Al-Mustaqbal University
College of Pharmacy
5th Stage
Applied therapeutics II
Lecture: 3

Depressive Disorders

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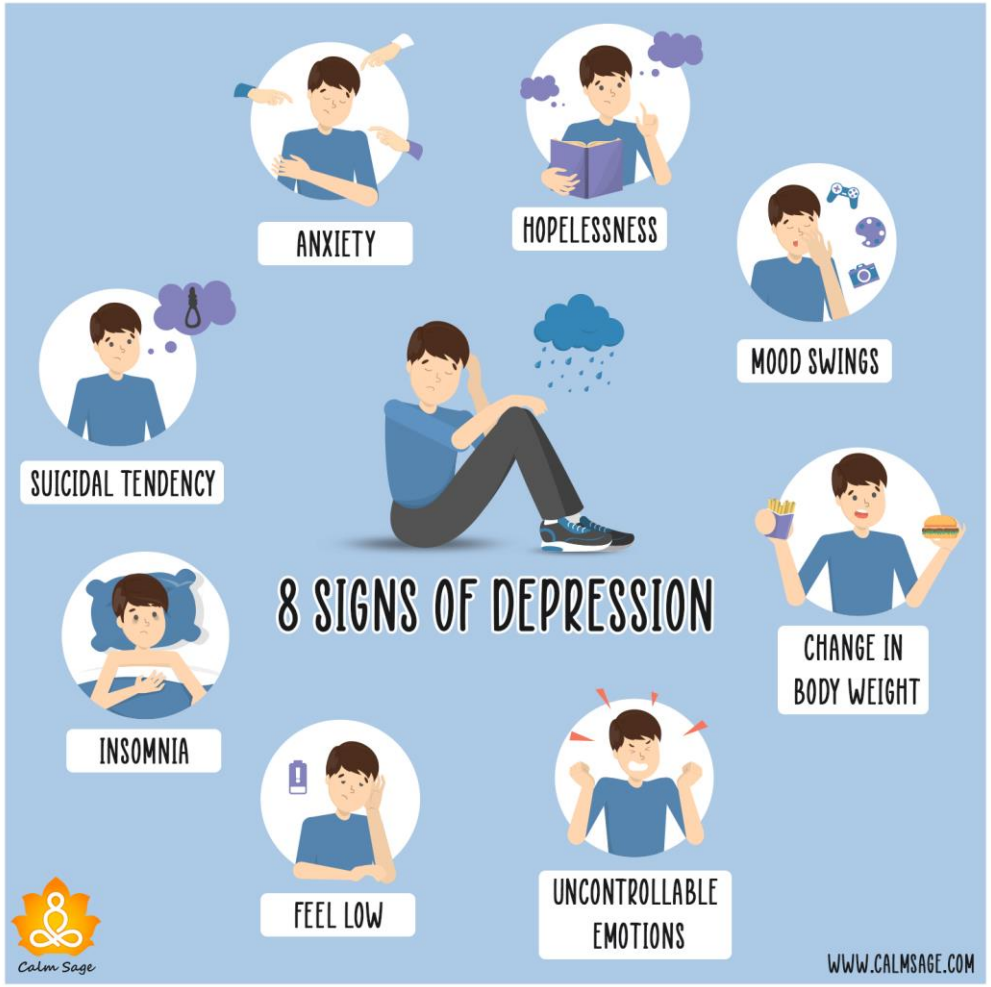
Introduction

- **Depression** is a **common mental** health condition that causes a **persistent feeling** of **sadness** and **changes** in how you **think, sleep, eat and act**.
- The **essential feature** of major depressive disorder (MDD) is a clinical course characterized by:

