BIOLOGICAL INTERVENTION FOR DEPRESSION

I. Psychopharmacological Intervention -

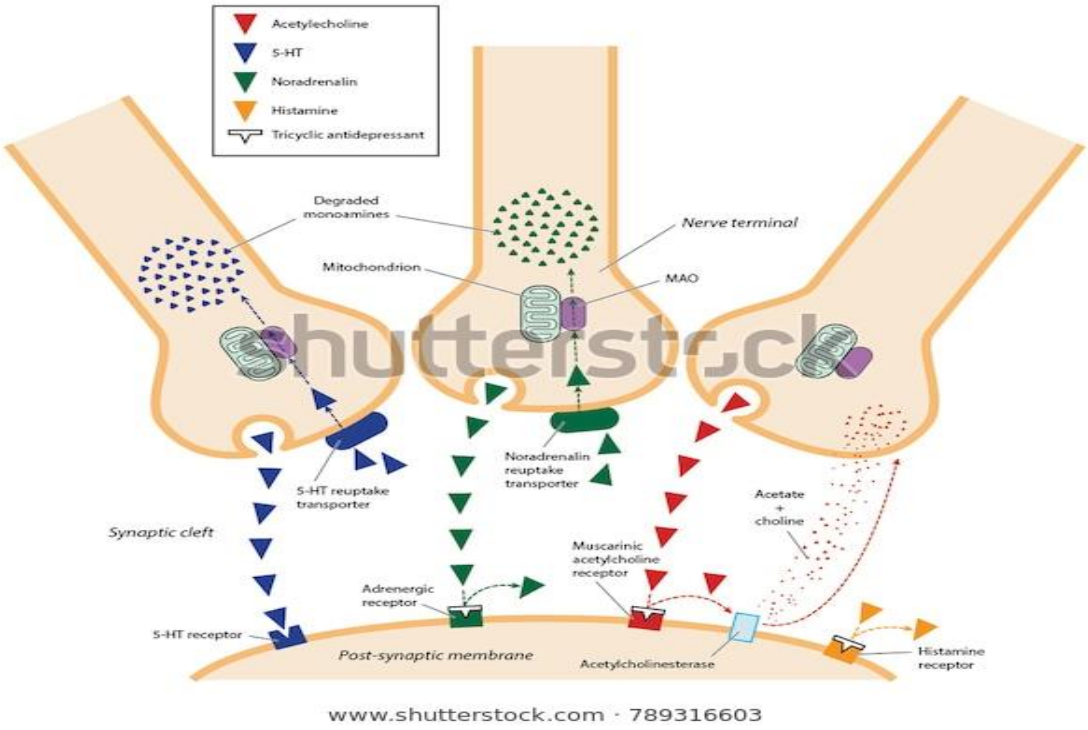
Antidepressants-are those drugs which help in the reduction in symptoms of depressive disorders by altering chemical imbalances of neurotransmitters in the brain. The antidepressants mostly inhibit reuptake of neurotransmitters through selective receptors thereby increasing the concentration of specific neurotransmitter around the nerves in the brain

A. Monoamine Reuptake Inhibitors-

Following release of the neurotransmitter into the synaptic gap, a specific transporter facilitates its reuptake into the presynaptic neurone. **Several classes of antidepressant act primarily via inhibition of this reuptake process. They are distinguished firstly by their selectivity for the transporter over receptors for other neurotransmitters, and secondly by their relative affinity for blockade of the reuptake of each of the monoamines.**

1. Tricyclic Antidepressants (TCAs)

- This heterogeneous group contains the earliest reuptake inhibitors.
- They basically inhibit the reuptake of serotonin and noradrenaline.
- TCAs also antagonize postsynaptic α1-adrenoceptors, histamine (H1) receptors, muscarinic cholinergic receptors and serotonin (5-HT2) receptors. These actions are responsible for the excess in side effects and toxic effects in comparison with more selective drugs such as the SSRIs.



