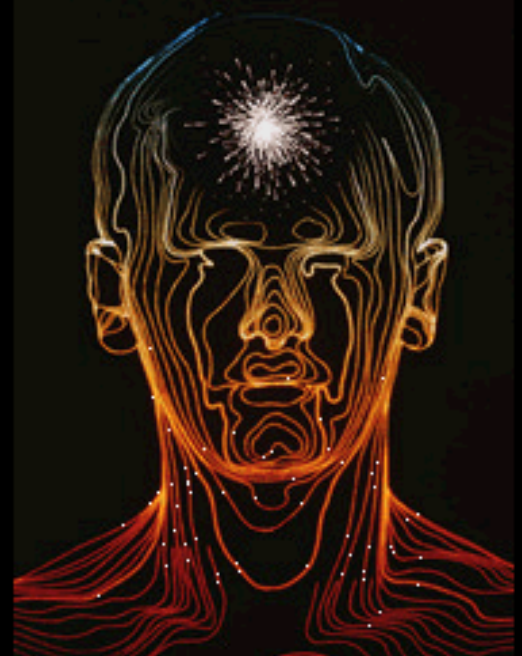


Antidepressants

CNS 1 Module

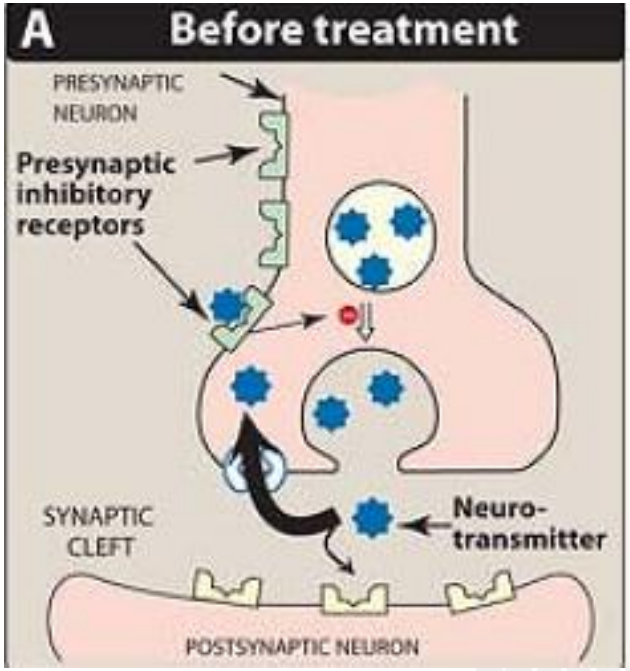
3rd Year MD

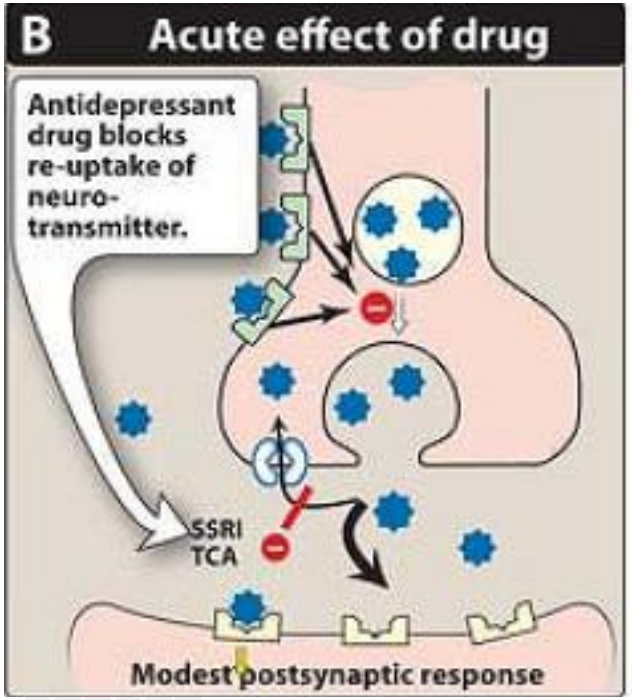
Dr. Laila Matalqah

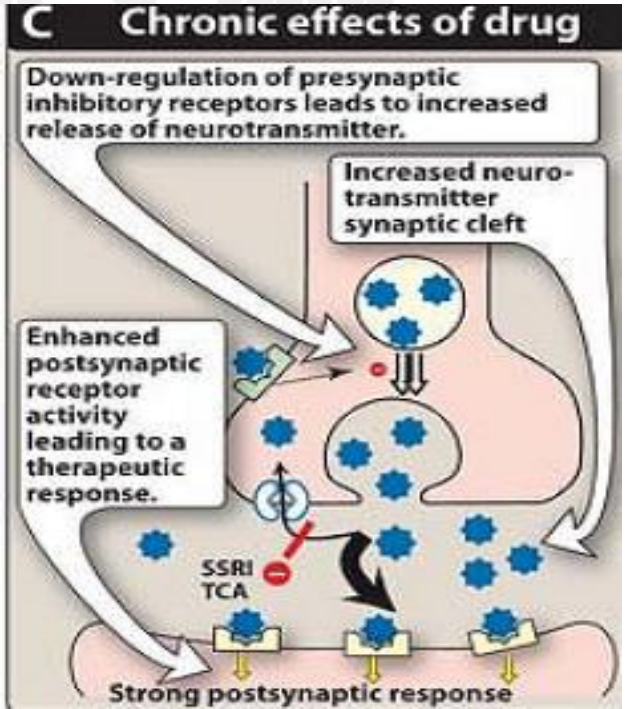
(Ph.D Clinical pharmacology)

Dr. Romany Helmy Thabet

(PhD, *Pharmacology)*


A
Before treatment
PRESYNAPTIC NEURON
Presynaptic inhibitory receptors
SYNAPTIC CLEFT
Neuro-transmitter
POSTSYNAPTIC NEURON


B
Acute effect of drug
Antidepressant drug blocks re-uptake of neuro-transmitter.
SSRI
TCA
Modest postsynaptic response


C
Chronic effects of drug
Down-regulation of presynaptic inhibitory receptors leads to increased release of neurotransmitter.
Increased neuro-transmitter synaptic cleft
Enhanced postsynaptic receptor activity leading to a therapeutic response.
SSRI
TCA
Strong postsynaptic response

Selective Serotonin Reuptake Inhibitors

- SSRIs have greater selectivity for the serotonin transporter as compared to the norepinephrine transporter.
- This contrasts with the ***tricyclic antidepressants*** that ***nonselectively*** inhibit the uptake of norepinephrine and serotonin
- SSRIs take ***at least 2 weeks*** to produce significant improvement in mood, and maximum benefit may require up to 12 weeks or more.
- **Note:** These drugs do not usually produce CNS stimulation or mood elevation in normal individual

- SSRIs have ***little blocking activity at*** muscarinic, α1-adrenergic, and histaminic H1 receptors.

- Therefore, ***common side effects*** associated with tricyclic antidepressants, such as orthostatic hypotension, sedation, dry mouth, and blurred vision, are not commonly seen with the SSRIs.

- So, largely replaced tricyclic antidepressants and monoamine oxidase inhibitors as the drugs of choice in treating depression.

Therapeutic uses

- Depression
- Obsessive-compulsive disorder (the only approved indication for *fluvoxamine*),
- Panic disorder,
- Generalized anxiety disorder,
- Posttraumatic stress disorder,
- Social anxiety disorder,
- Premenstrual dysphoric disorder, and
- Bulimia nervosa (only *fluoxetine* is approved for this).

- ***Fluoxetine*** **differs from the other members of the class in two respects;**

