Central Nervous System Stimulants
CNS STIMULANTS

Are drugs that produce stimulation of CNS and enhancement in excitability of different portions of the brains or the spinal cord.
Classification

1. **Analeptics:** Picrotoxin, Nikethamide, Ethamiran, Pentylene tetrazole, Doxapram and Strychnine.

2. **Methylxanthines:** caffeine, theophylline, theobromine and pentoxifylline.

Central sympathomimetic agents (Psychomotor stimulants):

Amphetamine, Methamphetamine, Phentermine, Benzphetamine, Chlorphentermine, Fenfluramine, Clortermine, Phenmetrazine, Phendimetrazine, Mazindol, Methylphenidate and Pemoline.
Mono amino oxidase Inhibitors (MAOIs): Phenelzine, Isocarboxazid, Tranylcypromine, pargyline and clorgyline.

Tricyclic Antidepressants: Imipramine, Desipramine, Trimipramine Amitriptyline, Nortriptyline, Protriptyline, Doxepin and Maprotiline.

Psychedelics:
1. Indolethylamine: Bufotenine, Psilocybin, and Psilocyn.
2. Phenylethylamines: Mescaline.
3. Agents have both indolethylamine and phenyl ethylamine: (+) Lysergic acid diethylamide (LSD).
4. Dissociative agents: Phencyclidine (PCP).
5. Depressant-Intoxicant: Tetrahydrocannabinol (THC) and Euphoriant-stimulant: cocaine.
1. Analeptics

- Are drugs that used chiefly to counteract respiratory depression and coma.
- They cause stimulation of vasomotor centers, vasoconstriction and this may increase the peripheral resistance i.e. increase blood pressure.
- Analeptics used as antidote for the overdose of CNS depressants but under the control due to high degree of side effects.
- Also they stimulate emetic enter, so they may be used as emetics in case of poisoning.
Picrotoxin

A powerful CNS stimulant, used to treat the adverse effects resulting from overdoses of barbiturate and other central depressants. The margin between analeptic and convulsant dose is narrow.
Pentylene tetrazol

1,5-pentamethylenetetrazole used for the treatment of drug induced coma and as a convulsant for shock therapy.
Nikethamide

Coramine® ($N,N$-Diethyl nicotinamide) is a respiratory stimulant. It has an intermediate central effect, resembling that of the amphetamine but more potent than picrotoxin and Pentylene tetrazole.
Flurothyl "Halogenated Ether"

Indoklon® or bis (2,2,2-trifluoroethyl) ether used in place of electro-shock therapy in depressive disorders.

It is a central stimulant "convulsant".

\[ \text{CF}_3\text{-CH}_2\text{-O-CH}_2\text{-CF}_3 \]
2. Purines "xanthine derivatives"

Purines occur widely distributed among natural products (coffee). The 2,6-dihydroxylated purines or methylxanthines are:

- Caffeine.
- Theophylline.
- Theobromine.
Methylxanthines

<table>
<thead>
<tr>
<th>Compound</th>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caffeine</td>
<td>CH₃</td>
<td>CH₃</td>
<td>CH₃</td>
</tr>
<tr>
<td>Theophylline</td>
<td>CH₃</td>
<td>CH₃</td>
<td>H</td>
</tr>
<tr>
<td>Theobromine</td>
<td>H</td>
<td>CH₃</td>
<td>CH₃</td>
</tr>
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\( (E) \)
3. Psychomotor Stimulants (Sympathomimetic CNS stimulants)

Sympathomimetic agents, whose effects are manifested mainly in the periphery, a few simple structural changes in these peripheral agents produce central sympathomimetic agents that are:

1. More resistant to metabolism.
2. More non polar.
3. Better ability to cross blood brain barrier.
Neuronal Synapse - NE Mechanism

Goodman and Gilman, 9th Edition

Figure 19–1. Sites of action of antidepressants and lithium.
Amphetamine
Prototype phenylethylamine. The good, the bad, and the ugly

Methylphenidate
(Ritalin)
Used for attention-deficit-hyperactive disorder
Usually in children

Phenmetrazine
(Preludin)
Anorectic

Phendimetrazine (Plegine)
Anorectic
Structural Activity Relationship "SAR" of sympathomimetic CNS stimulants

