

## Depression Prescriptioncracker.com

## MANIA

- feelings of sadness, hopelessness, as well as inability to experience pleasure in usual activity along w changes in sleep patterns & appetite
- Loss of energy & suicidal thoughts

### o-Biogenic-Amine Theory

- depress. is due to deficiency of monoamines (nor-epi & serotonin)

\* However This Theory fails to explain the effect of antidepressant and anti-mania drug on neurotransmission - that occur immediately

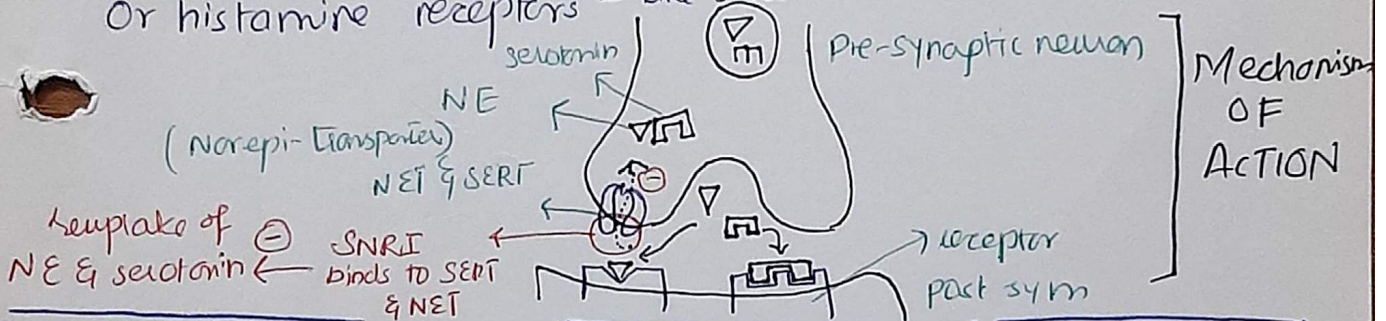
### \* - SEROTONIN/NOR-EPI Reuptake Inhibi-

- effective in pts in which SSRI are ineffective.

⇒ Similarity to TCA: - (Not present in SSRI).

(Due to their dual action on serotonin & NE ⇒ Effective in relieving pain also. e Diabetic periph. neuropathy, Lower back pain, fibromyalgia (widespread musculoske. pain & fatigue, & mood issues), and postherpetic neuralgia (viral skin infec. (shingles) complication that affect nerve fibers & skin causing burning pain)

⇒ Differ from TCA: less activity at  $\alpha$ -adrenergic, muscarinic or histamine receptors - like SSRI



## VENLAFAXINE

- Normal dose = Serotonin reuptake Inhi (Potent)
- Med-high dose = NE reuptake Inhi
- minimal Inhi. CYP450
- Substrate of CYP2D6
- N/Constipation, Headache
- Insomnia, dizziness, sedation
- SEXUAL DYSFUNCTION
- ↑BP & HR — at high dose

## DESVENLAFAXINE

- Active methylated metabo. of venla
- Inhib. of both NET & SERT
- ADRs similar to venlafaxine
- Levomilnacipran (L- enantiomer of milnacipran)
- Older SNRI

## DULOXETINE

- Inhi of both SERT & NET
- meta. by liver
- Inhib. of CYP2D6 (so ↑ conc. of drugs)
- metab. by this e.g. antidepressants
- N/Constipation, dry mouth
- Insomnia, somnolence
- SEXUAL DYSFUNCTION
- ↑BP & HR



## SELECTIVE SEROTONIN Reuptake INHIBITORS

- 300-3000 times more selectivity for serotonin transporters
- less activity on adrenergic, histamine & muscarinic receptors

