CNS Stimulant DRUGS

1. Cortical stimulants

2. Brainstem stimulants

3. Spinal cord stimulants

1- Cortical Stimulants

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

1-Amphetamine and amphetamine-like drugs

Amphetamine and dextroamphetamine, together with methamphetamine and methylphenidate, comprise a group of drugs with very similar pharmacological properties. They are substrates for the neuronal uptake transporters for noradrenaline, serotonin and dopamine, and cause release of these mediators producing the acute effects described below. With prolonged use, they are neurotoxic, causing degeneration of amine-containing nerve terminals and eventually cell death. This effect is probably due to the accumulation of reactive metabolites of the parent compounds within the nerve terminals. Amphetamine, and related drugs such as methamphetamine are a group of drugs that act by increasing levels of norepinephrine, serotonin, and dopamine in the brain.
It includes prescription CNS drugs commonly used to treat attention-deficit disorder (ADD) and attention-deficit hyperactivity disorder (ADHD) in adults and children. It is also used to treat symptoms of narcolepsy and chronic fatigue syndrome. Initially it was more popularly used to diminish the appetite and to control weight.

<table>
<thead>
<tr>
<th>The main central effects of amphetamine-like drugs are:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• locomotor stimulation</td>
</tr>
<tr>
<td>• euphoria and excitement</td>
</tr>
<tr>
<td>• stereotyped behaviour</td>
</tr>
<tr>
<td>• anorexia.</td>
</tr>
</tbody>
</table>

In addition, amphetamines have peripheral sympathomimetic actions such as:

- producing a rise in blood pressure
- Inhibition of gastrointestinal motility.

In experimental animals, amphetamines cause increased alertness and locomotor activity, and increased grooming; they also increase aggressive behaviour. With large doses of amphetamines, stereotyped behaviour occurs. This consists of repeated actions, such as licking, gnawing, rearing or repeated movements of the head and limbs. These activities are generally inappropriate to the environment, and with increasing doses of amphetamine they take over more and more of the behaviour of the animal. These behavioural effects are evidently produced by the release of catecholamines in the brain, because pretreatment with 6-hydroxydopamine, which depletes the brain of both noradrenaline and dopamine, abolishes the effect of
amphetamine, as does pretreatment with α-methyldopa, an inhibitor of catecholamine biosynthesis. Similarly, tricyclic antidepressants and monoamine oxidase inhibitors potentiate the effects of amphetamine, presumably by blocking amine reuptake or metabolism.

Amphetamine-like drugs cause marked anorexia, but with continued administration this effect wears off in a few days and food intake returns to normal.

In humans, amphetamine causes euphoria; with intravenous injection, this can be so intense as to be described as 'orgasmic'. Subjects become confident, hyperactive and talkative, and sex drive is said to be enhanced.

Fatigue, both physical and mental, is reduced by amphetamine, and many studies have shown improvement of both mental and physical performance in fatigued, although not in well-rested, subjects. Mental performance is improved for simple tedious tasks much more than for difficult tasks, and

Amphetamines have been used to improve the performance of soldiers, military pilots and others who need to remain alert under extremely fatiguing conditions.

It has also been in vogue as a means of helping students to concentrate before and during examinations, but the improvement caused by reduction of fatigue can be offset by the mistakes of overconfidence.
Clinical uses:

- Appetite suppressant
- ADHD
- Narcolepsy and chronic fatigue syndrome
- Treatment-resistant depression

Along with methylphenidate, amphetamine is one of the standard treatments for ADHD. Beneficial effects for ADHD can include:

- Improved impulse control
- Improved concentration
- Decreased sensory over stimulation
- Decreased irritability and decreased anxiety.

Amphetamines are sometimes used to augment anti-depressant therapy in treatment-resistant depression.

