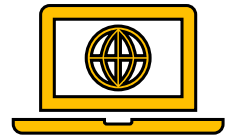
PC
Pharmacology Concepts
By Rajesh Choudhary

CNS Pharmacology



Website

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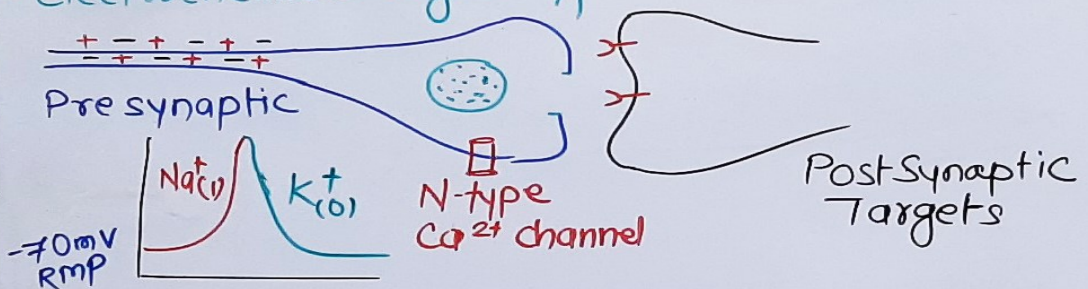
Pharmacology 3 | U 3

CNS PHARMACOLOGY / PATHOLOGY

Neurohumoral Transmission – Transfer of a nerve impulse from presynaptic to postsynaptic target by means of a endogenous humoral agent (NTs)

- Electrochemical Signaling –



Neurotransmitter :– are the endogenous chemicals that transmit signals across a synaps from one neuron to another neuron or target cells and regulate the physiology of postsynaptic cells. Criteria for NTs —

1. Should be present on Nerve end on Synaptic Vesicle
2. should be release on stimulation of the nerve
3. Metabolic enzyme for NT should also present on same neuron
4. Every NT has specific target Receptor

Types of NTs –

1. Amino acid – (i) Excitatory – Glutamate, Aspartate
   (ii) Inhibitory → GABA, Glycene
2. Amines – Dopamine, Nor-Ep., Serotonin (5HT)
3. Peptides – Vasopressin, Sometostatin, Neurotensin, Enkephalines, Endorphine, Dynorphin
4. Others – Acetyl cholin, Nitric oxide, Histamine

Neuropeptides → Neuromodulators
→ Sub P, Neuropeptide Y, VIP, enkephalin

NTs & Specific Role in CNS

NTs	Functn	Disorders
Dopamine (D1 to D5 R)	Extrapyridial Effect	Parkinson
	Behavioral –	Psychosis
	↓ Prolactin Sec	Galactorrhoea
	CTZ Stimulatn	Vomiting
	Control GH Sec	Acromegali
5HT (5H1-5HT7)	Mood, behavioral, Temp, pain, etc	Mania Depression Hallicination Anxiety, Seizure, Hypnotic-sedative ↓ Hyper-reflexia
GABA (GABA A - GABA C)	Inhibitory NT (–) CNS activity	
Glycene (GR)	↓ CNS activity	
Glutamate (NMDA)	Excitatory NT	– Epilepsy
Nor-Ep	Reward System ↓ mood	– Depression, mania
Ach	Behavioral, Memory	Alzhiemer
	EPS	Parkinson

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NEUROTRANSMITTER METABOLISM

Amino Acids

Glutamine —(Glutaminase / Glu. Synthase)→ Glutamate —(Glu. α decarboxylase)→ GABA

Glutamate + Glyoxylate —(Transaminase)→ α-oxoglutarate + Glycene

GABA —(GABA Transaminase)→ Succinic Semialdehyde → Succinate → Oxaloacetate

Biogenic Amines

Tyrosine —(T. Hydroxylase)→ DOPA —(decarboxylase)→ Dopamine —(β-hydroxylase)→ Norepinephrine —(N-methyl Transferase)→ Epinephrine

- Metabolised by - MAO & COMT (ANS')

Tryptophane —(hydroxylase)→ 5-hydroxy tryptophane —(decarboxylase)→ 5-Hydroxy Tryptamine (Serotonin) —(MAO, ADH)→ 5hydroxy indol acetic acid

Histamine

L-Histidine —(decarboxylase)→ Histamine

Histamine —(N-me Transferase)→ N-me histamine

Histamine —(diamine oxidase)→ Imidazole acetic α

Acetylcholine –

choline + Acetyl CoA —(choline acetyl transferase)→ Ach + CoA

Nitric Oxide (NO)

L-Argenine —(NO Synthase; NADPH, O_2)→ Nitric Oxide + L-Citrulline

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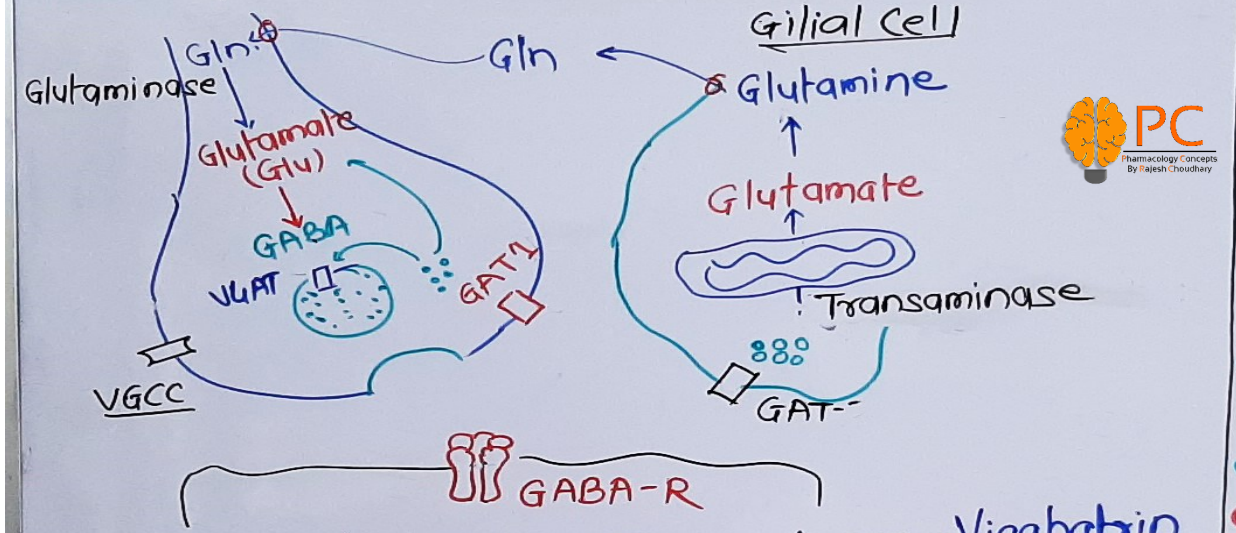
GABA Receptor Pharmacology

