Chapter 68: Depressive Disorders

INTRODUCTION

- The essential feature of *major depressive disorder* (MDD) is a clinical course characterized by one or more major depressive episodes without a history of manic or hypomanic episodes.
- Refer to guidelines published by the American Psychiatric Association, the British Association of Psychopharmacology, and the Canadian Network for Mood and Anxiety Treatments (CANMAT) because they have similarities in their recommendations.

PATHOPHYSIOLOGY

- *Monoamine hypothesis:* Decreased brain levels of the neurotransmitters norepinephrine (NE), serotonin (5-HT), and dopamine (DA) may cause depression.
- *Postsynaptic changes in receptor sensitivity:* Studies have demonstrated that desensitization or downregulation of NE or 5-HT_{1A} receptors may relate to onset of antidepressant effects.
- *Dysregulation hypothesis:* Failure of homeostatic neurotransmitter regulation, rather than absolute increases or decreases in their activities.
- *Inflammatory hypothesis*: Chronic stress and inflammation may alter glutamatergic and GABA transmission. Brain-derived neurotrophic factor (BDNF) is a primary mediator of neuronal changes as well as synaptogenesis whose expression is reduced due to stress and may be associated with depression.
- Neuroactive steroids are a growing area of research for depression.

CLINICAL PRESENTATION

- *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.
- *Physical symptoms*: Weight gain or loss, fatigue, pain (especially headache), sleep disturbance, decreased or increased appetite, loss of sexual interest, and gastrointestinal (GI) and cardiovascular complaints (especially palpitations).
- *Cognitive symptoms*: Decreased ability to concentrate, poor memory for recent events, confusion, and indecisiveness.
- *Psychomotor disturbances*: Psychomotor retardation (slowed physical movements, thought processes, and speech) or psychomotor agitation.

DIAGNOSIS

- MDD is characterized by one or more major depressive episodes, as defined by the *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. Five or more of the above symptoms must have been present nearly every day during the same 2-week period and cause significant distress or impairment. Depressed mood or loss of interest or pleasure must be present in adults (or irritable mood in children and adolescents). **Table 68-1** outlines a common acronym for MDD diagnostic criteria.
- The depressive episode must not be attributable to 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 requires a medication review, physical examination, mental status examination, a complete blood count with differential, thyroid function tests, and electrolyte determination.
- Many chronic illnesses (eg, stroke, Parkinson disease, traumatic brain injury, hypothyroidism) and substance 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.

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.

TREATMENT

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

Nonpharmacologic Treatment

- Psychotherapy (eg, cognitive therapy, behavioral therapy, or interpersonal psychotherapy) is recommended as primary treatment for mild to moderately severe major depressive episode. For severe depression, it may be used in combination with medications as its effect is considered additive. Psychotherapy alone is not recommended for acute treatment of severe and/or psychotic MDD.
- Electroconvulsive therapy (ECT) may be considered when a rapid response is needed, risks of other treatments outweigh potential benefits, there is history of a poor response to drugs, and the patient prefers ECT. A rapid therapeutic response (10–14 days) has been reported.

- Repetitive transcranial magnetic stimulation has demonstrated efficacy and does not require anesthesia as does ECT.
- Recent data suggest the benefit of physical activity in patients with MDD, and the American Psychiatry Association has endorsed inclusion of exercise into MDD treatment plans.

Pharmacologic Therapy

General Approach

- **Figure 68-1** shows an algorithm for treatment of uncomplicated MDD. **Table 68-2** guides adult dosing of antidepressants.
- 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 response. Dosing recommendations to aid in the interpretation of results are available through the Clinical Pharmacogenomics Implementation Consortium (CPIC) as well as the FDA-approved package inserts.
- 50%–60% of patients with varying types of depression improve with drug therapy.
- At least a 6-week trial of an antidepressant at maximum dosage is considered an adequate trial of that medication.
- The acute phase of treatment lasts 6–12 weeks, and the goal is remission (ie, absence of symptoms). The continuation phase (4–9 months after remission) seeks to eliminate residual symptoms or prevent relapse. The maintenance phase (12–36 months or more) seeks to prevent recurrence of a new episode of depression.
- Give older patients one-half of the initial dose given to younger adults, and increase the dose more slowly. Older patients may require 6–12 weeks of treatment to achieve the desired antidepressant response.
- Early in treatment, all antidepressants can increase suicidal thinking and behavior in children, adolescents, and young adults less than 25 years of age. Suicide risk may also be elevated in the 30 days after discontinuation.
- 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.
- **Table 68-3** shows antidepressant potency and relative selectivity for inhibition of various receptors. Specific adverse effects seen with select antidepressants are given in **Table 68-4**.
- The ability of any antidepressant to inhibit or induce the CYP450 enzymes can be a significant factor determining its capability to cause a pharmacokinetic drug–drug interaction.

