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

DEPRESSIVE DISORDERS

Dr Qassim A zigam

DEPRESSIVE DISORDERS

- Major depression is a **common**, seriously **disabling** disorder **nonresponsive** to volitional efforts to **feel better**.
- Individuals with MDD experience pervasive symptoms **affecting mood**, **thinking**, **physical health**, **work**, and **relationships**.
- **Inadequately** treated MDD increases the risk of **suicide**.
- The **essential clinical feature** of MDD is one or more major depressive episodes **without** a history of manic or hypomanic episodes.

PATHOPHYSIOLOGY

1. Monoamine hypothesis:

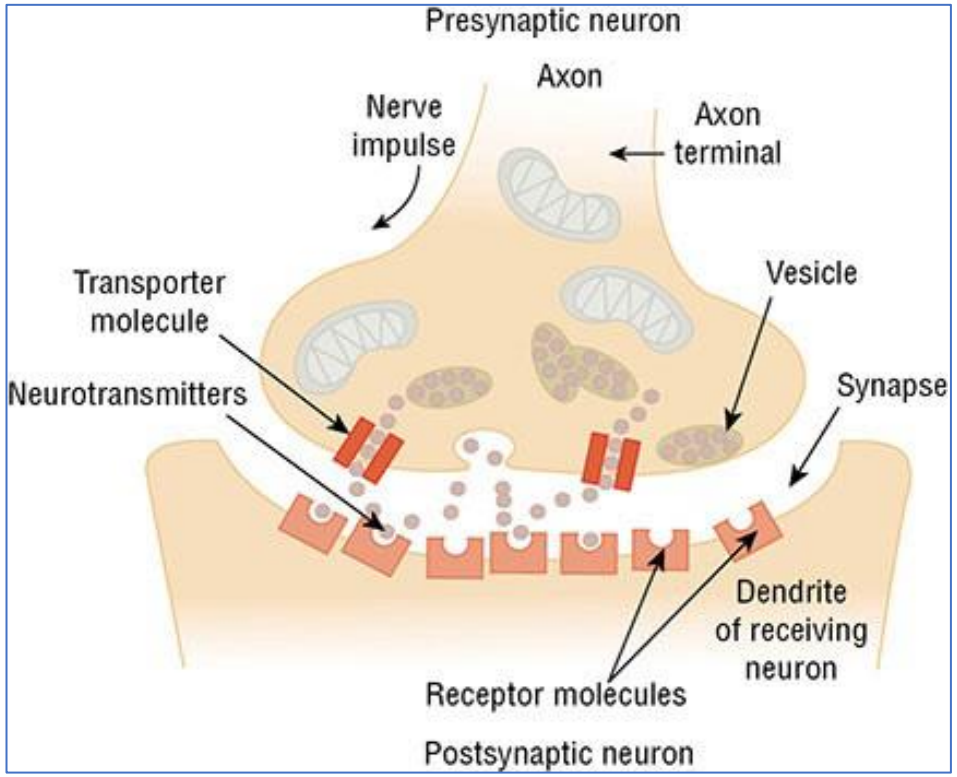
- **Decreased** brain levels of the **neurotransmitters** norepinephrine (NE), serotonin (5-HT), and dopamine (DA) may cause **depression**.

2. Postsynaptic changes in receptor sensitivity:

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

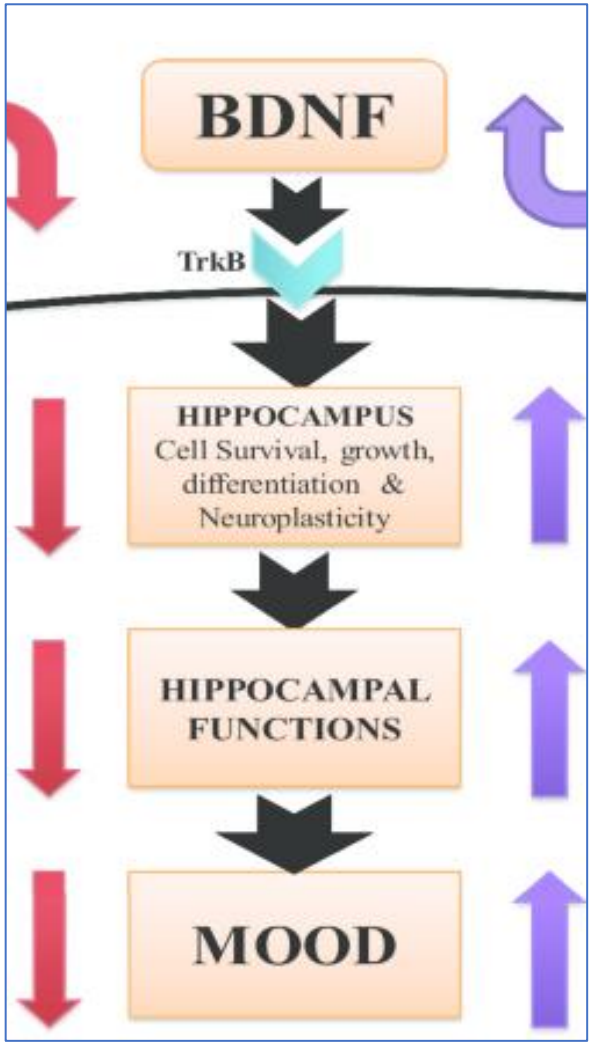
3. Dysregulation hypothesis:

- **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.



5. Neuroactive steroids:

- They 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**.

CLINICAL PRESENTATION

2. Physical symptoms:

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

3. Cognitive symptoms:

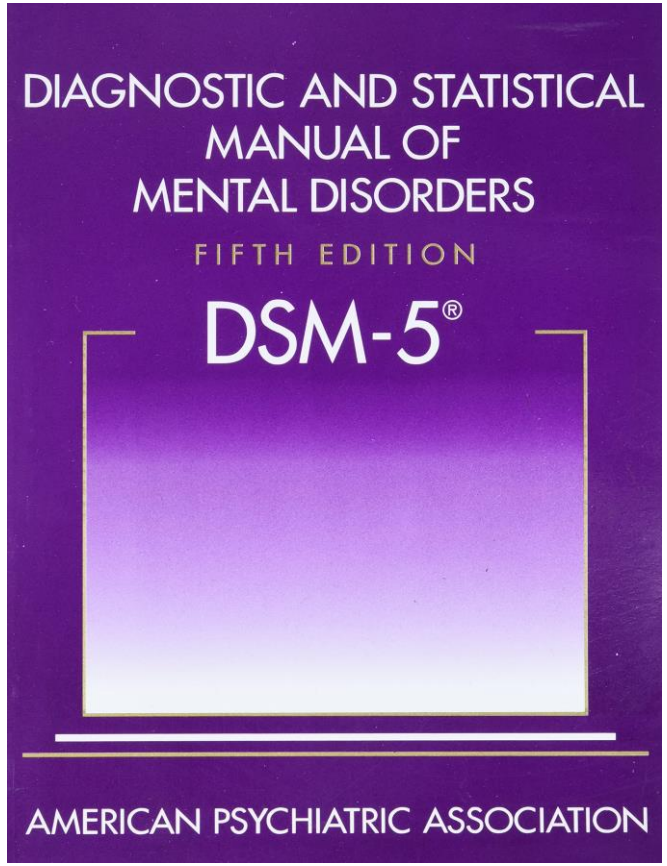
- Decreased ability to **concentrate**, poor **memory** for **recent** events, **confusion**, and **indecisiveness**.

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 DSM-5.
- **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**).
- The depressive **episode must not be** attributable to the physiological effects of a substance or medical condition.
- There **must not be a history** of manic-like or hypomanic-like episodes **unless** they were induced by a substance or medical condition.



DIAGNOSIS (Sig E caps)

TABLE 68-1	Diagnostic Criteria for Major Depressive Episode
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.

DIAGNOSIS

- **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's disease, traumatic brain injury, hypothyroidism) and **substance abuse** and **dependence disorders** are associated with depression.
- **Medications** associated with depressive symptoms include many **antihypertensives**, oral **contraceptives**, **isotretinoin**, **interferon-β_{1a}**, and many others.
- **Standardized rating scale** should be used to **diagnose** depression and **evaluate** treatment.

