MAJOR DEPRESSIVE DISORDER

Shimelis Engida

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Introduction

- A diagnosis of MDD is given when an individual experiences one or more major depressive episodes without a history of manic, mixed, or hypomanic episodes.
- Depression is associated with significant functional disability, morbidity, and mortality.
- Selective serotonin reuptake inhibitors (SSRIs), are effective and better tolerated than older agents, like Tricyclic Antidepressants(TCAs), MAOIs.

Epidemiology

- Prevalence is influenced by both genetic and environmental factors.
- Has the highest lifetime prevalence (almost 17 percent) of any psychiatric disorder.
- The yearly incidence is 1.59 percent (women, 1.89 percent; men, 1.10 percent).
- Adults 18 to 29 years of age experience the highest rates of major depression during any given year.

Etiology

- Too complex to be totally explained by a single social, developmental, or biologic theory.
- Several factors appear to work together to cause or precipitate depressive disorders.
  - Biologic
  - Genetic
  - Psychosocial

Pathophysiology[1]

1. BIOLOGICAL FACTORS

Biogenic Amine Hypothesis

- The cause of depression was linked to decreased brain levels of the neurotransmitters NE, 5-HT, and DA.
  - Reserpine depleted neuronal storage of NE, 5-HT, and DA…..significant depression occurs.

Pathophysiology[2]

- **Postsynaptic Changes In Receptor Sensitivity**
- This theory Provides a convincing explanation of the delayed onset of therapeutic response of antidepressant drugs.

Dysregulation Hypothesis: Emphasis is placed on a failure of homeostatic regulation of NTs, Not on absolute increases or decreases in NT activities.

  - Effective antidepressant agents restore efficient regulation to the dysregulated neurotransmitter system.

Pathophysiology[3]

- **ROLE OF DA IN DEPRESSION**

- Evidence suggests that;
  - DA transmission is decreased in depression.
  - Agents that increase dopaminergic transmission have been found to be effective antidepressants.
- The complexity of the interaction between 5-HT, NE, and possibly DA is gaining greater appreciation.

Diagnosis (DSM V Criteria)

- A. Five (or more) of the following symptoms have been present during the same 2-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.

Diagnosis (DSM V Criteria)

- 1. Depressed mood most of the day, nearly every day. (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.

Diagnosis (DSM V Criteria)[2]

3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day.
4. Insomnia or hypersomnia nearly every day.
5. Psychomotor agitation or retardation nearly every day.
6. Fatigue or loss of energy nearly every day,

Diagnosis (DSM V Criteria)[3]

7. Feelings of worthlessness or excessive or inappropriate guilt nearly every day.
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day.
9. Recurrent thoughts of death , recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

Diagnosis (DSM V Criteria)[4]

B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C. The symptoms are not due to the direct physiologic effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

Note: Criteria A-C represent a major depressive episode

Diagnosis (DSM V Criteria)[5]

D. The 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 episode or a hypomanie episode.

Clinical Presentation[1]

EMOTIONAL SYMPTOMS:

- a persistent, diminished ability to experience pleasure.
- Patients appear sad or depressed,
- they are often pessimistic and believe that nothing will help them feel better.
- The presence of feelings of worthlessness or inappropriate guilt ------risk for suicide.
- Anxiety symptoms are present in almost 90%
- View their present illness as a punishment.

Clinical Presentation[2]

- **Physical Symptoms**
- Chronic fatigue is a common complaint.
- Complaints of pain, especially headache, often accompany fatigue.
- Sleep disturbances generally present
- Appetite disturbances
- loss of sexual interest or libido
- GI and cvs complaints

Clinical Presentation[3]

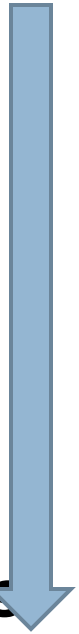
- **Intellectual Or Cognitive Symptoms**
- a decreased ability to concentrate,
- slowed thinking, and a poor memory for recent events.
- Patients can appear confused and indecisive.

Psychomotor Disturbances

- slowed or retarded in physical movements, thought processes, and speech (psychomotor retardation).
- Conversely, there can be psychomotor agitation.

Suicidal Ideation

- The 3rd leading cause of death in those aged 15 to 24 yrs.
- The 2nd leading cause of death in those aged 25 to 34 yrs.
- **suicidal plans/attempts,**
- **being of male gender,**
- **being single or living alone,**
- **inpatient status,**
- **having feelings of hopelessness**



decreasing order of frequency

Treatment

DESIRED OUTCOME

- To reduce the symptoms of acute depression,
- To facilitate the patient's return to a level of functioning before the onset of illness,
- To prevent further episodes of depression.

