Lecture 8: Central Nervous System (CNS)
# 1. Treatment of Neurodegenerative Diseases:
(Parkinson's Disease & Alzheimer disease)

<table>
<thead>
<tr>
<th><strong>I. Anti-Parkinson’s (D &amp; ACh)</strong></th>
<th><strong>II. Anti-Alzheimer’s (ACh):</strong></th>
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<tbody>
<tr>
<td>1. Levodopa Carbidop</td>
<td>1. Anticholine Esterase:</td>
</tr>
<tr>
<td>2. MAOIs:</td>
<td>*Donepezil</td>
</tr>
<tr>
<td>*Selegline</td>
<td>*Rivastigmine</td>
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<tr>
<td>*Rosagline.</td>
<td>*Galantamine</td>
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<td>3. COMT inhibitors:</td>
<td>*Tacrine</td>
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<tr>
<td>*Entacapone</td>
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<tr>
<td>*Tolcapone.</td>
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<td>4. Amantadine (antiviral)</td>
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<td>5. D- Agonists (BARPR):</td>
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<tr>
<td>*Bromocriptine</td>
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<tr>
<td>*Apomorphine</td>
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<tr>
<td>*Ropinirole</td>
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<td>*Pramipexole</td>
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<td>*Rotigotine</td>
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<td>6. Anti-Muscarinic (TBBP):</td>
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<tr>
<td>*Trihexyphenidyl</td>
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<td>*Biperiden</td>
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<tr>
<td>*Benztropine</td>
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<td>*Procyclidine</td>
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### *Neurotransmitters of the Central Nervous System (CNS):*

#### I. Biogenic Amines:
All are Excitatory except 5-HT → Excitatory/Inhibitory.

<table>
<thead>
<tr>
<th><strong>1. Acetyl Choline</strong></th>
<th>Excitatory: Involves in Arousal, Short term memory, Learning &amp; Movement (ASLM).</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2. Nor-epinephrine:</strong></td>
<td>Excitatory: Arousal Wakefulness, Mood &amp; CV regulation (AWMR).</td>
</tr>
<tr>
<td><strong>3. Dopamine:</strong></td>
<td>Excitatory: Emotions, Reward System &amp; Motor Control (ERM).</td>
</tr>
</tbody>
</table>

#### II. Amino Acids:

| **1. GABA:**            | Inhibitory:↑ Cl⁻ influx→ Hyperpolarization.                                   |
| **2. Glycine:**         | Inhibitory:↑ Cl⁻ influx→ Hyperpolarization.                                   |
| **3. Glutamine:**       | Excitatory:↑ Na⁺ influx→ Depolarization.                                      |

#### III. Neuropeptides:

| **1. Substance P:**     | Excitatory: mediates Nociception (pain) within spinal cord.                  |
| **2. Met-Enkephalin:**  | Centrally Inhibitory→ mediates analgesia.                                    |
*Synaptic potentials: CNS receptors at most synapses are coupled to ion ch.

A) **Excitatory pathways:** Excitatory post synaptic potential (EPSP): by Na⁺ entry → Depolarization.

B) **Inhibitory pathways:** Inhibitory post synaptic potentials (IPSP) by either influx of Cl⁻ or efflux of K⁺ → Hyperpolarization.

C) **Combined Effect of EPSP & IPSP:** Most neurons in CNS receive both EPSP & IPSP input.
I. Parkinson disease: ↓ of activity of inhibitory dopaminergic neurons in Substantia Nigra & Corpus Striatum parts of brain’s basal ganglia that are involved in motor control.

*Characteristics of disease:
1. Tremors & muscle rigidity.
2. Bradykinesia (Slowing of carrying out voluntary movements).
3. Postural & gait abnormalities
4. Masked face.

1st Parkinsonism: cause is unknown & ttt is palliative.
2nd Parkinsonism is due to:
1. Viral Encephalitis & Syphilis.
2. Drugs such as Phenothiazines & Haloperidol which blocks dopamine receptors in brain (Pseudoparkinsonism).
3. Toxins as Ca²⁺, Mn & Hg.

*Drugs Used in Parkinson disease (V.Imp):

A. Levodopa/ Carbidopa:
N.B. Dopamine doesn't cross BBB.
*M.O.A: [Levodopa]→dopa decarboxylase in CNS [Dopamine] "Therapeutic effect".
↓ Metabolism in GIT & Peripheral tissues [Dopamine] "Side effects"
by Dopa decarboxylase
∴ Carbidopa: dopa decarboxylase inhibitor that doesn't cross BBB so
↑ availability of Levodopa to the CNS & ↓ Severity of S.E of peripherally formed dopamine (N, V, Arrhythmia & Hypotension).
∴ ↓ dopamine dose (4-5 folds).

*Uses: Parkinson's → very effective in the 1st 3 years.
↓ After 4-5 years → Effectiveness ↓ due to ↓ in receptors
(Wearing off effect).

*Absorption & Metabolism: Taken on empty stomach (45 min before meals).
1. Meals high in protein content e.g. leucine & isoleucine compete with Levodopa for absorption (so taken 45 min before meal)
2. Antacids: rapid complete absorption of Levodopa by ↓ gastric emptying time

<table>
<thead>
<tr>
<th>*Adverse effects:</th>
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<tbody>
<tr>
<td>*Peripheral effects:</td>
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<tr>
<td>*Stimulation of Emetic center → Nausea &amp; vomiting</td>
</tr>
<tr>
<td>*Arrhythmia &amp; Hypotension.</td>
</tr>
<tr>
<td>*Mydriasis</td>
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<td>*Blood dyscariasis</td>
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<tr>
<td><strong>Diplopia</strong>: double vision.</td>
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<thead>
<tr>
<th>*CNS effects:</th>
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</thead>
<tbody>
<tr>
<td>*Visual &amp; auditory hallucinations.</td>
</tr>
<tr>
<td><em>Dyskinesia</em>: Abnormal involuntary movements.</td>
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<tr>
<td>*Depression &amp; Anxiety.</td>
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<thead>
<tr>
<th>*Interactions: (VVV.Imp)</th>
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<tbody>
<tr>
<td>1. Vitamin B6 (Pyridoxine):</td>
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<tr>
<td>*vitamin B6 is a co factor for dopa decarboxylase</td>
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<tr>
<td>∴ peripheral breakdown of Levodopa ∴ ↓ effect.</td>
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<tr>
<td>2. MAO-Inhibitors</td>
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<tr>
<td>Hypertensive crisis</td>
</tr>
<tr>
<td>3. Antipsychotic drugs &quot;Neurolyptics&quot;:</td>
</tr>
<tr>
<td>Dopamine blockers → Parkinsonian syndrome</td>
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<td>4. Antihypertensives &amp; TCAs:</td>
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<td>↑ Hypotensive effect.</td>
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<td>5. Patients with Glaucoma</td>
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<tr>
<td>↑ IOP</td>
</tr>
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<td>6. Malignant melanoma:</td>
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<tr>
<td>Dopamine activation → Melanin pigment:</td>
</tr>
<tr>
<td>∴ 1. Activation of Malignant Melanoma: ttt by interferon α</td>
</tr>
<tr>
<td>2. Saliva &amp; urine are stained brownish color. ***</td>
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### B. Indirect Acting Dopamine agonists:

1. **MAO-Inhibitors: Selegline "deprenyl" & Rosagline.**

*MOA:* Selectively inhibits MAO₈ which metabolizes dopamine but doesn't inhibit MAOA which metabolizes N.E & Serotonin.

*Uses:* As adjunct with Levodopa/ Carbidopa (in wearing off phenomena) → ↑ action & ↓ dose of them.

*S.E:* 1. At low doses → No HTN crisis, but **At High doses** loses selectivity → HTN Crisis.
2. Selegline → **Meth Amphetamine** → Amphetamine → **Insomnia** if taken after mid afternoon.
3. Rosagline > Selegline 4-5 in potency.
4. Rosagline is not metabolized to amphetamine.

*Drug Interactions:* Avoid Use with Mepridine (Opiate), Dextromethorphan, SSRIs & Dextroamphetamine.

2. **Amantadine (Antiviral):**

*MOA:* 1) ↑ Dopamine release
2) Blocking Cholinergic Receptors
3) Inhibit N-methyl-D- aspartate (NMDA) receptor of glutamine.

*S.E:* 1. Anticholinergic S.E (dry mouth, Urinary retention)
2. Hallucinations 3) ↑ doses → Toxic psychosis
*Tolerance:* develops within 6-12 months → ↑ dose or add another drug.
N.B *Drug has little effect on Tremors but is more effective than Anticholinergics against Rigidity & Bradykinesia. 
*Anticholinergics→↑ Amantadine effect.

