Antidepressants

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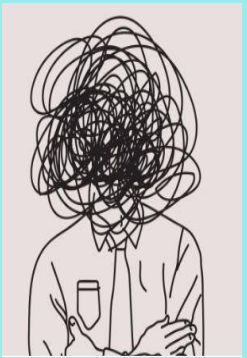
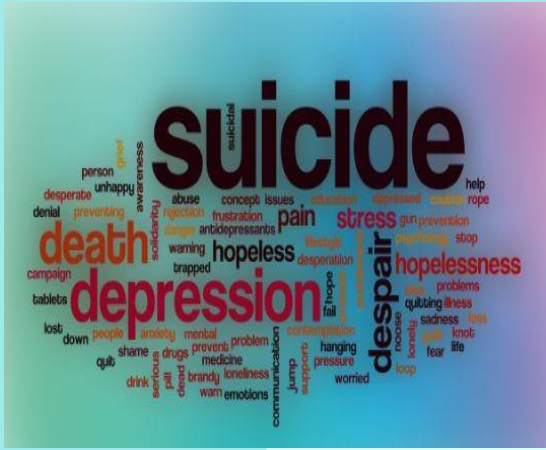
Depression

- It is a serious common disorder of mood .
- It is affects 300 million adults worldwide .
- women is more affected than men .





WORST SUICIDE?

