MAJOR DEPRESSIVE DISORDER

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LEARNING OBJECTIVES

- Explain the pathophysiologic mechanisms underlying Depression
- List the major symptoms of Major Depression
- Recommend an appropriate antidepressant therapy based on treatment phase and patient history
- Apply pharmacokinetic principles and patient specific data to choose the most appropriate pharmacologic therapy
- Evaluate response to therapy and treatment side effect

DEFINITION

- Mood state, as indicated by feelings of sadness, despair, anxiety, emptiness, discouragement, or hopelessness; having no feelings; or appearing tearful
- Syndrome, which is a constellation of symptoms and signs (eg, major depression or minor depression)
- Mental disorder that identifies a distinct clinical condition (eg, unipolar major depression)

ASSESSMENT

- History of present illness
  - Depressive symptoms and their context
  - Suicide risk
  - General medical illness
- Family history
- Social history
- Mental status examination
- Physical examination
- Laboratory evaluation
- Screening for depression
- Diagnostic instruments

EPIDEMIOLOGY

- Estimated lifetime prevalence is 12 percent
  - Developed countries like United States and Europe ➔18%
  - Developing countries like Peoples' Republic of China, Mexico, and Brazil ➔9%
- World Health Organization
  - Unipolar major depression is the 11th greatest cause of disability and mortality in the world
- United States
  - Major depression ranks second among all diseases and injuries as a cause of disability, and persistent depressive disorder (dysthymia) as the 20th
- Sex
  - Two times greater in females compared to males
- Race
  - Whites ➔18 %
  - Caribbean blacks ➔13 %
  - African Americans ➔ 10 %
- Age
  - Less common in older than younger adults living in the community

PATHOGENESIS

- Genetics
  - Pharmacogenetics may influence response to antidepressants
- Early life adversity
  - Childhood trauma
- Social factors
  - Isolation, poor social relationships, criticism from family members, and depression in one's friends and neighbors
- Psychologic factors
  - Negative patterns of thinking, early life losses, self-esteem, and difficulties in managing acute losses (real, imagined, or threatened) and interpersonal relationships
- Secondary depression
  - General medical disorders: Epilepsy, Parkinson, Heart Failure, HIV/AIDS, Cancer…
  - Medications: Glucocorticoids and Interferons

NEUROBIOLOGY

- Neurotransmitters
  - Monoamines (serotonin, norepinephrine, and dopamine)
  - Gamma-aminobutyric acid (GABA)
  - Glutamate

DIAGNOSTIC CRITERIA AND CLASSIFICATION

Criteria in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)

A. Five (or more) of the following symptoms have been present during the same two-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.
NOTE: Do not include symptoms that are clearly attributable to another medical condition.
1) Depressed mood most of the day, nearly every day, as indicated by either subjective report (eg, feels sad, empty, hopeless) or observations made by others (eg, appears tearful). (NOTE: In children and adolescents, can be irritable mood.)
2) Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation)
3) Significant weight loss when not dieting or weight gain (eg, a change of more than 5 percent of body weight in a month), or decrease or increase in appetite nearly every day. (NOTE: In children, consider failure to make expected weight gain.)
4) Insomnia or hypersomnia nearly every day
5) Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)
6) Fatigue or loss of energy nearly every day
7) Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)
8) Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by their subjective account or as observed by others)
9) Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide
B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
C. The episode is not attributable to the direct physiological effects of a substance or to another medical condition.
NOTE: Criteria A through C represent a major depressive episode.
NOTE: Responses to a significant loss (eg, bereavement, financial ruin, losses from a natural disaster, a serious medical illness or disability) may include the feelings of intense sadness, rumination about the loss, insomnia, poor appetite, and weight loss noted in Criterion A, which may resemble a depressive episode. Although such symptoms may be understandable or considered appropriate to the loss, the presence of a major depressive episode in addition to the normal response to a significant loss should also be carefully considered. This decision inevitably requires the exercise of clinical judgement based on the individual's history and the cultural norms for the expression of distress in the context of loss.
D. The occurence of the major depressive episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders.
E. There has never been a manic or hypomanic episode.
NOTE: This exclusion does not apply if all of the manic-like or hypomanic-like epsidoes are substance-induced or are attributable to the physiological effects of another medical condition.
Specify:
With anxious distress
With mixed features
With melancholic features
With atypical features
With psychotic features
With catatonia
With peripartum onset
With seasonal pattern

DIAGNOSTIC CRITERIA AND CLASSIFICATION

DSM-5 diagnostic criteria for manic episode

A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased activity or energy, lasting at least one week and present most of the day, nearly every day (or any duration if hospitalization is necessary).

B. During the period of mood disturbance and increased energy or activity, three (or more) of the following symptoms (four if the mood is only irritable) are present to a significant degree and represent a noticeable change from usual behavior:

1) Inflated self-esteem or grandiosity.

2) Decreased need for sleep (eg, feels rested after only three hours of sleep).

3) More talkative than usual or pressure to keep talking.

4) Flight of ideas or subjective experience that thoughts are racing.

5) Distractibility (ie, attention too easily drawn to unimportant or irrelevant external stimuli), as reported or observed.

6) Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation (ie, purposeless non-goal-directed activity).

7) Excessive involvement in activities that have a high potential for painful consequences (eg, engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments).

C. The mood disturbance is sufficiently severe to cause marked impairment in social or occupational functioning or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.

D. The episode is not attributable to the physiological effects of a substance (eg, a drug of abuse, a medication, other treatment) or to another medical condition.

NOTE: A full manic episode that emerges during antidepressant treatment (eg, medication, electroconvulsive therapy) but persists at a fully syndromal level beyond the physiological effect of that treatment is sufficient evidence for a manic episode and, therefore, a bipolar I diagnosis.

NOTE: Criteria A through D constitute a manic episode. At least one lifetime manic episode is required for the diagnosis of bipolar I disorder.

DSM-5 diagnostic criteria for hypomanic episode

A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased activity or energy, lasting at least four consecutive days and present most of the day, nearly every day.

B. During the period of mood disturbance and increased energy and activity, three (or more) of the following symptoms (four if the mood is only irritable) have persisted, represent a noticeable change from usual behavior, and have been present to a significant degree:

1) Inflated self-esteem or grandiosity.

2) Decreased need for sleep (eg, feels rested after only three hours of sleep).

3) More talkative than usual or pressure to keep talking.

4) Flight of ideas or subjective experience that thoughts are racing.