As appetite suppressants in humans and weight loss is still approved in some countries, but is regarded as obsolete and dangerous in others because of its tendency to cause pulmonary hypertension, which can be so severe as to necessitate heart-lung transplantation.
Adverse effects:

1- **Cardiovascular:**
   - Vasoconstriction
   - Tachycardia
   - Palpitation

2- **Ear, nose, and throat:**
   - Decongestant
   - Xerostomia

3- **Eye:**
   - Mydriasis
   - Relaxation of ciliary muscle

4- **Gastrointestinal:**
   - Decreased secretions
   - Decreased peristalsis

5- **Genitourinary:**
   - Urinary retention
   - Erectile dysfunction

6- **Others:**
   - Decrease in appetite/weight loss
   - Euphoria
   - Insomnia
   - Visual disturbance
   - Aggressiveness

**Amphetamines Summary:**

- The main effects are:
  - increased motor activity
  - euphoria and excitement
  - anorexia
  - with prolonged administration, stereotyped and psychotic behaviour.
- Effects are due mainly to release of catecholamines, especially noradrenaline and dopamine.
- Stimulant effect lasts for a few hours and is followed by depression and anxiety.
• Tolerance to the stimulant effects develops rapidly, although peripheral sympathomimetic effects may persist.
• Amphetamines may be useful in treating narcolepsy, and also (paradoxically) to control hyperkinetic children (ADHD). They are no longer used as appetite suppressants because of the risk of pulmonary hypertension.
• Amphetamine psychosis, which closely resembles schizophrenia, can develop after prolonged use.

Contraindications

- CNS Stimulants
- Agitated states
- Patients with a history of drug abuse
- Glaucoma
- MAOI use

Stimulants such as amphetamines elevate cardiac output and blood pressure making them dangerous for use by patients with a history of heart disease or hypertension. Also, patients with a history of drug dependence or anorexia should not be treated with amphetamines due to their addictive and appetite suppressing properties. Amphetamines can cause a life-threatening complication in patients taking MAOI antidepressants. Amphetamine is not suitable for patients with a history of glaucoma.

Amphetamines have also been shown to pass through into breast milk. Because of this, mothers taking medications containing amphetamines are advised to avoid breastfeeding during their course of treatment.
2- Methylphenidate

Methylphenidate (MPH) is a prescription stimulant commonly used to treat Attention-deficit hyperactivity disorder, or ADHD. It is also one of the primary drugs used to treat the daytime drowsiness symptoms of narcolepsy and chronic fatigue syndrome. The drug is seeing early use to treat cancer-related fatigue. Brand names of drugs that contain methylphenidate include Ritalin (Ritalina, Rilatine, Attenta, Methylin, Penid, Rubifen.

Mechanism of action:

The means by which methylphenidate affects people diagnosed with ADHD are not well understood. Some researchers have theorized that ADHD is caused by a dopamine imbalance in the brains of those affected. Methylphenidate is a norepinephrine and dopamine reuptake inhibitor, which means that it increases the level of the dopamine neurotransmitter in the brain by partially blocking the dopamine transporter (DAT) that removes dopamine from the synapses. This inhibition of DAT blocks the reuptake of dopamine and norepinephrine into the presynaptic neuron, increasing the amount of dopamine in the synapse. It
also stimulates the release of dopamine and norepinephrine into the synapse. Finally, it increases the magnitude of dopamine release after a stimulus, increasing the salience of stimulus. The stimulants do not work paradoxically. They stimulate portions of the brain that are underactive by increasing dopamine and norepinephrine in the striatum and prefrontal cortex. An alternate explanation which has been explored is that the methylphenidate affects the action of serotonin in the brain.
Indications

1. **ADHD**
2. **Narcolepsy**
3. **Treatment-resistant depression**
4. **Appetite suppressant**
5. **Antidepressant augmentation**

Methylphenidate is a central nervous system (CNS) stimulant, reducing impulsive behavior, and facilitating concentration on work and other tasks. Adults who have ADHD often report that methylphenidate increases their ability to focus on tasks and organize their lives.