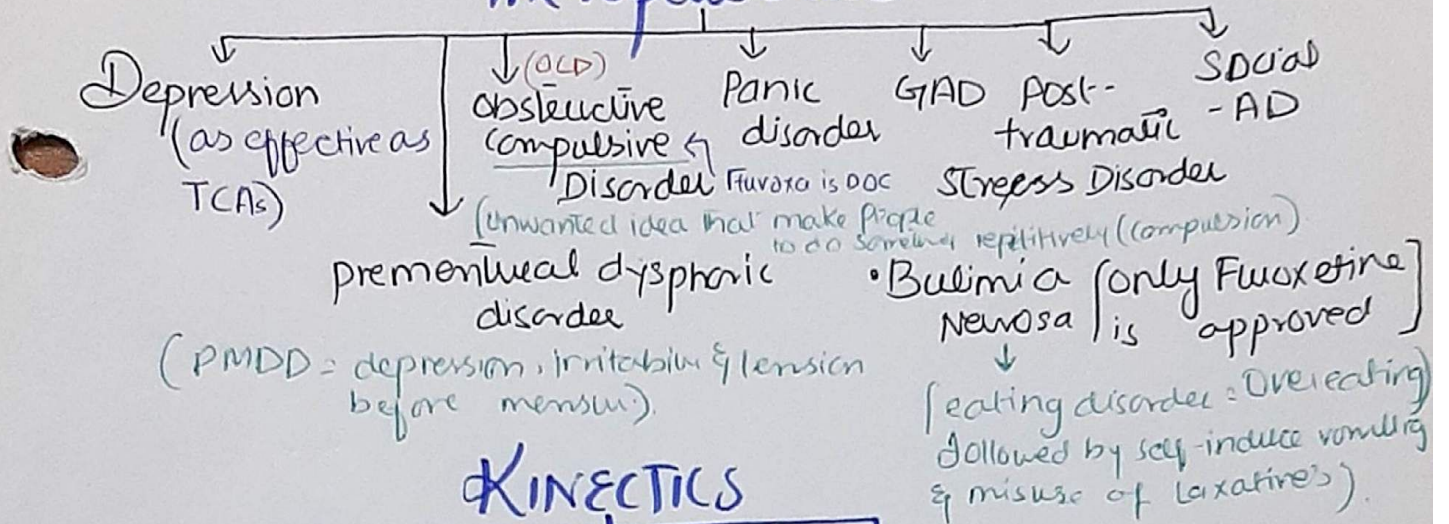
↓ ADRs (as compared to TCA) ⇒ DOC in Depression (have replace TCA & MAOI)

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## ACTION

- Block reuptake of serotonin  $\Rightarrow$  ↑ serotonin level in synaptic cleft.
- Typically take 2 weeks to produce effect - max 12 weeks

### Therapeutic uses



# KINETICS

## Absorption

- Well-absorbed
- peak = 2-8 hr
- Food = 1 abs. of Sertraline
  - little effect on other
- $t_{1/2}$  = 16-36 hr (majority)
- Fluoxetine = 50 hrs =

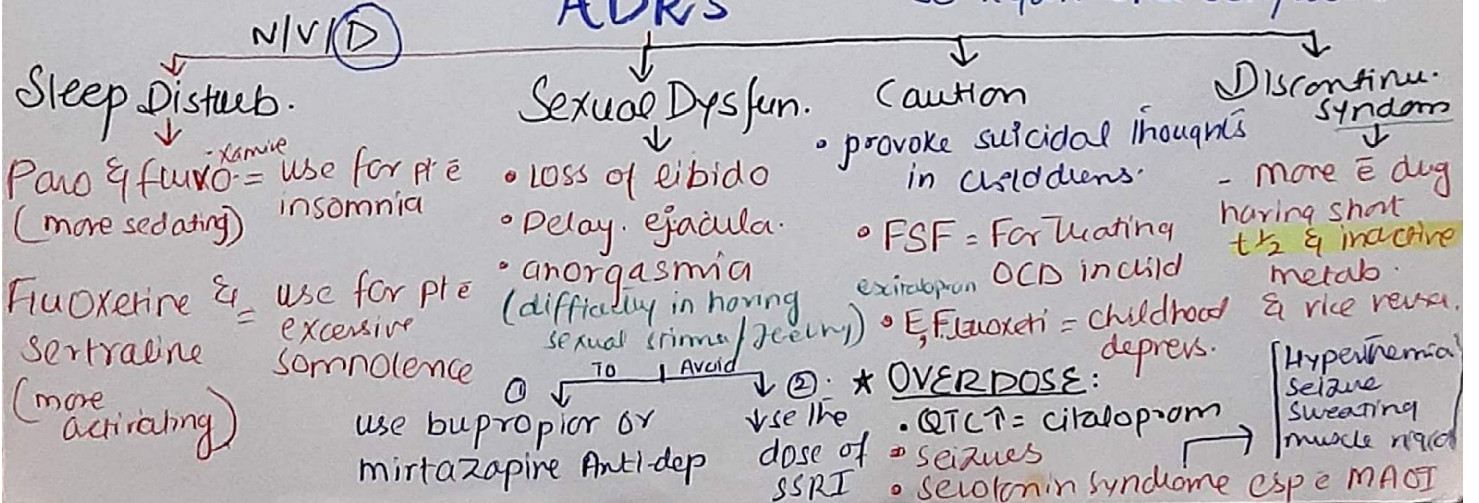
## Metabolism

- Metabolism**
- CYP450 → (glucuronide or sulfate conjug)
  - Fluoxe. & paroxetine → Inhib. of CYP 2D6 isoenzyme

200 (TCA- $\beta$ -receptor- $\beta$ -agonist)  $\swarrow$   
 To-chrad.  
 venous  
 Flow  $\uparrow$  and some anti-arrhythmic &  
 $\beta$ -antagonist drug's metabo.

active metabolite (S-norfluoxetine = today)  $\Rightarrow$  Avail as sustained release formula so require once dose/week.