5) Distractibility (ie, attention too easily drawn to unimportant or irrelevant external stimuli), as reported or observed.

6) Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation.

7) Excessive involvement in activities that have a high potential for painful consequences (eg, engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments).

C. The episode is associated with an unequivocal change in functioning that is uncharacteristic of the individual when not symptomatic.

D. The disturbance in mood and the change in functioning are observable by others.

E. The episode is not severe enough to cause marked impairment in social or occupational functioning or to necessitate hospitalization. If there are psychotic features, the episode is, by definition, manic.

F. The episode is not attributable to the physiological effects of a substance (eg, a drug of abuse, a medication, or other treatment).

NOTE: A full hypomanic episode that emerges during antidepressant treatment (eg, medication, electroconvulsive therapy) but persists at a fully syndromal level beyond the physiological effect of that treatment is sufficient evidence for a hypomanic episode diagnosis. However, caution is indicated so that one or two symptoms (particularly increased irritability, edginess, or agitation following antidepressant use) are not taken as sufficient for a diagnosis of a hypomanic episode, nor necessarily indicative of a bipolar diathesis.

NOTE: Criteria A through F constitute a hypomanic episode. Hypomanic episodes are common in bipolar I disorder but are not required for the diagnosis of bipolar I disorder.

Case-based Learning

Chief Complaint

- "I don't know if I can handle this anymore."

HPI

- Geneva Flowers is a 41-year-old woman who is referred by her family physician to an outpatient mental health clinic. She complains of feeling down and sad, with crying spells, trouble sleeping, increased eating, impaired concentration, and fatigue. She has not worked in over 2 months and has used up her vacation and sick leave from work.
- Things were going fairly well for her after her treatment and she remarried approximately 8 months ago. Arguments with her teenage sons about family issues and past incidents have made her increasingly depressed over the past few months. Her older son, 17, moved out to live with his father. Her younger son, 12, moved to live with his paternal grandparents.
- She divorced the boys' father after approximately 10 years of marriage when she discovered that he was having an affair with another woman. She left her second husband after approximately 2 years because of problems involving his children that caused increasing conflict with her then-husband. Without a second income in the household, she accumulated large credit card debts. Her present husband, her third, has been supportive of her, but she feels guilty about her failed previous marriages and her sons, worries about her debt, and has become more despondent. She has taken a leave of absence from her job as an administrative assistant at an elementary school.
- The patient sought treatment for depression 3 months ago from her family physician, who prescribed mirtazapine. Her spirits have not improved, and she says the medication made her gain weight. Because of vague references that the physician believed could possibly indicate suicidal ideas, she has been referred for psychiatric evaluation.

Case-based Learning

PMH

- Childhood illnesses: she has had all of the usual childhood illnesses. She was hospitalized at age 3 for bacterial meningitis but knows of no residual effects.
- Adult illnesses: no current nonpsychiatric adult illnesses; no previous psychiatric treatment.
- Surgeries: Hx childbirth by C-section; tonsillectomy at age 6.
- Diet: no dietary restrictions. Despite not having much of an appetite, reports eating more since taking mirtazapine.
- Exercise: no regular exercise program.
- Immunizations: uptodate

Case-based Learning

FH:

- Father is deceased, had coronary artery disease, but ultimately died of colon cancer. Mother has well-controlled HTN. A sister has depression and anxiety, takes antidepressant medication (patient does not know its name). A second sister committed suicide.

SH:

- High school graduate; works as an administrative assistant but on leave for approximately 2 months. Married approximately 8 months, two previous divorces. Lived with husband and sons until sons moved out in the last few weeks. Health insurance is through the school district where she is employed; includes adjusted copay on prescriptions. Reports heavy credit card debt. Attended church regularly in the past (Protestant), but not recently.
- Denies smoking. Drinks three to four cups of caffeinated coffee per day; usually drinks iced tea with evening meal; drinks colas as leisure beverage. Used marijuana a few times after high school, denies use in more than 10 years; denies present or past use of other illicit substances.

Case-based Learning

Meds

- Mirtazapine 30 mg PO QHS (started on mirtazapine 15 mg PO QHS approximately 3 months ago)
- St. John's wort 300 mg PO TID for the past 2 weeks at suggestion of husband (purchased at health food store)
- Acetaminophen 1000–1500 mg PO PRN headaches, two or three times a week
- Uses OTC antihistamines and decongestants for colds or allergies; none in recent months

Allergies:

- NKDA

ROS

- General appearance: pt c/o feeling tired much of the time
- HEENT: wears contact lenses; no tinnitus, ear pain, or discharge; no c/o nasal congestion; Hx of dental repair for caries
- Chest: no Hx of asthma or other lung disease
- CV: reports occasional feelings of "pounding heart"; no Hx of heart disease
- GI: reports infrequent constipation; takes MOM PRN; has gained 9 lb in last 2 months
- GU: has regular menses; LMP ended a week ago
- Neuromuscular: occasional headaches, worse over the past few months; no syncope, vertigo, weakness or paralysis, numbness or tingling
- Skin: no complaints

Case-based Learning

VS:

- BP 132/78 mm Hg, P 88 bpm, RR 22, T 36.9°C; Wt 187 lb, Ht 5′8″

Labs:

- Normal

Mental Status:

- When seen in the clinic, the patient is pale and appears moderately overweight, dressed in casual slacks and sweater. Grooming is fair and without makeup. She speaks slowly, often not responding to questions for approximately 30 seconds before beginning answers. She describes depressed mood and lack of energy and says she feels no pleasure in life. Her husband is good to her, but she feels everyone else she loves has left her. She has no social contacts other than occasional visits by her parents. She spends most of her time in bed. She feels worthless and blames herself for her problems. She feels particularly anguished about the incident with her son's friend even though she does not remember it. She is often anxious and worries about the future. She wonders if her sons love her and if they will ever return. She worries how she will repay her financial debts. Her speech is logical, coherent, and goal-oriented. She denies suicidal intent but says the future seems dim to her, and she wonders sometimes if life is worth living. She admits she sometimes wishes she could just go to sleep and not wake up. She denies hallucinations. Paranoid delusions are absent. There is no dysarthria (speech difficulty) or anomia (unable to recall names of objects).

Case-based Learning

Problem Identification

1.a. Create a list of this patient's drug therapy problems.

1.b. What signs, symptoms, and laboratory values indicate the presence of depression in this patient?

1.c. What factors in the family history support a diagnosis of depression?