Generic Drug names-

- amitriptyline
- clomipramine
- doxepin
- imipramine
- trimipramine
- amoxapine
- desipramine
- nortriptyline
- protriptyline

Side effects –

Many side effects may be related to the antimuscarinic properties of the TCAs. Such side effects are relatively common and may include dry mouth, dry nose, blurry vision, lowered gastrointestinal motility or constipation, urinary retention, cognitive and/or memory impairment, and increased body temperature.

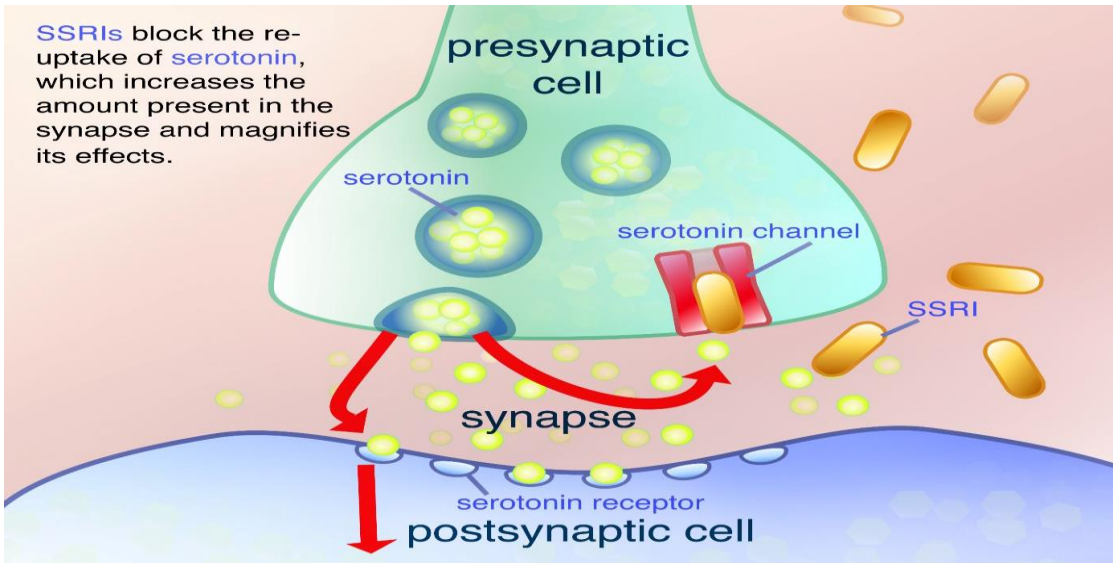
Other side effects may include drowsiness, anxiety, emotional blunting (apathy/anhedonia), confusion, restlessness, dizziness, hypersensitivity, changes in appetite and weight, sweating,

muscle twitches, weakness, nausea and vomiting, hypotension, tachycardia, and rarely, irregular heart rhythms. Rhabdomyolysis or muscle breakdown has been rarely reported with this class of drugs as well.

2. Selective serotonin reuptake inhibitors (SSRIs)

Although the development of the TCAs resulted in drugs that had greater affinity for the reuptake blockade of either serotonin or noradrenaline, the SSRIs are considered to be the first 'designer' antidepressants as they are highly selective for the 5-HT transporter.

Selective serotonin reuptake inhibitors (SSRIs) are believed to increase the extracellular level of the neurotransmitter serotonin by limiting its reabsorption into the presynaptic cell, increasing the level of serotonin in the synaptic cleft available to bind to the postsynaptic receptor. They have varying degrees of selectivity for the other monoamine transporters, with pure SSRIs having only weak affinity for the norepinephrine and dopamine transporters.