1. Has a much longer half-life (50 hours) and is available as a sustained-release preparation allowing ***once-weekly dosing***.
2. its metabolite is as potent as the parent compound. The half-life of the metabolite is quite long, averaging 10 days.

- *Fluoxetine* and *paroxetine* are ***potent inhibitors of a hepatic cytochrome P450*** isoenzyme (CYP2D6) responsible for the elimination of tricyclic antidepressant drugs, neuroleptic drugs, and some antiarrhythmic

Adverse effects

- Headache,
- Sweating,
- Anxiety and agitation,
- Gastrointestinal effects (nausea, vomiting, diarrhea),
- Weakness and fatigue,
- Sexual dysfunction,
- Changes in weight,
- Sleep disturbances (insomnia and somnolence), and
- Drug-drug interactions
- **Discontinuation syndrome;** *Fluoxetine* has the lowest risk *(headache, malaise and flu-like symptoms, agitation and irritability, nervousness, and changes in sleep pattern)*

Serotonin-Norepinephrine Reuptake Inhibitors

- *Venlafaxine* and *duloxetine* selectively inhibit the re-uptake of both serotonin and norepinephrine.
- SNRIs may be effective in treating depression in patients in whom SSRIs are ineffective.
- Furthermore, depression is often accompanied by chronic painful symptoms, such as backache and muscle aches, against which SSRIs are also relatively ineffective.

- SNRIs and tricyclic antidepressants, with their dual actions of inhibiting both serotonin and norepinephrine reuptake are sometimes effective in relieving physical symptoms of neuropathic pain, such as diabetic peripheral neuropathy.

- SNRIs unlike the tricyclic antidepressants, have little activity at adrenergic, muscarinic, or histamine receptors and, thus, have fewer of these receptor-mediated adverse effects than the tricyclic antidepressants.
- May precipitate a discontinuation syndrome

Atypical Antidepressants

Bupropion

- Acts as a weak dopamine and norepinephrine reuptake inhibitor
- Short half-life so, may require more than once-a-day dosing or the administration of an extended-release formulation
- A very low incidence of sexual dysfunction, and
- An increased risk for seizures at high doses.
- It assists in decreasing the craving and attenuating the withdrawal symptoms for *nicotine* in tobacco users trying to quit smoking.