Depression types

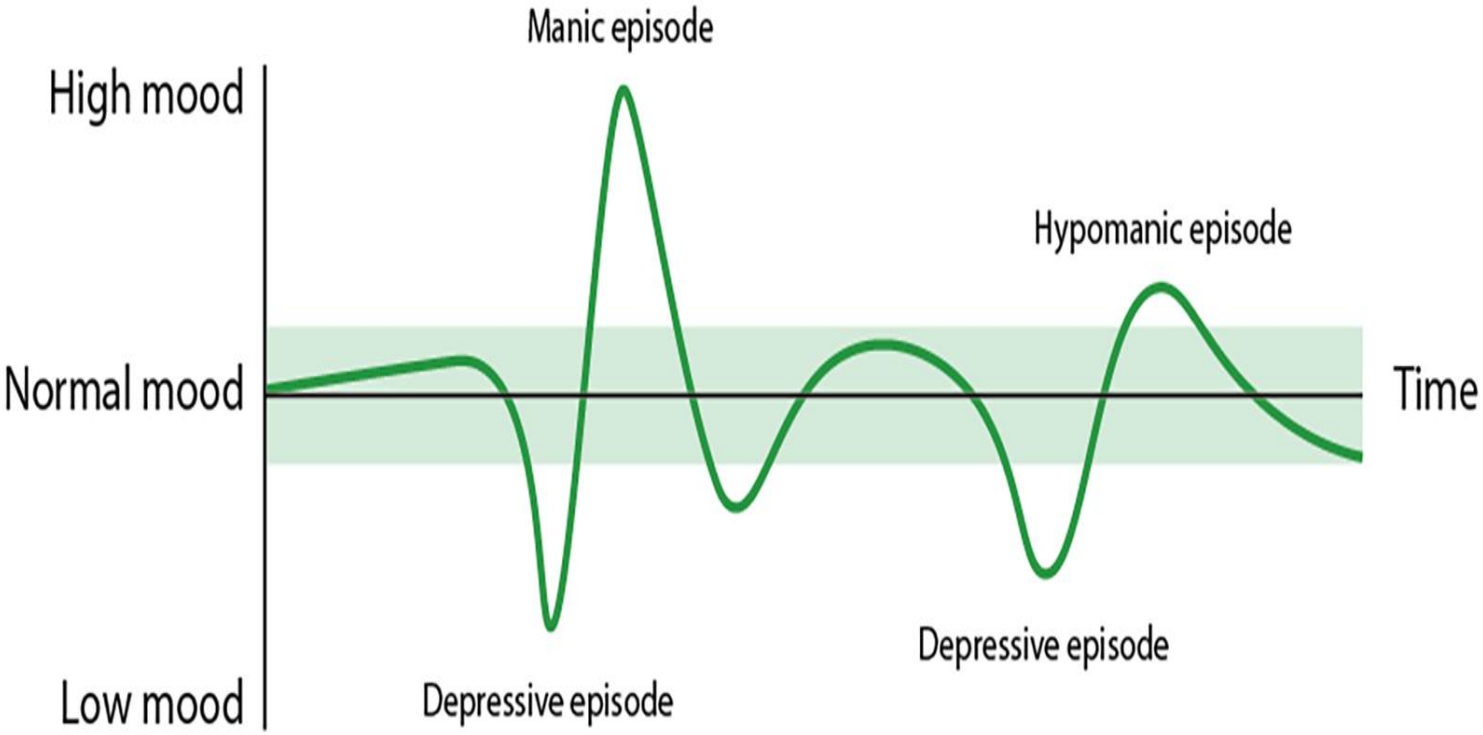
unipolar

- major depression disorder (95%)

bipolar

- manic depressive disorder (5%)