Generic Names-

- Citalopram
- Escitalopram
- Fluoxetine
- Paroxetine
- Sertraline

Possible side effects of SSRIs may include, among others:

- Nausea, vomiting or diarrhea
- Headache
- Drowsiness
- Dry mouth
- Insomnia
- Nervousness, agitation or restlessness
- Dizziness
- Sexual problems, such as reduced sexual desire, difficulty reaching orgasm or inability to maintain an erection (erectile dysfunction)
- Impact on appetite, leading to weight loss or weight gain
- Serotonin Syndrome

SEROTONIN SYNDROME –

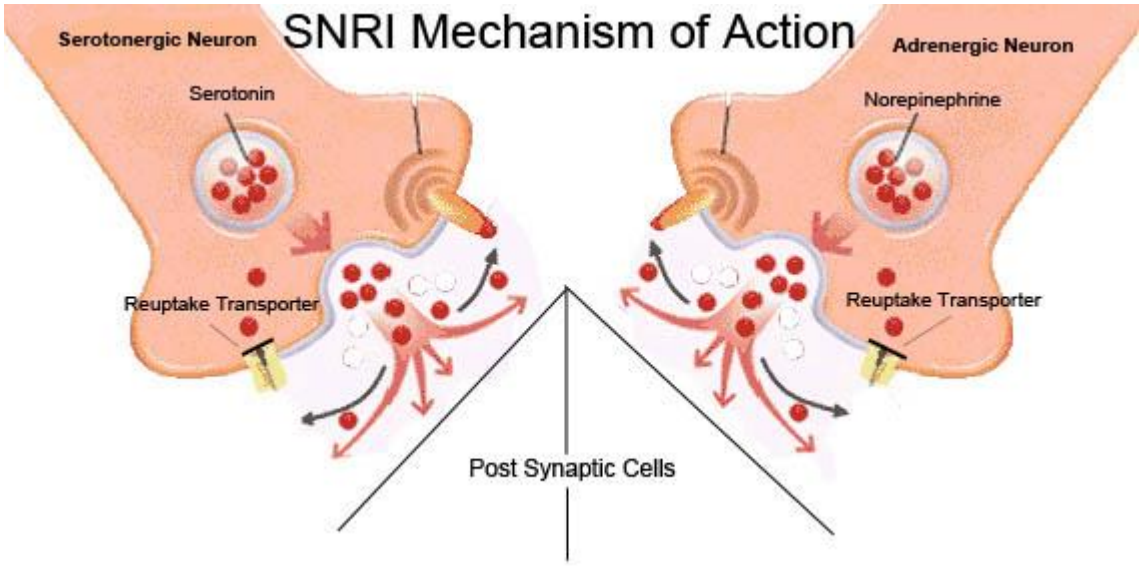
Serotonin syndrome occurs when you take medications that cause high levels of the chemical serotonin to accumulate in your body.Serotonin is a chemical our body produces that's needed for your nerve cells and brain to function. But too much serotonin causes signs and symptoms that can range from mild (shivering and diarrhea) to severe (muscle rigidity, fever and seizures). Severe serotonin syndrome can cause death if not treated.

Serotonin syndrome can occur when you increase the dose of certain medications or add a new drug to your regimen. Some illegal drugs and dietary supplements also are associated with serotonin syndrome. Milder forms of serotonin syndrome may go away within a day of stopping the medications that cause symptoms and, sometimes, after taking drugs that block serotonin.

3. Serotonin–norepinephrine reuptake inhibitors

Serotonin–norepinephrine reuptake inhibitors (SNRIs) are potent inhibitors of the reuptake of serotonin and norepinephrine. These neurotransmitters are known to play an important role in mood. SNRIs can be contrasted with the more widely used selective serotonin reuptake inhibitors (SSRIs), which act mostly upon serotonin alone.

The human serotonin transporter (SERT) and norepinephrine transporter (NET) are membrane proteins that are responsible for the reuptake of serotonin and norepinephrine. Balanced dual inhibition of monoamine reuptake can possibly offer advantages over other antidepressants drugs by treating a wider range of symptoms.