*More effective for tremors & Rigidity more than Bradykinesia.
*Play only adjunct role in Parkinsonism ttt.
*S.E: 1) dry mouth 2) ↓ GIT motility 3) Urinary retention.
4) C.I in glaucoma.
*Amantadine ↑ anticholinergic S.E.

C. Direct Dopamine agonists:

<table>
<thead>
<tr>
<th>Bromocriptine &amp; Pergolide:</th>
<th>Pramipexole &amp; Ropinirole: (oral)</th>
</tr>
</thead>
</table>
| 1. Ergot derivatives:→ Vasoconstriction  
↓Pulmonary  
& Retroperitoneal Fibrosis. | 1. Non Ergot derivatives: → No V.C  
↓No Fibrosis. |
| 2. They have duration of action > Levodopa so it’s effective in pts exhibiting Fluctuations in their response to Levodopa. | |
| 3. Less risk of developing dyskinesia. | |
| 4. They are effective in pts with advanced Parkinson disease complicated by motor Fluctuations & dyskinesia but they are ineffective in patients who have shown no therapeutic response to Levodopa. | |

*Pergolide is 100 x more potent than Bromocriptine.
*C.I: Psychiatric pts  
Ulcer pts.  
*They may delay the use of Levodopa in early Parkinsonism.  
*Pramipexole→renal excretion so Cimetidine reduce renal clearance→ ↑ t1/2 by 40 %.  
*Ropinirole→ Hepatic metabolism & Floroquinolone inhibit metabolism.

*Apomorphine→ I.V in severe & advanced cases  
*Rotigotine→ transdermal (once daily).

D. Catechol-O-Methyl Transferase/COMT inhibitors: Tolcapone or Entacapone

Levodopa [COMT 3-O- methyl dopa]  
(competes with Levodopa for active transport in CNS).

*COMT is minor pathway for Levodopa metabolism but when peripheral
dopamine decarboxylase inhibited by Carbidopa → significant amount of 3-O methyl dopa is formed.

<table>
<thead>
<tr>
<th>TOLCAPONE</th>
<th>ENTACAPONE</th>
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<tbody>
<tr>
<td>1. They reduce the symptoms of wearing off phenomena (in pts on Levodopa).</td>
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<tr>
<td>2. Penetrate BBB &amp; inhibit COMT in CNS</td>
<td>2. Doesn't penetrate CNS.</td>
</tr>
<tr>
<td>3. Long duration of action (3 doses/day)</td>
<td>3. Short duration of action (8 doses/day).</td>
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<tr>
<td>4. S.E: As Levodopa/ Carbidopa including dyskinesia.</td>
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<tr>
<td>Hepatic necrosis**</td>
<td>Doesn't exhibit this toxicity &amp; largely replaced Tolcapone.</td>
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</table>

*D.I: 1) Potentiates Levodopa  
2) Avoid MAOI.

II. Alzheimer Disease: (↓↓ Ach) ttt by (↑ Ach):

*Features: 1) Accumulation of Senile plaques "B-amyloid accumulation".  
2) Loss of cholinergic neurons.  
3) Formation of neurofibrillary tangles.

*ttt:

** A) Anticholine esterase:

↓ Non-Competitive: DONEPZIL, Tacrine, RIVASTIGMINE.  
↓ Competitive: GALANTAMINE.  
*↑ Ach by inhibiting Acetyl choline esterase enzyme.  
*May cause: tremors, bradycardia & diarrhea.  
*Tacrine → causes hepatotoxicity.

** B) NMDA receptor antagonist: MEMANTINE

*Overstimulation of glutamate receptors → neurodegeneration.  
*Memantine → partial blockade → ↓ Ca²⁺ influx but doesn’t cause inhibition.  
∴ Memantine activation for NMDA receptors for vital action

* Always used in combination with Ach Esterase inhibitors.
III. Anxiolytics & Hypnotics:

<table>
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<th>1. ANXIOLYRICS:</th>
<th>2. OTHER ANXIOLYRICS:</th>
<th>3. HYPNOTICS:</th>
<th>4. OTHER HYPNOTICS:</th>
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<tr>
<td><strong>BENZODIAZEPINES</strong></td>
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<tr>
<td>Flurazepam (F)</td>
<td>Buspiron</td>
<td>Amobarbital</td>
<td>Antihistamines</td>
</tr>
<tr>
<td>Quazepam (Q)</td>
<td>Hydroxyzine</td>
<td>Thiopental</td>
<td>Ethanol</td>
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<tr>
<td>Estazolam (E)</td>
<td>Antidepressants</td>
<td>Phenobarbital</td>
<td>Chloral Hydrate</td>
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<tr>
<td>Clonazepam (C)</td>
<td></td>
<td>Secobarbital</td>
<td>Esczopiclone</td>
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<tr>
<td>Lorazepam (L)</td>
<td></td>
<td>Phentobarbital</td>
<td>Zoleplone</td>
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<td>Diazepam (D)</td>
<td></td>
<td></td>
<td>Zolpidem</td>
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<td>Oxazepam (O)</td>
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<td>Ramelteon</td>
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<tr>
<td>Clorazepate (C)</td>
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<td>Triazolam (T)</td>
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<td>Temazepam (T)</td>
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<tr>
<td>Alprazolam (A)</td>
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<tr>
<td>Chlordiazepoxide (C)</td>
<td>Used in alcohol withdrawal.</td>
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**BENZODIAZEPINES' ANTAGONIST:**

Flumazenil

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A. ANXIOLYRICS: علاج التوتر/مرض العصر

**I. BENZODIAZEPINES:**

*MOA: Binds to GABA₃ receptors → Cl⁻ influx → Hyperpolarization. ((↑The frequency of channel opening) → Enhance inhibitory effect of GABA).

*Actions: 1) ↓ Anxiety. 2) Muscle Relaxation. 3) Sedative & Hypnotic 4) Anterograde Amnesia 5) Anti-convulsant.

*Uses:
1. Anxiety disorders: *Clonazepam, Lorazepam & Diazepam (CLD) are used for long term ttt. *Alprazolam → D.O.C in panic disorders & cause withdrawal symptoms.

2. Muscular disorders: *Diazepam is used for muscle spasm.

3. Sedative: *Triazolam, Flurazepam & Temazepam (TFT) are used to induce sleep. *Esczopiclone, Zolepzone & Zolpidem (other hypnotics) → don't affect sleep stages → preferred.


5. Anticonvulsants: *Diazepam & Lorazepam are used to ttt Grand mal & Status Epilepticus

*Notes: 1) Chlordiazepoxide: used for ttt delirium tremors (shaking due to withdrawal from alcohols)
2) Triazolam: is used to induce sleep → used intermittently due to withdrawal symptoms.
3) Flurazepam: Used for both inducing sleep & ↓ Awakening.
4) Temazepam: used to ↓ awakening frequency only.

*Duration of Action of BDZs:

<table>
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<tr>
<th>Long Acting (1-3 days):</th>
<th>Intermediate Acting (10-20 hrs):</th>
<th>Short Acting (3-8 hrs):</th>
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</thead>
<tbody>
<tr>
<td>Clorazepate C</td>
<td>Alpazolam A</td>
<td>Oxazepam</td>
</tr>
<tr>
<td>Chlordiazepoxide C</td>
<td>Estazolam E</td>
<td><em>Triazolam</em> (Produces short term amnesia (Anterograde amnesia) in some pts).</td>
</tr>
<tr>
<td>Diazepam D</td>
<td>Lorazepam L</td>
<td></td>
</tr>
<tr>
<td>Flurazepam F</td>
<td>Temazepam T</td>
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<tr>
<td>Quazepam Q</td>
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</table>

*Dependence: Physiological & physical dependence can develop.
*Withdrawal symptoms are more common with short acting (Triazolam & Oxazepam) than long acting (Flurazepam).

*Precautions should be taken with:
patients having Liver disorder or Narrow angle glaucoma.
*They are C.I in pregnancy & Lactation.

II. Benzodiazepines antagonist: Flumazenil.
*I.V only with short t1/2.
∴ Frequent injection may be necessary to eliminate action of long acting BDZs.

III. Other Anxiolytics:

A. Buspiron (Buspar®): *M.O.A: 1) 5-HT1A receptors (acting on inhibitory presynaptic neurons) → ↓ 5-HT release. 2) 5-HT2A 3) DA2 Receptors.
*↑ Prolactin, ↑ Growth hormone but causes Hypothermia (2↑ & 1↓).
*No action on muscle, sedation, convulsions with no tolerance.
(Antiolytic with no other CNS depressant activities).
B. Hydroxyzine & Meprobamate:
*Antihistamines in ttt of Nausea & Vomiting.
*No tendency for habituation → Used prior to dental procedures.