✓**one or** more major depressive **episodes**

✓**without** a history of **manic** or **hypomanic episodes**

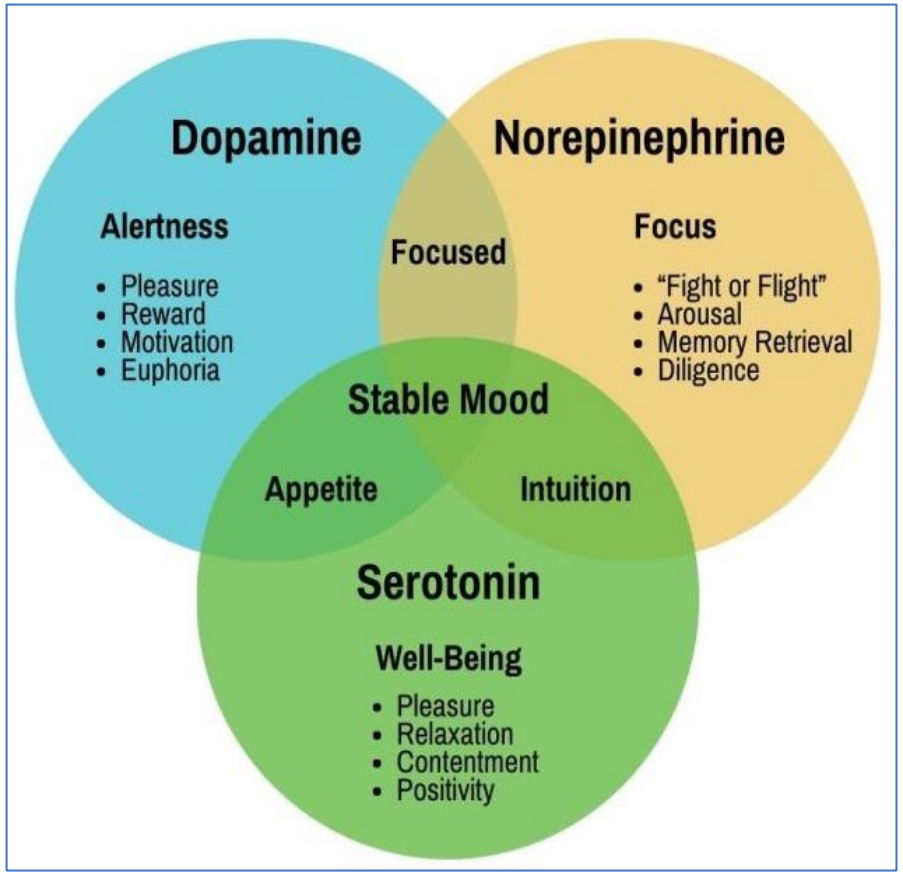


1. Monoamine hypothesis:

- **Decreased** brain levels of the neurotransmitters **norepinephrine (NE), serotonin (5HT), and dopamine (DA)** may cause depression.

2. Postsynaptic changes in receptor sensitivity:

- Studies have demonstrated that **desensitization or down- regulation** of **NE or 5HT1A receptors** may relate to onset of antidepressant effects.



3. Dysregulation hypothesis:

- **Failure** of **homeostatic** neurotransmitter regulation, **rather than** absolute **increases** or **decreases** in their activities.

4. Inflammatory hypothesis:

- **Chronic stress and inflammation** may alter **glutamatergic and GABA** transmission.
- Brain-derived neurotrophic factor (**BDNF**) is a **primary mediator** of **neuronal changes** as well as **synaptogenesis** whose expression is **reduced** due to **stress** and may be associated with **depression**.
- **Neuroactive steroids** are a growing area of **research** for depression.

Clinical presentation

1. Emotional symptoms:

- **Diminished** ability to experience pleasure, loss of interest in usual activities, sadness, pessimism, crying, hopelessness, anxiety, feelings of worthlessness or guilt, and **psychotic features** (eg, **auditory hallucinations and delusions**).
- **Recurrent** thoughts of **death, suicidal ideation without** a specific **plan**, **suicide attempt**, or a **plan** for committing suicide.

2. Physical symptoms:

- **Weight gain or loss**, fatigue, pain (**especially headache**), sleep disturbance, decreased or increased appetite, loss of sexual interest, and gastrointestinal (GI) and cardiovascular complaints (**especially palpitations**).

Clinical presentation

3. Cognitive symptoms:

- Decreased ability to **concentrate, poor memory for recent events, confusion, and indecisiveness**.

4. Psychomotor disturbances:

- Psychomotor **retardation** (**slowed physical movements, thought processes, and speech**) or psychomotor **agitation**.