GABA – γ-Amino Butyric acid (Major Inhibitory NT)

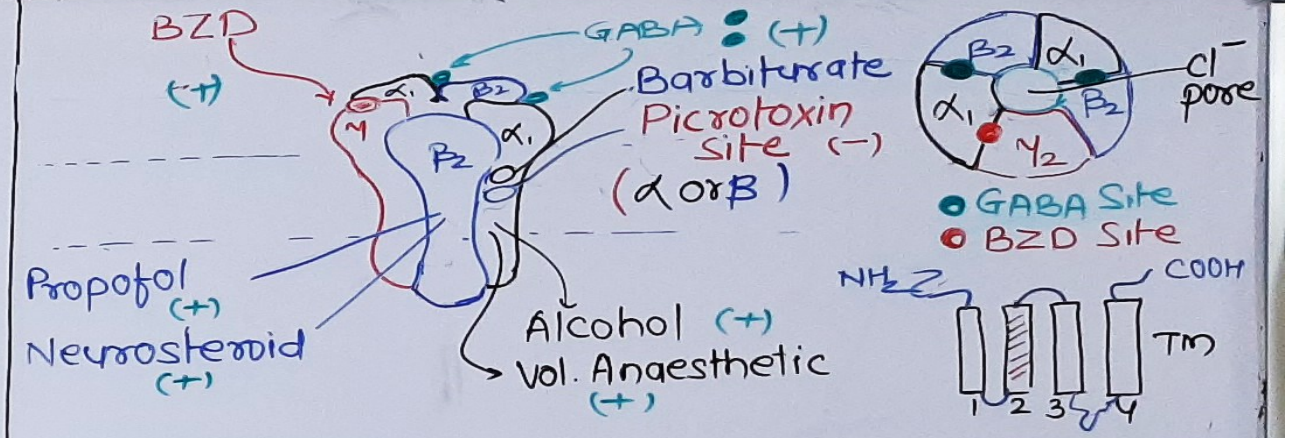


GAT —x— Tigabin , GABA-Transaminase – Vigabatrin

Receptors – $GABA_A R$, $GABA_B R$, $GABA_C R$

$GABA_A$ Receptor

- Ionotropic / Ligand Gated ion channel (Cl^-) – Hyperpolarize
- Effect – IPSP (Inhibitory post synaptic potential) – ↓ –70mV
- Structure → Pentameric Transmembrane Receptor having – 5-Subunit ($*B_2\alpha_1 B_2\alpha_1 \gamma_2$) → Anticlock
- Subunits – α(1-6), β(1-3), γ(1-3), δ, ε, π, θ, *ρ(1-3) → $GABA_C R$
- Distribution :– CNS, Placenta, Immune cells, Liver, Endocrine tissue



- GABA Agonist → GABA, Muscimol, Gaboxadol, Isoguavacin, Taurine, Progabide
- GABA Antagonist → Bicuculline, Gabazine
- BZD-R Agonist → Benzodiazepens
  - ↳ Facilitate GABA actⁿ & ↑ Frequency of opening
- BZD Antagonis – Flumazenil
- BZD Inverse Agonist → β-Carboline (DMCM)
- Picrotoxin (Non competitive GABA Antagonist)
- Barbiturates (Allosteric GABA Agonist)
  - ↳ prolong GABA action & open Cl^- channel
- (+) Neurosteroides → Alphaxalone (Steroidal Anesthetic) pregnanolone, Alloprenandone
  - ↳ They facilitate GABA actⁿs ↑ channel opening time and Frequency

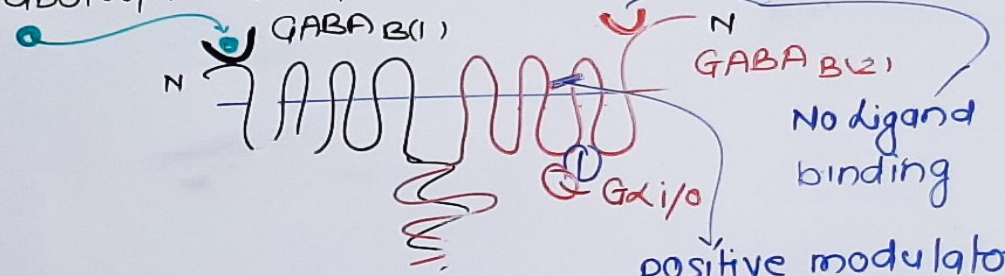
α_1 – Sedative action
α_2 – Anxiolytic action
α_3 – anxiolytic & anticonvulsant
α_5 – learning & memory (Amnesia)

– BZD action
– (Histidine)

GABA Receptor Pharmacology

GABA B

→ Metabotropic Receptor – Gi/o PCR (↓cAMP Pathway)

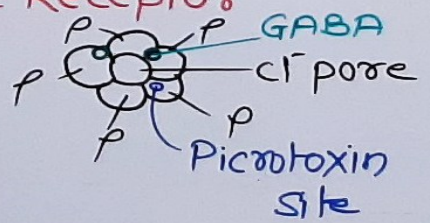


GABA B(1) Agonist – GABA, Beclofen
Antagonist – CGP 35348, CGP54626

Distribution – CNS & PNS
Effect – IPSP, GiPCR – ↓cAMP, ↑K⁺ & ↓Ca²⁺ conductⁿ
Action → 1° site is spinal cord (depress both polysynaptic & monosynaptic reflex), usefull in pain management, spinal injury, multiple Sclerosis, central musde relaxant

GABA C Receptor

Ionotropic/L.G.I.C. – Cl⁻ ion channel → Hyperpolarizatⁿ
Pentameric transmembrane Receptor
GABA C R – 5 ρ subunit
Lake of modulatⁿ by BZD, Barbiturates