1.d. Is there anything in the patient's medication history that could cause or worsen depression?

TREATMENT GOALS

- The goal of initial treatment for depression is:
  - Symptom remission
  - Restoring baseline functioning

Case-based Learning

Desired Goals

2. What are the goals of pharmacotherapy in this case?

CLASSIFICATION

- **MILD TO MODERATE MAJOR DEPRESSION**
- SEVERE MAJOR DEPRESSION

MILD TO MODERATE MAJOR DEPRESSION

- Manifestations:
  - Either no suicidal or homicidal ideation or behavior, or the presence of ideation that does not pose an imminent risk (eg, thoughts that family members would be better off if the patient was dead; or fleeting thoughts of killing oneself, with nonexistent or vague plans to commit suicide and no intent)
  - No psychotic features (eg, delusions or hallucinations)
  - Little to no aggressiveness
  - Intact judgment such that the patient or others are not at imminent risk of being harmed
- Mild to moderate depression can generally be treated in an outpatient setting or partial (day) hospital program

Case-based Learning

Problem Identification

1.b. What signs, symptoms, and laboratory values indicate the **severity of depression in this patient**?

MILD TO MODERATE MAJOR DEPRESSION

- Treatment
  - Antidepressants plus psychotherapy
  - Antidepressants
    - Classes of AD
    - Selecting an AD
    - Side effects
    - Dose
    - Response
    - Adequate trial
  - Psychotherapy

Antidepressants plus psychotherapy

- Randomized trials indicate that the combination of pharmacotherapy and psychotherapy (eg, cognitive-behavioral therapy or interpersonal psychotherapy) is more efficacious than either pharmacotherapy alone or psychotherapy alone

- However, psychotherapy is often not available or is declined

Antidepressants

- Second-generation antidepressants
  - Selective serotonin reuptake inhibitors (SSRIs)
  - Serotonin-norepinephrine reuptake inhibitors
  - Atypical antidepressants
  - Serotonin modulators

- Older, first-generation antidepressants
  - Tricyclic antidepressants
  - Monoamine oxidase inhibitors (MAOIs)

Selective serotonin reuptake inhibitors (SSRIs)

SSRIs	Dose (mg/day)	Administration	DDI	Metabolism & elimination
Citalopram (Cipram®)	20 – 40	QD	None	Liver
Escitalopram (Cipralex®)	10 – 20	QD	None	Liver
Sertraline (Zoloft®)	50 – 200	QD	2D6 (potent at doses > 200 mg per day), 2B6, 2C9, 2C19, and 3A4	Liver
Paroxetine (Seroxat®)	20 – 40 (CR: 25-50)	QD	2D6 (potent) and 2B6 (potent)	Liver
Fluoxetine (Prozac®)	20 – 60	QD Active mtb: norfluoxetine (4 - 16 days)	2D6 (potent), 2C9, 2C19, 2B6, and 3A4	Liver
Fluvoxamine (Faverin®)	50 – 200	QD	1A2 (potent), 2C19 (potent), 2B6, 2C9, and 3A4	Liver

Selective serotonin reuptake inhibitors (SSRIs)

- Use
  - Frequently used as first-line antidepressants because of their efficacy, tolerability, and general safety in overdose
- Pharmacology
  - SSRIs inhibit the serotonin reuptake pump and increase postsynaptic serotonin receptor occupancy
  - SSRIs are selective in that they have relatively little affinity for other types of receptors
- Efficacy
  - There is no compelling evidence that one SSRI is more efficacious than another
  - Choice is based upon cost, individual patient tolerance, and clinician experience

Selective serotonin reuptake inhibitors (SSRIs)

- Side Effects

Drug	Agent specific SE	Common SE to all SSRIs
Citalopram	QT Prolongation	• Insomnia/agitation • Orthostatic hypotension (OH) • Transient nausea and GI discomfort upon initiation or dose increase • Weight gain • Sexual dysfunction
Escitalopram	QT Prolongation	
Sertraline	QT Prolongation, Diarrhea	
Paroxetine	Anticholinergic, Drowsiness	
Fluoxetine	QT Prolongation	
Fluvoxamine	Drowsiness	

- **Sexual dysfunction** ➔ anorgasmia in women and erectile dysfunction in men, and increase ejaculation latency in men
- **Weight gain** ➔ improved appetite, increased carbohydrate craving, and changes in serotonin 2C receptor activity

Selective serotonin reuptake inhibitors (SSRIs)

- Switching between antidepressants
  - Cross-tapering is the best technique
  - Dose of the current antidepressant is gradually reduced over a one to two week period or longer, while the dose of the new antidepressant is gradually increased to therapeutic range over the same time period

Selective serotonin reuptake inhibitors (SSRIs)

- Discontinuation of antidepressants
  - Antidepressant dose should be reduced by 25% per week so as to minimize the occurrence of discontinuation side effects
  - Taper over two to four weeks
  - DO not discontinue abruptly to avoid **discontinuation syndrome**

  - **Discontinuation syndrome**
    - **Cause ➔ Abrupt cessation of SSRIs**
    - **Symptoms ➔ dizziness, nausea, fatigue, muscle aches, chills, anxiety, and irritability, electric shock sensations**
    - **Symptoms are mild with fluoxetine (long half-life) and can be particularly severe with paroxetine and fluvoxamine**

Selective serotonin reuptake inhibitors (SSRIs)

- Serotonin syndrome
  - Potentially life-threatening condition associated with increased serotonergic activity in the central nervous system
  - Caused by overstimulation of central and peripheral serotonin receptors
    - It can occur after initiating or increasing a single serotonergic drug
  - Clinical features include:
    - Anxiety, agitation, delirium, diaphoresis, tachycardia, hypertension, hyperthermia, gastrointestinal distress, tremor, muscle rigidity, myoclonus (sudden involuntary jerking of muscles), and hyperreflexia (overactive or over responsive reflexes)