Diagnosis

- MDD is characterized by **one or more major depressive episodes**, as defined by the Diagnostic and Statistical Manual of Mental Disorders, 5th ed (**DSMD-5**).
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- **Five or more** of the above **symptoms** must have been present **nearly every day during the same 2-week period** and cause significant **distress or impairment**.

- **Depressed mood or loss of interest or pleasure** must be present in **adults** (or **irritable mood** in **children and adolescents**). (Table 69-1 SIG E CAPS).

- The depressive episode must **not be attributable** to physiological effects of a substance or medical condition.

Diagnosis

- There must **not be a history** of **manic like or hypomanic like episodes** unless they were induced by a substance or medical condition.
- **Diagnosis requires** a medication review, physical examination, mental status examination, a complete blood count with differential, thyroid function tests, and electrolyte determination.
- **Many chronic illnesses** (eg, stroke, Parkinson disease, traumatic brain injury, hypothyroidism) and substance use disorders are **associated with depression**.
- **Medications associated** with depressive symptoms include many **antihypertensives, oral contraceptives, isotretinoin, interferonβ1a**, and many others.
- **Standardized rating scale** should be used to **diagnose** depression and **evaluate** treatment.

Diagnosis

TABLE 69-1	Diagnostic Criteria for Major Depressive Episode (SIG E CAPS)
S	Suicidal ideation with or without plan, suicide attempt; recurrent thoughts of death
I	Interest—loss of interest or pleasure in activities; anhedonia
G	Guilt—inappropriate or excessive in nature; feelings of worthlessness
E	Energy decreased
C	Concentration decreased; difficulty making decisions
A	Appetite changes; typically decreased; resulting in 5% change in weight from baseline
P	Psychomotor agitation or retardation
S	Sleep impairment; typically insomnia but may be hypersomnia

- At least five symptoms must be consistently present over a 2-week period.
- Symptoms must include depressed mood or anhedonia.
- Symptoms must cause substantial distress or impairment in functioning.
- Other medical conditions or substance use do not account for symptoms.

Treatment

Goals of Treatment:

- **Resolution** of current symptoms (ie, remission), **prevention** of further episodes of depression (ie, relapse or recurrence), and **prevention** of suicide.
- It include:

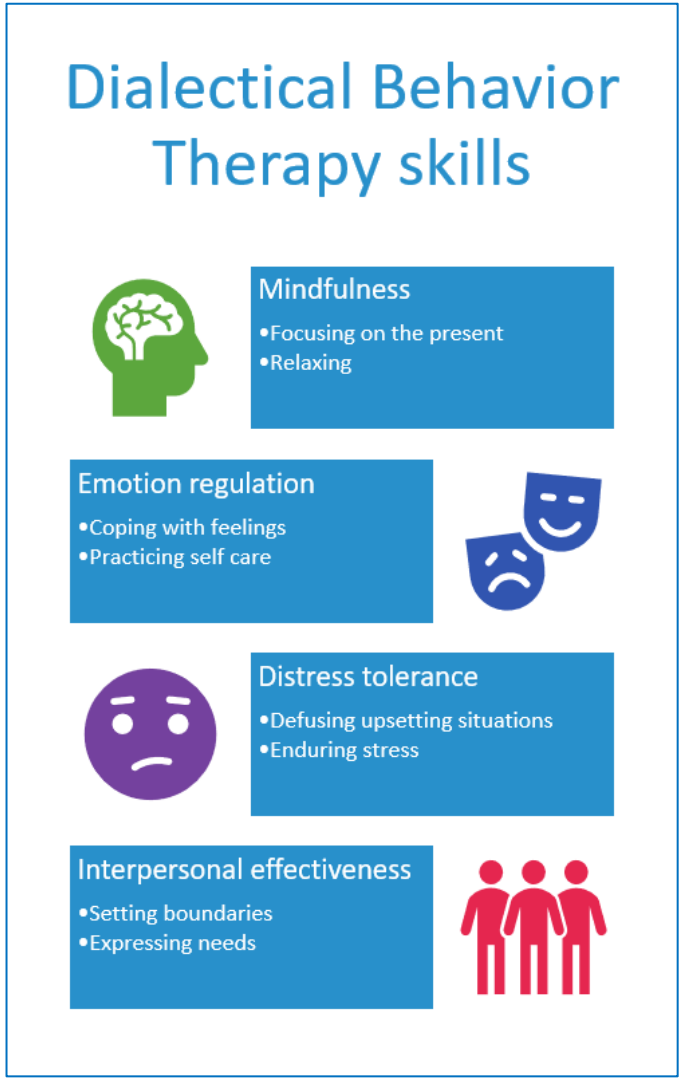
✓**Nonpharmacologic Therapy**

✓**Pharmacologic Therapy**

Nonpharmacologic Therapy

1. Psychotherapy:

- **Psychotherapy** (eg, cognitive therapy, dialectical behavior therapy, or interpersonal psychotherapy) is **recommended as primary** treatment for **mild to moderately severe** major depressive episode.
- For **severe depression**, it may be used in **combination** with medications as its effect is **considered additive**.
- Psychotherapy **alone** is not recommended for **acute treatment of severe and/or psychotic MDD**.



Nonpharmacologic Therapy

2. Electroconvulsive therapy (ECT):

- It may be considered **when** a **rapid response is needed**, **risks** of other treatments **outweigh potential benefits**, there is **history of a poor response** to medications, and the **patient prefers ECT**.
- A **rapid** therapeutic response (**10–14 days**) has been reported.

3. Repetitive transcranial magnetic stimulation (TMS):

- It has demonstrated **efficacy** and does **not require anesthesia** as does **ECT**.

4. Physical activity:

- **Recent** data suggest the **benefit of physical activity** in patients with MDD, and the **American Psychiatry Association** has endorsed **inclusion of exercise** into MDD treatment plans.

Pharmacologic Therapy - General Approach

- **Antidepressants** are considered **first line** and are **equal** in **efficacy** when administered in comparable doses.
- They are often **classified by chemical structure and/or presumed mechanism**.
- The **initial choice** of antidepressant is often **made empirically** and **influenced** by
    1. the patient's or family member's **history of response**
    2. **concurrent medical conditions**
    3. **medications** the patient is taking
    4. presenting **symptoms**
    5. potential for **medication interactions**
    6. medication **adverse effect** profiles
    7. **patient preference**
    8. **medication cost**.

Pharmacologic Therapy - General Approach

- An individual's **pharmacogenomics** may be useful when choosing therapy as a way to better predict antidepressant adverse effects or response.
- Dosing **recommendations** to **aid in the interpretation of results** are available through the Clinical Pharmacogenomics Implementation Consortium (**CPIC**) as well as the **FDA** approved package inserts.
- About **50%–60%** of patients with varying types of depression **improve** with **pharmacologic treatment.**
- **At least a 6week trial** of an antidepressant **at maximum dosage** is considered an **adequate trial**.

Pharmacologic Therapy - General Approach

- The **acute phase** of treatment lasts **6–12 weeks**, and the **goal is remission** (ie, absence of symptoms).
- The **continuation phase** (**4–9 months after remission**) seeks to **eliminate residual symptoms or prevent relapse**.
- The **maintenance phase** (**12–36 months or more**) seeks to **prevent recurrence** of a new episode of depression.
- **Some guidelines recommend lifelong maintenance therapy** for persons at **greatest risk for recurrence** (ie, younger than 40 years of age with two or more prior episodes or any age with three or more prior episodes).

Pharmacologic Therapy - General Approach

- Give **older** patients **one-half** of the initial dose given to **younger adults**, and **increase** the dose more **slowly**.
- **Older** patients may require **6–12 weeks** of treatment to **achieve** the **desired antidepressant response**.
- **Early** in treatment, **all antidepressants** can **increase suicidal thinking** and **behavior** in children, adolescents, and young adults less than 25 years of age.
- **Suicide risk** may also be **elevated** in the **30 days after discontinuation**.
- **Educate** patients and their **support systems** about the **delay** in antidepressant **response** (typically **2–4 weeks**) and the **importance of adherence** before starting therapy and throughout treatment.
- **Occurrence** of a **withdrawal syndrome** with some antidepressants may be **reduced with a slow taper** over weeks or months when the medication is being discontinued.
- The ability of any antidepressant to **inhibit or induce the CYP450** enzymes can be a significant factor determining its capability to cause **pharmacokinetic interactions**.

