Therapy of Major Depression

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Therapy of Major Depression

- The symptoms of major depressive disorders consistently reflect changes in brain monoamine neurotransmitters, specifically norepinephrine (NE), serotonin (5-HT), and dopamine (DA).
- Antidepressants are generally considered equally effective, and drug selection depends on the adverse effect profile mainly.
- The patient should be informed that adverse effects might occur immediately, while resolution of symptoms may take 2 - 4 weeks or longer.

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- **The disease is chronic and treatment is long-term, thus, drug tolerability is important because adverse effects may lead to medication nonadherence.**
- **The selective serotonin reuptake inhibitors (SSRIs), are effective and generally better tolerated than older agents (tricyclic antidepressants [TCAs] and the monoamine oxidase inhibitors [MAOIs]).**

Medications Associated with or Exacerbating Depressive Symptoms

1. Acne treatment: Isotretinoin
2. Neurological drugs: Levetiracetam, Topiramate, Vigabatrin, Lamotrigine, …, Benzodiazepines, Alcohol, opioids, Levodopa/carbidopa, Triptans
3. Cardiovascular medications: β-Blockers, Clonidine, Reserpine, Methyldopa
4. Asthma medications: Montelukast
5. Hormonal therapy: Gonadotropin-releasing hormone, Oral contraceptives, Hormonal replacement therapy, Tamoxifen

Medications Associated with or Exacerbating Depressive Symptoms

6. Corticosteroids: prednisone
7. Immunologic agents: Interferons
8. Smoking cessation medications: Varenicline
9. Proton pump inhibitors: Omeprazole, pantoprozole
10. Histamine H_2- blockers: Famotidine
11. Histamine H_1- blockers: Citrizine
12. Statins: Atorvastatin, Simvastatin

Medical Conditions Associated with Depression

1. Stroke.
2. Parkinson's disease.
3. Traumatic brain injury.
4. Hypothyroidism.
5. Withdrawal from cocaine, amphetamines and other stimulants commonly present with depressive symptoms.

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Desired Outcomes:

- **The goals of treatment are:**

A. The resolution of current symptoms (remission).

B. The prevention of further episodes (relapse and recurrence).

- **~ 50 - 60% of patients improve with acute drug therapy, compared with about 30 - 40% who improve with placebo.**

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The decision to hospitalize the patient depends on:

1. **Patient's risk of suicide.**
2. **Physical state of health.**
3. **Social support.**
4. **Presence of a psychotic depression.**

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Phases of therapy:

1. **The acute phase lasting 6 - 12 weeks in which the goal is remission (disappearance of symptoms).**
2. **The continuation phase lasting 4 - 9 months after remission in which the goal is to eliminate residual symptoms or prevent relapse (return of symptoms within 6 months of remission).**
3. **The maintenance phase lasting 12 - 36 months in which the goal is to prevent recurrence (a separate episode of depression which returns months-years after recovery).**

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Duration of therapy:

- **The duration of antidepressant therapy depends on the risk of recurrence, which increases as the number of past episodes increases.**
- **Some recommend life-long maintenance therapy for patients > 40 years of age with ≥ 2 prior episodes, and patients of any age with ≥ 3 prior episodes.**
- **An alternative approach is to treat for at least 2 years in patients considered to be at high risk for relapse.**

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- The decision when to taper/discontinue an antidepressant regimen depends on patient- and drug-specific variables.
- There are no universally agreed upon approaches.
- The precise rate of the antidepressant taper typically depends on medication half-life, and patient sensitivity to withdrawal symptoms.
- Therefore, monitoring for discontinuation signs and symptoms and for a return of depressive symptoms is very necessary.