Serotonin Syndrome

Examples of drugs that can precipitate serotonin syndrome

Mechanism	Drugs involved
Increases serotonin formation	Tryptophan
Increases release of serotonin	Amphetamines (including dextroamphetamine, methamphetamine)
	Cocaine
	MDMA (Ecstasy)
	Amphetamine derivatives (including fenfluramine, dexfenfluramine, phentermine)
	Levodopa, Carbidopa-levodopa (indirectly causes release serotonin)
Impairs reuptake from the synaptic cleft into the presynaptic neuron	Cocaine
	MDMA (Ecstasy)
	Meperidine
	Tramadol
	Pentazocine
	Selective serotonin reuptake inhibitors (SSRIs) (including citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline)
	Serotonin-norepinephrine reuptake inhibitors (SNRIs) (including desvenlafaxine, duloxetine, milnacipran, and venlafaxine)
	Dopamine-norepinephrine reuptake inhibitors (including bupropion)
	Serotonin modulators (including nefazodone, trazodone, and vilazodone)
	Tricyclic antidepressants (TCAs) (including amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, maprotiline, nortriptyline, protriptyline, trimipramine)
	St. John's wort (*Hypericum perforatum*)
	5-HT3 receptor antagonists (including dolasetron, granisetron, ondansetron, palonosetron)
	Metoclopramide
	Valproate
	Carbamazepine
	Sibutramine
	Dextromethorphan
	Cyclobenzaprine
Inhibits serotonin metabolism (ie, inhibits monoamine oxidase activity)	Monoamine oxidase inhibitors (MAOIs) (including phenelzine, tranylcypromine, isocarboxazid, moclobemide, selegiline, rasagiline, linezolid, tedizolid, methylene blue, procarbazine, Syrian rue [*Peganum harmala*, harmine])
Direct serotonin agonist	Buspirone
	Triptans (including sumatriptan, rizatriptan, others)
	Ergot derivatives (including ergotamine, methylergonovine)
	Fentanyl
	Lysergic acid diethylamide (LSD)
Increases sensitivity of postsynaptic receptor	Lithium

Serotonin Syndrome

Clinical and laboratory features
The Hunter Criteria for serotonin syndrome (SS) are fulfilled if the patient has taken a serotonergic agent and has one of the following:
Spontaneous clonus
Inducible clonus and agitation or diaphoresis
Ocular clonus and agitation or diaphoresis
Tremor and hyperreflexia
Hypertonia
Temperature above 38°C and ocular clonus or inducible clonus
SS is a clinical diagnosis; no laboratory test can confirm the diagnosis. SS can manifest a wide range of clinical symptoms from mild tremor to life-threatening hyperthermia and shock.
Examination findings can include: hyperthermia, agitation, ocular clonus, tremor, akathisia, deep tendon hyperreflexia, inducible or spontaneous clonus, muscle rigidity, dilated pupils, dry mucus membranes, increased bowel sounds, flushed skin, and diaphoresis. Neuromuscular findings are typically more pronounced in the lower extremities.
The following tests may be helpful in severe cases of SS to narrow the differential and to monitor potential complications:
Complete blood count, basic electrolytes, creatinine and BUN
Creatine phosphokinase, hepatic transaminases, coagulation studies
Blood culture, urinalysis, urine culture
Chest radiograph
Head computed tomography, lumbar puncture
Differential diagnosis
Neuroleptic malignant syndrome
Anticholinergic toxicity
Malignant hyperthermia
Sympathomimetic toxicity
Meningitis or encephalitis
Treatment
Discontinue serotonergic agents
Sedate using benzodiazepines (eg, lorazepam 1 to 2 mg IV per dose; 0.02 to 0.04 mg/kg/dose in children): goal is to eliminate agitation, neuromuscular abnormalities (eg, tremor, clonus), and elevations in heart rate and blood pressure; titrate dose to effect
Provide: oxygen (maintain SpO2 ≥94); IV fluids; continuous cardiac monitoring
Anticipate complications; in severe SS vital signs can fluctuate widely and rapidly
If benzodiazepines and supportive care fail to improve agitation and abnormal vital signs, give cyproheptadine (12 mg orally or by orogastric tube for initial adult dose; pediatric doses included in main text)
Treat patients with temperature >41.1°C with immediate sedation, paralysis, and endotracheal intubation; treat hyperthermia with standard measures; avoid antipyretics such as acetaminophen

Serotonin-norepinephrine reuptake inhibitors (SNRIs)

SNRIs	Dose (mg/day)	Administration	DDI	Metabolism & elimination
Levomilnacipran	-	QD	CYP3A4 substrate	Renal
Milnacipran (Ixel®)	100 - 200	BID	None	Renal and hepatic
Duloxetine (Cymbalta®)	60 - 120	QD	Inhibits CYP2D6	Renal and hepatic
Desvenlafaxine (Pristiq®)	50 - 100	QD	None	Renal and hepatic
Venlafaxine (Effexor XR®)	XR: 75 - 225	XR: QD Active mtb (desvenlafaxine)	None	Renal and hepatic

Serotonin-norepinephrine reuptake inhibitors (SNRIs)

- Use
  - Initial treatment of major depression, treatment resistant depression, and other disorders
  - Duloxetine may be used in diabetic peripheral neuropathy and fibromyalgia

- Pharmacology
  - Initially blocking presynaptic serotonin and norepinephrine transporter proteins ➔ Inhibits reuptake of these neurotransmitters and leads to increased stimulation of post-synaptic receptors
  - Little or no effect on dopaminergic, cholinergic, histaminergic, or alpha1-adrenergic receptors

Serotonin-norepinephrine reuptake inhibitors (SNRIs)

- Side Effects

SNRIs	Agent specific SE	Common SE to all SNRIs
Levomilnacipran	• Urinary hesitancy • May increase DBP and HR (monitor BP regularly)	• Transient nausea and GI discomfort upon initiation or dose increase • Sexual dysfunction • Anticholinergic like effects such as dry mouth and constipation – Caution in narrow angle glaucoma
Milnacipran	• Drowsiness • May increase DBP and HR (monitor BP regularly)	
Duloxetine	• Insomnia/agitation	
Desvenlafaxine	• Insomnia/agitation • May increase DBP and HR (monitor BP regularly)	
Venlafaxine	• Drowsiness • Insomnia/agitation • QT prolongation • Use XR formulation because of less nausea • May increase DBP and HR (monitor BP regularly)	

Atypical antidepressants

Atypical Antidepressants	Administration	DDI	Metabolism and elimination
Bupropion	QD	Inhibit CYP 2D6	Liver and kidney
Agomelatine (Valdoxan®) (not available in the United States)	QD QHS	None	Liver
Mirtazapine (Remeron ®)	QD	None	Liver and kidney

Atypical antidepressants

Atypical Antidepressants	Administration	DDI	Metabolism and elimination

Esketamine intranasal (Spravato ®)	• Induction phase
	  • Week 1-4: twice per week
	• Maintenance phase
	  • Week 5-8): once weekly
	  • Week 9 and after: Q2weeks or once weekly
		Multiple drugs	Liver and kidney