1. Selective Serotonin Reuptake Inhibitors

- The SSRIs **inhibit the reuptake** of 5HT into the **presynaptic neuron**.
- They are generally chosen as **first line antidepressants** because of their relative **safety** in overdose and improved **tolerability** compared with earlier agents.
- **Nonresponse** to one SSRI **does not** predict **nonresponse** to an **alternative** SSRI.
- The SSRIs may have a **nonlinear pattern of accumulation** with **chronic dosing**.
- **Hepatic impairment, renal impairment, and age** can influence SSRI **pharmacokinetics**.
- **Any antidepressant** that **enhances serotonergic activity** can be associated with **serotonin syndrome** characterized by mental status changes, autonomic instability, and neuromuscular abnormalities.
- **Combining** an SSRI with another 5HT augmenting agent is also a **risk**.

1. Selective Serotonin Reuptake Inhibitors

- The **primary adverse effects** for SSRIs are nausea, vomiting, diarrhea, headache, insomnia, fatigue, and sexual dysfunction and have a **reduced incidence** of sedative, anticholinergic, and cardiovascular adverse effects or weight gain.
- A **few patients** have **anxiety symptoms early** in treatment which may be **reduced** by **starting with lower** doses and **slowly titrating up**.
- **Citalopram** and **escitalopram** may to an **increase in QT interval** at doses **above 40 mg/day**.
- **Potentially fatal reactions** may occur when any **SSRI and MAOI** are **co-administered**. ?
- A **5 week washout** after **fluoxetine discontinuation** is critical **before starting an MAOI**.
- If an **SSRI is added** to a regimen which includes **interacting medications** the SSRI **starting dose should be low and slowly titrated**.
- **CYP2D6 and 3A4** are responsible for the **metabolism** of **more than 80%** of current medications.

2. Selective Norepinephrine Reuptake Inhibitors

- **Venlafaxine** may have a **slight efficacy advantage** compared to other antidepressants.
- Common **adverse effects** may be **dose related** and include nausea, sexual dysfunction, activation, and hyperhidrosis.
- **Venlafaxine** may cause a **dose-related increase in diastolic blood pressure**, which may **require dosage reduction** or **discontinuation** if **sustained** hypertension occurs.
- **Nausea and vomiting** may be worse with venlafaxine and there may be **higher** adverse effect **related discontinuation** rates with **venlafaxine** and **duloxetine** than with the **SSRIs**.
- The most common adverse effects of **duloxetine** are nausea, dry mouth, constipation, decreased appetite, insomnia, and increased sweating.

3. Antidepressants with Mixed Serotonin Effects

- **Mirtazapine** enhances central **noradrenergic** and **serotonergic** activity by **antagonizing** central **presynaptic α2adrenergic auto**-receptors and **hetero-**receptors.
- It also **antagonizes 5HT2 and 5HT3** receptors and **blocks histamine receptors**.
- It may be an **option** for patients experiencing **sexual dysfunction** with other antidepressants.
- Mirtazapine's most common adverse effects are **somnolence, and weight gain**.
- **Levomilnacipran** is a **single isomer**, extended-release form of **milnacipran** (FDA approved to **treat fibromyalgia**).
- It **inhibits NE reuptake more than 5HT reuptake** and may **increase blood pressure and heart rate**.
- Its place in therapy for MDD is unknown.

3. Antidepressants with Mixed Serotonin Effects

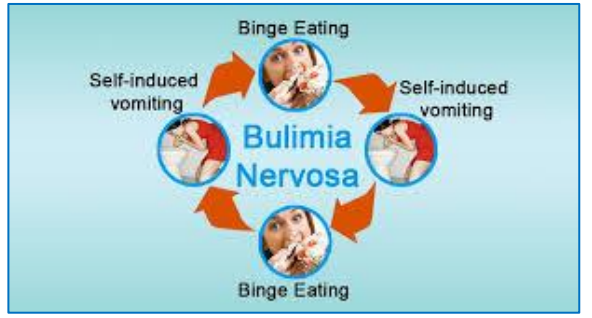
- **Trazodone** cause **minimal anticholinergic effects** and sedation, dizziness, and **cognitive slowing** are the **most frequent** dose limiting adverse effects.
- **Common** adverse effects with **nefazodone** are **dizziness, orthostatic hypotension, and somnolence**.
- **Priapism** occurs **rarely** with **trazodone** (1 in 6000 male patients), when occur **surgical intervention** may be required, and **impotence** may **result**.
- **Nefazodone** carries a black box warning for **life threatening liver failure**.
- **Do not** initiate nefazodone in individuals with **active liver disease** or **elevated** serum **transaminases**.