C. Antidepressants:
SSRIs, TCAs, Venlafaxine & Dulexetine & MAOIs are used.

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**B. Sedatives & Hypnotics**

I. Barbiturates:
*M.O.A:
1. Interact with GABA_A receptors → prolong opening of Cl^- channels →
Hyperpolarization (act on GABA receptor but at different site of BDZs).
2. No tendency for habituation → used prior to dental procedures.

*Duration of action & uses:

<table>
<thead>
<tr>
<th><em>Duration of action:</em></th>
<th><em>Drugs:</em></th>
<th><em>Uses:</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Short acting (3-8 hrs):</td>
<td>Pentobarbital Secobarbital Amobarbital (PAS)</td>
<td>*Sedative &amp; Hypnotic *Patient feel tired after waking up → Drug hangover.</td>
</tr>
<tr>
<td>Ultra-short acting (20 min):</td>
<td>Thiopental Na Methohexital Na</td>
<td>Anesthesia induction</td>
</tr>
</tbody>
</table>

Q) Barbiturates have been largely replaced by BDZs → why?
1. Physical dependence.
2. Tolerance.
3. Severe withdrawal symptoms (confusion, anxiety, agitation, restlessness, seizures & Cardiac arrest).
5. Poisoning → Why?
Barbiturates: low doses for sedation, ↑ dose for hypnosis, ↑ dose for anesthesia.
Overdose → suppress chemoreceptor response to CO₂ → Resp. depression.
∴ Central CV Depression

Coma & Death.

Q) ttt of Overdose → How?
1. Artificial respiration
2. Stomach evacuation.
3. Hemodialysis.
   *a. IV Sodium bicarbonate injection → why?
      because it is a weak acid, pKa 7.4 so alkalinization of urine → excretion.
   *b. IV Mannitol injection (osmotic diuretic).

**Notes:**
*Phenobarbital Na + Chloramphenicol → ppt of barbituric acid.
*Metabolism of Barbiturates: by oxidation then conjugation with sulfate (SO₄⁻).
*Put (T) Or (F): Phenobarbitone Na is acidic (F). Alkaline.

**II. Other Hypnotics:**

A. Zolpidem:
   *Acts on subset of Benzodiazepine receptors BZ
   *No anticonvulsant, muscle relaxant properties.
   *S.E: nightmares, dizziness & GIT upset.
   Onset of action < 30 min

B. Zaleplone: siesta ®
   *Similar hypnotic effect as Zolpidem with less effect on psychomotor & cognitive function compared to Zolpidem & BDZ.
   *Rapid elimination & short t½ (1 hr).

C. Esczopiclone: Night calm®
   *As Zolpidem & Zaleplone.
   *S.E: Unpleasant taste, headache & dry mouth.

D. Ramelteon:
   *Agonist for Melatonin receptors MT₁ & MT₂.
   *ttt of Insomnia in which falling asleep is the 1st complaint.
   *S.E: Dizziness, fatigue & ↑ Prolactin levels

E. Chloral hydrate:
   *Onset of action 30 min & duration is 6 hrs.
   *S.E: GIT irritation, unpleasant taste & Epigastric pain.

F. Ethanol:
   *Ethanol dehydrogenase → Acetaldehyde dehydrogenase → Acetate
   *Cause liver disease, cardiomyopathy with heavy users.

**Long term treatment for alcoholism:**
1. Carbamazepine is the D.O.C for ttt of withdrawal seizures.
2. Disulfiram causes flushing, tachycardia & hyperventilation (unpleasant effects due to accumulation of acetaldehyde).
3. Naltrexone (Opiate agonist) oral or IV for ttt of alcohol dependence.
4. **Acamprosate**: used for the same reason.

**Withdrawal symptoms of alcohol include:**
1. ↑ BP, ↑ Pulse, ↑ respiration & ↑ sweating.
2. Tremors, agitation & hallucination.
3. Anorexia & sleep disturbances.
Therapeutic disadvantages of benzodiazepines
- The BDZs may disturb intellectual functioning, memory, and learning.
- The BDZs have potential for dependence and withdrawal symptoms may occur.
- Withdrawal effects can result in rebound insomnia.

Therapeutic advantages of benzodiazepines
- Use in treatment of general anxiety disorder.
- DOC in generalised, anxiety, and panic disorders.
- As agents of choice in panic disorders.

Other agents
- Buspirone: chronic anxiety symptoms of irritability and hostility.
- Does not potentiate CNS depressants like alcohol.
- Low potential for addiction.
- Gradual withdrawal over six months.
- Show no withdrawal effects.
- Exhibit minimal rebound insomnia. A little and no tolerance occurs prolonged use.

Barbiturates
- Rapid onset of action.
- Prone to tolerance, drug metabolizing enzymes, and physical dependence, and show severe withdrawal symptoms.

BDZ antagonist: Flumazenil
IV. CNS Stimulants:

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<tr>
<th>Psychomotor Stimulants:</th>
<th>Hallucinogens:</th>
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<tbody>
<tr>
<td>*Amphetamine.</td>
<td>*Lysergic acid diethylamide (LSD).</td>
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<tr>
<td>*Dextroamphetamine</td>
<td>*Phencyclidine (PCP).</td>
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<tr>
<td>*Lisdexamphetamine</td>
<td>*Tetrahydrocannabinol (THC).</td>
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<tr>
<td>*Modafinil</td>
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<tr>
<td>*Armodafinil</td>
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<td>*Atomoxetine</td>
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<td>*Methylphenidate</td>
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I. CNS Stimulants:

A. Methyl Xanthines
(Theophylline، Theobromine، و Caffeine: قهوة، شاي، and كاكاو):

*M.O.A: 1) ↑ CAMP, CGMP by inhibition of phosphodiesterase.
2) Blockade of Adenosine receptors.

*Actions:

A) CNS
1) 1-2 cups of caffeine → ↓ fatigue & ↑ mental alertness.
2) 12-15 cups (1-5g) → Anxiety & tremors
3) 2-5g → stimulation of spinal cord.

B) C.V.S +ve chronotropic & inotropic effect.

C) Diuretic effect: ↑ diuresis

D) ↑ HCl secretion Avoided in peptic ulcer.

*Adverse Effects:
1) Moderate doses → Insomnia & anxiety.
2) High doses → Emesis & Convulsions.
3) Lethal doses → 10 g Caffeine.

B. Nicotine:

*M.O.A: Low doses → Ganglionic stimulation High doses → blockade.

*Actions:

A) CNS:
*Low doses → Euphoria, arousal & relaxation.
*High doses → respiratory paralysis & hypotension.
*Appetite suppressant.

B) Peripheral effects:
*↑ HR & ↑ BP
*↑ V.C so C.I with angina.
*↑ Motility of bowel.

BUT at High doses → reversal due to Ganglionic blockade

*N.B: Withdrawal symptoms are restlessness, irritability, headache & Insomnia.
*Buspiron (Antidepressant) can ↓ craving to cigarettes.

C. Varenicline:

*Partial agonist of neuronal nicotinic Ach receptors in the CNS.
*Used in the management of smoking cessation.
**D. Cocaine:**

*بيسموه السكر البني عشان يبحرق*

*M.O.A:* Inhibit reuptake of Monoamines (NE, Dopamine & Serotonin).

:*↑ Monoamine.*

*Actions:*

1) CNS:

*Euphoria & ↑ mental alertness.*

*High doses ➞ Tremors, Convulsions & Respiratory depression.*

2) CVS:

*↑ HR, ↑ PR & ↑ BP (by inhibiting baroreceptors reflux which buffers HTN).*

3) Hyperthermia:

May be fatal (Morbidity ↑ in hot weather). (imp)

*Uses: Used only as local anesthetic during eye, ear, nose & throat surgery.*

N.B: Cocaine is destrified & demethylated to benzoylecgonine which is used as a detector in urine for cocaine users.

*Adverse Effects: 1) HTN, Anxiety, ↑HR*

2) Depression (following euphoria).

3) Agitation ➞ ttt with BDZ & Phenothiazines

4) Seizures & CV arrhythmia ➞ Diazepam & propranolol.

N.B: Rapid but Short lived effects are achieved following I.V injection of Cocaine or by smoking the free base from the drug "Crack".

**E. Amphetamine: (Dextroamphetamine/ Methamphetamine)**

"Speed"

*M.O.A:* ↑ Release of Catecholamines from its stores.

*Actions:* 1) CNS: ↑ Alertness & ↓ fatigue.