TREATMENT

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

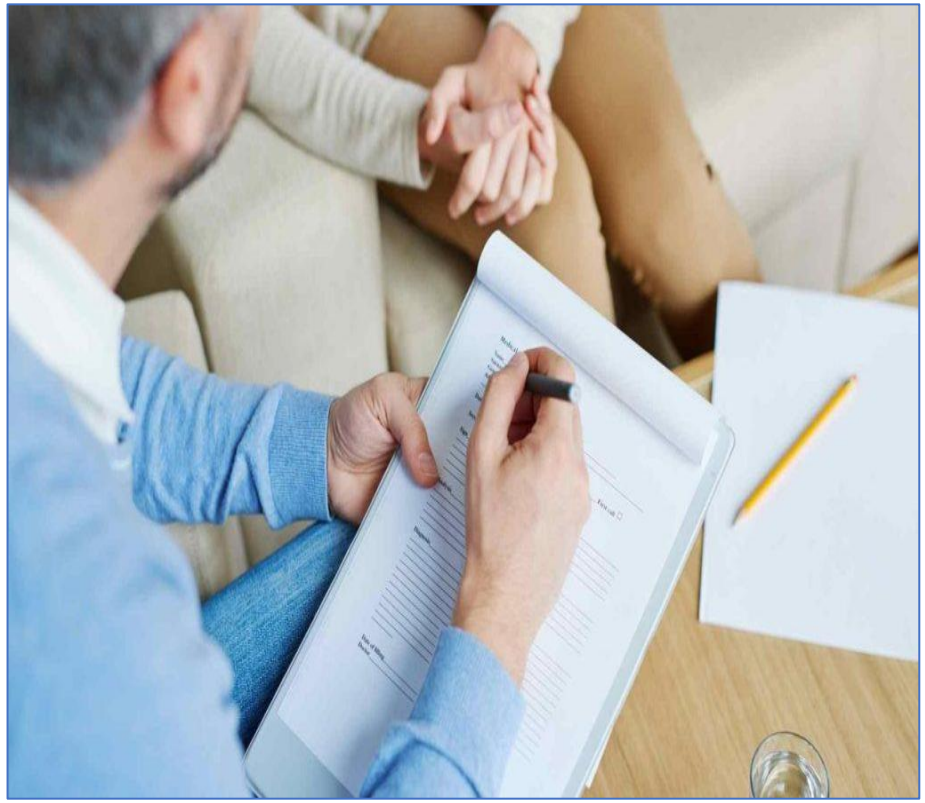
- There are **two types** of treatments:

1. **Nonpharmacologic** treatment
2. **Pharmacologic** treatment

NONPHARMACOLOGIC TREATMENT

1. Psychotherapy:

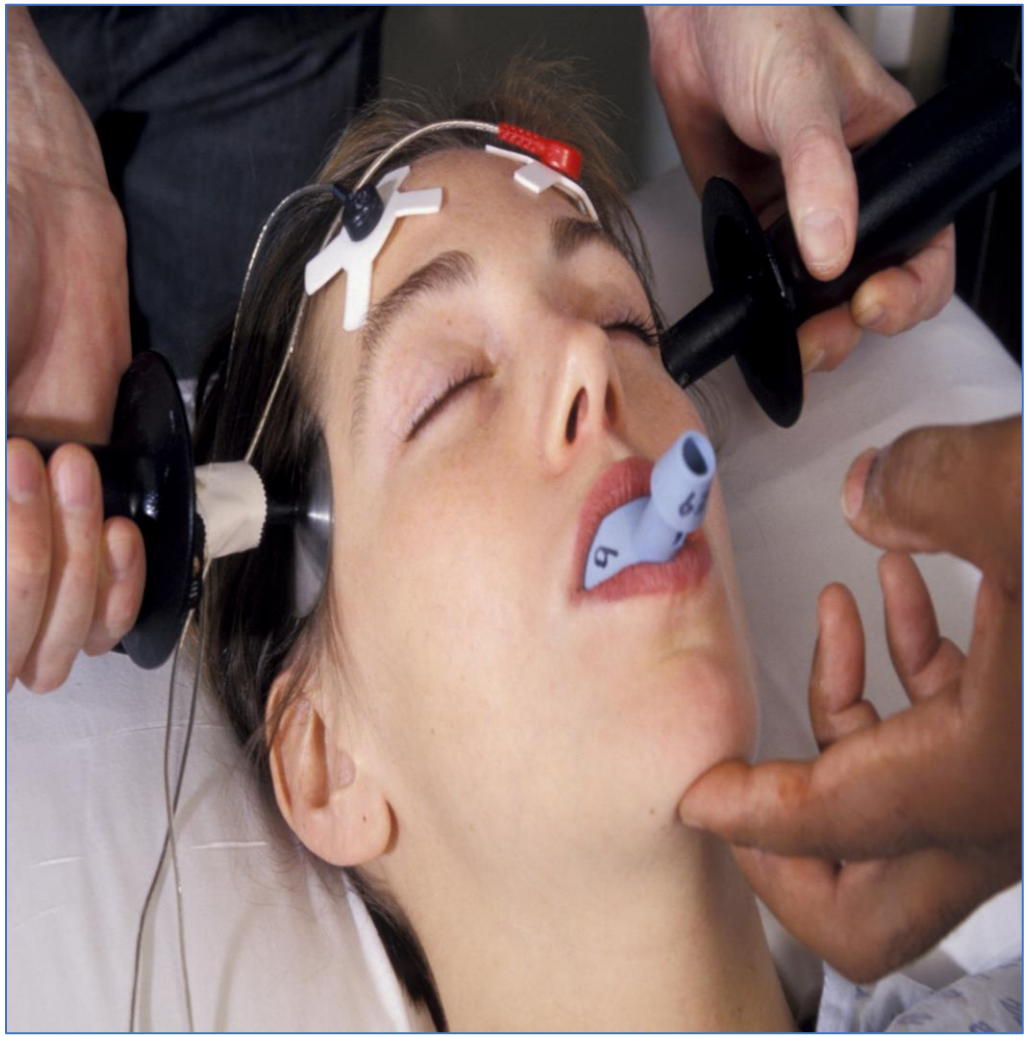
- Such as **cognitive therapy**, **behavioral therapy**, or **interpersonal psychotherapy** is recommended as **primary treatment** for **mild to moderate** major depressive episodes.
- For **severe depression**, it may be used in **combination** with **medications** as its effect is considered **additive**.
- Psychotherapy **alone is not recommended** for **acute** treatment of **severe and/or psychotic MDD**.