Generic names-

- Desvenlafaxine
- Duloxetine
- Levomilnacipran
- Venlafaxine

Side effects-

The most common possible side effects of SNRIs include:

- Nausea
- Dry mouth
- Dizziness
- Headache
- Excessive sweating

Other possible side effects may include:

- Tiredness
- Constipation
- Insomnia

- Changes in sexual function, such as reduced sexual desire, difficulty reaching orgasm or the inability to maintain an erection (erectile dysfunction)
- Loss of appetite

4. Other Reuptake inhibitors –

Norepinephrine-dopamine reuptake inhibitors

Norepinephrine and dopamine reuptake inhibitors (NDRIs) are antidepressant medications (Atypical ADM'S) that block the action of specific transporter proteins, increasing the amount of active norepinephrine and dopamine neurotransmitters throughout the brain.

The only drug used of this class for depression is bupropion.

Side effects of NDRIs can include-

- Insomnia.
- Agitation.
- Anxiety.
- Headache.
- Dizziness.
- Sweating.
- Dry mouth.
- Nausea.
- Abdominal pain.
- Weight loss.
- Constipation.
- High blood pressure.
- Tremors.
- Rash.
- Higher-than-normal energy levels and mood (hypomania – rare).

Norepinephrine reuptake inhibitors-

NRI are a type of drug that acts as a reuptake inhibitor for the neurotransmitter norepinephrine (noradrenaline) by blocking the action of the norepinephrine transporter (NET). This in turn leads to increased extracellular concentrations of norepinephrine. The first selective noradrenaline reuptake inhibitor to be marketed was reboxetine, an effective antidepressant (Atypical ADM'S) with reasonable tolerability.

