Drugs affecting the CNS

Major Neurotransmitters in CNS:

1. Noradrenaline → mood, B.P. regulation, wakefulness
2. Dopamine → Parkinson's, schizophrenia
3. Serotonin (5-HT) → Many functions, depression
4. Acetylcholine → Ach → dementia - Alzheimer's
5. GABA → Major inhibitory transmitter
6. Glutamate → Major excitatory transmitter

CNS drugs:
- Stimulants
- Depressants
CNS Stimulants

1. Cortical stimulants
2. Brainstem stimulants
3. Spinal cord stimulants

Cortical Stimulants

1) Psychomimetics
   - Amphetamine and related drugs
   - Cocaine
2) Psychotomimetics (Hallucinogens)
3) Methylxanthines
4) Nootropic drugs e.g. Piracetam
CNS stimulants

Examples:
Amphetamine and related drugs (khat, captagon, Ephedrine etc.)

Mechanism of action:
- Indirectly acting sympathomimetics
- Action in CNS and periphery
- Taken up by Noradrenergic neurons and cause release of NA
(Also cause release of dopamine and serotonin in the brain by similar mechanisms).

* Blocks NA reuptake, inhibits MAO & has direct effect on receptors.
Actions:

a) In the periphery:
   - Cardiovascular effects:
     - ↑ blood pressure
     - cardiac arrhythmias

b) In the CNS:
   - ↑ wakefulness
   - ↑ Alertness
   - ↓ fatigue
   - euphoria and ↑ mood
   - ↑ physical performance
   - ↓ mental performance
- Hallucinations followed by depression and fatigue, after large doses.
- ↓ appetite (causing loss of weight)
- Tolerance and psychic dependence (but no or little physical dependence)
Side effects (toxic effects):

- Insomnia
- Cardiac arrhythmias
- Dependence
- Drug abuse

Clinical uses:

- Narcolepsy
- To reduce body weight (fenfluramine is better)
- Attention – deficit hyperactivity disorder (ADHD)
Cocaine HCl

**Mechanism:**
Prevents reuptake of NA in the CNS and periphery (prolongs the action of NA).

**Actions:**
- Similar to amphetamine
- Also has local anaesthetic action.

**Side effects:**
- Similar to amphetamine
- Abused drug by sniffing and by injection
  - Sniffing leads to nasal puncture.
  - Injection → Risk of AIDS and Hepatitis.
- Abortion and premature labour in women.
- Cocaine base (Crack) is more toxic than the salt.
Clinical uses:

- Local anaesthesia (eye, nose & throat surgery)
- Eye drops cause mydriasis (used in eye examination).
Psychotomimetics

(Hallucinogens)

* Methoxylated amphetamines
  (mescaleine; dimethoxyamphetamine)
* High doses of amphetamine & analogus
* High doses of cocaine
* LSD inhibits firing of serotonergic
  neurons via stimulation of 5-HT2
  receptors
* Cannabis (marihuana and Hashish)
  contains δ-9- tetrahydrocannabinol
  (antiemetic in cancer patients)
* Nitrous oxide
  - auditory through endogenous morphine
  - Anaesthetic
* Pentazocine visual endogenous morphine
  - Analgesic

Mechanism of hallucination: via serotonin
(except Nitrous oxide and pentazocine).
- Abused drugs
- Cause tolerance and psychic dependence
Methylxanthines (theophylline, caffeine, theobromine)

Clinical uses:
- Theophylline ➔ asthma
- Aminophylline (theophylline + ethylene diamine) used in asthma
- Caffeine ➔ headache
  caffeine + ergot alkaloids ➔ migraine
- Pentoxiphylline (derivative of theobromine) for vascular disorders
Pharmacological properties:

1- Smooth muscle relaxation (esp. bronchi)
   Theophylline → most effective.
   - antiinflammatory in asthmatic lung.

2- CNS stimulatin (theophylline > caffeine).

3- Cardiovascular → Tachycardia & dysrhythmias at high doses.

4- Mild diuresis → inhibits Na⁺ reabsorption.
Mechanisms:

1. Inhibition of phosphodiesterase

   ![Diagram](image.png)

   - C-AMP + C-GMP
   - smooth muscle relaxation

2. Causes Ca\(^{++}\) release and prevents Ca\(^{++}\) depletion from cells and influx into cells.

3. Antagonism of adenosine receptors (inhibitory transmitter in CNS + autacoid in GIT)
**Adverse effects:**

- Insomnia
- Tachycardia
- Tolerance and withdrawal syndrome (headache + sleepiness)
- Reports of sudden death from I.V aminophylline.
Piracetam:
Nootropic drug (effects intellect)

M.O.A. Not clear
- Improves microcirculation in CNS
  - No central vasodilatation
  - Causes peripheral vasodilatation

Clinical uses:
- Loss of memory, vertigo, Alzheimer's disease
- Learning difficulties in children
- Chronic alcoholism and alcohol withdrawal
- Coma
adverse effects:
- few
  Nervousness
  anxiety
  sleep disturbances.
Brainstem Stimulants

(analeptics)

**Picrotoxin**: Clonic asymmetric convulsions
antagonist at postsynaptic GABA-A receptors.

**Pentylenetetrazole**: induces convulsions
Mechanism not clear
Respiratory stimulant

**Doxapram**: Respiratory stimulant
Induces convulsions at high dose
Used in recovery from general anaesthesia
Mechanism:
- Peripheral stimulation of chemoreceptors
  \[ \downarrow \]
  respiration
  \[ \uparrow \]
- Potentiates glutamate (excitatory transmitter)
Spinal cord stimulants

Strychnine:
Natural poison
Causes tonic symmetrical convulsions due to antagonism of glycine (inhibitory transmitter) of Renshaw cells in spinal cord.
Spinal Cord

Reshow cell

α-motor neuron

Ach

glycine

Skeletal muscle