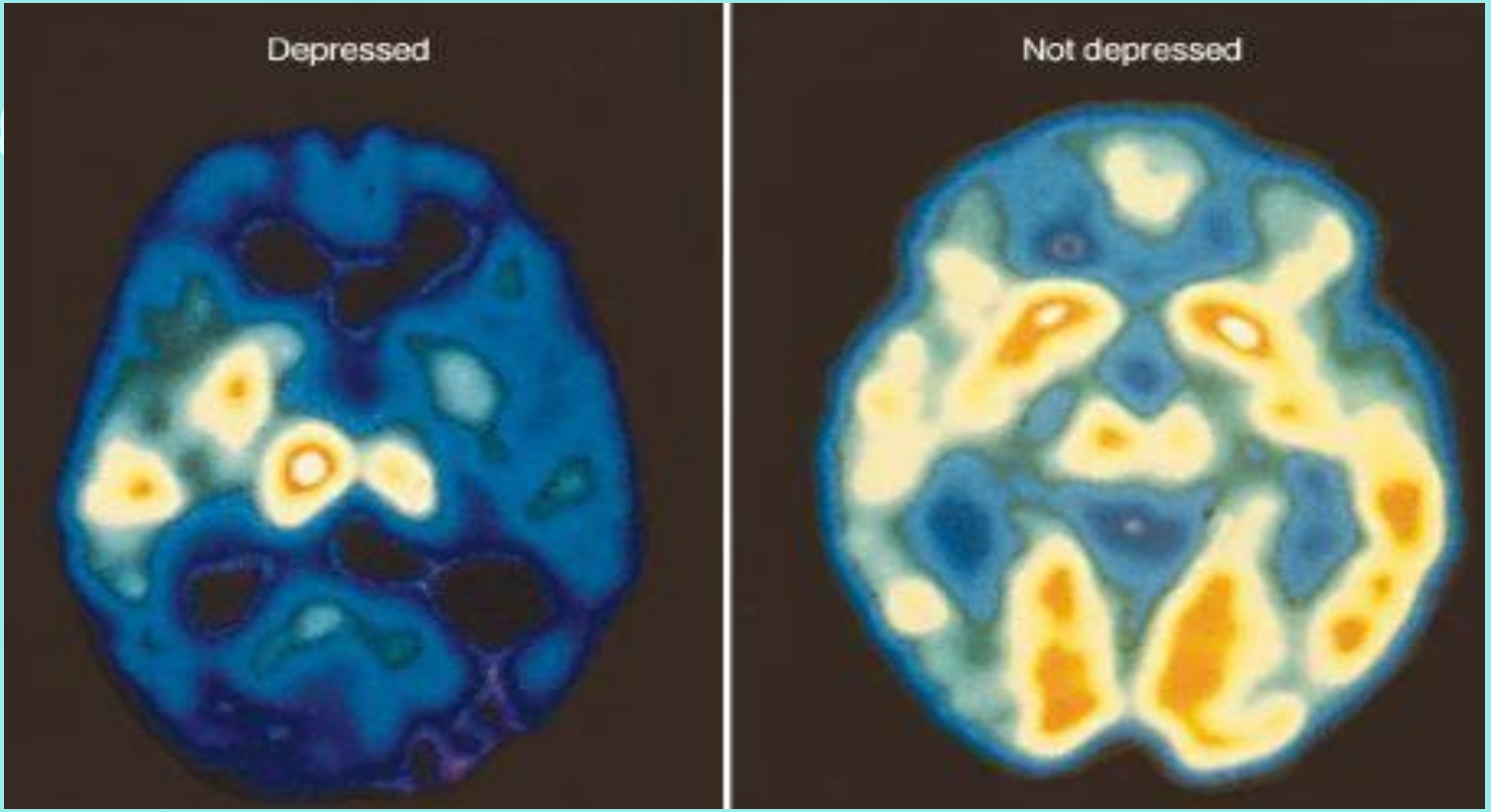
Bipolar disorder



PSYCHOLOGYTOOLS®

Pathophysiology of depression

- Genetics : to dates , 4 Genes were identified
- Biogenic amines and receptors theory :
  - low noradrenaline , serotonin and dopamine .
  - high 5HT2a and 5HT2 Receptor .
- Neurotrophic and cytokines theory :
  - Low brain derived neurotrophic factor (BDNF)
  - Proinflamatory cytokines