Distribution – Spinal cord & Retina
GABA C Agonist – GABA, TACA
Partial Agonit → muscimol, CACA (4-Amino-2-but-anoic ā)
Antagonist – Picrotoxin, TPMPA
Tetrahydro pyridine methy phosphonic ā

Role of GABA ($GABA_AR$)

Sedative & Hypnotics
Anxiolytic
Schizophrenia – VTA – α_3 $GABA_A$ (BZD)
Depression – α_2 $GABA_A$ – BZD
Anxiolytic action
mood regulation

Cognitive behavioral – α_5 $GABA_A$ – BZD

Stroke – α_5-$GABA_A$ (BZD)

Antiepileptic action

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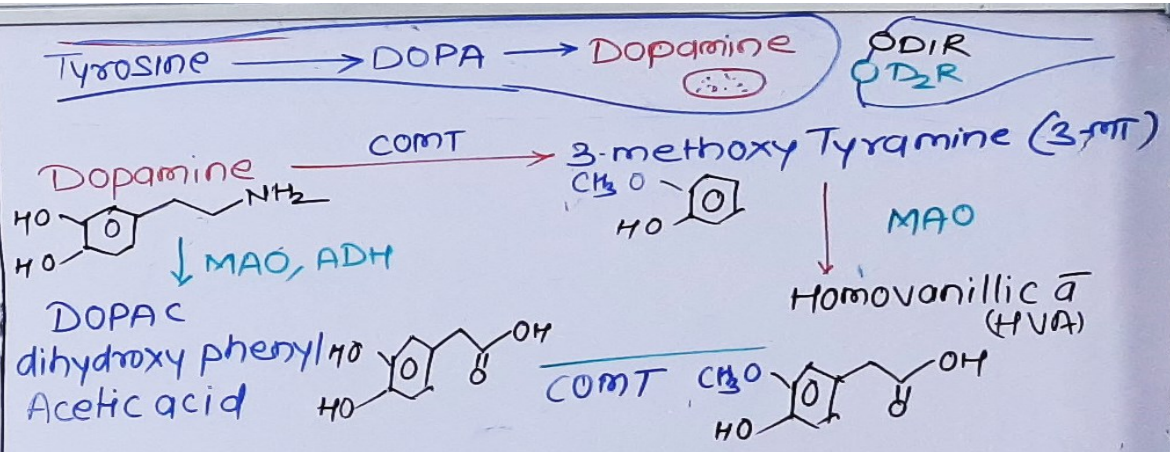
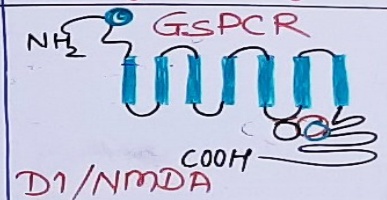
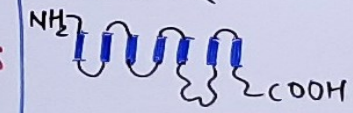
DOPAMINE RECEPTOR PHARMACOLOGY

Dopamine → Predominant Catecholamine NT present in the CNS. Dopaminergic neurons regulate the motor functn, Locomotion, learning & memory, mood/behavioral, Endocrine function, & Food intake in CNS. In PNS, it regulates the CVS, GI motility, Renal function, catecholamine release

RECEPTORS – 1 D1 like (D_1 & D_5 R) – GsPCR (Excitatory)
2 D_2 like (D_2, D_3, D_4 R) – GiPCR (Inhibitory)

Pathways – #Nigrostraital Pathway (motor contrc)
#Mesolimbic/mesocortical Pathways (behavioral)
#Tuberohypophyseal Pathways (Endocrine Contrc)



	Location	Signaling	Agonist	Antagonist	Function
D1R	Straitum, Limbic System, Thalamus Hypothalamus & Smooth mussels	 D1/NMDA	Dopamine Apomorphine Fenoldopam SKF 38393	SCH 23390 SCH 39166 Butaclamol (Inverse Ag)	Renal Vasodilitatn, +Inotropic, Cognitive functn, (+) NMDA R
D5 R	Midbrain, Hippocampus, Thalamus, Cerebral Cortex, straitum, vascular	GsPCR	Apomorphine Fenoldopam SKF 38393	SCH 23390 Butaclamol	↓ AT_1 Expression & Vascular proliferation
D2R	Pituitary gland, straitum, Hypothalamus	GiPCR 	Bromocriptin Pergolide Ropinirole	Haloperidol Sulpride Risperidone	Locomotion, learning & memory, Attention, motor function, sleep ↓ Prolactin ↑ GH, CTZ (Emesis) Reward
D3 R	Limbic System, Cortex, Hypothalamus	GiPCR	Pramiprexn Rotigotine Quinpirole	—11— Nafadotride	Presynaptic (↓dopaminergic) Locomotion, Cognition, Sleep
D4 R	Cortex, Limbic System, Amygdala	GiPCR			Cognition, impulse contrn, Sleep, reproductive behavior,

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ANTI-ANXIETY DRUGS

ANXIETY :- An emotional state, unpleasant in nature, associated with uneasiness, discom-ort, consern or fear about some defined or undefined future threats.

Somatic Symptoms –

- # Anaroxia
- # Breathlessness
- # Palpitation
- # Sweating
- # Paresthesia (Pins & needles Sansatn)

Treatments when excessive & dispropornate to the situation

Some depressed and Psychotic patients also feel Anxiety.

↳ Cardiac Neurosis → Fear to heart disease → palpitation, Pericardial pain.

↳ GI Neurosis → Reflex & Acidity

↳ Social Anxiety → fear to other thought

↳ OCD - Obsessive-compulsive disorder

↳ Post Traumatic stress disorder (PTSD)

↳ Phobia

ANXIOLYTIC DRUGS

CNS depressant drugs → Controll Symptoms

↳ have no effects on Schizophrenia

↳ Do not produce Extra pyrimidal Side effects

↳ have anticonvulsant property

↳ Produce Physical dependence

Ⓐ BZDs – Diazepam, Oxazepam, Alprazolam, Clonazepam

Ⓑ Azapirone – Buspirone, Gepirone, Ispapirone

Ⓒ Sed. Anti-H_1 → Hydroxyzine

Ⓓ B-blocker – Propranolol

DEPRESSION ☹

↳ Depression is a state of "Low Mood" that affects the person's "mood", "Feelings", "Behaviour", & "thought"
↳ Significant risk of Suicidal death

PAST ⟶ Present ⟹ Future

SYMPTOMS :⟹

Emotional Symptoms -

↳ Misery, Apathy, & pessimism
↳ Low Self Esteem :- Guilty, Inadequacy & Ugliness
↳ Indecisiveness, Loss of motivation

Biological Symptoms :-

↳ Retardat^{n} of thought & action
↳ Loss of Libido, Sleep disturbance, ↓ Appetite

TYPES :-

1. Major Depression - Sever Symptoms
2. Atypical Depression - Subtype of Major Depression, and can be treated with medicine
3. Dysthymia (Recurrent, mild depression)
4. Seasonal Affective Disorder (SAD) - Reduced day-light hour in winter may increase the depressive symptoms in some people.