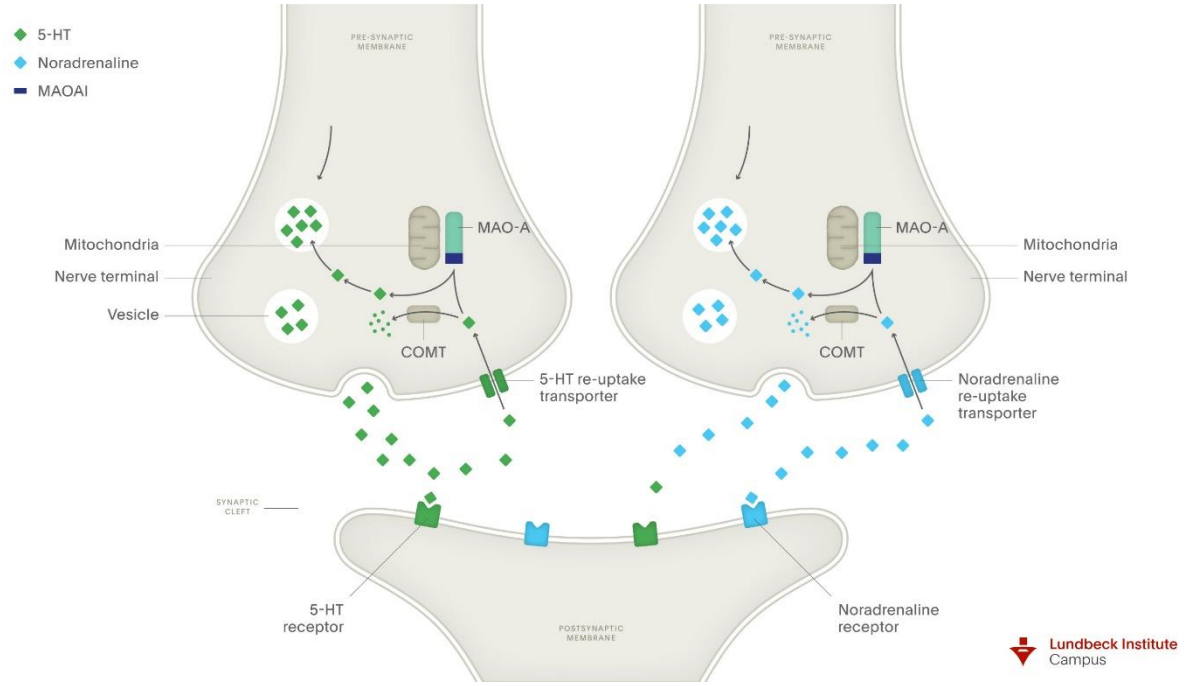
B. Monoamine Enzyme inhibitors

These drugs offer an alternative mechanism for increasing the synaptic availability of serotonin, noradrenaline and dopamine. The metabolism of these neurotransmitters within the presynaptic nerve terminal is inhibited by antagonism of monoamine oxidase enzymes. Antidepressant efficacy is similar to that of reuptake inhibitors but there is a distinct side-effect profile. The different mechanism of action of these drugs offers a strategy for treatment-resistant depression, and they have a historical clinical use in atypical depression.

1. Monoamine oxidase inhibitors

Monoamine oxidase inhibitors (MAOIs) are chemicals which inhibit the activity of the monoamine oxidase enzyme family. They have a long history of use as medications prescribed for the treatment of depression. They are particularly effective in treating atypical depression.

Because of potentially lethal dietary and drug interactions, monoamine oxidase inhibitors have historically been reserved as a last line of treatment, used only when other classes of antidepressant drugs (for example selective serotonin reuptake inhibitors and tricyclic antidepressants) have failed. Their clinical use is limited by their significant side-effect profile and overdose toxicity. Of particular concern is the risk of hypertensive crisis following the ingestion of foods containing tyramine (the 'cheese reaction') or drugs with sympathomimetic properties.



Generic drug names-

- Isocarboxazid
- Phenelzine
- Selegiline
- Tranylcypromine

Side effects of MAOIs

Because of side effects and safety concerns, MAOIs are most often tried when other antidepressants don't work.

The most common side effects of MAOIs include:

- Dry mouth
- Nausea, diarrhea or constipation
- Headache
- Drowsiness
- Insomnia
- Dizziness or lightheadedness
- Skin reaction at the patch site

Other possible side effects include:

- Involuntary muscle jerks
- Low blood pressure

- Reduced sexual desire or difficulty reaching orgasm
- Weight gain
- Difficulty starting a urine flow
- Muscle cramps
- Prickling or tingling sensation in the skin (paresthesia)

C. Monoamine Receptor blockers-

These drugs share the property of blockade of inhibitory presynaptic α2-adrenoceptors, resulting in an increase in the synaptic release of serotonin and noradrenaline, as well as acting at various postsynaptic receptors including the serotonin 5-HT2 receptor. This receptor mediates the agitation seen with other serotonergic antidepressants, so drugs in this class tend to have calming effects

Serotonin antagonists and reuptake inhibitors

Serotonin antagonist and reuptake inhibitors (SARIs) while mainly used as antidepressants, are also anxiolytics and hypnotics. They act by antagonizing serotonin receptors such as 5-HT2A and inhibiting the reuptake of serotonin, norepinephrine, and/or dopamine.

Additionally, most also act as α1-adrenergic receptor antagonists. The majority of the currently marketed SARIs belong to the phenylpiperazine class of compounds. They include Trazodone and Nefazodone.

Side effects -

That said, SARIs can produce some side effects. Commonly experienced side effects of trazodone are:

- Headache.
- Dizziness.
- Blurred vision.
- Drowsiness.
- Fatigue.
- Dry mouth.
- Constipation.

Potentially more serious side effects include:

- Erection lasting for more than 6 hours (priapism).
- Orthostatic hypotension (falling blood pressure when rising from a sitting position; increased risk of falls and injuries).
- Syncope (fainting).
- Serotonin syndrome (agitation, hallucinations, poor coordination, trouble walking, rapid heartbeat, nausea, vomiting).
- Low levels of sodium in the blood (hyponatremia).
- Irregular or fast heartbeat.
- Unusual bruising or bleeding.

Other than Antidepressant's –

Lithium (Li)-

Lithium has traditionally been the drug of choice for the treatment of manic episode (acute phase) as well as for prevention of further episodes in bipolar mood disorder. It has also been used in treatment of depression with less success.