2) CVS: ↑ HR, ↑ PR.

*Uses:* 1) ADHD "Hyperkinesia disorder" ➞ Also Atomoxetine is used.

Lisdexamphetamine GIT Metabolism Dextroamphetamine ➞ Pt attention, ↓ better function at school.

2) Narcolepsy (sleeping during day) ➞ Also Modafinil & Armodafinil are used.

*Adverse Effects:* 1) Amphetamine psychosis ➞ Suicidal tendency.

ttt with Chlorpromazine & Haloperidol.

2) T.C, V.C & HTN.

3) GIT ➞ Nausea, Vomiting & Anorexia.

4) CI: HTN, Glaucoma, CV disease & Hyperthyroidism.

**F. Methyl phenidate:**

*M.O.A:* Inhibit Dopamine uptake (As Cocaine).

*Used in ADHD & Narcolepsy as Amphetamine.

*S.E:* 1) Abdominal pain. 3) Anorexia.

2) Nausea. 4) Nervousness.

**Attention deficit hyperactivity disorder**
II. Hallucinogens:

A. Lysergic à diethylamide (LSD): "Stamps" الطوابع، العلبي، الخيال.Uzar al-hałūsah
*Agonist for 5-HT₁ & 5-HT₂.
*Haloperidol & Neuroleptics block action of LSD.

B. Tetrahydrocannabinol (THC) = Marijuana → CB₁ agonist. الحشيش
*Available as Dronabinol which is used as appetite stimulant or to ↓ severe emesis in chemotherapy.
*Rimonabant عكس الحشيش → CB₁ Antagonist → treat obesity.

C. Phencyclidine (PCP):
*Inhibit uptake of NE, D, 5-HT (As cocaine).
*As Ketamine causes dissociative anaesthesia (loss of pain but conscious).
*↑ Doses → Coma but eyes remain opened!
  العين مفتوحة و لكنه تائه.
V. **Opioids** = **Narcotic analgesics.**

<table>
<thead>
<tr>
<th>Strong Agonist:</th>
<th>Med./Low</th>
<th>Mixed</th>
<th>Antagonists</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl</td>
<td>Codeine.</td>
<td>Nalbupine.</td>
<td>Naltrexone</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>Propoxyphene.</td>
<td>Pentazocin.</td>
<td>Naloxone</td>
</tr>
<tr>
<td>Morphine</td>
<td></td>
<td>Buprenorphine.</td>
<td>Nalmefene</td>
</tr>
<tr>
<td>Mepridine</td>
<td></td>
<td>Butorphanol.</td>
<td></td>
</tr>
<tr>
<td>Heroin</td>
<td></td>
<td></td>
<td>Other Analgesics:</td>
</tr>
<tr>
<td>Oxycodone</td>
<td></td>
<td></td>
<td>Tramadol</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Tapentadol.</td>
</tr>
</tbody>
</table>

*Activation of Opioids receptors: \( \mu, \kappa, \delta \)*

- \( \downarrow \downarrow \) Ca\(^{2+} \) influx \( \rightarrow \) release of excitatory NT e.g. Glutamate.
- \( \uparrow \downarrow \) K\(^{+} \) efflux \( \rightarrow \) response (post synaptic) to the excitatory NT.

*Distribution of Opioid receptors:*

1. **Brain stem** \( \rightarrow \) Resp., Cough, N, V, BP, Pupil dilation & stomach secretion.
2. **Medial Thalamus** \( \rightarrow \) deep pain that is poorly loc. & em. infl.
3. **Spinal Cord** \( \rightarrow \) attenuation of painful afferent stimuli.
4. **Hypothalamus** \( \rightarrow \) Neuro-endocrine secretions.
5. **Limbic System** \( \rightarrow \) No analgesia but affect behavior.
6. **Periphery** \( \rightarrow \downarrow \) Ca\(^{2+} \) influx, \( \downarrow \) excitation.
7. **Immune cells.**

**I. Strong Agonist:**

1. **Morphine:**
   *M.O.A:* 1) Hyperpolarization nerve cells, inhibit nerve firing & presynaptic release of N.T.
   2) \( \kappa \)- receptors in lamina I & II of dorsal horn in spinal cord.
   3) \( \downarrow \) Release of substance p which modulates pain in the spinal cord.
   *Actions:*

   1. Analgesia: *\( \uparrow \) Pain threshold in spinal cord.*
      *Alterating pain perception in the brain.*
   2. Euphoria: *
   3. Resp. depression: *\( \downarrow \) Sensation of resp. center neurons to CO\(_2\)*
      It is the main cause of death due to Opioid overdose.
   4. Depression of Cough reflex: *Used as antitussive (Codeine).*
   5. Miosis: *Pin point pupil (\( \mu&\kappa \)) \( \rightarrow \) important in diagnosis.*
   6. Emesis: *Stimulates CTZ*
   7. G.I.T: *Constipation (\( \downarrow \) motility & \( \uparrow \) tone of intest. circular smooth M.
      \( \therefore \) Diphenoxylate is used to ttt diarrhea.*
   8. CVS: *\( \uparrow \) CSF this is due to resp. depression & CO\(_2\) retention.*
      \( \therefore \) C.I with pts having brain injury.
10. Hormonal Actions: *↓ Gonadotropin releasing H, ↓Corticotrophin RH, 
↓ Luteinizing & FSH, ↓ Test & cortisol. (6 ↓)
*↑ Growth h, Prolactin & ADH. (3 ↑)

11. Labor: Prolong 2nd stage of labor (↓ Uterine contraction).

*Therapeutic Uses:
1) Analgesia→ may be used with sleep inducing drugs.
2) Diarrhea. 3) Cough.
4) ttt of acute pulmonary oedema→ (I.V) ↓ dyspnea.

2. **Mepridine "Pethidine"****: μ & κ

*metabolism Nor-mepridine (active & toxic effects not reversed by Naloxone).

*Actions:
1) Resp. depression.
2) IV → ↓ PR, ↑ B. flow, ↑ H.R.
3) Doesn't cause pin-pupil, however dilate Atropine like action
   (anticholinergic like action).

*Therapeutic Uses: 1) Analgesia (not for long term ttt due to Nor-mepridine).
2) Cough & Diarrhea * NOT EFFECTIVE.
3) Opioid used in Obstetrics (less effect on uterine S.M).
4) Urinary retention less than morphine.

*Adverse Effects:
1) Anxiety, Tremors (due to Nor-mepridine) & muscle twitches.
2) Large doses→ dilatation of pupil.
3) Anti-muscarinic activity→ dry mouth & blurred vision.

3. **Methadone**: μ–receptors.

*Actions:
1) Analgesia= Morphine (Orally active).
2) Miotic. t 1/2 =24 hrs.
3) Resp. depression.
4) Constipation.

*Therapeutic Uses: 1) Analgesia
   2) Controlled withdrawal of depend. users of Heroin & Morphine.
   (Withdrawal symptoms are milder & more protracted (days-weeks).

*Adverse Effects: Can produce physical dependence.

4. **Fentanyl**: (both transdermal & transmucosal prep.)
1) Potency= 100 fold Analgesic effect of Morphine.
2) Duration (15-30 min).
3) Post-operative & during labor.
4) Cardiac surgery→ No effect on Myocardial Contractility.
5) Fentanyl patches→ hypoventilation→ death.
6) Pupillary constriction. 7) Transmucosal prep.→ In ttt of cancer pts.

Sufentanil> Fentanyl> Alfentanil> Remifentanil (in potency).

5. **Heroin "Diacetyl morphine"**: Synthetic Morphine diacetylation Heroin (3 folds > potency)/ Lipophilic→ cross
BBB → More Euphoria ∴ cause dependence.

**6. Oxycodone**: semi-synthetic derivative of morphine.
*In combination with Aspirin or Acetaminophen → moderate to severe pain.
*Abuse (SR Formulas) → ingestion of crushed tablets → death.