Depressed
Not depressed

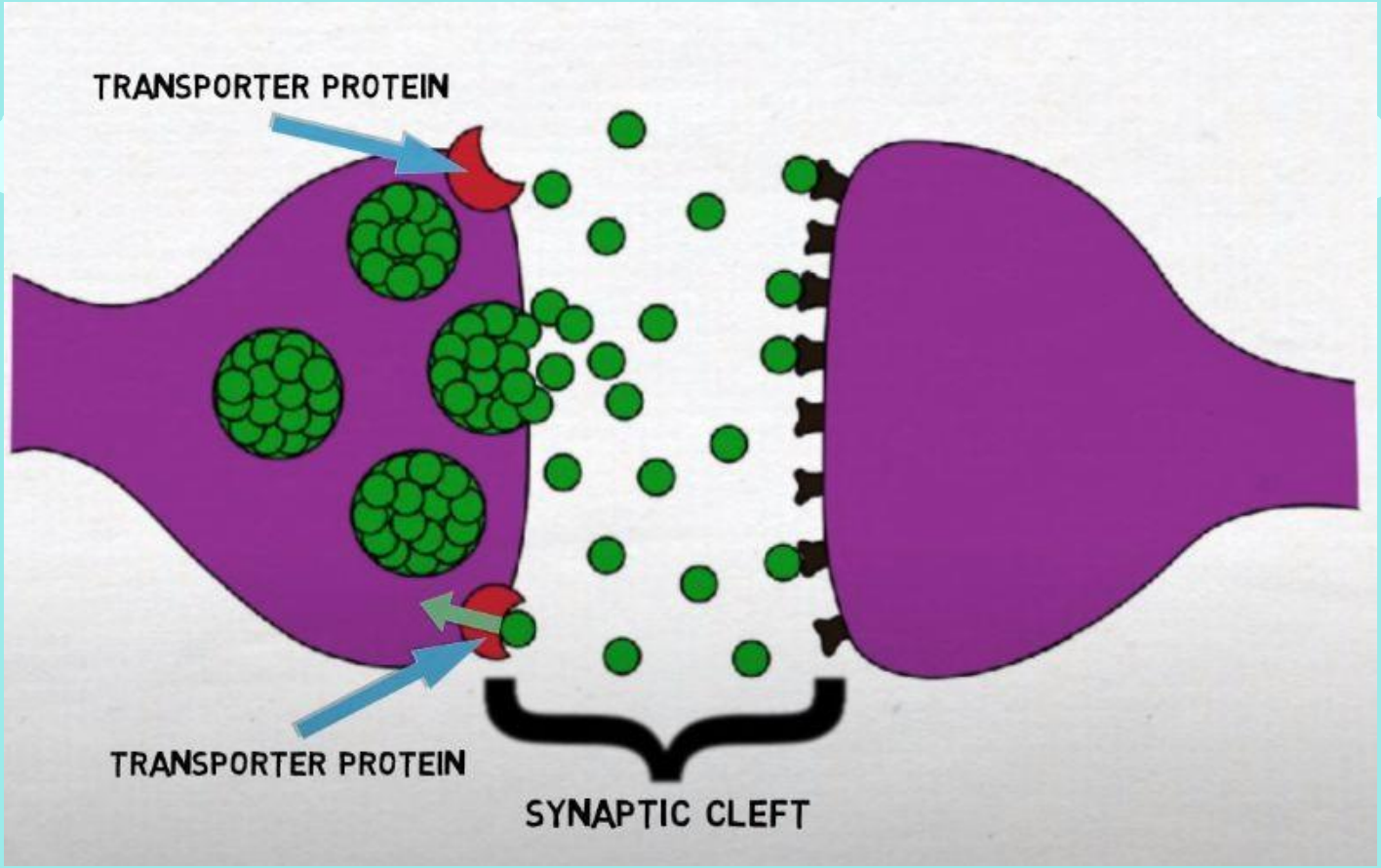
Antidepressants

- 1. Selective serotonin re-uptake inhibitors (SSRIs)
- 2. Tricyclic antidepressants (TCAs)
- 3. Atypical antidepressants >> (SNRI)
- 4. Monoamine oxidase inhibitors (MAOs)

SELECTIVE SEROTONIN REUPTAKE INHIBITORS

SELECTIVE SEROTONIN REUPTAKE INHIBITORS

- SSRIs block reuptake of serotonin, leading to increased concentrations of neurotransmitter in synaptic cleft and, ultimately, to greater postsynaptic neuronal activity , thus increasing the amount of serotonin in the brain.
- Safer and better tolerated than other classes of antidepressants .
- Because they have fewer adverse effects and are relatively safe even in overdose.


TRANSPORTER PROTEIN
TRANSPORTER PROTEIN
SYNAPTIC CLEFT

Examples of SSRIs include:

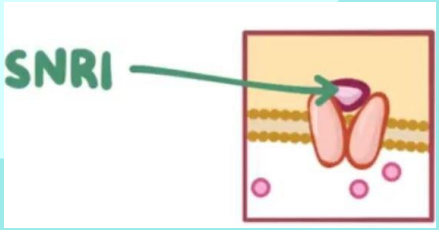
- **Fluoxetine (Prozac)—longest half-life with active metabolites**
- **Sertraline (Zoloft)-- evidence of for MI patient cause it is not cardiotoxic .**
- **Paroxetine (Paxil)—most serotonin specific, most activating (stimulant).**
- **Citalopram (Celexa)—used in Europe for 12 years prior to FDA approval in the United States.**
- **Escitalopram (Lexapro)—iso of citalopram; similar efficacy, fewer side effects .**

-SSRI can also be used in OCD and generalized anxiety disorder

SIDE EFFECTS SSRIs:

- orthostatic hypotension.
- serotonin syndrome.
- Sexual dysfunction.
- Headache
- gastrointestinal disturbance
- Sleep disturbances :sedation, insomnia
- Overdoses:seizures

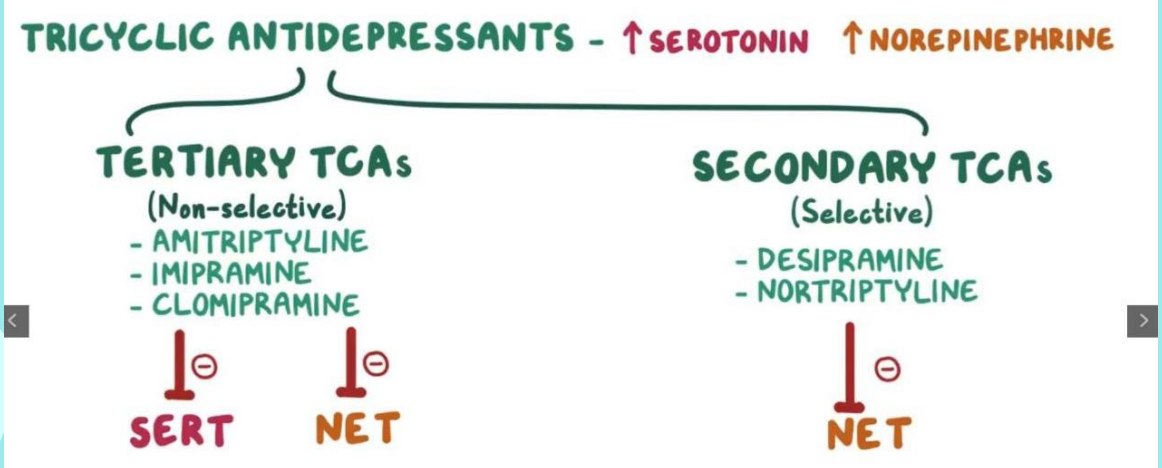
SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITORS (SNRIs)