I. UNIPOLAR DEPRESSIVE SYNDROME :- Mood swings are always in same direction.

→ Associated with stressful life Events.. Common symptoms are anxeity and agitation.. Reactive Depression (75%)
→ Endogenous Depression (25%) - Familial pattern

II. BIPOLAR DEPRESSION - Dep. alternates with Mania
↳ usually appears in early adult life
↳ Strong heriditary tendency.

ETIOLOGY - Stressful life Events, Medical Treatment, Psychiatric Syndrome, Genetic

PATHOPHYSIOLOGY :-

Monoamine Hypothesis - Proposed by "Schildkraut" in 1965. - "Depression is caused by functional deficit of Monoamine Transmitters (N-Ad, SHT) at certain site of Brain

Neuroendocrine mechanism

Hypothalamus $\xrightarrow{CRH}$ Pituitary $\xrightarrow{ACHT}$ Cortisole Sec.

Neuroinflammation & Immune mechanism

DRUG TREATMENTS -

1. Tricyclic Antidepressants (TCAs) -
NA & SHT Reuptake Inhibitor - Imipramine, Doxepine, Amitriptyline, Clomipramine, Trimipramine
NA reuptake inhibitors - Desipramine, Nortriptyline
2. SSRI - Fluoxetine, Fluvoxamine, Paroxetine
3. SNRI - Venlafaxine, Duloxetine
4. MAO-A Inhibitor - Meclobemide, clorgyline
5. Atypical Antidepressant - Trazodone, Mianserin, Mirazapine, Bupropione, Amoxapine

ANTI DEPRESSANT DRUGS

MAO (Mono-Amine-Oxidase) - Mitochondrial enzyme responsible for oxidative deamination of Biogenic Amines (NA, Adr, DA, & SHT)

MAO-A → NA & Serotonin ; MAO-B → Phenylethylamine

* Dopamine metabolised by both MAO-A & MAO-B

MAO-A :→ Peripheral Ad.-neuron, intestinal mucosa & human placenta. & Liver

INHIBITORS → Clorgyline & Moclobemide

MAO-B → Brain, Platelets & Liver

INHIBITOR → Selegiline

Isoniazid & Iproniazid (1951) - Anti-TB drugs
↓ degradatn of biogenic amine → ↑ Mood

1960s → Phenelzine, Isocarboxazide (INH Derv.)
Tranylcypromine (Amphetamine derv.)

↓

They are Non-selective MAO-Inhibitor, More toxic

ADR - Postural hypotension, Restlessness, insomnia sexual dysfunction,

CHEESE REACTION :→ MAO Inhibitors with Tyramine, dopa containing food/products (cheese, beer, Fish, Meat) Cause → "Hypertensive Crisis"

Similar reaction occurs with ephedrine, TCAs, SSRIs, SNRIs,

Hallucinatn & Atropine poisonig like symptoms occurs with - Alcohol, Sed.-Anti H_1, Barbiturates & opioids → ↓Res.

MAOIs + Pethidine → fever, Sweating, Excitatn, delirium, convulsion, Res. depression due to over productn of nor-pethidine

Moclobemide Pharmacology

MOA - Reversible MAO-A Inhibitor (Short duratn of action)

↳ Restriction of dietary is not required, because tyramine is able to displace from the enzyme

It has lack to anticholinergic, sedative, Cognitive, CVS, psychomotor side effects unlike TCAs.

Antidepressant alternative to older & heart patients. And in Social Phobia

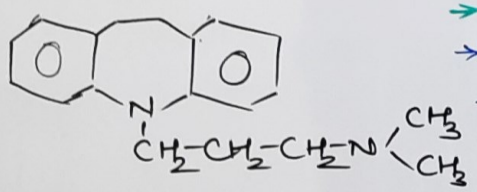
ADR = Nausea, diziness, headach, Insomnia
Rarely excitment & Liver damage

Contraindicated with - Alcohol, Pethidine, SSRIs & TCAs

TRICYCLIC ANTI-DEPRESSANT

NA + 5HT Reuptake Inhibitors →
Imipramine, Trimipramine, Clomipramine, Amitriptyline, Doxepin, Dothiepin,

NA - Reuptake Inhibitors → Desipramine, Nortriptyline



→ "Imipramine" - 1958
→ CPZ derivetive
→ Benificial in depression not in psychosis

TCAs : 1st Gen. Antidepressant

↳ # NA & 5HT Reuptake Inhibitor (NET & SERT)
Also act on cholinergic, Adr. & histaminergic R

Pharmacological Action : →

① **CNS** - A) In Normal Person → (+) Anxiety

B) In Depressed Patient → Acute Sedative effect, after 2-3 weeks of continous treatment, the mood is gradually elevated, Patients become more communicative in surrounding enviroment.

TCAs → Not euphorient - only antidepressant.
↳ At low dose → ↓ REM sleep (Hypnotic like)
↳ At high dose → disturbed sleep cycle
↳ ↓ Seizure threshold → (+) Convulsion
↳ Clomipramine & Bupropion
↳ overdose → Respiratory depression

② **ANS** - # Anticholinergic → Constipation, Blurred vision, etc.
Potentiate NA action, also have - α_1 - blocking actn
Antihistaminergic → Amitriptyline, Doxepin, Trimipramin

③ **CVS** → Tachycardia, Postural hypotension, Arrhythmia

Tolerance & Dependence -

Tolerance to anticholinergic & hypotensive effects
Addiction is rare, Physical dependence may occurs

P'KINETIC → Good Oral Abs, Vd = ~20L/kg, Metabolised - Liver
$t_{1/2}$ = 16-20 h, Therap. range → 50-200 ng/ml

ADR - # Anticholinergic # Antihistaminic - Sedation
↑ Appetite & wt gain # Seizure # CVS disorder
Dysphoria & Mania (Switch Over) # Sexual disturb.