---

**II. Moderate Agonists:**

| **1. Codeine:** | 1. Less analgesic effect than Morphine.  
2. Antitussive Effect.  
3. Less euphoria.  
4. Rarely dependence.  
5. Cough preparation (Codeine ↔ Dextromethorphan) → No analgesic effect & Low potential for abuse.  
*Actions:* 1) Analgesia.  
2) Euphoria  
3) Sedation.  
4) Dry cough.  
5) Constipation. |
| **2. Propoxyphene:** | It has 2 Isomers: Levoisomer → Anti-tussive effect.  
Dextroisomer → Analgesic effect = 1/2 Codeine.  
*Produce Nausea, Anorexia & Constipation.  
*Toxic doses: 1) Respiratory depression → tt with Naloxone.  
2) Cardiotoxicity → No solution. |

---

**III. Mixed Agonist- Antagonist & Partial agonists:**

| **1. Pentazocine:** | *κ → agonist  
Moderate pain.  
*μ & σ → antagonist  
-Less euphoria.  
-Doesn't antagonize the resp. depression caused by Morphine & can cause withdrawal symptoms. |
| **2. Buprenorphine:** | *Partial agonist.  
*Naive pts → Morphine like actions.  
*Opioid dependent → withdrawal symptoms.  
-Used in ↓ withdrawal symptoms & ↓ duration.  
-Tablets → cause Opioid dependence.  
-IV → moderate to severe pain.  
*Adverse effects: Respiratory depression which is not reversed by Naloxone. |
| **3. Nalbuphine & Butorphanol:** | As Pentazocine.  
*Less psychosis-like symptoms.  
*Less effect on BP & heart.  
*No oral forms. |

---

**IV. Others: Tramadol & Tapentadol:**
*Activates μ receptors.  
*Inhibits Serotonin/NE reuptake.  
*Less respiratory depression.
*Shouldn't be used with SSRIs/TCAs/MAOIs/Quinidine.
* Naloxone can partially reverse effect of Tramadol.

V. Opioid Antagonists:

<table>
<thead>
<tr>
<th>Opioid Antagonist</th>
<th>Effect/Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Naloxone:</td>
<td>*30 sec (I.V) → reverse respiratory depression of Heroin. *t\textsubscript{1/2} = 60-100 min.</td>
</tr>
<tr>
<td>2. Naltrexone:</td>
<td>*Longer t\textsubscript{1/2} (Oral) → blocks 48-hrs heroin effect. Used in combination with Clonidine &amp; Buprenorphine.</td>
</tr>
<tr>
<td>3. Nalmefene:</td>
<td>S.C/I.M t\textsubscript{1/2} = 8-10 hrs.</td>
</tr>
</tbody>
</table>
Relative potential for physical dependence on commonly abused substances:

- Caffeine
- Alcohol
- Cocaine
- Amphetamines
- Hallucinogens
  - LSD
  - Cannabis
  - Phencyclidine
- CNS Depressants
  - Ethanol
  - Barbiturates
  - Benzodiazepines
- Opioids
  - Morphine
  - Heroin

Low  High
# VI. Antidepressants:

<table>
<thead>
<tr>
<th>SSRI</th>
<th>SNRI</th>
<th>Atypical antidepressants</th>
<th>TCAs:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Escitalopram</td>
<td>Duloxetine</td>
<td>Mirtazapine</td>
<td>Amitriptyline</td>
</tr>
<tr>
<td>Citalopram</td>
<td>Venlafaxine</td>
<td>Nefazodone</td>
<td>Nortriptyline</td>
</tr>
<tr>
<td>Sertraline</td>
<td></td>
<td>Bupropion</td>
<td>Protriptyline</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td></td>
<td>Trazadone</td>
<td></td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td></td>
<td></td>
<td>Doxapine</td>
</tr>
<tr>
<td>Paroxetine</td>
<td></td>
<td></td>
<td>Anoxapine</td>
</tr>
</tbody>
</table>

**I. Selective Serotonin Reuptake Inhibitor (SSRIs):**

**Escitalopram Citalopram Sertraline Fluoxetine Fluvoxamine Paroxetine**

*M.O.A: 1) Selectively inhibit Serotonin uptake with no effect on Epinephrine.*
2) Inhibit little effect on M<sub>1</sub> & H<sub>1</sub> receptors Unlike TCAs
∵ No S.E as dry mouth, postural hypotension & blurred vision.

*Citalopram & Fluoxetine are racemic mixtures.*
*Escitalopram is the pure S-enantiomer of Citalopram.*
*Actions occur after 2 weeks & maximum effect after 12 weeks.

*Uses: 1) D.O.C in depression.*
2) **Fluvoxamine→OCD** (Obsessive compulsive disorder)**.*
3) **Fluoxetine→Bulimia Nervosa**.

*Pharmacokinetics:*
*t<sub>1/2</sub> range from 16-36 hrs*
*Fluoxetine is different in: a) t<sub>1/2</sub>= 50 hrs*
* b) Metabolite is 5-norfluoxetine (potent as the parent).*

*Inhibit CYP450.*
*Sertraline is the only one which is affected by food (↑ absorption).*

*They should be administered in the morning due to their stimulatory effects.*

**Adverse effects:**

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Sexual dysfunction:</td>
<td>↓ Libido &amp; delay ejaculation. <em>Can be replaced by Bupropion &amp; Mirtazapine.</em></td>
</tr>
<tr>
<td>3. Use in Children:</td>
<td>May ↑ suicidal thoughts (1 in each 50 child).</td>
</tr>
<tr>
<td>4. Overdose:</td>
<td>Doesn't cause Cardiac arrhythmia but ↑ seizures. May cause Serotonin syndrome (Hyperthermia &amp; muscle rigidity).</td>
</tr>
<tr>
<td>5. Discontinuation:</td>
<td><em>Abrupt cessation may cause symptoms with short acting &amp; inactive metabolites. (∵ Fluoxetine is the lowest risk to cause these symptoms.</em></td>
</tr>
</tbody>
</table>

---

22
II. Serotonin Norepinephrine Reuptake Inhibitors (SNRIs) Duloxetine & Venlafaxine.

*Inhibit uptake of both serotonin & NE.
*Effective in relieving symptoms of blockade, muscle aches & peripheral neuritis which may accompany depression (SSRIs don't ↓ these symptoms).
*Used when SSRIs are ineffective.
*No action on M₁, α₁ & H₁ receptors (unlike TCAs).

a. Venlafaxine: *(Effexor)®*  
* t₁/₂ = 11 hrs.  
*S.E: Nausea, dizziness, sexual dysfunction, ↑ BP & ↑ HR

b. Duloxetine:  
*Not recommended in pts in ESRD or hepatic dysfunction.  
*S.E as Venlafaxine.

III. Atypical Anti-depressants:

a. Bupropion:  
*Inhibit uptake of dopamine & NE (DNERI).  
*↓ Cravings to cigarettes.  
*Doesn’t cause sexual dysfunction.  
*Used as antidepressant & for seasonal affective disorders.

b. Mirtazapine:  
*Block α₂ receptors  NE & Serotonin.  
*Blocks 5-HT₂ receptors.  Sedating due to antihistaminic action.  
*Can be used with depressed pts having difficulty in sleeping.  
*Causes weight gain  used in pts with weight loss & depressed.  
*Doesn’t cause sexual dysfunction.

c. Trazadone & Nefazodone:  
*block 5-HT₂ receptors.  
*S.E: 1) Trazadone  priapism (persistent & painful erection of penis).  
2) Nefazodone  Hepatotoxicity.

IV. Tricyclic Antidepressants (TCAs): Low Therapeutic Index

AmitriptylineNor tryptilline  Protryptyline / TrimipramineImipramine  
ClomipramineDesipramine / Doxapin Amoxapine/ Maprotilline.

*Inhibit Uptake of Serotonin & NE. (SNRIs)
*Maprotilline & Desipramine are selective inhibitors for NE.
*Elevate mood, ↑ mental alertness & ↑ physical activity.
*Should be withdrawn gradually to ↓ withdrawal symptoms & cholinergic rebound effects.

*Uses: 1) Depression & Panic disorders.  
2) Imipramine  bed wetting in children> 6 years.  
3) Amitriptyline  Migraine headache & neuropathic pain (unknown)

*Adverse effects:

<table>
<thead>
<tr>
<th>Due to M-receptors:</th>
<th>α₁ receptors:</th>
<th>H₁-receptors:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Dry mouth</td>
<td>1) Orthostatic hypotension.</td>
<td>1) Sedation</td>
</tr>
<tr>
<td>2) Constipation</td>
<td>2) Reflex T.C</td>
<td>2) Drowsiness.</td>
</tr>
<tr>
<td>3) Urinary retention.</td>
<td>4) Blurred vision</td>
<td></td>
</tr>
</tbody>
</table>
**TCAs should be cautiously used with manic depression pts even in their depression state as they switch to manic behavior.**

*Interactions:

1) **With Ethanol or CNS depressants:** TCAs: → Toxic sedation.

2) MAOIs: → ↑ Hyperthermia, ↑ HTN & Convulsions.

3) **Indirect acting adrenergic drugs:** block their effect by preventing them from reaching site of action.

4) **Direct α₁-agonist:** Potentiate action by ↓ removal.