3. Antidepressants with Mixed Serotonin Effects

- **Vilazodone** and **vortioxetine** are antidepressants with **mixed serotonin** effects that are a combination **SSRI and 5HT1A** presynaptic receptor **partial agonists**.
- **Vilazodone** may be particularly useful for **depressed patients with anxiety**, and **vortioxetine** may be helpful for **depressed patients with cognitive difficulties**.
- **Vilazodone** is associated with nausea, diarrhea, dizziness, insomnia, and decreased libido, especially in males.
- **Vortioxetine** causes nausea and constipation and sexual dysfunction in males at the highest dose (**20 mg/day**).

4. Bupropion (NDRI)

- Bupropion **inhibits both the NE and DA reuptake** making it one of the most activating antidepressants.
- The **occurrence of seizures** with bupropion is **dose related** and may be **increased** by **predisposing factors** (eg, history of head trauma or central nervous system [CNS] tumor).
- At the **ceiling dose** (**450** mg/day), the **incidence of seizures is 0.4%**.
- **Other** adverse effects are nausea, vomiting, tremor, insomnia, dry mouth, and skin reactions.
- It is **contraindicated** in patients with **bulimia or anorexia nervosa**, due to a **higher risk for seizures**.
- It causes **less sexual dysfunction** than SSRIs.



5. Tricyclic Antidepressants

- **TCA** use has **diminished** given other **equally effective** therapies that are **safer** on overdose and **better tolerated**.
- They inhibit the **reuptake of NE and 5HT** and have affinity for **adrenergic, cholinergic, and histaminergic receptors**.
- TCAs cause **anticholinergic effects** (eg, dry mouth, blurred vision, constipation, urinary retention, tachycardia, memory impairment, and delirium) and **sedation**.
- **Additional** adverse effects include weight gain, orthostatic hypotension, cardiac conduction delay, and sexual dysfunction.
- **Desipramine** carries an increased **risk** of **death** in patients with a family history of sudden cardiac death, cardiac dysrhythmias, or cardiac conduction disturbances.
- **Abrupt withdrawal** of TCAs (especially high doses) may result in **cholinergic rebound** (eg, dizziness, nausea, diarrhea, insomnia, and restlessness).

5. Tricyclic Antidepressants

- TCA metabolism appears to be **linear** within the usual dosage range.
- Dose- related kinetics **cannot** be ruled out in older patients.
- **Factors** reported to **influence TCA plasma concentrations** include renal or hepatic dysfunction, genetics, age, cigarette smoking, and concurrent medications.
- In **acutely depressed patients**, there is a correlation between antidepressant effect and plasma concentrations for some TCAs (eg, amitriptyline, nortriptyline, imipramine, and desipramine).
- The best-established **therapeutic range** is for **nortriptyline**, and data suggest a **therapeutic window**.
- Some **indications** for **TCA plasma level monitoring** include inadequate response or relapse; adverse effects; use of higher than standard doses; suspected nonadherence; pharmacokinetic interactions; older, pediatric, and adolescent patients; pregnant patients; pharmacogenomic indications; and cardiac disease.

5. Tricyclic Antidepressants

- Obtain **steady state** plasma concentrations usually after a minimum of **1 week** at constant dosage, during the **elimination phase 12 hours** after the last dose.
- TCAs may **interact** with other **medications** that modify **hepatic cytochrome** P450 (CYP450) enzyme activity or **hepatic blood flow**.
- TCAs also are involved in **interactions** through **displacement** from protein binding sites.
- **Increased** plasma **concentrations** of TCAs and symptoms of **toxicity** may occur when CYP2D6 **inhibitors** are added.