- **Venlafaxine :**
- ■ Often used for depressive disorders, anxiety disorders like generalized anxiety disorder (GAD), and neuropathic pain.
- ■ Side-effect profile similar to SSRIs, with the exception of increased blood pressure (BP) in higher doses; do not use in patients with untreated or labile BP.
- **Duloxetine:**
- Often used for people with depression, neuropathic pain, and in fibromyalgia.
- ■ Side effects are similar to SSRIs, but more dry mouth and constipation relating to its norepinephrine effects.
- ■ Hepatotoxicity may be more likely in patients with liver disease or heavy alcohol use.

TRICYCLIC ANTIDEPRESSANTS

Imipramine, Clomipramine ,
Amitriptyline , Nortriptyline



Mechanism of action

- Block re-uptake of 5-HT and norepinephrine increased concentrations of monoamines in synaptic cleft

Also have “Broad spectrum” :

- Anti-histamine
- Anti-cholinergic
- Block alpha-1 receptors

Therapeutic Uses

1. Major depressive Disorder
2. Chronic pain condition e.g. fibromyalgia
3. Nocturnal enuresis in children: imipramine

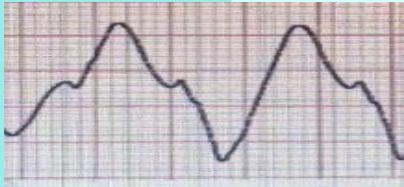
Side effects

-TCAs are highly protein bound and lipid soluble, and therefore can inter act with other medications that have high protein binding

-The side effects of TCAs are mostly due to their lack of specificity and interaction with other receptors

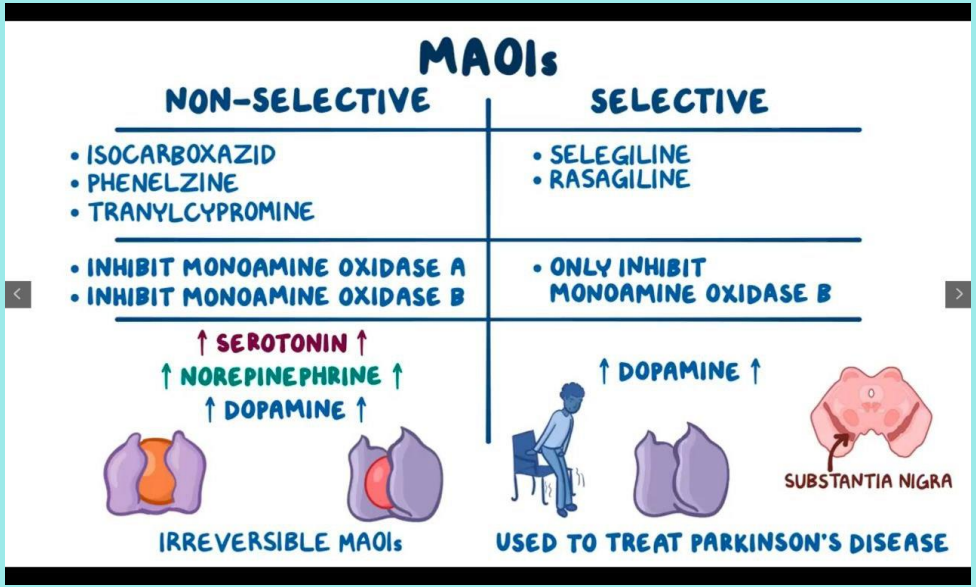
Side effects

- **Antihistaminic properties:** Sedation and weight gain.
- **Antiadrenergic properties** (cardiovascular side effects): Orthostatic hypotension, arrhythmias, and (ECG) changes (widening QRS, QT, and PR intervals).
- **Antimuscarinic effects** (also called anticholinergic): Dry mouth, constipation, urinary retention, blurred vision.
- **Lethal in overdose**—Symptoms of overdose include agitation, tremors, ataxia, arrhythmias, delirium, hypoventilation from central nervous system (CNS) depression, myoclonus, hyperreflexia, seizures, and coma.
- **Seizures:** (Higher risk of seizures at high doses and overdoses).
- **Serotonergic effects:** Erectile/ejaculatory dysfunction in males, anorgasmia in females



MONOAMINE OXIDASE INHIBITORS

Phenelzine , Tranylcypromine , Isocarboxazid .