Antipsychotics-

Antipsychotics are an important adjunct in the treatment of mood disorder. The commonly used drugs include risperidone, olanzapine, quetiapine, haloperidol, and aripiprazole. It is customary to use the atypical antipsychotics first, before considering the older typical antipsychotics. Some of the indications in Depression include:

Delusional depression- As stated above, antipsychotics are important adjuncts in the treatment of delusional depression. Once again, it is customary to use atypical antipsychotics such as olanzapine, quetiapine, risperidone, and ziprasidone first, although any antipsychotic can be used.

II. **Neuromodulation Therapeutic Techniques -**appears to be emerging gradually as **a new therapeutic field in psychiatric treatment.** It encompasses neuropsychiatric medical devices, such as **vagus nerve stimulation (VNS), transcranial magnetic stimulation (TMS), deep brain stimulation (DBS), and electroconvulsive therapy (ECT).** As a therapeutic approach to affective disorders, neuromodulation shifts the focus from the monoamine synapse to neural circuitry of the brain, which is dysregulated in depression. This neural circuitry has been elaborated on over the course of 15 years of neuroimaging research in mood disorders and is now believed to encompass disturbances in a frontolimbic network. These include reduced metabolism and blood flow in the prefrontal cortex and anterior

cingulate and pathologically increased activity in the subgenual cingulate and amygdala.

A. Electroconvulsive therapy (ECT)

Electroconvulsive therapy (ECT), formerly known as electroshock therapy, is a psychiatric treatment in which seizures in the brain are electrically induced in patients to provide relief from mental disorders.

The ECT procedure was first conducted in 1938 by Italian psychiatrist Ugo Cerletti and rapidly replaced less safe and effective forms of biological treatments in use at the time. ECT is often used with informed consent as a safe and effective intervention for major depressive disorder, mania, and catatonia.

A usual course of ECT involves multiple administrations, typically given two or three times per week until the patient is no longer suffering symptoms. ECT is administered under anesthesia with a muscle relaxant.

Indications-

The indications for electroconvulsive therapy are:

a. Major severe depression
b. With suicidal risk (This is the first and most important indication for ECT
c. With stupor.
d. With poor intake of food and fluids
e. With melancholia
f. With psychotic features
g. With unsatisfactory response to drug therapy
h. Where drugs are contraindicated, or have serious side effects

Contraindications-

Absolute-

The only absolute contraindication is the presence of *raised intracranial tension* (so an examination of the fundus oculi is an essential step). However, the APA Task Force Report on ECT recognises this too as a
relative contraindication.

Relative
These include:

1. Recent myocardial infarction (MI)
2. Severe hypertension
3. Cerebrovascular accident (CVA)
4. Severe pulmonary disease
5. Retinal detachment, and
6. Pheochromocytoma.

Techniques-

The techniques used for ECT administration are of two types:

i. ***Direct ECT*** is administered in the absence of muscular relaxation and general anaesthesia. All the other steps are the same as in modified ECT. This method of treatment is nowadays very infrequently used and not understandably encouraged by most guidelines.

ii. ***Modified ECT*** is modi fied by drug-induced muscular relaxation and general anaesthesia administered by an anaes thetist.

After the anaesthesis procedure, mouth gag is inserted between teeth, to prevent tongue bite during convulsion and pressure is applied on mandible to approximate upper and lower teeth till convulsions stop. The electrodes (usually U-shaped) are moistened with saline or 25% bicarbonate solution and are applied on head. **According to the position of application of electrodes, ECT is of two types:**

i. **Bilateral ECT:** This is the standard form of ECT used most commonly. Each elec trode is placed 2.5-4.0 cm (1-1½") above the midpoint, on a line joining the tragus of the ear and the lateral canthus of the eye.

ii. Unilateral ECT*:* In this type, electrodes are placed only on one side of head, usually the non-dominant side (right side of head in right handed individual). There are various positions described for the electrode placement. The unilateral ECT is safer, with much fewer side effects, particularly those of memory impairment. However, according to the APA ECT Task Force Report, bilateral ECT is superior to unilateral ECT in effectiveness.