FIGURE 68-1

Algorithm for treatment of uncomplicated MDD. Note: Both the BAP guidelines and the STAR*D trial suggest that switching and augmentation strategies are supported by stronger evidence compared to dose increases (among poor antidepressant responders).

(SSRI, selective serotonin reuptake inhibitor.)

image

TABLE 68-2

Adult Dosing Guidance for Currently Available Antidepressant Medications

Drug (Brand Name)	Initial Dose (mg/day)	Usual Dosage Range (mg/day)	Comments (eg, Maximum Daily Dosage, Suggested Therapeutic Plasma Concentration)[a]
Selective serotonin reuptake inhibitors (SSRIs)			
Citalopram (Celexa)	20	20–40	Doses >40 mg/day not recommended due to QT prolongation risk; maximum 20 mg/day for CYP2C19 poor metabolizers or coadministration with CYP2C19 inhibitors; 20 mg/day recommended for patients older than 60 years of age
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
			Maximum 300 mg/day (ER formulation)
Paroxetine (Paxil)	20	20–50	Maximum 50 mg/day (IR formulation); titrate 10 mg/day increments weekly
			Maximum 62.5 mg/day (CR formulation); titrate 12.5 mg/day increments weekly
Sertraline (Zoloft)	50	50–200	Maximum 200 mg/day; titrate 25 mg/day increments weekly
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. Dose reductions or discontinuation may be required if sustained hypertension occurs
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 or discontinuation may be required if sustained hypertension occurs

Levomilnacipran (Fetzima)	20	40–120	Initial dose (20 mg) for 2 days before dose increases is recommended at intervals of 2 or more days. Dose adjustment or discontinuation may be required if sustained elevated heart rate or hypertension occurs
Tricyclic antidepressants (TCAs)			
Amitriptyline (Elavil)	25	100–200	Maximum 300 mg/day for MDD; depending on the total dose, it may be given as a single daily dose at bedtime or in divided doses throughout the day; therapeutic serum level 100–250 ng/mL (mcg/L; 370–925 nmol/L); parent drug plus metabolite (nortriptyline)
Desipramine (Norpramin)	25	100–200	Maximum 300 mg/day; suggested therapeutic concentration range for combined imipramine + desipramine: 150–300 ng/mL (mcg/L; 550–1100 nmol/L)
Doxepin (Sinequan)	25	100–200	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	100–200	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 (mcg/L; 550–1100 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 (mcg/L; 190–570 nmol/L)
Norepinephrine and dopamine reuptake inhibitor (NDRI)			
Bupropion (Wellbutrin)	150 (75 mg given twice daily)	150–450	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. Adhering to labeled maximum daily and maximum single doses minimizes effect on seizure threshold
Mixed serotonergic effects (mixed 5-HT)			
Nefazodone (Serzone)	100	200–400	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	20–40	Target dose 20–40 mg/day unless coadministered with CYP3A4 inhibitor (dose not to exceed 20 mg/day). Dose titration: 10 mg/day for 7 days, 20 mg/day for 7 days, and then may increase to 40 mg/day. Dose must be taken with food to ensure adequate drug absorption and bioavailability
Vortioxetine (Brintellix)	10	20	Maximum 20 mg/day; minimal difference in efficacy and side effects in clinical trials between 10 and 20 mg
Serotonin and α_2-adrenergic antagonist			
Mirtazapine (Remeron)	15	15–45	Maximum 45 mg/day; dose adjustment may be required for renal impairment
Monoamine oxidase inhibitors (MAOIs)			