Mechanism of action

- Prevent the inactivation of biogenic amines such as norepinephrine, serotonin, dopamine, and tyramine .
-By irreversibly inhibiting the enzymes MAO-A and B,MAOIs increase the number of neurotransmitters available in synapses.
- MAO-A preferentially deactivates serotonin and norepinephrine, and MAO-B preferentially deactivates phenethylamine; both types also act on dopamine and tyramine.

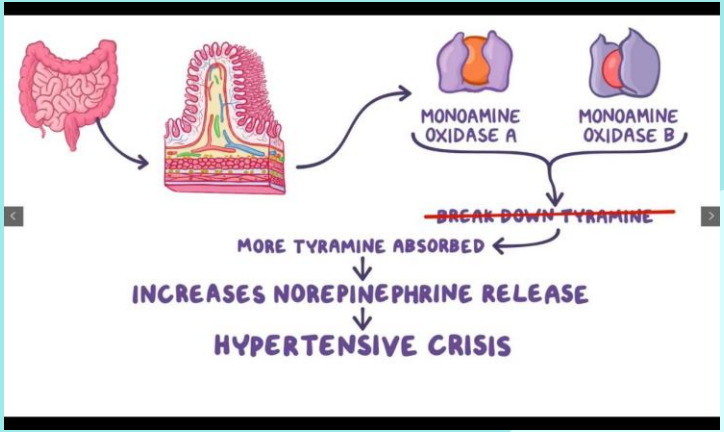
Therapeutic uses

-MAOIs are not used as first-line agents because of the increased safety and tolerability of newer agents, notably SSRIs/SNRIs. However, MAOIs are used for certain types of **refractory depression** and in refractory anxiety disorders

-MAO-B selective: selegiline • Used in Parkinson's

Side Effects

- **Serotonin syndrome** occurs when SSRIs and MAOIs are taken together.
- **Hypertensive crisis** "Cheese effect" : Risk when MAOIs are taken with tyramine-rich foods or sympathomimetics.
  -Foods with tyramine (cheese, chicken liver, fava beans, meats) cause a buildup of stored catecholamines.
- **Orthostatic hypotension** (most common).
- **Drowsiness.**



ATYPICAL ANTIDEPRESSANTS

Receptor blockers

-Serotonin Receptor Antagonists and Agonists (Trazodone , Nefazodone):

-Useful in the treatment of major depression, major depression with anxiety, and insomnia (secondary to its sedative effects)

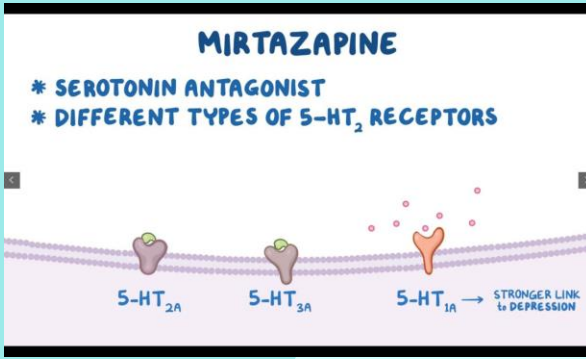
-Side effects include nausea, dizziness, orthostatic hypotension, cardiac arrhythmias, sedation, and priapism (especially with trazodone).

■ Because of orthostatic hypotension in higher doses, trazodone is not frequently used solely as an antidepressant.

- α2-Adrenergic Receptor Antagonists (Mirtazapine) :

-Useful in the treatment of major depression, especially in patients who have significant weight loss and/or insomnia.

■ Side effects include sedation, weight gain, dizziness, tremor, dry mouth, constipation.