INTERACTION → # Potentiate Sympathomimetic Action
+ Alcohol, Anti-H$_1$ → ↑↑ CNS depression
Protein binding displacement with Phenytoin, Aspirin, etc
Phenobarbitone, Carbamazepine → ↑ Metabolism of TCAs
SSRIs → ↓ Metabolism TCAs → Toxic action
Due to Anticholinergic → ↓ Absorption of own & other
+ MAO-Is → "Hypertensive crises"

Use - Antidepressant, Neuropathic pain, ADHD, Pruritis
Premature Ejaculatn, Migrain, Smoke Cessation

SELETIVE SEROTONIN REUPTAKE INHIBITORS AND SEROTONIN & NORADRENALINE REUPTAKE INHIBITORS

SSRIs → Fluoxetine, Fluvoxamine, Peroxetine, Sertraline, Dapoxetine, Escitalopram

SNRIs – Venlafaxine, Desvenlafaxine, Duloxetine

1980s → 2nd Gen Antidepressant drugs → SSRIs & SNRIs

They have minimal side effects unlike the TCAs.
- ↳ Cholinergic, histaminergic, CVS, neurological ADR
- ↳ Low Safety of margine
- ↳ Incomplete response or no response to TCAs

MOA :→ SSRIs → ↓5HT Reuptake (SERT)

SNRIs → ↓ 5HT (SERT) & NA (NET) Reuptake

Their efficacy is higher than TCAs & RIMAs

More safer at overdose & better torability

"SSRIs"

1st line drug for depression

Also used in Anxiety, Phobia, Panic, OCD & Related disorder

ADR = GI disturbance - Nausea (due to (+) $5HT_3R$), loose motion (due to 5HT uptake blockade & +5HTR), Sexual (ejaculation) problem, Insomnia, Nervousness, anorexia, dyskinesia, headache.
- > Epistaxis & Ecchymosis (due to platelet dysfunct°)

INTERACTION – + NSAIDs → ↑ Gastric blood loss

SSRIs (Enz Inhibitors) – ↓ metabolism of TCAs, Haloperidol, warfarin, β-blockers, etc.

+ MAOIs, Tramadol, Pethidine → (+) "Serotonin Syndrome" like agitat°, restlessness, rigidity, hyperthermia, delirium, sweating & twitching

"SNRIs" (Novel Antidepressant)

Similar effective as TCAs, but lesser side effects

Faster onsetup action

Uses – Antidepressant, mood changes in menopausal syndrome, social Anxiety & Eating disorder

ADR – Nausea, Vomiting, Sweating, anxiety, Dizziness, Impotance, withdrawal symptoms after discontinue

** Duloxetine → Little Sedative & antimuscarinic action

ATYPICAL ANTI-DEPRESSANT DRUGS

DRUGS – Trazadone, Mianserin, Mirtazapine, Bupropione, Amoxapine, Tianeptin, Amineptine

TRAZADONE – Block 5HT uptake, Prominant α-R & Weak $5HT_2$R blocker (Metabolite strong $5HT_2$R blocker)

Modest Antidepressant effect

ADR – Sedative (but not anticholinergic), ↓HR Nausea, Priapism (Painful Penile erection- α,R) Postural hypotension (α, R blockade)

MIANSERIN → Block α_2R → ↑NA Release

Also block $5HT_2$, $5HT_{1C}$, & H_1 Receptor

Antidepressant, Sedative → in Anxiety and Panic Attack.

ADR → Seizure in overdose, Blood dyscrasias, Liver dysfunction.

MIRTAZAPINE → Antidepression by blocking α_2R present presynaptic NA-neuron & hetero (Serotonergic) neurons. → ↑ NA & 5HT Release

→ (+) $5HT_1$R & block $5HT_2$ & $5HT_3$ receptors

→ Also known – Noradrenergic - Specific Serotonergic Antidepressant (NaSSA)

→ H_1 blocker (Sedative), mild anticholinergic

USE → in Depression with insomia

ADR – ↑ Appetite & weigh gain.

BUPROPIONE → DA & NA uptake inhibitor, → Excitant

↳ Amphetamine like metabolite → ↑ presynaptic release of DA & NA

Sustained release → Smoking Cessation with Nicotine patch

↑ Dopaminergic Reward function

ADR – Insomnia, Dry mouth, Agitation, nausea. Seizure (in Overdose)

Contraindicated – in Eating disorder & Bipolar illness.

USE → Along with SSRIs

AMOXAPINE → Tetracyclic compound

→ block D_2R & NA uptake

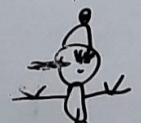
→ Antidepressant + Neuroleptic properties

– **ADR** → Seizure & EPS

TIANEPTIN :→ Antidepressant showing increase the uptake of 5HT (neither Sedative nor Stimulant)

→ Effective in Anxio-depressive patient with psychomimetic symptoms.

– **ADR** → Dry mouth, Epigastric pain, Flatulence, drawsiness, Insomnia, Tremor, bodyach



SCHIZOPHRENIA

↳ Schizophrenia is a chronic & sever mental disorder that is imp form of psychiatric illness affects how a person Thinks, Feels, & Behaves.

↳ They have lost touch with with reality.

A. Positive Symptoms - "Psychotic Behave"

Hallucinations # Delusions # Thought disorder
Abnormal behaviour # Movement disorder

B. Negative Symptoms

Flattening of emotional response
Withdrawal from social contact
Reduced feeling of pleasure

C. Cognitive Symptoms

Reduced Cognitive Function (Attention, learn, memory)

ETIOPATHOGENESIS

1. Genetics → Family history ↑ the risk
   ↳ Neuregulin-1 gene → Neuronal synaps & plasticity
   → NMDA Receptor Expression
   ↳ gene for d-amino acid oxidase (DAAO) → D-serine
   Allosteric modulator of NMDA Receptor

2. Enviromental Factors -
   ↳ Meternal viral infection - ↓ Neuronal development
   ↳ Cannabis consumption
   ↳ Drug Addiction
   ↳ Enivironmental toxins

NEUROCHEMICAL THEORIES - Pathophysiology

1. Dopamine Theory - Carlson proposed Dopamine theory & got Nobel prize in 2000.
   ⇒ ↑ Dopaminergic (D_2) pathway may responsible for psychotic behaviour.