General Approach To Treatment

- There are three phases of treatment of major depressive disorder:
  - (1) **the acute phase** lasting from 6 to 12 weeks in which the goal is remission.
  - (2) **the continuation phase** lasting 4 to 9 months - the goal is to eliminate residual symptoms or prevent relapse.
  - (3) **the maintenance phase** lasting at least 12 to 36 months - the goal is to prevent recurrence.

General Approach To Treatment[2]

- Acute and continuation treatment recommended for all patients with major depressive disorder (i.e., minimal duration of treatment = 7 months)
- Decision to prescribe maintenance treatment is based on the following:
  - Number of previous episodes
  - Severity of previous episodes
  - Family history of depression
  - Patient age (worse prognosis if elderly)
  - Response to antidepressant
  - Persistence of environmental stressors
- Indefinite maintenance treatment is recommended if any one of the following criteria are met:
  1. Three or more previous episodes (regardless of age)
  2. Two or more previous episodes and age older than 50 years
  3. One or more and age older than 60 years

General Treatment Rules

- Often takes……. 4-6 weeks for response
- Monitor for ……response versus remission
- Neurovegetative symptoms …….
  - tend to improve first, cognitive symptoms take longer
- SSRI's are ……
  - the first line of treatment for most MDD's

Non pharmacologic Therapy

- Psychotherapy: Cognitive behavioral therapy
- Should be employed whenever the patient is able and willing to participate.
- Somatic Interventions
  - Electroconvulsive therapy (ECT)
  - Transcranial magnetic stimulation (TMS)
  - Bright light therapy.
- Life style Adjustments(exercise, diet, substance, sleep and others)

Pharmacologic Therapy

At present, 26 medications have received FDA approval in the US for the treatment of depression.

Grouped into six categories:

1. SSRIs
1. 2. Serotonin norepinephrine reuptake inhibitors (SNRIs)
3. Norepinephrine reuptake inhibitors (NRIs)
4. TCAs
5. Monoamine oxidase inhibitors (MAO Is)
6. Miscellaneous (e.g., trazodone, atypical antipsychotics)

Pharmacologic therapy

- Antidepressants are of equivalent efficacy in comparable doses. The choice dependent on;
  - the patient's history of response,
  - history of familial antidepressant response,
  - patient's concurrent medical history, eg,for epilepsy, sertaline, escitalopram and venlfaxine are preferred.
  - potential for drug-drug interactions,
  - adverse events profile,
  - patient preference, and drug cost.

Pharmacology of Antidepressants

Medication	Serotonin	Norepinephrine	Dopamine	Bioavailability (Oral)	Protein Binding	Half-Life (hours) (Active Metabolite)
Selective Serotonin Reuptake Inhibitors						
Fluoxetine	++++	0/+	0	80%	95%	24–72 (146)
Sertraline	++++	0/+	+	>44%	95%	26 (66)
Paroxetine	++++	+	0	64%	99%	24
Citalopram	++++	0	0	80%	<80%	33
Escitalopram	++++	0	0	80%	56%	27–32
Serotonin Norepinephrine Reuptake Inhibitors						
Venlafaxine	++++	+++	0	92%	25%–29%	4 (10)
Desvenlafaxine	+++	+++	0	80%	30%	11 (0)
Duloxetine	++++	++++	0	50%	>90%	12 (8–17)
Norepinephrine Reuptake Inhibitors						
Bupropion	0/+	+	+	>90%	85%	10–21
Tricyclic Antidepressants						
Desipramine	+	++++	0/+	51%	90%	12–28
Nortriptyline	++	+++	0	46%–56%	92%	18–56
Amitriptyline	++++	++++	0	37%–49%	95%	9–46 (18–56)
Imipramine	+++	++	0/+	19%–35%	95%	6–28 (12–28)
Doxepin	+++	+	0	17%–37%	68%–85%	11–23
Others						
Mirtazapine	+++	++++	0	50%	85%	20–40

0, negligible; +, very low; ++, low; +++, moderate; ++++, high.