Brexanolone (Zulresso®)	• IV: Initiate 60-hour continuous infusion early enough in the day to allow for recognition of excessive sedation	Multiple drugs	Liver and kidney

Atypical antidepressants

- Use
  - Used in patients with inadequate responses or intolerable side effects during first-line treatment with SSRIs
  - First-line treatment if the drug has a desirable characteristic

    - Bupropion ➔ major depression, seasonal affective disorder, ADHD, tobacco dependence, hypoactive sexual disorder, and obesity
    - Agomelatine ➔ major depression + insomnia
    - Mirtazapine ➔major depression, generalized anxiety disorder, and tension type headaches
    - Esketamine ➔ treatment-resistant depression in conjunction with an oral antidepressant
    - Brexanolone ➔ treatment of postpartum depression (PPD) in adults

Atypical antidepressants

Atypical Antidepressants	**Pharmacology**
Bupropion	Dopamine norepinephrine reuptake inhibitor (DNRI)
Agomelatine	• Agonist at melatonin receptors (MT1 and MT2) ➔ normal circadian rhythms (preferred in insomnia) • 5-HT2C receptor antagonist ➔ increase release of dopamine and norepinephrine
Mirtazapine	• Presynaptic alpha-2 receptors antagonist ➔ increases release of norepinephrine and serotonin • Antagonist of postsynaptic serotonin 5-HT2 and serotonin 5-HT3 receptors ➔ increases neurotransmission mediated by serotonin 5-HT1 receptors • H1 receptor antagonist ➔ sedation • Low affinity for cholinergic, alpha-1 adrenergic, and dopaminergic receptors

Atypical antidepressants

Atypical Antidepressants	Pharmacology
Esketamine	• S-enantiomer of racemic ketamine • Nonselective, noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist (NMDA is a glutamate receptor) • The mechanism by which esketamine exerts its antidepressant effect is unknown.
Brexanolone	• Gamma-Aminobutyric Acid (GABA) A Receptor Positive Modulator

Atypical antidepressants

- Side effects

Atypical Antidepressants	**Agent specific SE**
Bupropion	• Seizures • Insomnia/agitation (more with IR and less with SR) • QT Prolongation • GI toxicity • NO SEXUAL DYSFUNCTION
Agomelatine	• Drowsiness • Insomnia/agitation • GI toxicity
Mirtazapine	• Drowsiness • Anticholinergic • QT prolongation • Increased appetite and weight gain • Sexual dysfunction

Atypical antidepressants

- Side effects

Atypical Antidepressants	**Agent specific SE**	
Esketamine	• Dissociation • Dizziness • Nausea • Vertigo • Sedation	• Headache • Dysgeusia • Hypoesthesia • Anxiety • Lethargy
Brexanolone	• Presyncope • Drowsiness • Sedation • Vertigo • Xerostomia	

Serotonin modulators

Serotonin modulators	Administration	DDI	Metabolism and elimination
Nefazodone	BID	CYP3A4 inhibitor P-gp inducer	Liver
Trazodone	BID	P-gp inducer	Liver
Vilazodone	QD	None	Liver
Vortioxetine	QD	None	Liver

Serotonin modulators

- First-line treatment if the drug has a desirable characteristic

- Use
  - Nefazodone ➔ major depression and premenstrual syndrome
  - Trazodone ➔ major depression, functional dyspepsia, hypnotic to treat insomnia in the context of depression, as well as insomnia associated with antidepressants
  - Vilazodone ➔ major depression
  - Vortioxetine ➔ major depression

Serotonin modulators

- Pharmacology

Atypical Antidepressants	Pharmacology
Nefazodone	• Antagonizes and down regulates postsynaptic 5-HT2A receptors, and weakly inhibits presynaptic serotonin and norepinephrine reuptake ➔ increase activity at the serotonin 5-HT1A receptors • Little to no affinity for alpha-adrenergic receptors, cholinergic, dopamine D2, and histamine H1 receptors
Trazodone	• Acts upon postsynaptic serotonin 5-HT2A and 5-HT2C receptors and weakly inhibits presynaptic serotonin reuptake ➔ dose dependent effects such that at low doses the drug acts as a serotonin antagonist and at high doses as a serotonin agonist • Effects on norepinephrine and dopamine reuptake are minimal • It blocks postsynaptic alpha-adrenergic receptors (orthostatic hypotension and priapism) and histamine H1 receptors (sedation) • Does not affect cholinergic receptors
Vilazodone	• Inhibits presynaptic reuptake of serotonin and also acts as a partial agonist at postsynaptic serotonin 5-HT1A receptors • Inhibition of norepinephrine and dopamine reuptake is minimal
Vortioxetine	• Serotonin reuptake inhibitor (SRI) • 5-HT1A receptor high-efficacy partial agonist/near-full agonist • 5-HT1B receptor partial agonist • 5-HT3A receptor antagonist • 5-HT7 receptor antagonist • Affinity for the β1-adrenergic receptor, though any actions at this site are unlikely to contribute to its therapeutic effects and likely only to contribute to side effects

Serotonin modulators

- Side effects

Serotonin modulators	Agent specific SE	Common SE to Serotonin Modulators
Nefazodone	• Anticholinergic • CAUTION: can cause liver failure	• Drowsiness • OH • GI toxicity
Trazodone	• QT Prolongation • Weight gain • Sexual Dysfunction (rare association with priapism)	
Vilazodone	• Insomnia/agitation • GI toxicity (higher rates of N/V/D)	• Sexual Dysfunction
Vortioxetine	• GI Toxicity	

Tricyclic antidepressants

TCAs	Type of amine	MOA	MOA: blocks	Administration	DDI	Metabolism and elimination
Amitriptyline (Tryptizol®)	Tertiary	More potent in blocking reuptake of 5-HT compared with NE 5HT > NE	H 1 and M1	QD	Substrate	Liver(has active metab: nortrip)
Clomipramine (Anafranil®)	Tertiary		H 1 and M1			Liver
Doxepin (Doxepin®)	Tertiary		Strongest H1 (sed/wt) and M1			Liver
Imipramine (Tofranil®)	Tertiary		Alpha, H1, and M1			Liver (has active metab: desip)
Trimipramine	Tertiary		H1 and less M1			Liver
Desipramine (Desipramine®)	Secondary	More potent in blocking reuptake of NE than 5-HT NE > 5HT	Less H1 and M1			Liver (is the active metab of imipramine)
Nortriptyline	Secondary		Less H1 and M1			Liver (is the active metab of amitrip)
Protriptyline	Secondary		Less H1 and M1			Liver
Maprotiline (Ludiomil®)	Tetracyclic		H1			Liver
Amoxapine	Different	More Potent NE reuptake inhibitor than 5-HT and blocks postsynaptic DA receptors	DA			Liver