The therapeutic adequacy of the treatment is usually gauzed by the occurrence of a generalized tonic-clonic seizure lasting for not less than 25-30 seconds. This is ensured by:
1. Observing the seizure (in direct ECT).
2. EEG recording during ECT (in modified ECT).
3. Occluding the circulation of one extremity with a BP apparatus cuff, before giving succinylcholine. Thus, the whole body is paralyzed but one extremity convulses and can be directly observed.

4. Observing plantar extension and eyelid contractions which may be seen despite the muscular relaxation (not a very reliable method).

The usual dose for obtaining an adequate seizure response is 90-150 volts (average 110 volts) for 0.1-1.0 seconds (average 0.6 seconds). The usual amount of current passed in an ECT session is 200-1600 mA. Earlier, the ECT machines used a *sine wave* to deliver the current (with a positive and a negative wave constituting a cycle). However, with *sine wave*, unnecessarily excessive and inefficient electrical stimulus is delivered. The newer ECT machines instead use a *brief pulse* wave form that delivers the electrical stimulus, usually in a 1-2 msec time period at a rate of 30-100 pulses/second. Therefore, the *brief pulse* current is more efficacious and safer than the *sine wave* current.

After seizure has occurred, the mouth gag is removed, secretions are removed by a suction machine from the oral cavity, and oxygen mask is applied. Till consciousness is regained, the patient is turned to one side to prevent aspiration. The vital parameters are constantly monitored till recovery occurs. The patient is made to rest, for about 30 minutes to 1 hour, on bed after the treatment is over.

Side Effects

1. Side effects associated with general anaesthesia: *Deaths* during ECT are usually due to the general anaesthesia, succinylcholine (in patients with deficiency of pseudo-cholinesterase) or drug interactions. According to the APA Task Force Report (2001), the approximate mortality rate is 1:10,000 patients (or 1:80,000 treatments), which is similar to any operative procedure under anaesthesia.

2. *Memory disturbances* (both anterograde and retrograde) are very common. These are usually mild and recovery occurs within 1-6 months after treatment. Unilateral ECTs cause much less memory disturbance than bilateral ECTs.

3. *Confusion* may occur in the postictal period. Like memory disturbances, confusion is much commoner with bilateral ECTs. Usually, no treatment is needed. Parenteral diazepam may be given for excitement during this period.

4. *Other side effects* include headache, prolonged apnoea, prolonged seizure, cardiovascular dysfunction, emergent mania, muscle aches and apprehension.

B. Vagus nerve stimulation (VNS)-

- Vagus nerve stimulation (VNS) is a medical treatment where a device similar to a pacemaker is implanted into the chest. A wire leading out of the device is passed under the skin and connected to the left vagus nerve in the neck. This nerve is connected to the brain. VNS involves periodically stimulating this nerve with electrical signals.

- A newer type of VNS has been developed that does not require surgery. In non-invasive or transcutaneous (across the skin) VNS, the vagus nerve is stimulated with a device that is placed on the skin over the vagus nerve. Usually, this device is placed in the outer part of the ear.
- VNS is an implanted device that has established efficacy in pharmaco-resistant epilepsy. It was approved by the FDA for the treatment of severe, recurrent unipolar and bipolar depression in July of 2005. VNS adopts a bottom-up approach to modulating the neural circuitry of depression by stimulating vagal afferent fibers in the neck, which carry impulses to the brain stem to target there the locus coeruleus and dorsal raphe nucleus.
- How does it work? -It is not clear exactly how VNS might help treat depression. The vagus nerve is connected to brain areas involved in mood regulation. Stimulating this nerve might help restore chemical imbalances involved in depression.
- Is it effective?-Only one randomized controlled trial has been conducted on VNS for people with diagnosed depression. Participants in this study who received VNS did not experience any greater reduction in their depression symptoms than those who received a placebo (dummy) treatment. Many more studies have been conducted where the treatment was not compared to a placebo. In these studies, more people experienced a reduction in depression symptoms if they had the VNS treatment compared to people who had only their regular treatment (for example, antidepressant medication). However, because there was no placebo group to compare to in these studies, we cannot be sure that the VNS intervention caused this effect.
- Are there any disadvantages? - Traditional VNS is an invasive procedure and requires surgery under general anaesthetic to implant the device. It is also an expensive procedure which may not be covered by Medicare. It may be many months before an improvement in symptoms is noticed. Side effects can include neck pain, voice changes, coughing, headaches and chest pain, amongst others. Non-invasive VNS does not require surgery, but it is not a widely accessible treatment.