6. Monoamine Oxidase Inhibitors

- **Isocarboxazide, phenelzine, and tranylcypromine increase** the concentrations of **NE, 5HT, and DA** within the neuronal **synapse** through **inhibition** of monoamine oxidase (**MAO**).
- They are **nonselective** inhibitors of MAOA and MAOB.
- **Selegiline**, available as a **transdermal patch** for treatment of major depression, inhibits brain **MAOA and MAOB** but has **reduced** effects on **MAOA in the gut**.
- The most common medication adverse effect is **postural hypotension** (more likely with **phenelzine** than tranylcypromine), which can be **minimized** by **divided dosing**.
- **Phenelzine** is mildly to moderately **sedating**, but **tranylcypromine** is often **stimulating**, and the last dose of the day is administered in the early afternoon.
- **Sexual dysfunction** in both genders is common.

6. Monoamine Oxidase Inhibitors

- **Phenelzine** has been associated with **hepatocellular damage and weight gain**.
- The potentially **fatal hypertensive crisis** can occur when **MAOIs** are taken concurrently with **foods high in tyramine** and with certain **medications**.
- **Symptoms** include occipital headache, stiff neck, nausea, vomiting, sweating, and sharply elevated blood pressure.
- It can be **treated** with agents such as **captopril**.

6. Monoamine Oxidase Inhibitors

- **Education regarding dietary** (e.g., aged cheese) and **medication** (e.g., Dextromethorphan, amphetamine, sympathomimetics, etc) **restrictions** are **critical**.
- Patients taking **transdermal selegiline patch** doses greater than **6 mg/24 hours** must follow the **dietary restrictions**.
- Potentially **fatal reactions** may occur when any **SSRI or TCA** is co-administered with an **MAOI**.
- However, TCAs and MAOIs can be **combined in refractory patients** by experienced clinicians with **careful monitoring**.

7. Ketamine

- Ketamine **modulates glutamate activity** via extra synaptic N-methyl-D- aspartate **(NMDA) receptor antagonism** resulting in **increased BDNF activity and synaptogenesis**.
- It has **rapid antidepressant effects** when used in **intravenous** doses of **0.5mg/kg** for treatment of **treatment-resistant depression** (**TRD**).
- **Esketamine** is the single **s-isomer** of ketamine that has a **higher affinity** for the NMDA receptor than the R-isomer.
- **Intranasal esketamine** is FDA approved and requires **supervised, in-clinic self administration** (1–3 sprays in each nostril per session) followed by **2 hours** of **in-clinic observation**.
- In **trials**, patients received doses **twice weekly for 4 weeks** and variable dosing thereafter.
- Medication adverse effects include **transient psychotomimetic/dissociative effects and blood pressure elevation** (10–20 mm Hg) with both agents.
- It has a mandatory Risk Evaluation and Mitigation Strategies (**REMS**).

8. Brexanolone

- **Brexanolone** (exogenous **allopregnanolone**) is thought to exert **antidepressant** effect by **allosteric modulation of GABAA receptors**, which may **increase 5HT** and **NE** transmission and is FDA approved for **postpartum depression**.
- **Administration** involves a **60 hour stepped dose**, **intravenous infusion** which is **very costly**.
- Common adverse effects are **headache, dizziness, and somnolence**.
- It also has a **REMS program** with Elements to Ensure Safe Use (**ETASU**) due to the incidence of excessive sedation or loss of consciousness.

9. Alternative Pharmacotherapy

- **St. John's wort**, a **herb** containing **hypericum**, may be effective some with **mild to moderate depression**.
- It is associated with **several medication interactions**.
- **Omega3** fatty acids, **S-adenosyl-L-methionine** (SAMe), and **folate** are additional pharmacotherapies that **could be considered**.
- **Evidence** regarding their use is **conflicting or still emerging**.
- **All** of these agents should be used with **caution**.

Special Populations - Older Patients

- In **older patients**, depressed mood may be **less prominent** than **other symptoms**, such as loss of appetite, cognitive impairment, sleeplessness, fatigue, physical complaints, and loss of interest in usual activities.
- The **SSRIs** are often considered **first choice** antidepressants for older patients.
- **Bupropion**, **venlafaxine**, and **mirtazapine** are also **effective** and **well tolerated**.
- **Hyponatremia** is more **common** in older patients.