Tricyclic antidepressants

- Use
  - 1958 ➔ TCAs were first-line treatment for depression for 30 years, until SSRIs were introduced
  - Major depression, panic attacks, generalized anxiety disorder, post-traumatic stress disorder, bulimia nervosa, smoking cessation, chronic daily headache and neuropathy
  - Taken once a day, usually at bedtime because of sedating side effects
  - Response: 4 weeks ➔ after reaching therapeutic dose, response should occur after at least 4 weeks
  - Adequate trial: 12 weeks ➔ after reaching therapeutic dose, 12 weeks should elapse before determining whether the medications have sufficiently relieved symptoms or not
  - Amoxapine ➔ antipsychotic effects

Tricyclic antidepressants

- Side effects

• Tertiary amines generally cause more side effects compared with secondary amines • More anticholinergic side effects (eg, constipation or blurred vision) + highly sedating (central effects on histamine)	

Cardiac	• Heart block, ventricular arrhythmias, and sudden death ➔ Before initiating treatment with any of the cyclic antidepressants, patients must be screened for cardiac conduction system disease, which precludes the use of these medications
	  • Patients ≥ 40 years should have a baseline ECG for this purpose
	  • Patients < 40 can be screened by history for evidence of cardiac disease and do not require an ECG if the history is negative

	• Orthostatic hypotension (alpha block)

Tricyclic antidepressants

- Side effects

Anticholinergic SE	Blurred vision, constipation, dry mouth (which may lead to dental caries), urinary retention, tachycardia, ocular crisis in patients with narrow-angle glaucoma, confusion and delirium
Antihistaminic SE	Sedation, increased appetite leading to weight gain, confusion, and delirium
Other SE	Decreased seizure threshold, sexual dysfunction, diaphoresis, and tremor
Toxicity	Dangerous in overdose by suicidal patients

Monoamine oxidase inhibitors (MAOIs)

Drug	Administration	DDI	Metabolism and elimination
Tranylcypromine	BID	MAO inhibitor CYP inhibitor	Urine
Phenelzine	TID	MAO inhibitor	Urine
Selegiline (Transdermal patch: EMSAM®)	QD	MAO inhibitor CYP inhibitor	Liver and kidney

Monoamine oxidase inhibitors (MAOIs)

- Use
  - Not considered first-line antidepressant
    - Dietary restrictions
    - Drug-drug interactions
    - Extensive side-effects
  - Useful for "atypical" depression
    - Depression with hyperphagia, hypersomnia, leaden paralysis (depressed patients who have a sense of heaviness in arms & legs), and rejection sensitivity (anxiously expect, readily perceive, and overreact to social rejection)
  - Effective in treatment-resistant depression

Monoamine oxidase inhibitors (MAOIs)

- Pharmacology
  - Inhibit MAOa and MAOb
  - **MAOa:** preferentially deaminate 5HT, melatonin, epinephrine, NE, DA, trace amines (like Tyramine)
  - **MAOb:** preferentially deaminate phenylethylamine, DA, and other trace amines (like Tyramine)

Monoamine oxidase inhibitors (MAOIs)

- Pharmacology
  - Tranylcypromine
    - Irreversible inhibitor of MAOa
    - Irreversible inhibitor of MAOb to a degree
    - Blocks reuptake of serotonin and catecholamines
  - Phenelzine
    - Irreversible inhibitor of MAOa and MAOb
  - Selegeline
    - Selective MAOb inhibitor at low doses and a non-selective MAO inhibitor at higher doses
    - Transdermal patch form “EMSAM” ➔ approved by FDA in 2006 for treatment of depression (bypasses gut)

Monoamine oxidase inhibitors (MAOIs)

- Side effects
  - Serotonin Syndrome
  - Sexual dysfunction, sleep disturbance, dry mouth, GI upset, urinary hesitancy, headache, and myoclonic jerks
  - Hypertensive Crisis
    - Blockade of MAOIa in the gastrointestinal tract is responsible for the "cheese reaction“
      - Severe hypertensive crisis that can occur after patients on MAOIs ingest foods containing the sympathomimetic tyramine
      - **Tyramine is usually metabolized in the gastrointestinal tract by MAOa**
      - **But** the **blockade of MAOa** allows it to **flow** into the **general circulation**

Monoamine oxidase inhibitors (MAOIs)

- Side effects
  - Hypertensive Crisis
    - Drug Restrictions
      - Cold remedies/asthma inhalants
      - Appetite suppressants
      - Methyldopa/reserpine
      - Narcotic pain killers
      - Amphetamines
      - Other MAOIs
      - Other antidepressants
      - Vasoconstrictors/sympathomimetics
      - All stimulants

Foods contraindicated during therapeutic use of monoamine oxidase inhibitors

Foods
Absolutely restricted:
Aged cheeses
Aged and cured meats
Improperly stored or spoiled meats, fish, or poultry
Banana peel; broad bean pods
Marmite
Sauerkraut
Soy sauce and other soy condiments
Draft beer
Consume in moderation:
Red or white wine (no more than two 4-ounce glasses per day)
Bottled or canned beer, including nonalcoholic (no more than two 12-ounce servings per day)

Monoamine oxidase inhibitors (MAOIs)

- Side effects
  - Hypertensive Crisis
    - Signs and Symptoms
      - Headache/neck stiffness or soreness
      - Nausea/vomiting
      - Sweating
      - Dilated pupils/photophobia
      - Sudden nose bleed
      - Tachycardia/bradycardia/chest pain
    - Management
      - Withhold medication and notify MD
      - Monitor vital signs
      - Sublingual captopril/nifedipine
      - Stand up and walk

Monoamine oxidase inhibitors (MAOIs)

- Discontinuation

From	Duration to wait	To
Antidepressants	2 weeks	MAOI
Fluoxetine	5 weeks	MAOI
MAOI	2 weeks	Antidepressants OR stopping MAOI diet

Antidepressants

- Selecting an antidepressant
  - Mild to moderate unipolar major depression
    - First line options:
      - SSRIs
      - SNRIs
      - Other options based on preference