2. Glutamate Theory — ↓ Glutaminergic pathway

3. Serotonin Theory — ↑ Serotonergic pathway

Serotonergic —— Dopaminergic

DRUG MANAGEMENT

1. Neuroleptics (D_2 Antagonist) = Typical

A. Phenothiazine - Chlorpromazine, Thioridazine, Fluphenazine

B. Butyrophenone - Haloperidol, Trifluperidol

C. Thioxanthine - Flupenthixol

2. Atypical Antipsychotic Drugs

- Clozopine, Risperidone, Olanzapine
  Ziprasidone, Zotepine,

NEUROLEPTICS (ANTI PSYCHOTIC DRUGS)

↳ "Chlorpromazine", Triflypromazine, Thioridazine
Trifluoperazine, Fluphenazine (phenothiazines)
↳ Haloperidol, Trifluperidol, Penfluridol (Butyrophenones)
↳ Flupenthixol (Thioxanthine)

MOA - D_2 Blockers (Limbic System & mesocortical)

PHARMACOLOGY OF CPZ

1) CNS - # In non psychotic → Paucity of thought, psychomotor slowing, emotional quietening "Neuroleptic Syndrome". & produce Extra pyrimidal motor side effect

In psychotic → Control Psychosis behaviour
↳ Aggressiveness ↳ Agitation
↳ Disturbed thought ↳ Anxiety
↳ Hyperactivity ↳ Hallucination

CPZ & Thioridazine → more Sedative action
Intelligence and performance - Unaffected
CPZ - ↓ Seizure threshold
CPZ at high dose - ↓ Body temp.
Other vital function → not affected (at therap. dose)
CPZ, Haloperidol → Antiemetic (CTZ)
Trifluopromazine

2) ANS - Anti-α and Anticholinergic (M1)
α blocking → CPZ = Trifluopromazine = Thioridazine > Fluphenazine > Haloperidol > Trifluperazine > Pimozole * more potent (D_2) - Less α blocking
Anticholinergic - Thioridazine > CPZ > Trifluopromazine > Trifluperazine = Haloperidol

3) Local Anesthetic → CPZ (mem. Stab. act^n)

4) CVS → ↓ BP & Reflex Tachycardia
at high dose → myocardial depression and prolonging QT & supress T wave

5) * Endocrine → ↑ prolactin Release
this may cause Glactorrhoea and Gynaecomastia
CPZ → ↓ GnH, GH, ADH release & ↓ ACTH response
↳ impaired Glucose tolerance → + Diabetes

Tolerance & Dependence

Tolerance to the sedative & hypnotic action develops within days or weeks, not for psychotic action.

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NEUROLEPTICS (ANTI PSYCHOTIC DRUGS)

PKinetics – CPZ

Oral Abs → unpredictable, BA = low, SO IM < IV
Highly tissue (brain) protein binding (Vd = 20 L/kg)
Metabolized by CYP2D6 # $t_{1/2}$ = 18-30 h
excretn through urine & Bile for month after discontinue the drug

* EPS Effect = Haloperidol = Trifluperazine > Triflupromazine > CPZ > Thioridazine

1) Triflupromazine → more potent than CPZ, Antiemetic, Muscle dystonia in children

2) Thioridazine – Low potency, marked anticholinergic, low EPS, *Arrhythmia, impaired sexual functn & eye damage

3) Trifluperazine & Fluphenazine → high potent, less ANS action, Marked EPS & dyskinesia

4) Haloperidol → most commonly used. potent antipsychotic similar piperazine derv., few ANS acts preffered for acute Schizophrenia, Huntington's disease and Gilles de la Tourette Syndrome

5) Flupenthixol - less sedative than CPZ used in Schizophrenia particularly in withdrawn & apathetic patient

6) Pimozide – Selective D_2 blocker not having ANS actn. used for maintanance. used in Gilles de la Tauretts syndrome

ATYPICAL ANTIPSYCHOTIC DRUG

↳ 2nd Generation newer antipsychotic drugs having minimal D_2 blocking activity but potent $5HT_2$ Antagonistic Activity.

↳ Drugs → Clozapine, Olanzapine, Risperidone Quetiapine, Aripiprazole, Ziprasidone

1. CLOZAPINE

Minimal D_2 blocking → low EPS effects
Mainly → $5HT_2$ Antagonistic action
Other → D_4 blocking, Anticholinergic (M_1) & Antihistamic (H_1) action
Control both +ve & -ve Schizophrenia
ADR – Agranulocytosis, Metabolic disfunction (Hyperlipidemia, weight gain, Diabetes) seizure may be induced, Sedation, unstable BP, Tachycardia, Myocarditis, Urinary incontinance.
Use – Reserve for Refractive Schizophrenia
• Also improve the cognitive function

2. Aripiprazole

Partial D_2 & $5HT_{1A}$ Agonist & $5HT_2$ Antagonist
Improve cognition & used in Schizophrenia (+/-)
May cause Hyperglycemia & ↑ QT interval
Also helpful in resistant depression & Bipolar

3. Ziprasidone

Antagonistic activity on D_2, $5HT_{2A/2C}$, H_1 & α_1
Agonist on $5HT_{1A}$ # Antagonist on $5HT_{1D}$
↓ reuptake of 5HT & NA (Antidepressant and anxiolytic action)
used in Schizophrenia & Mania
ADR – Sedation, Hypotension, weight gain, Hyperglycemia, "Low EPS"

4. Risperidone

D_2, $5HT_2$ - blockade → Antipsychotic Actn
α & H_1 blockade → Hypotension & Sedation
More potent D_2 blocker than clozapine but EPS shows at high dose > 6mg/day
ADR → ↑Prolactin, EPS
→ less Epileptogenic than clozapine
& weight gain, Diabetes may precipitate
# Use – 1st line drugs for Schizophrenia

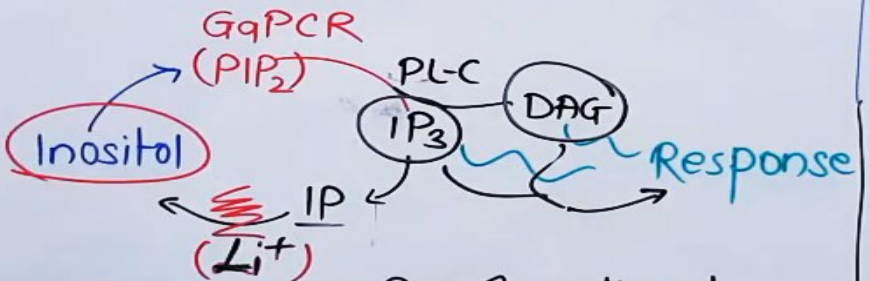
DRUG USED IN MANIA & BIPOLAR DISORDER

↳ Lithium Carbonate
↳ Antiepilepsy – Sod. Valproate, Carbamazepine Lamotrigine
↳ Antipsychotic → Olanzapine, Risperidone, Aripiprazole