Pharmacology of Antidepressants

	Reuptake Antagonism		Anticholinergic Effects	Sedation	Orthostatic Hypotension	Seizures[a]	Conduction Abnormalities[a]
	Norepinephrine	Serotonin					
Selective Serotonin Reuptake Inhibitors							
Citalopram	0						
Escitalopram	0						
Fluoxetine	0						
Fluvoxamine	0						
Paroxetine	0						
Sertraline	0						
Serotonin–Norepinephrine Reuptake Inh							
Duloxetine[b]	++++						
Venlafaxine[c] and desvenlafaxine	++++	++++	+	+	0	++	+
Tricyclic Antidepressants (TCAs)							
Amitriptyline	++	++++	++++	++++	+++	+++	+++
Desipramine	++++	+	++	++	++	++	++
Doxepin	++	++	+++	++++	++	+++	++
Imipramine	+++	+++	+++	+++	++++	+++	+++
Nortriptyline	+++	++	++	++	+	++	++
Mixed Serotonergic (Mixed 5-HT)							
Nefazodone	0	++	0	+++	+++	++	+
Trazodone	0	++	0	++++	+++	++	+
Vilazodone	0	++++	0	+	0	++	0
Norepinephrine and Dopamine Reuptake Inhibitor (NDRI)							
Bupropion[d]	+	0	+	0	0	++++	+
Serotonin and α_2-Receptor Antagonist							
Mirtazapine	0	0	+	++	++	0	+

++++, high; +++, moderate; ++, low; +, very low; 0, absent.

[a]These are uncommon side effects of antidepressant drugs, particularly when used at normal therapeutic doses; they may be dose-dependent, resulting in corresponding dose restrictions (e.g., citalopram 40 mg/day maximum due to QTc prolongation concerns).

[b]Duloxetine: balanced 5-HT and NE reuptake inhibition.

[c]Venlafaxine: primarily 5-HT at lower doses, NE at higher doses, and DA at very high doses.

[d]Bupropion: also blocks dopamine reuptake.

Pharmacology of Antidepressants

Adverse Effects of Antidepressant Medications

Medication	Sedation	Agitation/Insomnia	Anticholinergic Effects	Orthostasis	GI Effects (Nausea/Diarrhea)	Sexual Dysfunction	Weight Gain
Selective Serotonin Reuptake Inhibitors							
Fluoxetine	+	+ + + +	0/+	0/+	+ + + +	+ + + +	+
Sertraline	+	+ + +	0/+	0	+ + +	+ + +	+
Paroxetine	+ + +	+ +	+ +	0	+ + +	+ + + +	+ + +
Citalopram	+ +	+ +	0/+	0	+ + +	+ ++	+
Escitalopram	+	+ +	0/+	0	+ + +	+ + +	+
Serotonin Norepinephrine Reuptake Inhibitors							
Venlafaxine (Effexor)	+ +	+ +	+	0	+ + +	+ + +	+
Desvenlafaxine (Pristiq)	+ +	+ +	+	+	+ + +	+ +	0/+
Duloxetine (Cymbalta)	+ +	+ +	+	0	+ + +	+ +	0/+
Norepinephrine Reuptake Inhibitors							
Bupropion (Wellbutrin)	0	+ + +	+	0	+	0/+	0
Tricyclic Antidepressants							
Desipramine (Norpramin)	+ +	+	+ +	+ + +	0/+	+	+ +
Nortriptyline (Pamelor)	+ +	+	+ +	+ +	0/+	+	+ +
Amitriptyline (Elavil)	+ + + +	0/+	+ + + +	+ + + +	0/+	+ +	+ + +
Imipramine (Tofranil)	+ + +	0/+	+ + +	+ + + +	0/+	+ +	+ +
Doxepin (Sinequan)	+ + + +	0/+	+ + + +	+ + + +	0/+	+ +	+ +
Others							
Mirtazapine (Remeron)	+ + + +	0	+ +	0/+	+	0/+	+ + +

0, negligible; +, very low; + +, low; + + +, moderate; + + + +, high.

Pharmacology of Antidepressants

- **Adverse effects of Antidepressant**
- Management of SSRI-Induced Sexual Dysfunction
  - Patience (may improve after 2-4 weeks)
  - Reduced dosage (if possible)
  - Drug holidays
  - Antidotes: Bupropion SR 150 mg daily to BID, Sildenafil 50-100 mg daily PRN , Mirtazapine 7.5-I; mg at bedtime
  - Change of antidepressants (e.g., bupropion, mirtazapine)