NONPHARMACOLOGIC TREATMENT

2. Electroconvulsive therapy (ECT):

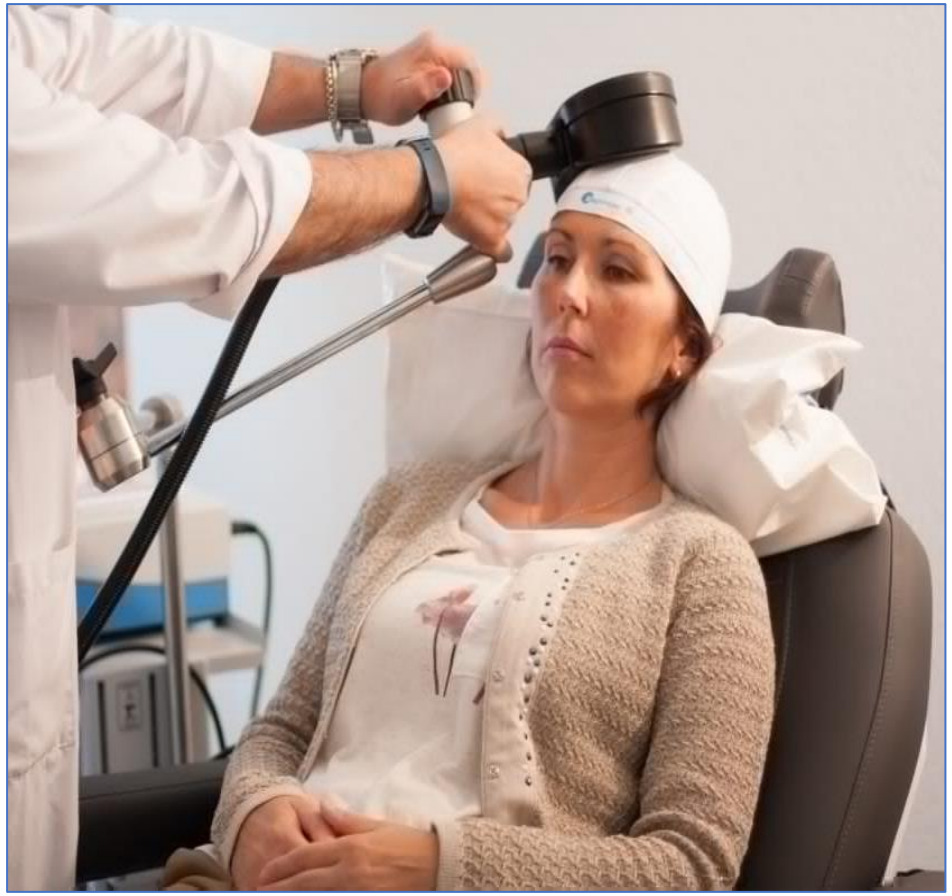
- It may be **considered** when:
  - ✓Rapid response is needed
  - ✓Risks of other treatments outweigh the potential benefits
  - ✓There is a history of a poor response to drugs
  - ✓The patient prefers ECT
- A **rapid therapeutic response (10–14 days) has been reported**.