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Classification of Antidepressants:

1. **Selective Serotonin Reuptake Inhibitors (SSRIs):**

- **Citalopram, Escitalopram, Fluoxetine, Fluvoxamine, Paroxetine, Sertraline.**
- **Escitalopram and sertraline demonstrate the 'best' effect and safety profile.**

2. **Norepinephrine - Dopamine Reuptake Inhibitors (NDRI):**

- **Bupropion.**
- **May be used also in smoking cessation programs.**

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3. **Serotonin–Norepinephrine Reuptake Inhibitors (SNRIs):**

A. Tricyclic antidepressants (TCAs):

- **Amitriptyline, Desipramine, Doxepin, Imipramine, Nortriptyline.**
- **TCAs affect other receptor systems (cholinergic, histaminergic, and α-adrenergic receptors).**
- **Therefore, they have frequent adverse reactions.**

B. Newer-generation SNRIs:

- **Venlafaxine, Desvenlafaxine, Duloxetine, Levomilnacipran.**
- **Venlafaxine may be associated with higher rates of response and remission.**

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4. **Mixed Serotonergic Effects:**

- **Nefazodone, Trazodone, Vilazodone, Vortioxetine.**
- **Trazodone act as both 5-HT_2 antagonists and 5-HT reuptake inhibitors.**
- **It may also enhance 5-HT_{1A}-mediated neurotransmission.**
- **It blocks α_1-adrenergic and histaminergic receptors leading to increased adverse effects (dizziness and sedation) that limit its use.**
- **It may be used adjunctively (in low doses) to induce sleep among depressed patients who are taking other antidepressant medications.**

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5. Serotonin and α_2-Adrenergic Antagonists (Mirtazapine):

- **It enhances central noradrenergic and serotonergic activity through the antagonism of central presynaptic α_2-adrenergic autoreceptors and heteroreceptors.**
- **It also antagonizes 5-HT_2 and 5-HT_3 receptors as well as histamine receptors.**
- **The antagonism of 5-HT_2 and 5-HT_3 receptors has been linked to lower anxiety and GI adverse effects, respectively.**
- **Blockade of histamine receptors is associated with sedation.**

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6. Monoamine Oxidase Inhibitors (MAOIs):

- **Phenelzine, Selegiline, Tranylcypromine.**
- **MAOIs increase the concentrations of NE, 5-HT, and DA within the synapse through inhibition of the MAO enzyme.**
- **Similar to TCAs, chronic therapy causes downregulation of β-adrenergic, α-adrenergic, and serotonergic receptors.**
- **The MAOIs phenelzine and tranylcypromine are nonselective inhibitors of MAO-A and MAO-B.**
- **Selegiline inhibits both MAO-A and MAO-B in the brain, yet has reduced effects on MAO-A in the gut.**

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- **Antidepressants are considered first-line treatment for moderate - severe depressive episode.**
- **The choice of drug is empiric because one cannot predict which antidepressant will be the most effective in an individual patient.**

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Factors that often influence the choice of an antidepressant include:

1. **The patient's history of response.**
2. **Presenting symptoms.**
3. **Potential for drug–drug interactions.**
4. **Adverse effect profile.**
5. **Patient preference.**
6. **Drug cost.**

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Symptoms and Initial Antidepressant Choice

Symptoms	Preferred Antidepressant
Anxiety	Selective Serotonin Reuptake Inhibitors
Weight loss, Reduced appetite	Serotonin and α_2-Adrenergic Antagonists (Mirtazapine)
Sleep disturbance, Insomnia	Mirtazapine, TCAs, Mixed Serotonergic drugs (Trazodone)
Pain	Serotonin–Norepinephrine Reuptake Inhibitors
Cognitive difficulties	Selective Serotonin Reuptake Inhibitors

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Adverse Effects:

1. Selective Serotonin Reuptake Inhibitors:

- Less anticholinergic and cardiovascular adverse effects than the TCAs.
- Not usually associated with significant weight gain.
- The most common adverse effects are nausea, vomiting, diarrhea, sexual dysfunction in both males and females, headache, and insomnia.
- Citalopram and escitalopram produce dose-dependent prolongation of QT interval.
- Withdrawal syndrome.

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2. Serotonin–Norepinephrine Reuptake Inhibitors:

TCAs:

- The most common adverse effects are dose-related anticholinergic effects like dry mouth, constipation, blurred vision, urinary retention, dizziness, tachycardia, memory impairment, and, at higher doses, delirium.
- These effects interfere with patient adherence, particularly in the elderly and in those receiving long-term maintenance therapy.