Adult Dosing for Antidepressant Medications

Drug	Brand Name	Initial Dose (mg/day)	Usual Dosage Range (mg/day)	Comments (e.g., Maximum Daily Dosage, Suggested Therapeutic Plasma Concentration)[a]
Selective Serotonin Reuptake Inhibitors (SSRIs)				
Citalopram	Celexa	20	20–40	Doses greater than 40 mg/day not recommended due to QT prolongation risk; maximum 20 mg/day for CYP2C19 poor metabolizers or coadministration with CYP2C19 inhibitors
Escitalopram	Lexapro	10	10–20	Maximum 20 mg/day; dose may be increased to maximum daily dose after at least 1 week if needed; 5 mg tablet available for unique circumstances
Fluoxetine	Prozac	20	20–60	Maximum 80 mg/day; dose may be increased in 20 mg increments; doses of 5 or 10 mg/day have been used as initial therapy; doses >20 mg/day may be given in a single daily dose or divided twice daily
Fluvoxamine	Luvox	50	50–300	Maximum 300 mg/day; daily doses >100 mg total dose should be divided twice daily, with the larger dose given at night
Paroxetine	Paxil	20	20–60	Maximum 50 mg/day (IR); titrate 10 mg/day increments weekly Maximum 62.5 mg/day (CR); titrate 12.5 mg/day increments weekly
Sertraline	Zoloft	50	50–200	Maximum 200 mg/day; titrate 25 mg/day increments weekly

Adult Dosing for Antidepressant Medications

Serotonin–Norepinephrine Reuptake Inhibitors (SNRIs)				
Newer-generation SNRIs				
Desvenlafaxine	Pristiq	50	50	Doses up to 400 mg/day have been studied; however, AEs are increased and no additional benefit has been shown at doses exceeding 50 mg/day
Duloxetine	Cymbalta	30	30–90	Maximum 120 mg/day (given once or twice daily); doses exceeding 60 mg/day not shown to provide increased efficacy for the treatment of MDD
Venlafaxine	Effexor	37.5–75	75–225	Maximum 375 mg/day (IR); maximum 225 mg/day (ER); may increase in increments up to 75 mg/day at a minimum of every 4 days. Dose reductions may be required if sustained hypertension occurs
Tricyclic antidepressants (TCAs)				
Amitriptyline	Elavil	25	100–300	Maximum 300 mg/day for MDD; may be given as a single daily dose at bedtime or in divided doses throughout the day Therapeutic serum level 100–250 ng/mL (370–925 nmol/L); parent drug plus metabolite (i.e., nortriptyline)
Desipramine	Norpramin	25	100–300	Maximum 300 mg/day Suggested therapeutic concentration range for combined imipramine + desipramine: 150–300 ng/mL (550–1,100 nmol/L)
Doxepin	Sinequan	25	100–300	Maximum 300 mg/day; may be given in a single daily dose at bedtime (if tolerated) or in divided doses throughout the day; a single dose should not exceed 150 mg
Imipramine	Tofranil	25	100–300	Maximum 300 mg/day; may be given in a single daily dose at bedtime (if tolerated) or in divided doses throughout the day Suggested therapeutic concentration range for combined imipramine + desipramine: 150–300 ng/mL (550–1,100 nmol/L)
Nortriptyline	Pamelor	25	50–150	Maximum 150 mg/day; total daily may be given as a single daily dose (if tolerated) or 25 mg doses given three to four times daily Therapeutic serum level 50–150 ng/mL (190–570 nmol/L)

Adult Dosing for Antidepressant Medications

Norepinephrine and Dopamine Reuptake Inhibitor (NDRI)				
Bupropion	Wellbutrin	150	150–300	Please see text for proper dosing, which can help decrease seizure risk Maximum 450 mg/day (IR, ER), 400 mg/day (SR); ER dosed once daily; SR dosed once or twice daily; IR may be dosed up to three times daily
Mixed Serotonergic Effects (Mixed 5-HT)				
Nefazodone	Serzone	100	300–600	Maximum 600 mg/day; daily doses should be divided twice daily
Trazodone	Desyrel; Oleptro	50	150–300	Maximum 600 mg/day; IR daily dose should be divided three times daily and may increase by 50 mg/day increments every 3–7 days; ER dose titration initiated at 150 mg at bedtime and can be increased 75 mg/day every 3 days
Vilazodone	Viibryd	10	40	Target dose = 40 mg/day unless coadministered with CYP3A4 inhibitor (dose not to exceed 20 mg/day); doses greater than 40 mg/day have not been assessed Dose titration: 10 mg/day for 7 days, 20 mg/day for 7 days, and then 40 mg/day