NONPHARMACOLOGIC TREATMENT

3. Transcranial magnetic stimulation:

- Repetitive **transcranial magnetic stimulation** has demonstrated **efficacy** and does **not** require **anesthesia** as does ECT.



4. Physical activity

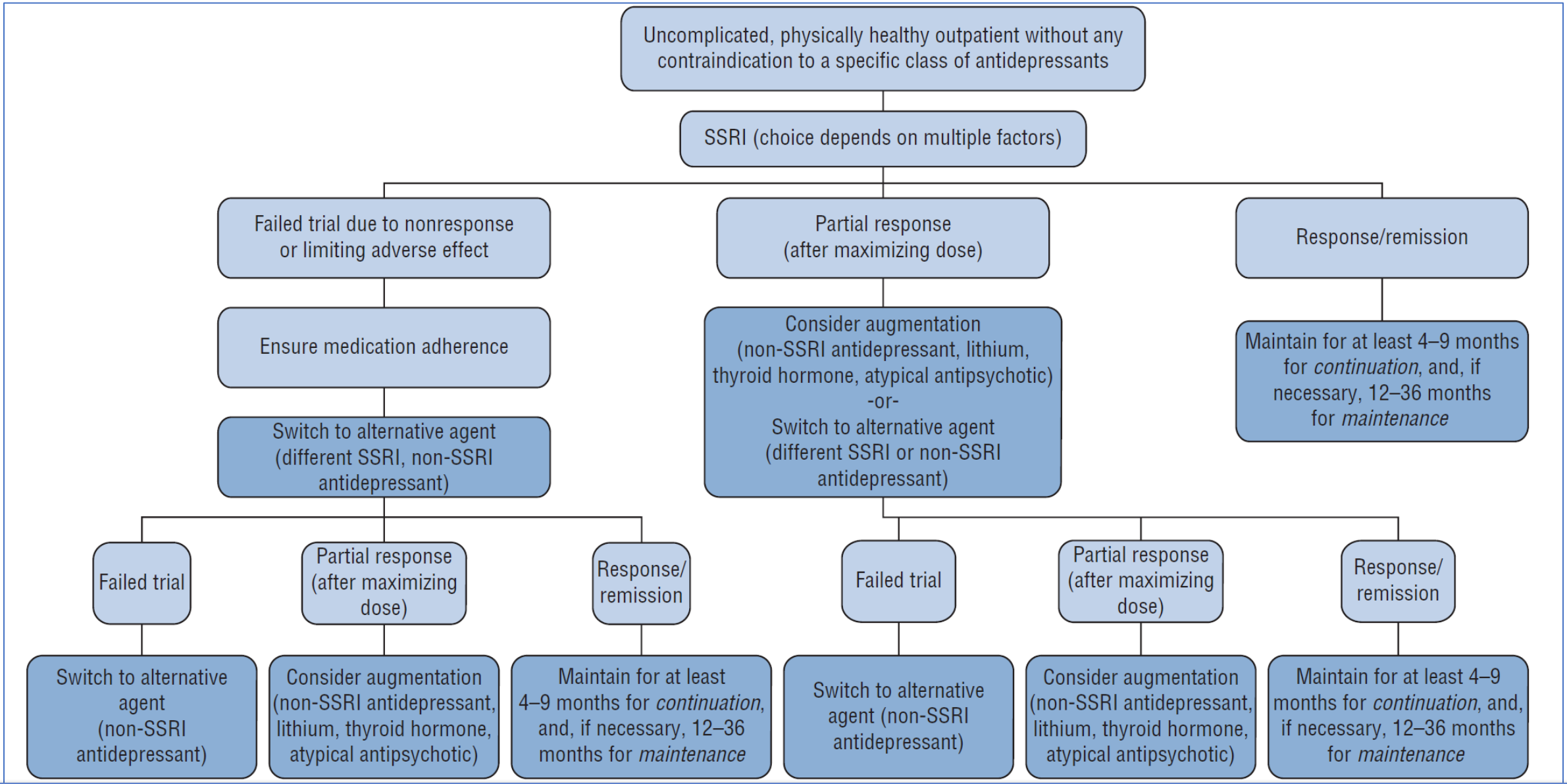
- Recent data suggest the benefit of **physical activity** in patients with MDD, and the American Psychiatry Association has **endorsed the inclusion of exercise** into MDD treatment plans.