---

**V. Monoamine Oxidase Inhibitors (MAOIs):**

**Selegline, Phenelzine, Tranylcypromine.**

*Inhibit MAO in brain, liver & Gut.

*Have an Amphetamine like stimulant effect → may produce agitation & insomnia

*Uses: 1) pts who are unresponsive or allergic to TCAs.
   2) pts with ↓ psychomotor activities → MAOIs are stimulants (Analpeptics**).
   3) Atypical depression (labile mood, rejection sensation & appetite disorders).

*Last line ttt due to their drug-drug interactions.

**Adverse effects:**

1) Headache.
2) Tachycardia.
3) HTN.
4) Nausea.
5) Seizures.
6) Stiff neck.

*Pts should be advised to avoid Tyramine containing food (Marmite, mature cheese).

*MAOIs are C.I with SSRI & a wash out period of 2 weeks should occur except for Fluxetine it should be 6 weeks.

*M AOI + Bupropion → Seizures.

---

**VI. ttt of Mania & Bipolar:** alteration bet. mania & depression.

Lithium salts used for manic-depressive pts in the ttt of manic episodes

**(Mood Stabilizers).**

*S.E: 1) Polyurea 2) Polydipsia 3) Polyphagia 4) GIT distress. 5) Sedation. Can be treated with Amiloride (K⁺- sparing diuretic).

*Adverse effects to lithium rarely occur when serum Li<1.5 mEq/L.

-Mild to moderate toxic reactions may occur at level 1.5-2.5 mEq/L

-Severe toxicity → seen above these levels.

*Pt is advised to drink 8-12 glasses of water/day → why?

because this will stabilize Li levels & prevent Li toxicity.

*Pts should NOT restrict Na⁺ in diet (avoid diuretics) → or toxicity.

*In monitoring Serum Li levels, blood samples are usually drawn just prior to taking a dose.

*Other approved mood stabilizers:

Carbamazepine, Valproic acid & Lamotrigine.
VII. Antipsychotic Drugs= Neuroleptics:

<table>
<thead>
<tr>
<th>1st Generation : Typical</th>
<th>2nd Generation: Atypical (↓D, ↑Ach)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOW POTENCY</td>
<td>HIGH POTENCY:</td>
</tr>
<tr>
<td>*Chlorpromazine</td>
<td>*Fluphenazine</td>
</tr>
<tr>
<td>*Prochlorperazine</td>
<td>*Haloperidol</td>
</tr>
<tr>
<td>*Thioridazine</td>
<td>*Pimozide</td>
</tr>
<tr>
<td></td>
<td>*Thiothixene</td>
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<td></td>
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</tbody>
</table>

*Schizophrenia*: is due to ↑D, ↑5-HT & ↓Glutamate.

**Antipsychotic drugs**:

*M.O.A.*

1) D-receptors blocking activity:

- $D_1$, $D_2$ → Excitation
- $D_2$, $D_3$, $D_4$ → Hyperpolarization.
- *Chlorpromazine* → $D_2$ (Typical) → mesolimbic system.
- *Clozapine* → $D_4$ (Atypical) (EPS) counteract → (Levodopa-Amphetamine-Bromocriptine).

2) Serotonin ($5HT_2A$):

- Atypical drugs have 5 HT$_2$ receptor antagonist action.

<table>
<thead>
<tr>
<th>Traditional Antipsychotics:</th>
<th>Atypical Antipsychotics:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mainly blocks dopamine (R)</td>
<td>Act more on Serotonin (5-HT$_2$) R.</td>
</tr>
<tr>
<td>Improve +ve symptoms but worsen –ve symptoms</td>
<td>Improves both +ve &amp; -ve symptoms.</td>
</tr>
<tr>
<td>More EPS &amp; Hyperprolactinemia</td>
<td>Less EPS &amp; Hyperprolactinemia.</td>
</tr>
</tbody>
</table>

**Neurolyptics:**

<table>
<thead>
<tr>
<th>Cholinergic:</th>
<th>α- adrenergic</th>
<th>Dopamine</th>
<th>Serotonin</th>
<th>H$_1$- receptors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thioridazine</td>
<td>Chlorpromazine</td>
<td>Haloperidol</td>
<td>Clozapine</td>
<td>Chlorpromazine</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td></td>
<td>Thiothixene</td>
<td>Risperidone</td>
<td>Clozapine</td>
</tr>
</tbody>
</table>
### *Actions:*

1) **Antipsychotic actions:**

- **+ve symptoms** → hallucination & delirium (All typical & Atypical).
- **-ve symptoms** → Apathy, Aphedonia & Impaired cognitive function.

*Not all only Clozapine may reduce –ve symptoms.

2) **Extrapyramidal effects (EPS):**

*Includes: Parkinson-like symptoms, Tardive dyskinesia & dystonia.

Atypical antipsychotics → less likely to cause EPS.

3) **Antiemetic:**

*Thioridazine, Chlorpromazine, Clozapine & Olanzepine.

Dry mouth (except Clozapine: ↑ saliva), blurred vision, ↓ urination & constipation.

4) **Anti-muscarinic:**

*Haloperidol & Prochlorperazine → Chemotherapy.

*Atypical doesn’t have antiemetic effect.

5) **Others:**

- **α–blocker** → Orthostatic hypotension.
- **Poikilothermia** → Temp. varies with environment.
- **H1–blockers** → Clozapine & Chlorpromazine (Sedation).
- **Sexual dysfunction.**

### *Therapeutic Uses:*

1) **ttt of Schizophrenia:**

- **Typical** → +ve
- **Atypical** → -ve

*Clozapine is reserved for pts unresponsive to other Neurolyptics.

S.E: Blood Dyscariasis

2) **Prevention of Nausea & Vomiting:**

*Prochlorperazine → for drug induced vomiting

3) **Others:**

- a) Tranquilizers.
- b) In combination with Narcotic analgesics for ttt of Chronic pain in severe anxiety.
- c) For Tics of Tourette's disorder → Pimozide/ Haloperidol/ Risperidone.

### *Adverse Effects:*

1) **EPS:**

- **a) Anticholinergic** → Benztropine.
- **Thioridazine** → has Anti-M. effect → less EPS.
- **Haloperidol & Fluphenazine** → No M. effect → ↑ EPS.

- **b) Atypical:**

- **Risperidone** → 1st line (Paliperidone).
- **Clozapine** → last choice → Bone marrow depression, CV, Seizures.

**ttt of EPS**: Reserpine, BZDs, Valproic à, Baclofen & Vit E.

2) **Tardive dyskinesia:**

*Due to blockade of D2 receptors.

*↑ no of D- receptors that are sensitized as compensatory mechanism making the receptor supersensitive to dopamine.

**Tardive dyskinesia**: May be irreversible even upon stopping the drug.

3) **Neurolyptic Malignant syndrome:**

Muscle rigidity, fever, unstable BP.

**ttt of Neurolyptic malignant syndrome**: Dantrolene & Bromocriptine.
**VIII. Epilepsy:**

*It is produced by abnormal excessive discharge of cerebral neurons. (Detected by ECG).*

<table>
<thead>
<tr>
<th>BB CD EFG LLO PPP TTZ or EFC GLLO BB PPP TTZ</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ethosuximide- Felbamate- Carbamazepine- Divalproex</strong></td>
</tr>
<tr>
<td><strong>Gabapentin- Lamotrigine- Levetiracetam- Oxacarbazepine-</strong></td>
</tr>
<tr>
<td><strong>Barbiturates- Benzodiazepines- Phenytoin- Pregabalin- Primidone-</strong></td>
</tr>
<tr>
<td><strong>Topiramate- Tiagabine- Zonisamide.</strong></td>
</tr>
</tbody>
</table>

**EF CD GLLO BB PPP TTZ**

<table>
<thead>
<tr>
<th><strong>Barbiturates:</strong></th>
<th><strong>Hydantoins:</strong></th>
<th><strong>Succinimides:</strong></th>
<th><strong>Oxazolidinediones:</strong></th>
<th><strong>BDZs:</strong></th>
<th><strong>Miscellaneous:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenobarbital</td>
<td>Phenytoin</td>
<td>Ethosuximide</td>
<td>Paramethadione</td>
<td>Clonazepam</td>
<td>Lamotrigine</td>
</tr>
<tr>
<td>Primidone</td>
<td>Mephenytoin</td>
<td>Methsuximide</td>
<td>Trimethadione</td>
<td>Diazepam</td>
<td>Felbamate</td>
</tr>
<tr>
<td>Mephobarbital</td>
<td>Ethotoin</td>
<td>Phensuximide</td>
<td></td>
<td></td>
<td>Gabapentin</td>
</tr>
<tr>
<td></td>
<td>Fosphenytoin</td>
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<td>Carbamazepine</td>
</tr>
</tbody>
</table>

**Classification of Epilepsy:**

**1] Partial:** *involve a portion of the brain (part of one lobe of one hemisphere) *

*consciousness is preserved.