Side effects:

1. **Cardiovascular:** Arrhythmia or increase in blood pressure
2. **Endocrinal:** Appetite loss
3. **Eye:** Blurred vision
4. **Gastrointestinal:** Nausea/vomiting, abdominal pain
5. **Musculoskeletal:** Muscle twitches
6. **Neurological:** Insomnia, drowsiness, dizziness, headache
7. **Psychological:** Psychosis (abnormal thoughts or hallucinations)

Contraindications:

Use of tricyclic antidepressants: (e.g. desipramine), as methylphenidate may dangerously increase their plasma concentrations, leading to potential toxic reactions (mainly, cardiovascular effects).
suspected risks to health:

In a 2005 study, only "minimal effects on growth in height and weight were observed" after 2 years of treatment."

In February 2005, a team of researchers from The University of Texas M. D. Anderson Cancer Center led by R.A. El-Zein announced that a study of 12 children indicated that methylphenidate may be carcinogenic.

3- Methamphetamine

Methamphetamine, also known as methylamphetamine, N-methylamphetamine or desoxyephedrine, is a psychostimulant and sympathomimetic drug. It is a member of the family of phenylethylamines. The dextrorotatory (S-isomer) dextromethamphetamine can be prescribed to treat attention-deficit hyperactivity disorder, though unmethylated amphetamine is more commonly prescribed. Narcolepsy and obesity can also be treated by the aforementioned isomer under the brand name Desoxyn. It is considered a second line of treatment, used when amphetamine and methylphenidate cause the patient too many side effects. It is only recommended for short term use (~6 weeks) in obesity patients because it is thought that the anorectic effects of the drug are short lived and produce tolerance quickly, whereas the effects on CNS stimulation are much less susceptible to tolerance. It is also used illegally for weight loss and
to maintain alertness, focus, motivation, and mental clarity for extended periods of time, and for recreational purposes.

Methamphetamine enters the brain and triggers a cascading release of norepinephrine, dopamine and serotonin. To a lesser extent methamphetamine acts as a dopaminergic and adrenergic reuptake inhibitor and in high concentrations as a monamine oxidase inhibitor (MAOI). Since it stimulates the mesolimbic reward pathway, causing euphoria and excitement, it is prone to abuse and addiction. Users may become obsessed or perform repetitive tasks such as cleaning, hand-washing, or assembling and disassembling objects. Withdrawal is characterized by excessive sleeping, eating, and depression-like symptoms, often accompanied by anxiety and drug-craving. Users of methamphetamine sometimes take sedatives such as benzodiazepines as a means of easing their "come down".

Methamphetamine has the potential to cause addiction. An addiction to methamphetamine typically occurs when a person begins to use the drug as a stimulant, because of its enhancing effects on pleasure and sex, alertness and ability to concentrate. Over time, however, the effectiveness decreases, and users find that they need to take higher doses to get the same results.

Pharmacology

Methamphetamine is a potent central nervous system stimulant which affects neurochemical mechanisms responsible for regulating heart rate, body temperature, blood pressure, appetite, attention, mood and responses associated with alertness or
alarm conditions. The acute physical effects of the drug closely resemble the physiological and psychological effects of an epinephrine-provoked fight-or-flight response, including increased heart rate and blood pressure, vasoconstriction (constriction of the arterial walls), bronchodilation, and hyperglycemia (increased blood sugar). Users experience an increase in focus, increased mental alertness, and the elimination of fatigue, as well as a decrease in appetite.

The methyl group is responsible for the potentiation of effects as compared to the related compound amphetamine, rendering the substance on the one hand more lipid soluble and easing transport across the blood brain barrier, and on the other hand more stable against enzymatic degradation by MAO. Methamphetamine causes the norepinephrine, dopamine and serotonin (5HT) transporters to reverse their direction of flow. This inversion leads to a release of these transmitters from the vesicles to the cytoplasm and from the cytoplasm to the synapse (releasing monoamines in rats with ratios of about NE:DA = 1:2, NE:5HT = 1:60), causing increased stimulation of post-synaptic receptors. Methamphetamine also indirectly prevents the reuptake of these neurotransmitters, causing them to remain in the synaptic cleft for a prolonged period (inhibiting monoamine reuptake in rats with ratios of about: NE:DA = 1:2.35, NE:5HT = 1:44.5).