LITHIUM CARBONATE

↳ Monovalent cation. In 1949, it was found to Sedative action in animals and beneficial effects in manic patients

MOA :-



1) CNS – Mood Stabilizer in Bipolar disorder
→ Supress the manic episode, taking 1-2 weeks
→ Markedly reduce sleeptime in manic patient
Li^+ - Replace the Na^+ and distributed equally and affect the ionic flux.
↓ the presynaptic release of NA and DA without affecting 5HT

2) Other action – ↓ action of ADH and may cause diabetes insipidus.
→ Insulin-like action on Glucose metabolism

P'Kinetic → Orally well absorbed but neither protein bound nor metabolised
→ uniform distribution – plasma ⇌ CSF
→ Vd = 0.8 L/kg
→ Excreted through urine, 80% are reabsorbed
→ Narrow margin of Safety, 0.5–0.8 mEq/L for maintenance therapy
→ > 1.5 mEq/L → Toxic Action

ADR : → Nausea, Vomiting, mild diarrhoea, Thirst, Polyurea, Tremor, CNS Toxicity (Tremor, rigidity, Ataxia, Motor incoordination, mental confusion, slurred speech)
-> 2 mEq/L → muscle twitching, convulsion, etc
↳ Treatment → Osmotic diuresis, $NaHCO_3$

Interaction # Diuretics → ↑ Li^+ reabsorption
NSAIDS, ACEIs → Li^+ retention
Li^+ → ↓ pressor response of NA
Li^+ → ↑ sulfonyl urea & insulin action

Uses → Acute mania & Bipolar disorder

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HALLUCINOGEN (PSYCHOTOMIMETICS)

INDOLE AMINE :- "Lysergic acid diethylamide (LSD)", Lysergic acid amide, Psilocybin, Harmine, Bufotenin

PHENYLALKYL AMINE → Mescaline, Ecstasy, Yaba

ARYLCYCLOHEXYL AMINE → "Phencyclidine"

CANNABINOID - "Tetrahydrocannabinol"

"LSD"

* Synthesized by "Hofmman" (1938) from "Ergot" and himself feel hallucinogenic effect.
# Most potent - 25-50 ug produces all effects.
# shows 'mental effects' and stimulates centrally sympathetic system
# MOA = $5HT_2$ Receptor Agonist

"CANNABINOIDS"

↳ "Cannabis indica" (Marijunna)

↳ "Bhang", "Ganja", "Charas" - use "world wide"

↳ Cannabis is the drug of abuse having the lowest acute toxicity, even habitual use is not associate with serious neurotoxicity or damage to any other organ toxicity.

Thought, Personalities, and Psychiatric problem are more common in cannabis user.

Young → Amotivational Syndrome

Cannabinoid Receptor - CB_1R (CNS) (+) — CB_2R (Peripheral)

"Anandamide" (Ethanolamide of arachidonic a)

Actions - # Antiinflammatory - Analgesic

Antiemetic - Cancer chemo-induced, "nabilone" & "dronabilone" ++

To relieve anxiety & migraine

↓ IOP - Glaucoma

Bronchodialators (Asthma)

Apetite stimulant

↳ Hallucinogens (Marijunna) produce dream like state with disorientation.

↳ Produce tolerance & Psychological dependence.

CNS-STIMLANTS

The drug which stimulate the CNS or improve specific function of Brain

1. CONVULSANT – Strychnine, Picrotoxin, Bicuculline, Pentylenetetrazole (PTZ)
2. ANALEPTIC – Doxapram
3. PSYCHOSTIMULANT – Amphetamine, Methylphenidate, Atomoxatine, Modafinil, Armodafinil, Cocain, Caffeine

CONVULSANT

1. Strychnine → alkaloid - "Strychons nux-vomica"
   → ↓ Glycene transmission
2. Picrotoxin → obtain from "Fish-berries" (Anamirta Cocculus") → $GABA_AR$ allosteric antagonist
3. PTZ → ↳ Depolarize the CNS neurons
   ↳ ↓ GABA Transmission

ANALEPTIC (RESPIRATORY STIMULANT)

Restrictive used in Coma or fainting at Sub convulsive dose, (Margin of safety in narrow)

1. Doxapram → IV inj. in fainting, barbiturate poisoning ventilatory failure in COPD, suffocation, etc.

PSYCHOSTIMULANT

1. Amphetamine → Sympathetic stimulation
2. Methylphenidate → ↑ release of NA & DA Centrally
   → used in ADHD in children
   → used in Narcolepsy (Adult)
3. Atomoxatine – NA reuptake inhibitor, Not (+) CNS, but improve attention & Behaviour in ADHD
4. Modafinil → Newer psychostimulant is popular with night-Sift (Call Centre) workers & others.
   ↳ Improve alertness & keep awake.
   ↳ ↓ NA & DA uptake, Modulate GABA & Glutamate
   ↳ Used in - day time sleepness due to narcolepsy, Sleep-apnoea syndrome, Sift-Work disorder.
   # ↓ Cocain withdrawal symptoms & Dependence
5. Caffeine – Xanthene derivetive → (+) CNS
   MOA → # PDE-Inhibitor # Antagonise Adenosine R
   # Antagonise BZD R, # ↑ Ca^{+2} Signaling
   Use → Combination → Analgesics, Migrain
   → Apnoea in infant alternate to theophylline
   → CNS stimulant

ALZHEIMER'S DISEASE (AD)

AD is the commonest progressive, dementing, neurodegenerative disease in elderly (>65y)

* "Alois Alzheimer", a German Scientist described symptoms & pathology - "Neuronal loss, "Plaques" & Neurofibrillary tangles

Major Affected Area → Cerebral Cortex

Clinical Sign & Symptoms :→

1. Mild → memory loss, Language problem, behavioral changes, Judgement impairment
2. Moderate: - Behavioral/Personality changes, unable to learn & recall new info., Long-term memory loss, Confusion, Aggression
3. Sever: → + motor disturbance