**A] Simple:**

*Patient doesn’t lose consciousness*  
*Abnormal activity in one limb or group of muscles.*

**B] Complex**

**Partial**  
**Seizures:**  
-Complex sensory hallucination  
-Mental disturbance  
-Motor dysfunction➔chewing movement /diarrhea/urination  
-Consciousness may be altered

**2] Generalized:** *Immediate loss of consciousness*

*Involves both hemispheres

**A] Tonic-Clonic**  
**[Grand-mal]:**  
➔Loss of consciousness.  
Alteration between Tonic (continued contraction) Clonic phases(rapid contraction and relaxation) phases.

**B] Absence**  
**[Petit-mal]:**  
-3-5 years ➔puberty  
-brief self limiting loss of consciousness  
-stares/rapid eye blinking

**C] Myoclonic:**  
muscle contraction may re occur for several minutes  
after awakening and exhibit brief jerks of limbs.

**D] Febrile:**  
-3 months-5 years. ➔fever  
-short duration tonic clonic

**E] Status Epilepticus:**  
-Two or more seizures without recovery between attacks With full consciousness.  
-Partial or generalized /convulsive or non convulsive  
-Life threatening➔emergency
**Aim of ttt:** 1) Block initiation of the electric discharge from the focal area e.g. Na⁺ Ch. blockers as phenytoin.
2) Prevent spread of abnormal electric discharge to adjacent brain area by:
   a) **Enhancement of GABA** (inhibitory transmission).
   b) **Inhibit** Excitatory transmission (Glutamate).
   c) **Ca²⁺ ch. blockers** → ↓ spread by ↓↓ release of excitatory transmission.

**Drug Choice:**

<table>
<thead>
<tr>
<th>Newly diagnosed epilepsy</th>
<th>1st Choice:</th>
<th>Next choices:</th>
<th>Vagal stimulation:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First-choice drug</strong></td>
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<tr>
<td>● Choose drug appropriate for the patient's type of seizure.</td>
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<tr>
<td>● Consider toxicity of the agent.</td>
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</tr>
<tr>
<td>● Consider characteristics of the patient.</td>
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<tr>
<td>● Gradually titrate the dosage to that which is maximally tolerated and/or produces optimal seizure control.</td>
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<tr>
<td>Seizures persist</td>
<td>Seizure free</td>
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<td></td>
</tr>
<tr>
<td><strong>Second-choice drug</strong></td>
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<tr>
<td>● The second drug is titrated to a therapeutic level that controls seizures before tapering and discontinuing the original antiseizure agent.</td>
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<tr>
<td>● If the first drug is associated with significant adverse effects, it should be tapered while the second drug is added.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seizures persist</td>
<td>Seizure free</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Type of Epilepsy:**

1) **Partial**
   a. Simple or Complex:  LLT Rest/ Z ✓
   b. Elderly: Lamotrigine Gaba/ Carba ✓

2) **Generalized**
   1) Absence: DL Ethus-Topiramate ✗
   2) Myoclonic: DL Benz Topir- Lamo ✗
   3) Tonic Clonic: LLT D & Z ✓
   4) Status Epilepticus: Benz-Pheny Lbarbiturates ✗

3) **Epilepsy syndrome:**
   a. Benign rolandic: GL LTD ✗
   b. Infantile spasms (West syndrome): ACTH-Vigab. Z ✗
   c. Lennox gastaut: DLT Felbamate-Z ✓
## Anti-epileptic Drugs:

<p>| 2) Carbamazepine: LME Inducer, can potentiate its own metabolism | → Reduces the propagation of abnormal impulses in the brain by blocking Na channels -used in partial and generalized tonic clonic seizures -trigeminal neuralgia and bipolar disease - hyponatremia with elderly -shouldn’t be used in absence -→ will increase seizures S.E Cause NSIADH -→ exam question |
| 3) Divalproex: | → combination between Valproic acid and sodium Valproate -used in partial and generalized epilepsy -teratogenicity M.O.A → Na channel blockade/ blockade of GABA transaminase and action on the T type of Ca channel |
| 4) Ethosuximide: | → inhibit propagation of abnormal impulses in the brain by inhibiting T-type of Ca channels. -used in generalized absence |
| 5) Felbamate: | M.O.A →- block Na channels -block Ca channels -GABA agonist -(NMDA)glutamate antagonist Used in Lennox-Gastaut due to high risk of Aplastic anemia and hepatic failure. |
| 6) Gabapentine: not metabolized so can be used in liver failure. | → analog of GABA -partial seizures and post-herpetic neuralgia -well tolerated by elderly |
| 7) Lamotrigine: | → block Na and Ca channels -used in partial seizures/generalized/absence and Lennox-Gastaut -Valproic acid increase concentration by 50% -well tolerated by elderly |
| 8) Levetiracetam: | → in partial seizures, tonic clonic and Myoclonic |
| 9) Oxcarbazepine: | → Na channel blocker -Used in partial seizures |
| 10) Phenobarbital: | → enhancement of inhibitory effect of GABA -used in status epilepticus and is only considered for chronic therapy when the patient is refractory to other drugs due to adverse effects and Cytochrome P 450 inducing effect |
| 11) Phenytoin and Fosphenytoin: | → block Na channels / at high doses Ca channel blockade -partial and generalized tonic clonic / status epilepticus -Gingival hyperplasia in elderly/peripheral neuropathy and osteoporosis -can cause nystagmus (oscillation of the eye ball) -Fosphenytoin → I.M &amp; I.V while phenytoin cause tissue damage &amp; necrosis |
| 12) Pregabalin: | → bind to alpha 2 and delta site of Ca channel -→ inhibit excitatory effect -partial seizures / Neuropathic pain(diabetic and herpes) -drowsiness, blurred vision and weight gain |
| 13) Primidone: | Has 2 active metabolites 1-phenobarbital 2-phenylethylmalonide -used for patients refractory to other drugs -→ S.E |
| 14) Tiagabine: | GABA uptake inhibitor -partial seizures -Post marketing sum -→ increase epilepsy in normal ones. |</p>
<table>
<thead>
<tr>
<th></th>
<th><strong>Topiramate:</strong></th>
<th><strong>Zonisamide:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>15)</td>
<td>M.O.A: 1-1-Na channels blocker</td>
<td>M.O.A -(\rightarrow) 1-Na channels blocker</td>
</tr>
<tr>
<td></td>
<td>2-L type Ca channel</td>
<td>2-T type Ca channels blockers</td>
</tr>
<tr>
<td></td>
<td>3-carbonic anhydrase inhibitor</td>
<td>3-carbonic anhydrase inhibitor</td>
</tr>
<tr>
<td></td>
<td>4-binding to GABA A receptors -(\rightarrow) increase Cl channel opening</td>
<td>-partial seizures</td>
</tr>
<tr>
<td></td>
<td>-partial and generalized/migraine</td>
<td>-partial and generalized/migraine</td>
</tr>
<tr>
<td></td>
<td>-somnolence, weight gain, ataxia, renal stones, hyperthermia</td>
<td>-kidney stones, oligohidrosis, increase in body temp</td>
</tr>
</tbody>
</table>
**IX. Anesthetics:**

<table>
<thead>
<tr>
<th>Benzodiazepines I.V:</th>
<th>Barbiturates:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relieve anxiety</td>
<td>Sedation</td>
</tr>
<tr>
<td>e.g. Midazolam or Diazepam</td>
<td>e.g. Phenobarbital</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Antihistamines:</th>
<th>Antiemetics:</th>
<th>Anticholinergic:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevent allergic reactions e.g. Diphenhydramine.</td>
<td>Prevent aspiration of stomach contents &amp; postsurgical nausea &amp; vomiting. e.g. Ondansetron</td>
<td>Prevent bradycardia &amp; fluid secretion into respiratory tract. e.g. Scopolamine or Atropine.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Opioids I.V:</th>
<th>Muscle relaxants:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Provide analgesia e.g. Fentanyl &amp; Sufentanyl</td>
<td>Facilitate intubation &amp; relaxation. e.g. Vecuronium, Atricuronium &amp; Succinyl choline</td>
</tr>
</tbody>
</table>

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**Stages of Anesthesia:** V.I

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>How to overcome?</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Analgesia</td>
<td>Loss of pain sensation</td>
</tr>
<tr>
<td>II</td>
<td>Excitement</td>
<td>Delirium &amp; Combative behavior</td>
</tr>
<tr>
<td>III</td>
<td>Surgical Anesthesia</td>
<td>Surgery proceeds during this stage.</td>
</tr>
<tr>
<td>IV</td>
<td>Medullary paralysis</td>
<td>Respiratory center depression→ death.</td>
</tr>
</tbody>
</table>

**A. Induction Of Anesthesia:** How to overcome stage II?
By using anesthetics with rapid onset of action:
e.g. I.V→ Thiopental Na, Methohexital Na.
Inhalation→ Halothane or Sevoflurane (for children without I.V access).