Methamphetamine is a potent neurotoxin, shown to cause dopaminergic degeneration. High doses of methamphetamine produce losses in several markers of brain dopamine and serotonin neurons. Dopamine and serotonin concentrations, dopamine and 5HT uptake sites, and tyrosine and tryptophan hydroxylase activities are reduced after the administration of
methamphetamine. It has been proposed that dopamine plays a role in methamphetamine induced neurotoxicity because experiments which reduce dopamine production or block the release of dopamine decrease the toxic effects of methamphetamine administration. When dopamine breaks down it produces reactive oxygen species such as hydrogen peroxide. It is likely that the oxidative stress that occurs after taking methamphetamine mediates its neurotoxicity. It has been demonstrated that a high ambient temperature increases the neurotoxic effects of methamphetamine.

Indications:

1- Attention deficit hyperactivity disorder
2- Extreme obesity
3- Narcolepsy

Methamphetamine addicts may lose their teeth abnormally quickly, a condition known as "meth mouth". This effect is not caused by any corrosive effects of the drug itself, which is a common myth. According to the American Dental Association, meth mouth "is probably caused by a combination of drug-induced psychological and physiological changes resulting in xerostomia (dry mouth), extended periods of poor oral hygiene, frequent consumption of high calorie, carbonated beverages and tooth grinding and clenching." Similar, though far less severe symptoms have been reported in clinical use of other amphetamines, where effects are not exacerbated by a lack of oral hygiene for extended periods.

Like other substances which stimulate the sympathetic nervous system, methamphetamine
causes decreased production of acid-fighting saliva and increased thirst, resulting in increased risk for tooth decay, especially when thirst is quenched by high-sugar drinks.

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.

**Clinical uses:**
- Local anaesthesia (eye, nose & throat surgery)
- Eye drops cause mydriasis (used in eye examination).

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

**2- Hallucinogens**

1- Methoxylated amphetamines (mescaline; dimethoxyamphetamine)
2- High doses of amphetamine & analogus
3- High doses of cocaine
4- L S D: inhibits firing of serotonergic neurons via stimulation of 5-HT2 receptors
5- Cannabis (marihuana and Hashish)
contains δ-9-tetrahydrocannabinol
(antiemetic in cancer patients)

3- Methylxanthines
(theophylline, caffeine, theobromine)

Mechanisms:
1. Methylxantines inhibit phosphodiesterase enzyme which convert 3,5 cyclic AMP to the inactive 5-AMP, thus increasing concentration of cyclic AMP and cyclic GMP in the tissues.
2. Xanthines inhibit adenosine receptors. This action is responsible for their Bronchodilator effect.

Pharmacological actions:
1. Smooth muscle: relaxation (esp. bronchi)
   - Theophylline most effective.
2. CNS stimulation (theophylline > caffeine).
3. Cardiovascular: Tachycardia & dysrhythmias at high doses.
4. Systemic blood vessels: Vasodilation
5. Cerebral Blood vessels: Vasoconstriction resulting in decrease in cerebral blood flow (relief hypertensive headache).
4. Mild diuresis inhibits Na reabsorp

Clinical uses:
1. Theophylline: Bronchial asthma
   - Aminophylline (theophylline + ethylene diamine) used in asthma
2. Caffeine headache
   - caffeine + ergot alkaloids migraine
3. Pentoxiphylline (derivative of theobromine) for vascular disorders
2- **Brainstem Stimulants**  
(analeptics)

1- **Picrotoxin**: Clonic convulsions  
Asymmetric  
Coordinated  
Spontaneous in origin  
intermitted  
Mechanism: GABA A receptors Antagonist.  
Now obsolete

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

3- **Doxapram**:  
- Respiratory stimulant  
- Induces convulsions at high dose  
- Used in recovery from general anaesthesia.

3- **Spinal cord stimulants**

1- **Strychnine**  
- Natural poison  
- Causes tonic convulsions  
symmetric  
uncoordinated  
reflex in origin  
continuous  
During convulsion, the body is arched in hyperextension, a posture described as **OPISTHOTONUS**.  
Mechanism: Competitive antagonism for glycine receptors