Special Populations - Pediatric Patients

- **Symptoms** of depression in childhood include boredom, anxiety, failing adjustment, and sleep disturbance.
- Data supporting **efficacy** of antidepressants in children and adolescents are **sparse**.
- **Fluoxetine and escitalopram** are FDA approved for patients **below 18 years** of age.
- **All antidepressants** carry a black box warning for use in this population regarding increased risk for **suicidal ideation and behavior**.
- The FDA recommends specific **monitoring** parameters.
- Several cases of **sudden death** have been reported in children and adolescents taking **desipramine** and baseline electrocardiogram (**ECG**) is **recommended**.

Special Populations - Pregnancy and Lactation

- Individuals who **discontinued** antidepressant therapy during pregnancy were **five times** more likely to have a **relapse** during their pregnancy than those who **continued** treatment.
- The **absolute risk** of antidepressant use in pregnancy is **unknown**.
- **Risks** reported with **SSRIs** use in pregnancy include **low birth weight, respiratory distress, and congenital heart defects**.
- The **risks and benefits** of drug therapy during pregnancy **must be weighed**, including concerns about **untreated depression**.
- There is a **great deal** of **uncertainty** regarding long-term antidepressant exposure in infants exposed through human milk **due to the lack of data**.

Relative Resistance and Treatment-Resistant Depression

- **One in three** patients who **did not achieve remission** with an antidepressant may become **symptom free** when an **additional medication** (eg, bupropion SR or buspirone) is added.
- **One in four** may **achieve remission** after **switching to a different** antidepressant (eg, venlafaxine XR or bupropion, or sertraline).
- The current antidepressant may also be **augmented by addition of another agent** (eg, lithium or triiodothyronine [T3]), or **another antidepressant** can be added.
- A **second generation antipsychotic** (eg, aripiprazole, quetiapine, brexpiprazole) can be used to **augment** antidepressant response.
- **New medications** such as **ketamine** and **esketamine** may be **considered**.

Relative Resistance and Treatment-Resistant Depression

- The practice guideline of the American Psychiatric Association (**APA**) recommends that **after 6–8 weeks** of treatment, **partial responders** should consider **changing** the dose, **augmenting** the antidepressant, or **adding** psychotherapy or ECT.
- For patients with **no response**, options include **changing** to another antidepressant or the **addition** of psychotherapy or ECT.
- **Before changing** treatment, **evaluate** the **adequacy** of the medication dosage and **adherence**, as most "treatment resistant" depressed patients have received inadequate therapy.

Relative Resistance and Treatment-Resistant Depression

- **Issues** to be **addressed** in assessing the patient who has not responded to treatment include asking:
- (1) Is the diagnosis correct?
- (2) Does the patient have a psychotic depression?
- (3) Is the dose and duration of treatment adequate?
- (4) Do adverse medication reactions preclude adequate dosing?
- (5) Is patient adherence appropriate?
- (6) Was a stepwise approach to treatment used?
- (7) Was treatment outcome adequately measured?
- (8) Is there a coexisting or preexisting medical or psychiatric disorder?
- (9) Are there other factors interfering with treatment?
- (10) May pharmacogenomics be impacting treatment?

Evaluation of therapeutic outcomes

- **Several** monitoring **parameters**, in addition to **plasma concentrations**, are useful.
- Monitor regularly for **adverse effects, remission** of target symptoms, and **changes** in **social or occupational** functioning.
- Assure **regular monitoring** for **several months after discontinuation** of antidepressants.
- Regularly monitor **blood pressure** of patients given serotonin–norepinephrine reuptake inhibitors.
- A **pretreatment ECG** is recommended before starting **TCA therapy in children, adolescents, and patients over 40** years of age, and perform **follow up ECGs periodically**.
- Monitor for **suicidal ideation** after initiation of any antidepressant, **especially** in the **first few weeks** of treatment and up to **30 days after treatment discontinuation**.
- In addition to the **clinical interview**, use **psychometric rating instruments** to rapidly and reliably measure the **nature and severity** of depressive and associated symptoms.

THANK YOU FOR YOUR ATTENTION