**B. Maintenance of anesthesia:**
By administration of volatile anesthetics + Opioids
minute to minute control of anesthesia analgesics…. why?
Coz inh. anesthetics aren't good analgesics.

**C. Recovery:**
Due to redistribution rather than metabolism.
I. General Anesthetics:

A. Inhalation:
Used primarily for Maintenance of anesthesia after administration of I.V agent.

*Common Features:
1. Non flammable & Non explosive.
2. Decrease Cerebrovascular resistance → increase perfusion of the brain.

*M.O.A:
They enhance binding of GABA to its receptor → Greater entry of Cl⁻ → Hyperpolarization → ↓ neural excitability.

*Potency:
Def: The Median alveolar Conc. [MAC]
MAC: it is the end tidal conc. of anesthetic gas needed to eliminate movement among 50% of patients.
MAC: is usually expressed as conc. of the gas in the mixture.
- MAC = Median effective dose [ED₅₀] of the anesthetic.
- Potency α 1/MAC.
- ↑ Lipid solubility → ↓ conc. of anesthetic required to produce anesthesia → ↑ potency.
Halothane > Nitrous oxide in potency.

*Uptake & Distribution of inhalation anesthetics:
. The partial pressure of gas at the respiratory pathway is the driving force that moves the gas into → alveolar space → blood → brain & other body parts.

. Steady state is achieved when the partial pressure in body parts is equal to that in the inspired mix.

*The time required to attain steady state depend on:
1) Alveolar wash in: replacement of normal lung gases with inspired mix.
   *Time required for this step → directly proportional to functional residual capacity of the lung.
   → Inversely proportional to ventilatory rate.
   → Independent on gas physical properties.

2) Anesthetic uptake: it depends on:
   a) Solubility in the blood "depend on gas physical properties"
      blood/ gas partition coefficient = Total amount of gas in blood.
      Equilibrium btn inhaled anesthetic & blood.
      ↑ Blood solubility → High amount of gas & long time required to raise arterial blood pressure & reach equilibrium → ↑ time of induction & recovery.
**Halothane-Enflurane-Isoflurane-Sevoflurane-Desflurane-Nitrous oxide.
   ↑ Blood solubility
   ↑ Blood / gas partition coefficient.
   ↑ Time of induction & recovery.
b) Cardiac output:
\[ \downarrow \text{Cardiac output} \rightarrow \text{Slow delivery of anesthetic.} \]

c) Alveolar to Venous partial pressure gradient of anesthetic.

3) Effect of different tissue types on anesthetic uptake:

<table>
<thead>
<tr>
<th>Tissue Types</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain, Heart, Liver, Kidney &amp; Endocrine glands:</td>
<td>Highly perfused tissues (\rightarrow) rapidly attain a steady state with partial pressure of anesthetic in the blood.</td>
</tr>
<tr>
<td>Skeletal muscles:</td>
<td>Poorly perfused &amp; have large volume (\rightarrow) (\uparrow) time to reach steady state.</td>
</tr>
<tr>
<td>Fat:</td>
<td>Poorly perfused &amp; High capacity to store very lipid soluble anesthetics (\rightarrow) (\uparrow) time to reach steady state.</td>
</tr>
<tr>
<td>Bone, Ligaments &amp; Cartilage:</td>
<td>Poorly perfused + low capacity to store anesthetics (\rightarrow) No effect on anesthetics</td>
</tr>
</tbody>
</table>

4) Wash out:

A. Halogenated Hydrocarbons:
1. They are weak analgesics so used with opioids or nitrous oxide.
2. Vagomimetic \(\rightarrow\) bradycardia.
3. They produce conc. dependant Hypotension so Phenyl ephrine is given or Methoxamine.
4. Malignant Hyperthermia as well as Succinyl choline.
   - In very small percentage of patients.
   - Due to dramatic \(\uparrow\) in Mycoplasma \(\text{Ca}^{2+}\).
   - Dantrolene is given as the anesthetic mixture is withdrawn.
5. Cause Hepatitis:
   - Halothane: 1:10,000 individual \(\rightarrow\) 50% of them die of hepatic necrosis.
   - Isoflurane: 1:500,000 individual (low incidence).

B. Nitrous Oxide (laughing gas):
   a) Potent analgesic but weak general anesthetic:
      - 30% Nitrous oxide + oxygen \(\rightarrow\) analgesia for dental surgery.
      - 80% \(\rightarrow\) can't produce anesthesia so used with halogenated HCs.
   b) Rapid induction & recovery:
      - Nitrous oxide + Halogenated HCs \(\rightarrow\) rapid intake of Nitrous oxide \(\rightarrow\) Concentration of Halogenated HC in alveoli (2nd gas effect).
      - Within closed body parts Nitrous oxide increase volume \(\rightarrow\) causing pneumothorax or \(\uparrow\) pressure in sinuses.
      - Retard oxygen uptake during recovery \(\rightarrow\) Diffusion Hypoxia.
   c) No Muscle relaxant properties.
**It is the **Safest anesthetic** but at least 20% oxygen must be administered simultaneously.

<table>
<thead>
<tr>
<th>Halothane:</th>
<th>Enflurane:</th>
<th>Isoflurane:</th>
<th>Sevoflurane:</th>
<th>Desflurane:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metab: Trifluoroethanol+ Br(^-) → fever followed by anorexia, nausea &amp; vomiting especially in females.</td>
<td>F(^-) → excreted by kidney so C.I in patients with renal failure.</td>
<td>Little metabolism(\rightarrow) little F(^-)</td>
<td>(\rightarrow) F(^-) (\rightarrow) C.I in renal failure.</td>
<td>Degradation is minimal(\rightarrow) toxicity is rare.</td>
</tr>
<tr>
<td>1. Relative uterine muscle(\rightarrow) can be used in obstetrics.</td>
<td>Potent muscle relaxant (Curare- like effect)</td>
<td>Dilate Coronary vessels(\rightarrow)↑ blood flow &amp; O(_2) consumption by heart(\rightarrow) Useful in pts with ischemic heart disease.</td>
<td>Induction of children anesthesia.</td>
<td>Rapid onset so used for anesthesia for outpatient surgery.</td>
</tr>
<tr>
<td>2. Not hepatotoxic in children &amp; have pleasant odor(\rightarrow) induction of children anesthesia.</td>
<td>3. Relax bronchioles(\rightarrow) asthma pts.</td>
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</tr>
<tr>
<td>*Cause cardiac arrhythmia. *↑ Cardiac sensitivity to Catecholamines.</td>
<td>Causes CNS excitation at twice MAC(\rightarrow) C.I in seizure pts.</td>
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Causes CNS excitation at twice MAC\(\rightarrow\) C.I in seizure pts.  

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Have low volatility so given by vaporizer.
### B. Intravenous:

<table>
<thead>
<tr>
<th></th>
<th>THIOPENTAL</th>
<th>ETOMIDATE</th>
<th>KETAMINE</th>
<th>PROPOFOL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction of anesthesia</td>
<td>Not analgesic</td>
<td>Not analgesic</td>
<td>Analgesic</td>
<td>Not analgesic</td>
</tr>
<tr>
<td><em>C.I:</em></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>1) Hypovolemic or shock patient due to hypotension.</td>
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<tr>
<td>2) Asthmatic patient due to cough &amp; laryngospasm.</td>
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<tr>
<td><em>Adv:</em></td>
<td>No effect on heart &amp; circulation so only used for patients with coronary disease or Cardiovascular dysfunction.</td>
<td><em>C.I:</em> Hypertension or stroke patients.</td>
<td>*Less depressant effect than volatile anesthetics on CNS-evoked potentials as somatosensory evoked potentials so it is suitable for spinal tumors resection surgery in which somatosensory evoked potentials are monitored to assess spinal cord function.</td>
<td></td>
</tr>
</tbody>
</table>

### II. Local Anesthetics:

**Procaine, Lidocaine, Tetracaine, Bupivacaine**

- Bupivacaine: cardiotoxic.
- Procaine: allergic reactions.