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- **Weight gain (may be due to blockade of 5-HT_2 receptors that regulate appetite, hunger and feeling of fullness).**
- **Sexual dysfunction.**
- **Orthostatic hypotension (adrenergic receptors blockade).**
- **Cardiac conduction delays and heart block (may be due to their blockade of fast sodium channels like class 1 antiarrhythmics which overrides their anticholinergic effect).**
- **TCA overdose can produce severe cardiac arrhythmias and increased risk of death due to prolongation of QT_c interval.**

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3. Newer-generation SNRIs:

- **The most common adverse effects of venlafaxine are sexual dysfunction, and nausea and vomiting.**
- **It may cause a dose-related increase in blood pressure.**
- **It may produce dry mouth, constipation, decreased appetite, insomnia, and increased sweating.**

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4. Mixed Serotonergic Medications:

- **Trazodone and nefazodone have minimal anticholinergic adverse effects and less 5-HT agonist adverse effects (sexual dysfunction), but may cause orthostatic hypotension.**
- **Sedation, cognitive slowing, and dizziness are the most frequent dose-limiting adverse effects associated with trazodone.**
- **A rare but potentially serious adverse effect of trazodone and nefazodone is priapism.**

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5. Norepinephrine and Dopamine Reuptake Inhibitor:

- **Bupropion may cause nausea, vomiting, tremor, insomnia, and dry mouth.**
- **Dose-dependent seizures.**
- **It is contraindicated in patients with eating disorders (bulimia and anorexia) which are prone to electrolyte abnormalities and increased risk for seizures.**
- **Activation or agitation due to adrenergic stimulation.**

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6. Serotonin and α_2-Adrenergic Receptor Antagonists:

- **The most common adverse effects of mirtazapine are somnolence, weight gain, dry mouth, and constipation (strong antihistaminergic effects).**

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7. Monoamine Oxidase Inhibitors:

- The most common adverse effect is postural hypotension (more likely with phenelzine than with tranylcypromine).
- Weight gain and sexual dysfunction.
- Phenelzine has mild - moderate sedating effects, while tranylcypromine may exert a stimulating effect (insomnia).
- Fever, myoclonic jerking, and brisk deep tendon reflexes may occur.
- Hypertensive crisis, a potentially serious and life-threatening but rare adverse reaction, may occur when MAOIs are taken concurrently with certain foods, especially those high in tyramine, or some medications.

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Dietary and Medication Restrictions for Patients Taking Monoamine Oxidase Inhibitors:

- **Food:** Aged cheese, Sour cream, Yogurt, Cottage cheese, American cheese, Mild Swiss cheese, Wine (especially Chianti and sherry), Beer, Sardines, Canned, aged, or processed meat, Monosodium glutamate, Liver (chicken or beef, more than 2 days old), Raisins, Pods of broad beans (fava beans), Yeast extract and other yeast products, Soy sauce, Chocolate, Coffee, Ripe avocado, Sauerkraut, Licorice.
- **Medications:** Amphetamines, Levodopa, Appetite suppressants, Local anesthetics containing sympathomimetic vasoconstrictors, Asthma inhalants, Meperidine, Buspirone, Methyldopa, Carbamazepine, Methylphenidate, Cocaine, Other antidepressants, Cyclobenzaprine, Other MAOIs, Decongestants (topical and systemic), Reserpine, Dextromethorphan, Rizatriptan, Dopamine Stimulants, Ephedrine, Sumatriptan, Epinephrine, Sympathomimetics, Guanethidine, Tryptophan

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Serotonin Syndrome (SS):

- **Any antidepressant that increases serotonergic neurotransmission can be associated with SS.**
- **The typical triad of symptoms of SS includes mental status changes, autonomic instability, and neuromuscular abnormalities.**
- **First step in management is to discontinue all medication that increase serotonin, followed immediately by supportive care which may need admission to intensive care when severe.**

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Pharmacokinetic Drug Interactions:

- **Tremendous.**

Mechanisms:

1. **Inhibition of metabolism of other co-administered drugs by antidepressants.**
2. **Displacement of highly protein bound drugs from their binding sites.**
3. **Drugs that decrease hepatic blood flow may reduce the metabolism of some antidepressants.**