PHARMACOLOGIC TREATMENT

Antidepressants include:

1. **Selective serotonin reuptake inhibitors (SSRIs):** Citalopram, Escitalopram, Fluoxetine, Norfluoxetinec, Fluvoxamine, Paroxetine, and Sertraline.
2. **Serotonin–norepinephrine reuptake inhibitors (SNRIs):** Desvenlafaxine, Duloxetine, levomilnacipran, and Venlafaxine.
3. **Tricyclic Antidepressants (TCAs):** Amitriptyline, Nortriptyline, Desipramine, Doxepin, Imipramine, and Nortriptyline.
4. **Mixed serotonergic (mixed 5-HT):** Nefazodone, Trazodone, Vilazodone, and Vortioxetine.
5. **Norepinephrine/Dopamine reuptake inhibitor (NDRI):** Bupropion.
6. **Serotonin and α2-adrenergic antagonists:** Mirtazapine.
7. **Monoamine Oxidase Inhibitors (MOIs) :** Isocarboxazide, phenelzine, and tranylcypromine, and Selegiline

PHARMACOLOGIC TREATMENT



PHARMACOLOGIC TREATMENT

- Antidepressants are **equal** in **efficacy** when administered in **comparable doses**, and they are often **classified** by chemical structure and/or presumed mechanism.
- The **initial choice** of antidepressant is often made empirically and **influenced by** the patient's or family member's **history of response**, **concurrent** medical conditions, **medications** the patient is taking, presenting **symptoms**, potential for **drug-drug interactions**, **side effect** profiles, **patient preference**, and **drug cost**.
- An individual's **pharmacogenomics** may be useful when choosing therapy as a way to better **predict** antidepressant side effects or responses.
- **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.

PHARMACOLOGIC TREATMENT

- At least a **6-week trial** of an antidepressant at **maximum dosage** is considered an adequate **trial** of that medication.

1. The **acute phase** of treatment lasts **6–12 weeks**, and the **goal is remission** (ie, absence of symptoms).
2. The **continuation phase** (**4–9 months after remission**) seeks to **eliminate residual** symptoms or **prevent relapse**.
3. The **maintenance phase** (**12–36 months or more**) seeks to **prevent the recurrence of a new episode of depression**.

- **50%–60%** of patients with varying types of depression **improve with drug therapy**.
- 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.

PHARMACOLOGIC TREATMENT

- **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**.
- Some clinicians recommend **lifelong therapy** for persons **younger than 40 years** with two or more prior episodes and for **all persons** with three or more prior episodes.
- **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.

Selective Serotonin Reuptake Inhibitors (SSRIs)

- The SSRIs **inhibit the reuptake of 5-HT 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.
- The SSRIs, with the possible **exceptions** of citalopram and sertraline, may have a **nonlinear pattern** of drug accumulation with chronic dosing.
- **Hepatic** impairment, **renal** impairment, and **age** can **influence** the pharmacokinetics of SSRIs.
- 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 5-HT augmenting agent is also a risk.

Selective Serotonin Reuptake Inhibitors (SSRIs)

- The **primary adverse effects** of 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 increase in QT interval at doses above 40 mg/day.
- Potentially **fatal reactions** may occur when any **SSRI** and **MAOI** are **co-administered**.

Selective Serotonin Reuptake Inhibitors (SSRIs)

- A **5-week washout** after fluoxetine discontinuation is critical **before** starting an MAOI.
- If an SSRI is **added** to a regimen that includes drugs known to **interact with SSRIs**, the SSRI **starting** dose should be **low and slowly titrated**.
- **CYP2D6 and 3A4** are responsible for the **metabolism** of more than **80%** of currently marketed drugs.
- Consult the **drug interaction** literature for detailed information concerning any real or potential psychotherapeutic drug interactions.

Serotonin–Norepinephrine Reuptake Inhibitors (SNRIs)

- SNRIs include **venlafaxine, desvenlafaxine, duloxetine,** and **levomilnacipran**.
- Some studies suggest a **slight efficacy advantage** for **venlafaxine** compared to other antidepressants.
- **Common side effects** for these medications may be **dose-related** and include nausea, sexual dysfunction, activation, and hyperhidrosis.
- **Venlafaxine** may cause a dose-related increase in **diastolic blood pressure**.
- Dosage **reduction** or **discontinuation** may be **necessary** if **sustained hypertension** occurs.