Bupropion :

- Norepinephrine-dopamine reuptake inhibitor.
- Relative lack of sexual side effects as compared to the SSRIs.
- Some efficacy in treatment of (ADHD)
- Effective for smoking cessation.
- Weight neutral
- Side effects include increased anxiety, as well as increased risk of seizures and psychosis at high doses.
- Contraindicated in patients with epilepsy or active eating disorders .

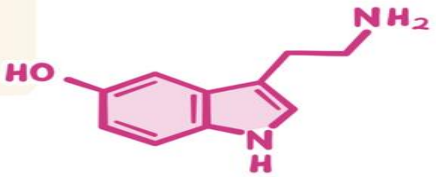
Selective Serotonin Reuptake Inhibitors (SSRIs) briefly...

SSRI	*Significant distinguishing features (evidence level)*
Citalopram	No significant inhibition of hepatic enzymes (P) Possibly less safe in overdose[1] (III)
Fluoxetine	Long elimination half-life (P) Inhibition of hepatic enzymes (P) Slower onset of antidepressant action[1] (I) Possibly causes more agitation and adverse dermatological reactions[1] (I–II) Abrupt treatment interruption least likely to cause discontinuation reactions[1] (I) Probably safe in pregnancy and breast-feeding (III) Associated with most stable pattern of prescription in primary care[1] (II)
Fluvoxamine	Inhibition of hepatic enzymes (P) Less well tolerated, especially in higher doses[1] (I) More severe gastrointestinal side-effects[1] (II) Possibly less sexual dysfunction[1] (I)
Paroxetine	Inhibition of hepatic enzymes (P) Possibly causes more sedation and sexual dysfunction1 (II) Possibly more weight gain during long-term use[1] (I) Abrupt treatment interruption most likely to cause discontinuation reactions[1] (I–II)
Sertraline	Little significant inhibition of hepatic enzymes (P) Relatively safe in breast-feeding (III)

Serotonin Syndrome

BACKGROUND

* LIFE-THREATENING TOXICITY caused by EXCESS SEROTONIN
  - "SEROTONIN TOXICITY" or "SEROTONIN TOXIDROME"



CAUSES

* ANTIDEPRESSANT MEDICATION
  - SSRIs & SNRIs
  - TCAs
  - MAOIs
* OPIOIDS
  - TRAMADOL
* OTHER MEDICATIONS
  - ONDANSETRON
  - CIPROFLOXACIN
  - SUMATRIPTAN
* ILLICIT DRUGS & DIETARY SUPPLEMENTS

DIAGNOSIS

* PRESENTATION
* EXCLUDING OTHER POSSIBLE CAUSES
* HUNTER SEROTONIN TOXICITY CRITERIA (HSTC):
  - 1. MUST TAKE SEROTONERGIC MEDICATION
  - 2. SPONTANEOUS CLONUS
* RULE OUT NEUROLEPTIC MALIGNANT SYNDROME (NMS)

SIGNS & SYMPTOMS

3 A's:

* ALTERED MENTAL STATE
  - AGITATION, RESTLESSNESS, or ANXIETY
* NEUROMUSCULAR ABNORMALITIES
  - OCULAR CLONUS, HYPERREFLEXIA, TREMORS, RIGIDITY of MUSCLES
* AUTONOMIC HYPERACTIVITY
  - TACHYCARDIA, HYPERTENSION, DIAPHORESIS, MYDRIASIS, FLUSHED SKIN, ARRYTHMIAS, VOMITING, or DIARRHEA

MILD:

* TREMORS, SWEATING, TACHYCARDIA, HYPERTENSION, & NAUSEA

SEVERE:

* FEVER, HYPERACTIVE BOWEL SOUNDS, CLONUS, AGITATION, HYPERTHERMIA, & DELIRIUM
* AS CONDITION WORSENS, RHABDOMYOLYSIS, MYOGLOBINURIA, RESPIRATORY & KIDNEY FAILURE

TREATMENT

* DISCONTINUE SEROTONERGIC MEDICATION
* SUPPORTIVE CARE
* OFTEN RESOLVES within 24 HOURS of CESSATION
* RARELY, INTUBATION & VENTILATORY SUPPORT
* SUPPORTIVE MEASURES INSUFFICIENT
  - SEROTONIN ANTAGONISTS to REVERSE EFFECTS