Discontinuation of Antidepressants

- Withdrawal syndrome
  - Worse with paroxetine, venlafaxine
  - Symptoms: dizziness, nausea, paresthesias, anxiety/insomnia, flulike symptoms
  - Onset: 36-72 hours
  - Duration: 3-7 days

Discontinuation of Antidepressants

- **Taper schedule, for patients on long term treatment , (every 1-2 weeks).**
  - Fluoxetine and Bupropion : generally unnecessary

    Paroxetine and Citalopram: decrease by 5-10 mg
  - Escitalopram: decrease by 5 mg every 1-2 weeks
  - Venlafaxine and sertaline : decrease by 25-50 mg

    Nefazodone: decrease by 50-100 mg
  - Tricyclics:decreaseby10%-25%

Special Populations

- **Elderly patients**
- Bupropion and venlafaxine are often selected because of milder anticholinergic and less frequent cardiovascular side effects.
- Mirtazapine has been shown to be an effective antidepressant in the elderly (at least 65 years of age) and better tolerated than the SSRI paroxetine.

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** is the only FDA approved antidepressant for treating depression in patients below 18 years of age.

Special Populations

- **Pregnant and lactating mothers**
- Approximately 14% of pregnant women develop a serious depression during pregnancy .
- The risks and benefits of drug therapy during pregnancy must always be weighed, and concerns about the risks of untreated depression during pregnancy should be considered.
- SSRIs, the most commonly used and best-tolerated treatment for depression in this population group.

Treatment Resistant Depression

- Treatment-resistant depression is;
- A depression which has not achieved remission even after two optimal antidepressant trails.
- Three pharmacologic approaches that have been used :
  - Switching to other antidepressants
  - Augmentation: Bupropion , Lithium Thyroid supplements
  - Atypical antipsychotic Agents, apriprazole, olanzapine in combination with Fluoxetine

Treatment Resistant Depression

- The APA practice guideline advised that if patients fail to respond to medication after 6 to 8 weeks, a reappraisal of the treatment regimen should be considered.
- **Partial responders** should consider changing the dose, augmenting the antidepressant, or adding psychotherapy or ECT.
- **With no response**, options include changing to a second antidepressant or the addition of psychotherapy or ECT.

Evaluation of therapeutic outcomes

- Monitor for adverse effects as they affect Adherence
- Patients >40 years of age should receive a pretreatment ECG before starting TCA therapy, and follow up ECGs should be performed periodically.
- Patients should be monitored for the emergence of suicidal ideation after initiation of any antidepressant.
- Assess Psychometric rating before and after 6 -8 weeks of therapy, then periodically.

Evaluation of therapeutic outcomes

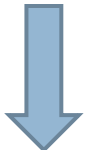
- Patients can be taught to manage side effects such as sedation, constipation, and dry mouth.
- Potential side effects such as weight gain and sexual dysfunction should be discussed with the patient and monitored at each visit.
- Venlafaxine may increase blood pressure, and patients should have their blood pressure checked at each visit.

Evaluation of therapeutic outcomes

- Patients taking TCAs such as amitriptyline, imipramine, nortriptyline, or desipramine should have antidepressant serum levels checked if overdose, side effects, or nonadherence is an issue.
- Patients should be monitored for serotonin syndrome if they are taking two or more serotonergic medications.

Evaluation of therapeutic outcomes

- **Definition of therapeutic outcome**
- (a) non response is less than 25% decrease in baseline symptoms,
- (b) partial response is a 26% to 49% decrease in baseline symptoms, and
- (c) partial remission or response is greater than a 50% decrease in baseline symptoms.
- Remission is a return to baseline functioning with no symptoms present.



Adverse Drug Reactions and Monitoring Parameters

Drug	ADR(s)	Monitoring	Comments
Antidepressants from Each Pharmacologic Class			
Common to all antidepressants			
	Suicidality	Behavioral changes Mental status	(U.S. boxed warning) for all antidepressants; caregivers should be alerted to monitor for acute changes in behavior
Selective Serotonin Reuptake Inhibitors (SSRIs)			
Common to all SSRIs			
	Anxiety or nervousness	Assess severity and impact on patient functioning and quality of life	Most prominent on initial treatment; generally subsides over time as antidepressant causes neurochemical adaptations
	Insomnia	Sleep patterns	Among SSRI class: fluoxetine may be more activating; fluvoxamine and paroxetine may be more sedating
	Nausea	Frequency and severity	
	Serotonin syndrome	Autonomic function (e.g., pulse, temperature); neuromuscular function	Criteria include mental status change, clonus, hyperthermia, diaphoresis, and tachycardia
	Sexual dysfunction	Assess severity and impact on patient functioning and quality of life	Spontaneous self-reporting may be low; clinician should assess symptoms; reversible on drug discontinuation