C. Transcranial magnetic stimulation (TMS)-

Transcranial magnetic stimulation (TMS), also known as repetitive transcranial magnetic stimulation (rTMS), is a non-invasive form of brain stimulation in which a changing magnetic field is used to cause electric current at a specific area of the brain through electromagnetic induction. An electric pulse generator, or stimulator, is connected to a magnetic coil, which in turn is connected to the scalp. The stimulator generates a changing electric current within the coil which induces a magnetic field; this field then causes a second inductance of inverted electric charge within the brain itself.

This forceful magnetic field is generated on the surface of the scalp, without any intrusion into the skin, muscles or bones, making its electrical stimulation electrodeless . Levels of excitability of neuronal stimulation can be regulated, either by high (10 to 20 Hz) or low (1 Hz)

frequency. The generated magnetic field is about 1.5 Tesla, similar in strength to that of magnetic resonance imaging . Patients being treated with TMS undergo five daily treatment sessions over three to six weeks, resulting in a total of 20 to 30 sessions during treatment.

High-frequency stimulation of the left DLPFC alleviates depressive symptoms, whereas low-frequency cortical stimulation of the right DLPFC helps to relieve the symptoms of both depression and anxiety. This was validated by a case series in which the effects of TMS on either side of the prefrontal cortex were evaluated in 16 healthy individuals aged 24 to 75 years. Patients who underwent stimulation of the left DLPFC showed a drop in salivary cortisol level in the morning. However, the results of this study were limited due to the small sample size and limited number of TMS sessions . Many randomized clinical trials have shown that daily TMS of the left prefrontal cortex was effective in treating depressive mood symptoms, with remission rates of 30% to 40% of cases. Similar to antidepressants, TMS resulted in sustained improvement in mood symptoms but with fewer side effects .

Another randomized multicenter trial showed that this non-invasive treatment method had significant antidepressant effects with remission rates four-fold higher than placebo. A multicenter observational study involving 307 patients in a clinical setting showed that the depression severity scale decreased after treatment with TMS. Moreover, therapeutic responses were maintained in patients treated with TMS

The neurobiological phenomena underlying the effectiveness of TMS as an antidepressant are not well understood, although studies have suggested a correlation between cerebral metabolic activity and TMS effectiveness.

TMS is regarded as an effective and safe stimulation technique. However, it has a few side effects that might affect treatment compliance. Commonly reported adverse effects include transitory and/or recurrent headaches that respond to over the counter analgesics, a tingling sensation on the scalp and face, and ipsilateral lacrimation. Seizure activity is rare, and one patient was reported to develop trigeminal autonomic cephalalgia after the administration of rTMS for refractory depression

III. **Psychosurgery (ablative)-** is an extremely rarely used method of treatment and is resorted to only in exceptional circumstances. In depressive episode, which is either chronic or persistently recurrent with a limited or absent response to other modes of treatment, one of the following procedures may very rarely be performed:

i. Stereotactic subcaudate tractotomy, or
ii. Stereotactic limbic leucotomy.

In carefully selected patients, the results are reported to be satisfactory. However, in the current day and age, psychosurgery is hardly ever considered in routine clinical practice.