# ADRS





# MONOAMINE OXIDASE INHIBITORS

- MAO → mitochondrial enzyme found in nerve, gut & liver.
- function as safety valve - oxidatively deaminate & inactivate excess NT (NE, serotonin & dopam.) that may leak out of syn. vesicle when neuron is as rest.
- MAO = in liver & gut catalyze oxido. deamin. of drugs & potentially toxic subs. such as Tyramine in certain food
- Thus MAOIs = high Drug-Drug & Drug-food Interac
- **Sellegiline** = adm. as TDDS = ↓ inhi. of liver & gut MAO at low doses as it avoids first-pass metab. (use in Parkinson's Dis.)

**ACTIONS:** Although MAO is fully inhibited after several days of treatment, the anti-dep. effect is Delay Action like SSRI, SNRI & TCAs

- **Sellegiline** & **tranylcypromine** = have amphetamine-like stimulant effect = agitation & insomnia

## Therap. uses

- Use for pts who are
  - ↳ unresponsive to TCA/SSRI
  - ↳ Allergic to
- or who experience = strong Anxiety and Atypical Depression
- Due to high D-D & D-F interactions
- Last-Line agents
- complicated dietary restrictions

## KINETICS

- well-absorb after oral
- may. regeneration occur several week after termination of drug So,
- terminating of MAOI
  - 2 week gap
  - starting another Anti-dep gap
- Hepatic metab.
- Excreted in urine

## ADRS

- aged cheese & meats
- chicken liver
- pickled or smoked fish
- Red wine
- contain Tyramine
- ⊖ ↑ ← MAOI
- Inactiv by MAOI
- Hypertensive crisis
- (management) phentolamin & prazosin
- ↓ ⊖
- occipital headache
- stiff neck
- Tachycardia
- Nausea
- arrhythmia
- seizures
- stroke.

⇒ Other ADRs: Constipation, blurred vision, **ortho. hypo.**, dry mouth

(SSRI)

⇒ must have wash out period of 2 weeks.

[risk of serotonin syndrome]

Fluoxetine

termin (6 weeks gap)

MAOI starting

Watch pharmacology lectures on Pharmaco-Study YouTube channel



**OXIDASE INHIBITORS**  
 enzyme found in  
 ve. - oxidatively  
 (e.g. dopam-) that me  
 catalyze oxida.  
 ch as Tyramine  
 Drug & Drug-  
 DDS = ↓ inhi. of  
 avoids first-po  
**CTIONS**: Although MAO  
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 stimulant

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 responsive to  
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**INECTICS**  
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**RS**  
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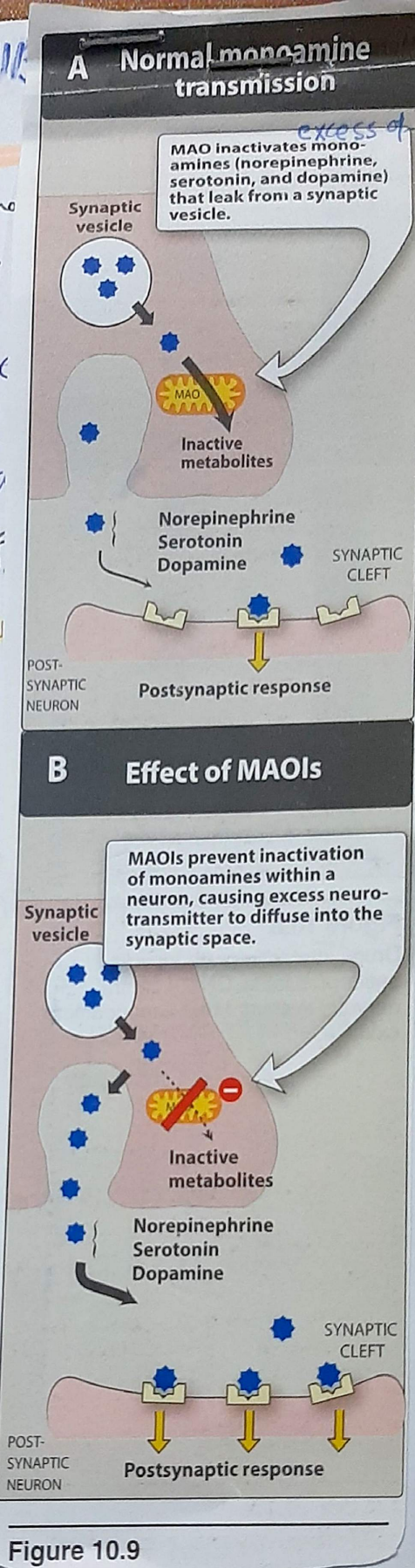