Adverse Drug Reactions and Monitoring Parameters

SSRI-Specific			
Citalopram	QT interval prolongation	Electrocardiogram; electrolytes (e.g., potassium, magnesium)	Caution use in "at-risk" patients (e.g., electrolyte disturbance); discontinue if QTc persistently >500 milliseconds
Fluoxetine	Anorexia	Weight (over time)	SSRIs are generally considered weight neutral
Fluvoxamine	Somnolence	Mental status	May be less tolerable than other SSRIs
Paroxetine	Anticholinergic effects	Symptoms: dry mouth, constipation, urinary retention, mental status	Paroxetine possesses relatively more anticholinergic effects than other SSRIs

SSRI Side Effect Management

- **Insomnia**
  - may use trazodone or low-dose benzo temporarily
- **Anxiety**
  - start low and increase slow--tends to be transient
  - may need to use a benzodiazepine initially
- **GI Distress**
  - lower dose or take with food
  - temporary--but occasionally need to switch to a different antidepressant
- **Headache**
  - specific for SSRI's--may need to switch

Adverse Drug Reactions and Monitoring Parameters

Serotonin–Norepinephrine Reuptake Inhibitors (SNRIs)			
Common to all SNRIs			
	Insomnia	Sleep patterns	Possibly less likely with duloxetine
	Nausea	Frequency and severity	
	Serotonin syndrome	Autonomic function (e.g., pulse temperature); neuromuscular function	Criteria include mental status changes, clonus, hyperthermia, diaphoresis, and tachycardia
	Sexual dysfunction	Assess severity and impact on patient functioning and quality of life	Spontaneous self-reporting may be low; clinician should assess symptoms; reversible on drug discontinuation
SNRI-Specific			
Desvenlafaxine	Hyperlipidemia	Lipid profile	Elevations in total cholesterol, low-density lipoproteins, and triglycerides
Duloxetine	Orthostatic *hypo*-tension	Blood pressure, pulse	Initial treatment or on dose increase
Venlafaxine	Dose-related *hyper*-tension	Blood pressure, pulse	May need to lower dose or discontinue
Mixed Serotonergic Effects (Mixed 5-HT)			
Nefazodone	Liver toxicity	Liver function tests	Nefazodone use is extremely limited in the United States due to concerns about liver toxicity
Trazodone	Orthostatic hypotension	Blood pressure, pulse	May be more severe as compared with other antidepressants rate-limiting side effect
	Priapism	Patient report of sexual side effects, especially painful erection	Patient should seek medical attention for prolonged erection (i.e., >4 hours)
Vilazodone	Serotonin syndrome	Autonomic function (e.g., pulse temperature); neuromuscular function	Criteria include mental status changes, clonus, hyperthermia, diaphoresis, and tachycardia
Serotonin and α_2-Adrenergic Antagonist			
Mirtazapine	Weight gain	Body weight	Frequently occurring and significant (>7%) weight gain amor adults
Norepinephrine and Dopamine Reuptake Inhibitor (NDRI)			
Bupropion	Seizure activity	Electroencephalogram	See text for proper dosing, which can help decrease seizure risk; caution use in patients with eating disorders or alcohol use disorders

SSRI – Serotonin Syndrome

- A "serotonin syndrome" may occur, where mental status changes along with .....
  - Agitation
  - Shivering
  - Diarrhea
  - fever may develop
  - sweating
  - tremors
  - uncoordination
- This syndrome may be life-threatening.

SSRI – Serotonin Syndrome

- SSRIs should not be used with any drug that increases serotonin concentrations, including….
  - MAO inhibitors
  - Tramadol
  - Sibutramine
  - Meperidine
  - Sumatriptan
  - Lithium
  - St. John's wort
  - Ginkgo biloba, and
  - Some anti-psychotic agents.

Patient education

1. Depression is NOT a personality flaw or a weakness of character..
2. All antidepressants are equally effective.
3. Most patients receiving antidepressants will experience some side effect(s) initially.
4. Antidepressants should be taken at the same time daily.
5. The response to antidepressants is delayed.
6. Antidepressants must be taken for at least 6 to 9 months.
7. Antidepressants are NOT addictive substances.
8. Avoid alcohol and other CNS depressants.

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Thank you!