Serotonin–Norepinephrine Reuptake Inhibitors (SNRIs)

- Nausea and vomiting may be worse with **venlafaxine** and there may be higher side effect-related **discontinuation rates** with venlafaxine and duloxetine than with the SSRIs.
- The most **common** side effects of **duloxetine** are nausea, dry mouth, constipation, decreased appetite, insomnia, and increased sweating.
- **Levomilnacipran** is a single-isomer, **extended-release** form of **milnacipran** which is FDA-approved to treat **fibromyalgia** and pharmacologically **inhibits NE reuptake more than 5-HT reuptake**.
- This agent may **increase** blood pressure and heart rate and its place in therapy for MDD is unknown.

Serotonin and α2-adrenergic antagonists

- **Mirtazapine** enhances **central** noradrenergic and serotonergic activity by antagonizing central **presynaptic α2-adrenergic autoreceptors** and **heteroreceptors**.
- It also **antagonizes 5-HT2 and 5-HT3 receptors** and **blocks histamine receptors**.
- It may be an **option** for patients who **experience sexual dysfunction** taking other antidepressants.
- Mirtazapine's most **common** adverse effects are somnolence, weight gain, dry mouth, and constipation.

Mixed serotonergic (mixed 5-HT)

- **Trazodone** and **nefazodone** antagonize the 5-HT2 receptor and inhibit the reuptake of 5-HT, they can also enhance 5-HT1A neurotransmission.
- **Trazodone** blocks **α1-**adrenergic and **histaminergic** receptors increasing dizziness and sedation.
- **Trazodone** cause **minimal anticholinergic** effects. Sedation, dizziness, and cognitive slowing are the most frequent **dose-limiting** side effects with trazodone.
- **Priapism** occurs rarely with **trazodone** (1 in 6000 male patients), **surgical** intervention may be required, and **impotence** may result.
- **Common** side effects of **nefazodone** are dizziness, orthostatic hypotension, and somnolence.
- **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**.

Mixed serotonergic (mixed 5-HT)

- **Vilazodone** and **vortioxetine** are other antidepressants with mixed serotonin effects that are a **combination** of **SSRI and 5-HT1A 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 men.
- Vortioxetine causes nausea and constipation and sexual dysfunction in men at the highest dose (20 mg/day).

Norepinephrine/Dopamine reuptake inhibitor (NDRI)

- **Bupropion** inhibits both the NE and DA reuptake which makes 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** side effects are nausea, vomiting, tremor, insomnia, dry mouth, and skin reactions.
- It is **contraindicated** in patients with **bulimia or anorexia nervosa**, as these patients have a higher risk for seizures.
- It causes **less sexual dysfunction** than SSRIs.

Tricyclic Antidepressants (TCAs)

- TCAs use has **diminished** because of the **availability** of equally **effective** therapies that are **safer** on overdose and better **tolerated**.
- They inhibit the reuptake of NE and 5-HT and have an affinity for adrenergic, cholinergic, and histaminergic receptors.
- TCAs cause **anticholinergic side 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.

Tricyclic Antidepressants (TCAs)

- **Abrupt withdrawal** of TCAs (especially high doses) may result in **cholinergic rebound** (eg, dizziness, nausea, diarrhea, insomnia, and restlessness).
- **Maprotiline**, a tetracyclic drug, causes **seizures** at a higher incidence than do standard TCAs and is **contraindicated** in patients with a history of **seizure** disorder.
- **Metabolism** of the TCAs appears to be **linear** within the **usual** dosage range, and dose-related kinetics cannot be ruled out in older patients.
- **Factors** reported to influence TCA plasma conc. include **renal** or **hepatic dysfunction**, **genetics**, **age**, **cigarette smoking**, and **concurrent** drug administration.

Tricyclic Antidepressants (TCAs)

- In acutely depressed patients, there is a **correlation** between antidepressant effect and **plasma conc.** for some TCAs (eg, amitriptyline, nortriptyline, imipramine, and desipramine).
- Some **indications** for TCA plasma level **monitoring** include inadequate response; relapse; serious or persistent adverse effects; use of higher than standard doses; suspected non-adherence, toxicity, pharmacokinetic interactions; **elderly**, **pediatric**, and adolescent patients; pregnant patients; patients of African or Asian descent (because of **slower metabolism**); cardiac disease; and **changing** brands.

