-Amphetamine Behavioral Stimulants

**Pemoline (Cylert)**
- Structurally dissimilar to amphetamine & methylphenidate
- Decreases ADHD symptoms by potentiating dopaminergic transmission
- May cause hepatitis-like liver damage

**Modafinil**
- Potentiates glutamate neurotransmission, and inhibits activity of GABA neurons
- Used in treatment of ADHD, narcolepsy and causes cognitive improvement in Alzheimer’s patients
Psycho-mimetic Drugs (Hallucinogens)

- Produce changes in thought patterns and mood.
- These drugs have the ability to induce altered states of perception similar to dreams but in the awake state.
- These drugs have no therapeutic indications*.
LSD (Lysergic acid diethylamide)

- This drug acts as a serotonin (5-HT) agonist at presynaptic receptors in the midbrain.
- Activation of the sympathetic nervous system occurs, causing pupillary dilation, hypertension, piloerection and hyperthermia.
- Hallucinations and mood alteration occur, tolerance and physical dependence may occur.
- High doses may produce long-lasting psychotic changes in susceptible individuals.
- Hallucinations may be rapidly aborted by the use of haloperidol, a major anti-psychotic agent particularly effective in the treatment of schizophrenia.
Tetrahydrocannabinol (THC)

- This agent may produce euphoria, relaxation drowsiness, impair short-term memory and **slow mental activity**.

- It decreases muscle strength and impairs skilled motor activity. It produces dry mouth, delusions, enhanced sensory activity and is an appetite stimulant.

- THC (marinol) is prescribed for the anorexia associated with HIV/AIDS and as an anti-emetic for chemotherapy patients.

- THC receptors are found on inhibitory presynaptic nerve terminals.

- THC is highly lipid soluble and it is metabolized and excreted through the biliary system.

- At high doses a toxic psychosis can develop, recent data suggests that chronic use beginning during adolescence may promote the development of schizophrenia.

- Tolerance and physical dependence can develop with chronic use.
• **Endocannabinoids**: have been identified and may act as local neuromodulators.

• **Dronabinol**: (oral THC) the appetite stimulation may last for up to 24 hours.

• **Rimonabant**: antagonist for THC-receptors used for treatment of obesity as it decrease the appetite
Phencyclidine (PCP):

- This impressive agent inhibits the re-uptake of DA, 5-HT and NE. The major action of PCP is to block the ion channels regulated by the NMDA subtype of glutamate receptor, this blocks the influx of Ca\(^{+2}\) through the channel.

- **PCP** is an analog of ketamine and causes a dissociative anesthesia and analgesia (awake but feeling no pain).

- Other effects include slurred speech, hyper-salivation, ataxia and muscular rigidity. Hostile, bizarre and violent behavior can occur, as one would expect these individuals are quite difficult to manage.
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