

# **Therapy of Major Depression**

**Yacoub M. Irshaid MD. PhD, ABCP**  
**Department of Pharmacology**

A 48-year-old female complains of a feeling of hopelessness and emptiness. She had over the past 4 weeks decreased appetite, poor ability to concentrate, difficulty falling asleep, feeling tired after waking up in the morning and experiencing headaches. Over the last 2 weeks, she started to experience feelings of worthlessness, and transient thoughts of death/suicide. There is a family history of major depression on the mother side and her brother committed suicide. She took previously antidepressants. She was adherent to the drugs but not comfortable with.

# Therapy of Major Depression

- The symptoms reported by patients with MDD 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.

# Therapy of Major Depression

- 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. Anticonvulsants: **Levetiracetam, Topiramate, Vigabatrin**

3. Antimigraine agents: **Triptans**

4. Cardiovascular medications:

**β-Blockers, Clonidine, Reserpine, Methyldopa.**

5. Hormonal therapy:

**Gonadotropin-releasing hormone, Oral contraceptives, Steroids (prednisone), Tamoxifen.**

6. Immunologic agents:

**Interferons**

7. Smoking cessation medications:

**Varenicline**

# Medical Conditions Associated with Depression

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

# Therapy of Major Depression

## Desired Outcomes:

- **The goals of treatment are:**

- A. The resolution of current symptoms (remission).**

- B. The prevention of further episodes (relapse or recurrence).**

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

# Therapy of Major Depression

**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.**



# Therapy of Major Depression

## 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 ).

# Therapy of Major Depression

## 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  $\geq 2$  prior episodes, and patients of any age with  $\geq 3$  prior episodes.
- An alternative approach is to treat for at least 2 years in patients considered to be at high risk for relapse.

# Therapy of Major Depression

- 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.**

# Therapy of Major Depression

## Nonpharmacologic Therapy:

- **Psychotherapy** may be useful in combination with pharmacologic therapy **but not alone**.
- **Cognitive therapy, behavioral therapy, and interpersonal psychotherapy appear equally effective.**
- **Electroconvulsive therapy (ECT) is a safe and effective treatment for certain severe mental illnesses, including MDD.**

# Therapy of Major Depression

## Classification of Therapeutic Drugs:

### 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.

# Therapy of Major Depression

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

### A. Tricyclic antidepressants (TCAs):

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

### B. Newer-generation SNRIs:

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

# Therapy of Major Depression

## 4. Mixed Serotonergic Effects:

- **Nefazodone, Trazodone, Vilazodone, Vortioxetine.**
- **Trazodone act as both 5-HT<sub>2</sub> antagonists and 5-HT reuptake inhibitors.**
- **It may also enhance 5-HT<sub>1A</sub>-mediated neurotransmission.**
- **It blocks  $\alpha_1$ -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.

# Therapy of Major Depression

## 5. Serotonin and $\alpha_2$ -Adrenergic Antagonists (Mirtazapine):

- It enhances central noradrenergic and serotonergic activity through the antagonism of central presynaptic  $\alpha_2$ -adrenergic autoreceptors and heteroreceptors.
- It also antagonizes 5-HT<sub>2</sub> and 5-HT<sub>3</sub> receptors as well as histamine receptors.
- The antagonism of 5-HT<sub>2</sub> and 5-HT<sub>3</sub> receptors has been linked to lower anxiety and GI adverse effects, respectively.
- Blockade of histamine receptors is associated with sedation.



# Therapy of Major Depression

## 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  $\beta$ -adrenergic,  $\alpha$ -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.

# Therapy of Major Depression

- **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.**

# Therapy of Major Depression

**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.**

# Therapy of Major Depression

## Symptoms and Initial Antidepressant Choice

Symptoms	Preferred Antidepressant
Anxiety	Selective Serotonin Reuptake Inhibitors
Weight loss, Reduced appetite	Serotonin and $\alpha_2$ -Adrenergic Antagonists (Mirtazapine)
Sleep disturbance, Insomnia	Mirtazapine, TCAs, Mixed Serotonergic drugs (Trazodone)
Pain	Serotonin–Norepinephrine Reuptake Inhibitors
Cognitive difficulties	Selective Serotonin Reuptake Inhibitors

# Therapy of Major Depression

## 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.**

# Therapy of Major Depression

## 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.

# Therapy of Major Depression

- **Weight gain and sexual dysfunction.**
- **Orthostatic hypotension** (adrenergic receptors).
- **Cardiac conduction delays and heart block.**
- **TCA overdose can produce severe cardiac arrhythmias and increased risk of death .**

# Therapy of Major Depression

## 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.



# Therapy of Major Depression

## 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**.

# Therapy of Major Depression

## 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.

# Therapy of Major Depression

## 6. Serotonin and $\alpha_2$ -Adrenergic Receptor Antagonists:

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

# Therapy of Major Depression

## 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.

# Therapy of Major Depression

## 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

# Therapy of Major Depression

## 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**.
- However, the presence of any of the following symptom clusters is highly diagnostic of SS:
  1. Tremor + hyperreflexia.
  2. Spontaneous clonus.
  3. Muscle rigidity + temperature  $> 38^{\circ}\text{C}$  + ocular clonus or inducible clonus.
  4. Ocular clonus + agitation or diaphoresis.
  5. Inducible clonus + agitation or diaphoresis.

# Therapy of Major Depression

## 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.

# Therapy of Major Depression

## 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**



# Therapy of Major Depression

## Pharmacodynamic Drug Interactions:

- 1. When SSRIs are coadministered with other drugs that increase serotonin at the synapse such as linezolid, patients may develop the “serotonin syndrome”.**
- The TCAs, SNRIs, and SSRIs can also potentially by themselves produce the SS.**

# Therapy of Major Depression

- 2. 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.**
- 3. 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**.

# Therapy of Major Depression

## 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.**

# Therapy of Major Depression

- **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.**

# Therapy of Major Depression

## Relative Resistance and Treatment-Resistant Depression:

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

# Therapy of Major Depression

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).**



# Therapy of Major Depression

- 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.**

# Therapy of Major Depression

## 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.