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Examples on inhibitors of cytochrome P450:

1. **Duloxetine: inhibits CYP2D6**
2. **Fluoxetine: inhibits CYP2D6 > CYP3A4**
3. **Fluvoxamine: inhibits CYP1A2 > CYP2C**
4. **Paroxetine: inhibits CYP2D6**
5. **Sertraline: inhibits CYP2D6**

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Pharmacodynamic Drug Interactions:

1. **When SSRIs are coadministered with other drugs that increase serotonin at the synapse such as linezolid, opioids (fentanyl, tramadol), antimigraine drugs (triptans), Attention deficit hyperactivity disorder stimulants, Dextromethorphan (antitussive), MDMA (Ecstasy) amphetamine derivative, St. John's Wort, ,patients may develop the "serotonin syndrome".**
2. **The TCAs, SNRIs, and SSRIs can also potentially by themselves produce the SS.**

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3. **Increased risk of bleeding when combined with NSAIDs (upper GI and intracranial hemorrhage) may be due to inhibition of serotonin uptake by platelets, thus reducing platelet aggregation.**
4. **Hypertensive crisis that may result following the coadministration of MAOIs and other medications that increase vasopressor response.**

Therapy of Major Depression in Special Populations

Elderly Patients:

- In the elderly, depression may be mistaken for dementia.
- SSRIs are usually the antidepressants of first-choice in the elderly.
- Bupropion and venlafaxine may be used because of milder anticholinergic and less frequent cardiovascular adverse effects.
- Mirtazapine can be used in the elderly.

Therapy of Major Depression in Special Populations

Pediatric Patients:

- No antidepressant, except fluoxetine and escitalopram, is FDA-approved for the treatment of depression in patients younger than 18 years of age.
- There is an increased risk for suicidal ideation and behavior when antidepressants are used in children.
- Several cases of sudden death, that may be due to cardiac causes, have been reported in children and adolescents taking antidepressants, such as desipramine.

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Pregnancy:

- **Pregnancy does not protect against the occurrence of depression.**
- **Approximately 14% of pregnant women develop a serious depression during pregnancy.**
- **Women who have discontinued antidepressant therapy have high relapse during pregnancy.**
- **Both antidepressant treatment and untreated depression have been associated with potential problems in pregnant women.**

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- **Maternal depression adversely affects child development.**
- **Prenatal exposure to SSRIs was associated with an increased risk of low birth weight.**
- **There is a high risk of persistent pulmonary hypertension of newborn infants exposed to an SSRI after the 20th week of gestation.**
- **Despite all of that, SSRIs remain the most commonly used and best-tolerated treatment for depression during pregnancy.**

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Relative Resistance and Treatment-Resistant Depression:

1. **The majority of "treatment-resistant" depression may be due to inadequate therapy (relative resistance).**

- **Patients may achieve remission after switching to another antidepressant from the same class as well as a different class.**

2. **Treatment-resistant depression is depression that has not achieved remission even after two optimal antidepressant trails.**

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Successful pharmacotherapy of treatment-resistant depression include the following:

1. **The current antidepressant may be stopped and a trial with another agent initiated (switching).**
2. **The current antidepressant can be augmented by the addition of another agent such as lithium, or another antidepressant (combination antidepressant treatment).**

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3. **The use of atypical antipsychotic agents to augment the antidepressant response. Aripiprazole and quetiapine slow release have been recommended as first-line agents to augment an antidepressant medication.**

- **The antidepressant effect of atypical antipsychotics involves regulation of monoamines, glutamate, gamma-aminobutyric acid (GABA), cortisol, and neurotrophic factors.**

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Notes:

1. **Antidepressants can generally be classified as either activating or sedating and this is often a major consideration in antidepressant choice.**
2. **Medications that promote noradrenergic activity (venlafaxine) or serotonin (SSRIs) may be activating upon initiation and therefore are poor choices for a patient with significant insomnia.**
3. **In contrast, medications with antihistaminergic properties (mirtazapine) may be highly sedating and therefore appropriate for the depressed patient suffering from insomnia.**