- General order of preference in choosing an AD:
  - **SSRI ➔ SNRI ➔ atypical antidepressant ➔ serotonin modulator ➔ TCA ➔ MOAI**

Antidepressants

- Selecting an antidepressant
  - Given the lack of clear superiority in efficacy among antidepressants, selecting a drug is based upon other factors such as:
    - Patient response to antidepressants during prior depressive episodes
    - Safety
    - Side effect profile
    - Specific depressive symptoms
    - Comorbid illnesses
    - Concurrent medications and potential drug-drug interactions
    - Family (eg, first-degree relative) history of response to antidepressants
    - Ease of use (eg, frequency of administration)
    - Patient preference
    - Cost
    - Example:
      - Bupropion ➔ useful for patients who prefer to avoid sexual dysfunction or want treatment for comorbid tobacco dependence
      - Citalopram and escitalopram ➔ less likely to cause DDI
      - Mirtazapine ➔ not used in patients who prefer to avoid weight gain

Antidepressants

- Side effects
  - **Diarrhea** occurs more often with **sertraline** than bupropion, citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, and venlafaxine (16 versus 8 percent of patients)
  - **Nausea and vomiting** occurs more often with **venlafaxine** than SSRIs as a class (33 versus 22 percent)
  - **Sexual dysfunction** occurs more often with **escitalopram, fluoxetine, paroxetine, and sertraline** than bupropion (16 versus 6 percent; paroxetine is especially problematic)
  - **Somnolence** occurs more often with **trazodone** than bupropion, fluoxetine, mirtazapine, paroxetine, and venlafaxine (42 versus 25 percent)
  - **Weight gain** is greater with **mirtazapine** than fluoxetine, paroxetine, trazodone, and venlafaxine (0.8 to 3.0 kg after six to eight weeks of treatment)

Antidepressants

- Dose
  - Starting at low doses in order to reduce side effects and improve adherence
  - For depressed patients who do not respond to the minimum therapeutic dose of SSRIs, most clinicians increase the dose within the therapeutic dose range
  - Some patients benefit from doses that exceed the maximum therapeutic dose, provided the drug is safely tolerated
  - Pharmacogenetics
    - Patients may rapidly metabolize drugs due to genetic polymorphisms of hepatic enzymes ➔ Require larger doses
    - Other hepatic isoenzymes may lead to slow metabolism of antidepressants ➔ Need lower doses

Antidepressants

- Response to antidepressants
  - Response is seen after 4 weeks of treatment at adequate doses
- Duration of an adequate trial
  - Adequate trial is usually 12 weeks of treatment at adequate doses
- If patient cannot tolerate a drug due to side effects or intolerance, then switch to a different antidepressant

Psychotherapy

- Types
  - Cognitive-behavioral therapy (CBT)
  - Interpersonal psychotherapy
  - Family and couples therapy
  - Problem solving therapy
  - Psychodynamic psychotherapy
  - Supportive psychotherapy
- Efficacy of psychotherapy
  - Psychotherapy is efficacious for the initial treatment of mild to moderate unipolar major depression, based upon randomized trials
- Compared with antidepressants
  - The evidence indicates that the efficacy of psychotherapy compared with antidepressants at the end of treatment is generally comparable

Case-based Learning

Therapeutic Alternatives

3.a. What nonpharmacologic treatments are important in this case? Should nonpharmacologic treatments be tried before beginning medication?

Case-based Learning

Therapeutic Alternatives

3.b. What pharmacotherapeutic options are available for the treatment of depression?

CLASSIFICATION

- MILD TO MODERATE MAJOR DEPRESSION
- **SEVERE MAJOR DEPRESSION**

SEVERE MAJOR DEPRESSION

- Clinical features include:
  - Suicidal or homicidal behavior or ideation with a specific plan and intent
  - Psychotic features (eg, delusions or hallucinations)
  - Catatonia
  - Poor judgement that places the patient or others at imminent risk of being harmed
  - Grossly impaired functioning (eg, food and fluid refusal leading to malnutrition and dehydration)
- Severely ill patients should be referred to a psychiatrist for management and generally require hospitalization

SEVERE MAJOR DEPRESSION

- Choosing treatment
  - Initial treatment ➔ Combination of pharmacotherapy + psychotherapy
  - Alternative ➔ Pharmacotherapy alone
  - Another alternative ➔ Electroconvulsive therapy (ECT)
    - Especially for patients who require a fast response (eg, patients with suicidal ideation or behavior that is life-threatening)

- General order of preference in choosing an AD:
  - **SSRI ➔ SNRI ➔ atypical antidepressant ➔ serotonin modulator ➔ TCA ➔ MOAI**

SEVERE MAJOR DEPRESSION

- Choosing an antidepressant
  - Initial treatment ➔ SSRIs or SNRIs
  - Alternative ➔ any other class of antidepressants

- General order of preference in choosing an AD:
  - **SSRI ➔ SNRI ➔ atypical antidepressant ➔ serotonin modulator ➔ TCA ➔ MOAI**

ST. JOHN'S WORT

- *Hypericum perforatum*
  - OTC product
  - Has affinity to many neurotransmitter receptors
  - Efficacy studies have been conflicting
  - Significant drug interactions
  - Safety issues???
  - Never used in combination with other antidepressants

TREATMENT APPROACH

TREATMENT PHASES	ACUTE	CONTINUATION	MAINTENANCE
DURATION	12 Weeks	4-9 Months	12-36 Months
GOAL	Induce Remission	Preserve Remission	Prevent Recurrence

TREATMENT FAILURE

- If no response at therapeutic doses in 12 weeks or intolerance to antidepressant

- Several options
  - Switch to an agent from the same class
  - Switch to an agent from a different class
  - If failure after 2 different agents from different classes
    - Augmentation therapy
    - Electroconvulsive therapy
    - Combination therapy

- General order of preference in choosing an AD:
  - **SSRI ➔ SNRI ➔ atypical antidepressant ➔ serotonin modulator ➔ TCA ➔ MOAI**
- General order of preference in choosing an adjunctive medication:
  - **SGA ➔ Lithium ➔ Thyroid hormone ➔ second AD from a different class**

AUGMENTATION THERAPY

- Drugs added to therapy if response to antidepressants is inadequate

- Several options
  - Second Generation Antipsychotics SGA (Risperidone, aripiprazole, brexpiprazole)
  - Lithium (resistant depression)
  - Thyroid (add to TCAs)
  - *Anticonvulsants (CBZ, VA, Lamotrigine)*
  - *Buspirone*