- Our parameters are duration and potency.
- Structural requirements:

```
H       N
\    /
/     \\  \CH3
CH3

Ampetamine R= H
Methaphetamine R= CH3
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First Study: (Phenyl Ring)

Max. activity = unsubstituted by OH

Halogen → ↓ sympathomimetic activity
↑ serotonin + dopamine activity

Replacing the aromatic ring by cyclohexane → no activity

Any alkyl group → no activity

Any polar group → ↓ or no activity

OCH₃ → ↓ sympathomimetic + dopamine activity
Halogen Substituted Phenylethylamines

“The Halogen Rule”

Halogen substitutions provide for 5HT selectivity or specificity.

The halogen rule, also applies to reuptake inhibitors.

\[
\begin{align*}
\text{Cl} & \quad \text{CH}_2\text{CH} & \quad \text{NH}_2 \\
\text{4-chlorophenylethylamine} & \quad \text{5HT selective} \\
\text{CH}_3 & \quad \text{CH}_2\text{CH} & \quad \text{NH}_2 \\
\text{Phentermine} & \quad \text{DA selective} \\
\text{F}_3\text{C} & \quad \text{CH}_2\text{CH} & \quad \text{NH} & \quad \text{CH}_3 \\
\text{Fenfluramine} & \quad \text{5HT selective}
\end{align*}
\]
Second Study: (Side Chain)

2 Carbon atoms ↑ or ↓ → loss binding site
(separate the aromatic ring from N)

Unsubstituted phenylethylamine in α-position → highly metabolized by MAO and this will → no activity

α-Dimethyl group → less activity (Phentermine)

α-C has CH₃ → more potent (amphetamine)

Ethyl or propyl group at α-C → no activity
• **α-methyl phenyl amine derivatives**: They are more resistant to the metabolism → longer duration of action like amphetamine.

• The sympathomimetics like amphetamine have polarity more than peripheral amines and less metabolized, which used clinically as CNS stimulant "abuse" and anorexiants.
• α-substituted may be part of the ring → the activity retained like Phenmetrazine and methylphenidate.
• This C atom is either *dextro* or *levo* isomer, the *dextro* is more potent (D >> L).

![Chemical structure](image)

• β-Carbon either CH₂ or part of the ring, if we add OH group on β-carbon → ↓ activity.
Third Study: Terminal N amino

1° (-NH₂) or 2° (-NHR)

3° amine (-N R₂) → ↓ activity

N is 4° (-N⁺R₃) → no activity

Has group like CH₃ or CH₂

Some times it is cyclic amine or open chain

Phenmetrazine

Methylphenidate

Ampetamine R= H
Methaphetamine R= CH₃
Amphetamine Sulfate

The racemic mixture has a higher proportion of cardiovascular effects than the *dextro*-isomer. For most medical uses the dextrorotatory is preferred.
Chlorphentermine Hydrochloride

Chlorphentermine is structurally interesting because of the $p$-chloro substituent on $\alpha,\alpha$-dimethylphenylethylamine. It is an effective anorexiant with less abuse potential than dextroamphetamine.

$p$-chloro-$\alpha,\alpha$-dimethylphenethylamine hydrochloride
Benzphetamine Hydrochloride

• It’s *N*-benzyl substituted methamphetamine. The large (benzyl) *N*-substituent decrease excitatory properties.

• The compound has been observed to share mechanism of action characteristic with methylphenidate. The agent reduces appetite with fewer CNS excitatory effects than dextroamphetamine.
Methylphenidate Hydrochloride (Ritalin®)

It is a potent CNS stimulant. Indications include narcolepsy and attention-deficit hyperactive disorder ADHD.

There are two asymmetric centers in methylphenidate and four possible isomers, but evidences indicate that the \(2R,3R\) isomer of the *threo*-racemic mixture is responsible for almost all actions.
MONOAMINE OXIDASE INHIBITORS

Inhibit liver MAOs in addition to brain MAOs, thereby allowing dietary pressor amines that normally would be inactivated to exert their effects.

A number of severe hypertensive responses, sometimes fatal, have followed ingestion of foods high in pressor amines.
1. Non selective MAO A and B inhibitors:

A. Hydrazines:
- Isocarboxazid
- Isoniazid
- Nialamide
- Procarbazine
- Hydracarbazine

B. Non Hydrazines:
- Tranylecypromine
2. Selective MAO inhibitors

A. Selective MAO A inhibitors:
   • Moclobemide (reversible)
   • Pirindole
   • Toloxytamine

B. Selective MAO B inhibitors:
   • Rasagiline
   • Selegeline
They are converted by MAO to agents that inhibit the enzyme irreversibly.

Moclobemide is a reversible inhibitor of MAO-A, it is considered to be an effective antidepressant and permits dietary tyramine to be metabolized.

Moclobemide
Tricyclic Antidepressant Compounds
(and Mechanistically Related)

• Almost all of the original agents block neuronal reuptake of NE, 5-HT, and DA.

• As with the MAOIs, there is a time lag before antidepressant effect which is due:

  1. Desensitization of receptors ($\alpha_2$, $\beta$ and 5-HT$_2$).
  2. They are extremely lipophilic and, accordingly, highly tissue-bound outside the CNS.
The SARs for the TCAs

A large, bulky group encompassing two aromatic rings, preferably held in a skewed arrangement by a third central ring and a three- or sometimes two-atom chain to an aliphatic amino group that is mono methyl- or dimethyl substituted.

Fully extended *trans* conformation of the β-aryl amines. The dimethylamino compounds tend to be sedative. The mono-methyl relatives tend to be stimulatory.
As is typical of dimethylamino compounds, anticholinergic and sedative effects tend to be marked.

Metabolic inactivation proceeds mainly by oxidative hydroxylation in the 2-position, followed by conjugation with glucuronic acid.
Amitriptyline Hydrochloride

It is one of the most anticholinergic and sedative TCAs, because it lacks the ring electron-enriching nitrogen atom.

- Metabolic inactivation mainly proceeds at the benzylic 10-position. Conjugation produces excretable metabolites.
- By $N$-demethylation nortriptyline is produced, which has a less anticholinergic, less sedative, and more stimulant action than amitriptyline.
Maprotiline Hydrochloride

Ludiomil® is described as a tetracyclic antidepressant. The description is chemically accurate.

It can be viewed as a TCA with an ethylene-bridged central ring.

The compound has been noted to have stimulant properties.
Serotonin Reuptake Inhibitors

Fluoxetine
Paroxetine
Sertraline
Fluvoxamine

Serotonin reuptake inhibitors have received much favorable attention as an antidepressant.

They look like the protonated amino group, H-bonding to the ether oxygen to generate the β-aryl amino-like group with the bulge on the side.
Selective Serotonin Reuptake Inhibitors SSRI

- Citalopram
- Escitalopram

Escitalopram is the (S)-stereoisomer (left-enantiomer) of citalopram.
• Cocaine as a euphoriant-stimulant psychotomimetic, and drug of abuse amphetamine, with which it shares many biologic properties.

• At low doses, it produces feelings of well-being, decreased fatigue, and increased alertness.