* Aphasia - Disturbance in language function
* Apraxia - Impaired motor function
* Agnosia - Inability to recognise name of objects
* Executive Functioning - Inability to think abstractly

Risk Factors - ① Aging >65y ⇒ Progressive neuronal loss
② Hypertension ③ Diabetes ④ Hyperlipidemia
⑤ Down Syndrome ⑥ Smoking & Alcohol

6) Genetic - mutationon - # Amyloid Precurssor Proteins (APP)
Presenilin gene (PSEN1 & PSEN2)
β-secretase (BACE1)
γ-secretase # ε4 allele of apolipoprotein E (APO-E)

Pathophysiology -

1. Neuronal Damage - loss of neurons & synaps, cerebral atrophy, ↓ Cholinergic neurone, Imbalance of Glutaminergic neurons.
2. Genetic mutation
3. Diposition of β-Amyloid protein - resulting in Neuritic "Senile" Plaque - Neurotoxic
4. Neurofibrillary Tangles - are fillamentous collection of neurofillaments & microtubules within the cytoplasm of neuron

Management -

1. Nutrients - ω-3-Fatty a, Curcumin, vit E, Ginkgo
2. Cognitive Enhancer: -

a. Anti-cholinesterase - Rivastigmine
Donepezil Galantamine

b. Glutamate Antagonist - Memantine

c. others - Piracetam, Citicoline, Pyritinol
Dihydroergotoxin, Ginkgo biloba

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ANTI-ALZHIEMER'S DRUGS

Cognition Enhancer / Cerebroactive Drugs

A) CHOLINERGIC ACTIVATORS (ChE Inhibitors)
↳ Rivastigmine, Donepezil, Galantamine, Tacrine

RIVASTIGMINE :→ Carbamate derv. of physostigmine ∆
↳ Inhibits both AchE & BuChE, but is more selective for G_1 isoform of AchE that predominant in Brain.
↳ highly lipid soluble — easily cross BBB
↳ ↑ cholinergic transmission in brain
↳ 3.8 point improvement in Alzhiemer Disease Assessment Scale (ADAS-cog)
↳ Other symptoms apathy, delusion, agitation, and hallucination are also improved
↳ No/min. peripheral side effects
↳ Used in mild to moderate AD

B) NMDA ANTAGONIST → "MEMANTINE"
↳ Newer NMDA-receptor blocker related to Amantadine
↳ Block the excito-toxicity of Glutamate transmission
↳ use - moderate to Sever AD (better tolerated)
↳ Also effective in PD
↳ Side effects — constipation, headach, tiredness, dizziness, ∆ drawsiness

"PIRACETAM" - Cyclic GABA derivetive but no GABA action, "Nootropic drug" - Improve the efficiency of higher telencephalic integrative activities.
↳ Reduce blood viscosity
↳ Improve cognitive impairement & dementia in elderly as well as mental retardatn in children.
↳ In UK, approved for adjunctive treatment of cortical myoclonus

"PYRITINOL" (Pyrithioxine) - 2 mole. of pyridoxine bind with disulphide bridge
↳ No Vit B_6 Activity
↳ ↑ Glucose transport in brain,
↳ ↑ regional blood flow in ischemic brain area.

"PIRIBEDIL" - Dopaminergic agonist

"CITICOLINE" - Derived from choline & cytidine that involved in synthesis of Lecithine
↳ Improve cerebral blood flow
↳ Indicated in impaired brain func. due to Ischemia, stroke, PD, ∆ head injury.

GINKGO BILOBA → Ginkgolide-B → PAF Antagonist
→ Improve blood flow

MORPHINE PHARMACOLOGY

MORPHINE is an alkaloid present in Opium (Papaver somniferum) & it is a phenanthrene derivative.

MOA – (+) Opioid Receptor (GiPCR) mainly μR

PHARMACOLOGICAL ACTION –

1) CNS – Analgesia# → # Visceral Pain is relieved better than Somatic pain
Nociceptive pain is relieved better than Neuropathic
Pain associated reaction are also relieved.
Modulate the pain pathway in spinal & Supra-spinal region by inhibiting Excitatory Transmitter

Sedation# – drawsiness – Sleep – "Coma"
Euphoria#, Respiratory depression – Death, Supression of cough, Hypothermia in cold condⁿ, Depressed vasomotor Centre → ↓ BP

* Stimulatory Actions → # + CTZ → Vometing/nausea
# (+) Edinger-Westphal nucleus of III nerve by ↓ GABA-ergic interneuron ⇝ Miosis
# (+) Vagal Centre → Bradycardia (↓ HR)

2) NEURO-ENDOCRINE ACTION = Modulate hypothalamic - Pituitary function → ↓ FSH, LH, ACTH
↑ Prolactin & GH
↳ Also ↓ Sex hormone & Cortisole level

3) PERIPHERAL ACTION –

a) CVS → ↳ Vasodilation (due to histamine release)
↳ ↓ vasomotor Centre → ↓ BP

b) GIT → ↓ GI motility – Antidiarrhoeal action.

c) Other Smooth muscle –
↑ Spasm of sphincter of oddi → ↑ Intrabiliary pressure → B. colic
↑ tone of Bladder & detrusor sphincter → Urine urgency
Bronchoconstriction (due to histamine)

P'KINETIC → unreliable oral abs., high 1st pass metabolism.
oral BA = 25%, PB-30%, widely distribution, small fraction of morphine enters Brain slowly, also cross placenta & affect foetus. #Metabolised by glucuronic conjugatⁿ & metabolite is more potent to μR. Morphine-3-Glucuronide → Neurotoxic
excretn through urine & Bile, $t_{1/2}$ = 2-3 h

ADR – # Sedative # Idosyncrasy & Allergy # Apnoea in new born (Antidote – Naloxone 10 μg/kg) # Dependence
Acute morphine poisoning → Res. dep., Miosis (pinpoint) coma, Flacidity, Fall in BP, Cyanosis, shock
↳ Antidote → Naloxone (0.4–0.8 mg, IV)

Contraindication → # Asthmatic patients # Infant
Pregnancy, # Hypotensive or Hypovolemic state
Head injury → ↑ CO_2, ↑ Intracranial pressure, Acidosis, Sedatn
Undiagnosed Acute abdominal pain

Use of Opioids → # As Analgesic # Anesthesia (Fentanyl) # Anxiety
cough
diarrhoea