TCAs

1. *The tertiary amines;* (the prototype drug), *amitriptyline*, *clomipramine*, *doxepin* and *trimipramine.*

2. *The secondary amines; desipramine* and *nortriptyline*

- Patients who do not respond to one TCA may benefit from a different drug in this group.
- These drugs are a valuable alternative for patients who do not respond to SSRIs

TCAs

e.g. *imipramine, amitriptyline*

- **Inhibition of neurotransmitter reuptake:** TCAs are potent inhibitors of the neuronal reuptake of norepinephrine and serotonin into presynaptic nerve terminals

- **Blocking of receptors:** TCAs also block serotonergic, α-adrenergic, histaminic, and muscarinic receptors

Therapeutic uses of TCAs

- Moderate to severe major depression
- Panic disorder
- *Imipramine;* control bed-wetting in children (older than 6 years) *by causing contraction of the internal sphincter of the bladder. (used cautiously because of the inducement of cardiac arrhythmias and other serious cardiovascular problems).*
- *Amitriptyline*, used to treat migraine headache and chronic pain syndromes (for example, neuropathic pain)

Adverse effects of TCAs

- ***Blockade of muscarinic receptors;*** blurred vision, xerostomia (dry mouth), urinary retention, constipation, and aggravation of narrow-angle glaucoma.
- ***Block α1-adrenergic receptors;*** orthostatic hypotension (*Imipramine* is the most likely).
- ***Block histamine H1 receptors;*** Sedation, especially during the first several weeks of treatment.
- Weight gain
- Sexual dysfunction

Monoamine Oxidase Inhibitors

- Three MAO inhibitors are currently available for treatment of depression:

1. *phenelzine*,
2. *tranylcypromine* and
3. *Selegiline;* the agent that was prior-approved for Parkinson's disease, but is now also approved for depression.

Therapeutic uses

- Depressed patients who are unresponsive or allergic to TCAs or who experience strong anxiety.
- Patients with low psychomotor activity may benefit from the stimulant properties of the MAO inhibitors.
- Phobic states.
- Atypical depression

Note; Despite their efficacy in treating depression, because of their risk for drug-drug and drug-food interactions, the MAO inhibitors are considered to be last-line agents in many treatment venues.

Adverse effects

- ***Cheese reaction;*** tyramine is contained in certain foods, such as aged cheeses and meats, chicken liver, pickled or smoked fish and red wines, is normally inactivated by MAO in the gut. Individuals receiving a MAO inhibitor are unable to degrade tyramine obtained from the diet. Tyramine causes the release of large amounts of stored catecholamines from nerve terminals, resulting in occipital headache, stiff neck, tachycardia, nausea, hypertension, cardiac arrhythmias, seizures, and possibly, stroke.

- Drowsiness,
- Orthostatic hypotension,
- Blurred vision, dry mouth, dysuria, and constipation.
- The MAO inhibitors and SSRIs should not be coadministered. Both types of drugs require washout periods of at least 2 weeks before the other type is administered, with the exception of *fluoxetine,* which should be discontinued at least 6 weeks before a MAO inhibitor is initiated.

Antidepressants in depression

- Treatment response
  - Weeks 1-2
    - Physical responses
      - Improvement in appetite and sleep
  - Weeks 3-4
    - Energy and cognitive responses
      - Improvement in energy
      - Improvement in guilt, concentration
  - Weeks 5-6
    - Emotional responses
      - Improvement in mood

Drug treatment mild depression

- ‘Antidepressants are not recommended for the initial treatment of mild depression, because the risk-benefit ratio is so poor’
- Start CBT (**cognitive behavioral therapy)**
- Persistent symptoms – start SSRI
- Mild depressive episode in those with a history of moderate or severe depression – treat with SSRI

Treatment of moderate to severe depression

- ‘In moderate depression, offer antidepressant medication routinely, before psychological interventions’
- Delay in onset of effect
- Risk assessment – See those considered high risk of suicide and less than 30 years old one week post initiation, limit quantity prescribed

Treatment of moderate to severe depression

- If increased agitation develops early in treatment with an SSRI, provide appropriate information and, if the patient prefers, either change to a different antidepressant (Mirtazapine, Moclobemide)or consider a brief period of concomitant treatment with a **benzodiazepine** followed by a clinical review within 2 weeks.

Special patient characteristics

- Women – poorer toleration of **imipramine**
- **Sertraline** 1st choice in those with recent MI or unstable angina
- ECG and BP must be checked before starting a **TCA** in a patient at significant risk of CVD
- Venlafaxine and TCA contraindicated in those with recent MI or high risk serious cardiac arrhythmias