SPECIAL POPULATIONS

- Elderly
  - Start at lower doses
  - Avoid TCAs
  - Reserve MAOIs for resistant/atypical patients
  - Venlafaxine (preferred), SSRIs, Bupropion
- Pregnancy
  - Pregnancy does not protect against depression
  - Weigh risks vs. benefits
  - Consider D/C therapy prior to conception

Drug	Pregnancy category
Citalopram	C
Escitalopram	C
Sertraline	C
Paroxetine	D
Fluoxetine	C
Fluvoxamine	C
Bupropion	C

SPECIAL POPULATIONS

- Pediatrics
  - Antidepressants increase the risk of suicidal thinking/behavior in children, adolescents and young adults
  - Antidepressants have a Black Box warning from the FDA
  - Monitor patients closely

Drug	Use in Children
Citalopram	Off label
Escitalopram	FDA ≥ 12 years
Sertraline	• Not for MDD • Given for OCD
Paroxetine	Not for MDD
Fluoxetine	FDA ≥ 8 years
Fluvoxamine	• Not for MDD • Given for OCD

Case-based Learning

Optimal Plan

4.a. What drug regimen (drug, dosage, schedule, and duration) is best for this patient?

4.b. How should the patient be advised about the herbal therapy, St. John's wort?

4.c. What alternatives would be appropriate if the patient fails to respond to initial therapy?

Case-based Learning

Outcome Evaluation

5. What clinical and laboratory parameters are necessary to evaluate the therapy for efficacy and adverse effects?

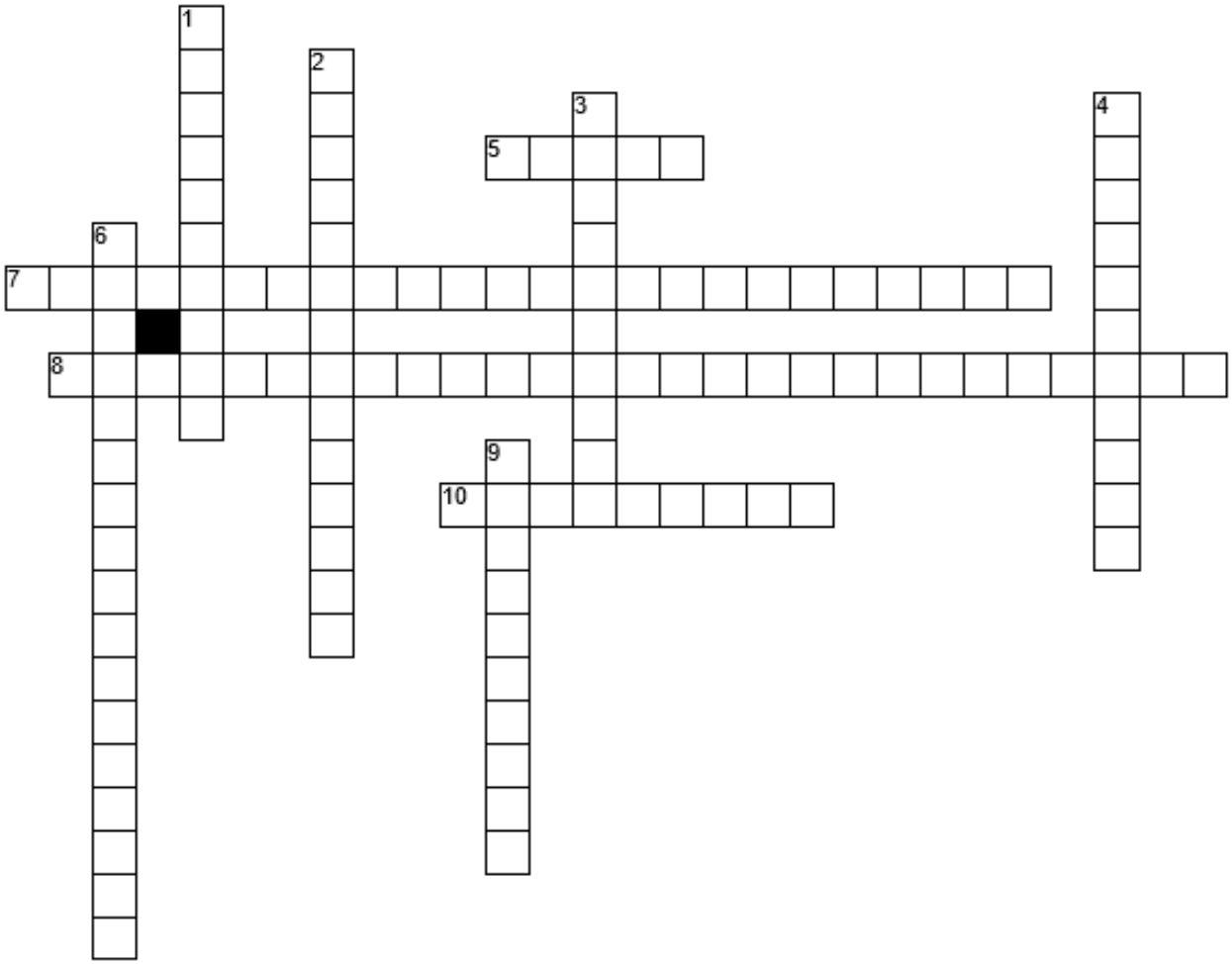
Case-based Learning

Patient Education

6. What information should be provided to the patient to enhance adherence, ensure successful therapy, and minimize adverse effects?

Treatments for Depression CROSSWORD

Treatments for Depression CROSSWORD



Treatments for Depression CROSSWORD

Across	Down
5. Citalopram belongs to this class of antidepressants **7. Only used in cases of severe circumstances.** **8. A type of talking therapy.** **10. Antidepressant that has least sexual dysfunction**	**1. SSRI associated with anticholinergic side effects** **2. Developed in the late 50s.** **3. Best technique for switching between antidepressants** **4. SNRI available as XR** **6. Potentially life-threatening condition associated with increased serotonergic activity in the central nervous system** **9. SNRI used in cases of fibromyalgia**

Bupropion Venlafaxine Serotonin Syndrome Cognitive Behavioural Therapy SSRIs Tricyclic Drugs Cross Taper Paroxetine Duloxetine Electroconvulsive Therapy

THANK YOU…