Tricyclic Antidepressants (TCAs)

- Plasma concentrations should be obtained at a **steady state**, usually after a minimum of **1 week** at constant dosage, during the elimination phase, and usually in **the morning 12 hours after** the last dose.
- TCAs may **interact** with other drugs 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 **fluoxetine** or **paroxetine** (both inhibitors of CYP2D6) are **added**.

Monoamine Oxidase Inhibitors (MAOIs)

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

Monoamine Oxidase Inhibitors (MAOIs)

- **Sexual dysfunction** in both genders is **common**.
- **Phenelzine** has been associated with **hepatocellular damage** and **weight gain**.
- **Hypertensive crisis** is a potentially fatal reaction that can occur when **MAOIs** are taken concurrently with **certain foods**, especially those high in **tyramine**, and with certain drugs.
- **Symptoms** of the hypertensive crisis include **occipital headache, stiff neck, nausea, vomiting, sweating,** and **sharply elevated blood pressure**.
- Hypertensive crisis may be **treated** with agents such as **captopril**.

Monoamine Oxidase Inhibitors (MAOIs)

- **Education** of patients taking **MAOIs** regarding **dietary** and **medication** restrictions is 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**.

Ketamine

- Ketamine is an older **anesthetic** agent, which modulates **glutamate activity** via extra-synaptic N-methyl-D-aspartate (**NMDA**) receptor **antagonism** resulting in **increased BDNF activity** and **synaptogenesis**.
- Ketamine has **rapid** antidepressant effects when used in **intravenous** doses of 0.5mg/ kg for the treatment of **refractory** MDD.
- **Esketamine** is the single **s-isomer** of ketamine that has a **higher affinity** for the NMDA receptor than the r-isomer.

Ketamine

- **Intranasal esketamine** is FDA-approved and requires **supervised**, in-clinic self-administration (2–6 sprays per session) followed by 2 hours of in-clinic **observation**.
- In trials, patients received doses twice weekly for 4 weeks and variable dosing thereafter.
- **Side effects** include **transient psychotomimetic/dissociative** effects and blood **pressure elevation** (10–20 mm Hg) with both agents.

Brexanolone

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

St. John’s Wort

- St. John’s wort, a **herb** containing **hypericum**, may be effective for **mild-to-moderate** depression.
- It acts as a **serotonin** reuptake inhibitor, as well as **dopamine** and **norepinephrine**.
- It is associated with several drug–drug **interactions**.
- All antidepressant regimens should be **overseen** by a trained healthcare professional.

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 the efficacy of antidepressants in children and adolescents are **sparse**.
- **Fluoxetine** and **escitalopram** are the **only** FDA-approved antidepressants for patients **below 18 years** of age.
- **All** antidepressants carry a **black box warning** for caution when using antidepressants in this **population**, and the FDA recommends specific monitoring parameters.
- Several cases of **sudden death** have been reported in children and adolescents taking **desipramine** and a baseline **ECG** is recommended.

SPECIAL POPULATIONS

- **Pregnancy**
- Approximately **14%** of pregnant women develop depression during pregnancy and women who **discontinued** antidepressant therapy were **five times** more likely to have a **relapse** during their pregnancy than were women who **continued** treatment.
- **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.
- **Lack** of current data exists regarding antidepressant exposure to **infants** during breastfeeding; however, **sertraline** may be **preferred**.
- The **Motherisk program** has the most up-to-date information.

Relative Resistance and Treatment-Resistant Depression

- Most “treatment-resistant” depressed patients have received **inadequate** therapy.
- The STAR*D study showed that **one in three** patients who did **not achieve remission** with an antidepressant became symptom-free when an **additional** medication (eg, bupropion SR or buspirone) was added, and **one in four** achieved **remission** after **switching** to a different antidepressant (eg, venlafaxine XR or bupropion, or sertraline).
- The current antidepressant may be **stopped** and a trial initiated with a **different** agent (eg, mirtazapine or nortriptyline).

Relative Resistance and Treatment-Resistant Depression

- **Alternatively**, the current antidepressant may be **augmented** by the addition of another agent (eg, lithium or triiodothyronine [T3]), or another antidepressant can be added.
- An **atypical antipsychotic** (eg, aripiprazole, quetiapine, brexpiprazole) can be used to **augment** antidepressant response.
- The practice guideline of the American Psychiatric Association **recommends** that after **6–8 weeks** of antidepressant 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.

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 the **blood pressure** of patients given serotonin-norepinephrine reuptake inhibitors.

EVALUATION OF THERAPEUTIC OUTCOMES

- 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