Figure 10.9



# TRICYCLIC-ANTI-Dep (TCA)

- Block NET & SET
- They include tertiary amines (imipramine = prototype) and secondary amines as well as N-demethylated metabolites of imipr & amitriptyline and tetracyclic antidepressants (amoxapine & meproboline).
- If one class doesn't respond → Try other drug of other class of TCA.

## Mechanism

### Inhibi of NE reuptake

- TCA & amoxapine = potent inhib. of neuro TCA's - block = serotonergic, NE & serotonin

- Maprotiline & Desipramine = NE reuptake inhibitors.

### Blocking of receptors

- d1-adrenergic = dizziness, vertigo
- block
- serotonergic, histaminic, & muscarinic recept = ↑ ADRs

## Action

- elevate mood, ↑ mental alertness
- ONSET = slow (2 week or longer)
- After therap. response = ↓ dose to ↑ tolerability
- ↑ se physical activity
- physical & psycholo. depend. rate

## THERAPEUTIC USES

- Depression & panic disorders
- Imipramine
  - control bed-wetting in child > 6yr
  - Replaced by Desmopressin & enuresis alarms
- Amitriptyline
  - Migraine
  - neuropathic pain
- lower dose of Doxepin in somnia.

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## KINETICS

- well absorb. after oral adm
- First-pass meta = ↓ Bioavail
- lipophilic nature
- Distribute in CSF
- Sensitive to drugs that ↑/↓ CYP450 isoenzyme
- Inactive metab via kidney

- Should be use w/ caution in bipolar disorder (mania + depressive episodes) even in depress state because treatment will shift state into mania

- TCA's = **NARROW THER. INDEX** (5-6 fold max. dose of imip = lethal)

- TCA = exacerbate = prostatic hypertrophy, epilepsy & pre-exis. arrhythmia

- Sex-Dys = MINIMAL
- Amitriptyline = **GI ↑**

## INTERACTIONS & co-adm.

- MAOI
  - ↑ BP
  - ↑ convuls
  - ↑ coma
  - Hyperpyrexia (high fever)
- Ethanol/CNS-depres
  - TOXIC
  - SEDA
- Direct-acting adrenergic
  - TCA ↓ prevent-removal of biogenic amines
  - ↑ effect of amines
- Indirect-acting
  - TCA ↓ Block their action by their preventing binding at intra-cell site



# TRICYCLIC-ANTI-Dep (TCA)

SET • They include tertiary amines (imipr and secondary amines as well metabolites of imipr & amitriptyline nortalep (amoxapin & meprobolone). doesn't respond → Try other drugs

## Mechanism

↓ NE reuptake

Blocking

Imipr = potent inhib. of neuro TCA's - block: NE & serotonin  
 & Desipramine = NE reuptake inhibitors • Amoxapin & meprobolone

## Action

mental alertness ✓ ↑ physical activity  
 (week or longer)  
 response = ↓ dose to ↑ tolerability

## THERAPEUTIC USES

Imipramine

Amitriptyline

- control bed-wetting in child > 6yr
- Replaced by Desmopressin & enuresis alarms
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## KINETICS

oral adm  
 Bioavail  
 Lipophilic nature  
 Distribute in CSF  
 Sensitive to drugs that ↑/↓ CYP450 isoenzyme  
 metab via kidney

caution in

(mania + depressive episodes)  
 treatment will shift state into mania

TER. INDEX

of imipr = 1 lethal

ostatic hyperkalemia

is. arrhythmia

↑

MAOI

↓

↑ BP

↑ convulsions

↑ coma

Hyperpyrexia (high fever)

## INTERACTIONS & co-adm.

Ethanol/  
 CNS-depres

↓

TOXIC

SEDAI

Direct-acting

adrenalg

↓

TCA prevent-removal of biogenic amines

↑ effect of amines

Indirect acting

↓

TCA Block their action by their preventing binding at intra-cellular sites

Weight gain



TCA

Dry mouth

M-block



Constipation

M-block



Urinary retention

M-block



M-block

Blurred vision

M-block

NET

α-blockade

Sinus reflex

Tachycardia

α-blockade



Arrhythmias



Nausea



Drowsiness

H<sub>2</sub>-receptor blockade