Phenelzine (Nardil)	15	30–90	Divided dosing 2–3 times daily; dosing may be increased to 90 mg/day based on tolerance and response
Selegiline (transdermal) (Emsam)	6	6–12	Not to exceed 12 mg/24 hours; dose may be increased by 3 mg/day increments every 2 weeks; site of application should be rotated
Tranylcypromine (Parnate)	10	20–40	Maximum 60 mg/day; divided dosing; increase by 10 mg at 1- to 3-week intervals
Isocarboxazid (Marplan)	10–20	30–60	Maximum 60 mg/day; divided dosing
Second-generation antipsychotics (SGA) as augmentation ($5HT_{2A}$ and D_2 modulators)			
Aripiprazole (Abilify)	2	2–15	FDA-approved for augmentation; CANMAT Level 1 evidence, 1st line
Brexpiprazole (Rexulti)	1	1–3	Not FDA-approved for augmentation; CANMAT Level 1 evidence, 2nd line
Olanzapine (Zyprexa)	2.5	2.5–10	Not FDA-approved for augmentation; CANMAT Level 1 evidence, 2nd line
Quetiapine (Seroquel)	50	150–300	FDA-approved for augmentation; CANMAT Level 1 evidence, 1st line
Risperidone (Risperdal)	1	1–3	Not FDA-approved for augmentation; CANMAT Level 1 evidence, 1st line
Alternative augmentation agents (not FDA-approved for antidepressant augmentation)			
Buspirone (Buspar)	10	10–60	Divided dosing 2–3 times daily
			5HT1A partial agonist
Lithium	300	600–1200	Dose based on therapeutic levels (target 0.6–1 mEq/L [mmol/L])
			Mechanism in depression not fully understood
Triiodothyronine (Cytomel)	0.025	0.025–0.05	Once daily dosing; monitor free T3 levels

[a]SI conversion for cases where reference ranges are for a mixture of parent drug and active metabolite is calculated based on a 1:1 ratio.

AE, adverse effects; CR, continuous release; ER, extended release; IR, immediate release; MDD, major depressive disorder; SR, sustained release; CANMAT, Canadian Network for Mood and Anxiety Treatments.

TABLE 68-3

Relative Potencies of Norepinephrine and Serotonin Reuptake Blockade and Selected Receptor Antagonism Profile of Antidepressants

	Reuptake Antagonism				
	NE	5-HT	M1	H1	α1
Selective serotonin reuptake inhibitors (SSRIs)					
Citalopram	0	++++	0	+	0
Escitalopram	0	++++	0	0	0
Fluoxetine	+	++++	0	0	0
Fluvoxamine	0	++++	0	+	0
Paroxetine	++	++++	+	+	0
Sertraline	0	++++	0	0	0
Serotonin–norepinephrine reuptake inhibitors (SNRIs)					
Duloxetine	+++	++++	+	0	+
Levomilnacipran	++++	+++	+	0	0
Venlafaxine[a] 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
Vortioxetine	0	++++	0	+	0
Norepinephrine and dopamine reuptake inhibitor (NDRI)					
Bupropion[b]	+	0	+	0	0

Serotonin and α_2-receptor antagonist					
Mirtazapine	0	0	0	++	++

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

[b]Bupropion: also blocks dopamine reuptake.

α1, antiadrenergic, hypotension; H1, antihistamine, sedation; M1, antimuscarinic/anticholinergic side effects.

++++, high; +++, moderate; ++, low; +, very low; 0, absent or not adequately studied.

TABLE 68-4

Adverse Drug Reactions and Monitoring Parameters Associated with Select Antidepressants

Drug	ADR(s)	Monitoring	Comments
Antidepressants from each pharmacologic class			
Common to all antidepressants			
	Suicidality	Behavioral changes	(US black box warning) for all antidepressants; caregivers should be alerted to monitor for acute changes in behavior (especially early in treatment)
		Mental status	
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; lower initial doses recommended in patients with prominent anxiety
	Hyponatremia	Serum sodium	More likely in older females; sodium may decrease within 72 hours of initiating antidepressant
	Nausea	Frequency and severity	May improve with slower dose titration
	Sleep changes (insomnia and somnolence)	Sleep patterns	Among SSRI class: fluoxetine may be more activating; fluvoxamine and paroxetine may be more sedating
	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
SSRI-specific			

Citalopram (possibly escitalopram)	QTc interval prolongation	Electrocardiogram; electrolytes (eg, potassium, magnesium)	Caution use in "at-risk" patients (eg, electrolyte disturbance); discontinue if QTc persistently >500 msec or increased >5 msec over baseline
Fluoxetine	Anorexia	Weight (over time)	SSRIs are generally considered weight neutral
Paroxetine	Anticholinergic effects	Symptoms: dry mouth, constipation, urinary retention, mental status	Paroxetine possesses relatively more anticholinergic effects than other SSRIs
Serotonin–norepinephrine reuptake inhibitors (SNRIs)			
Common to all SNRIs			
	Cardiovascular changes	Increases in blood pressure; heart rate	Possibly less likely with duloxetine; may need to lower/discontinue dose
	Insomnia	Sleep patterns	Possibly less likely with duloxetine
	Nausea	Frequency and severity	May improve with slower dose titration
	Sexual dysfunction	Assess severity and impact on patient functioning and quality of life	Spontaneous self-reporting may be low; clinicians should assess symptoms; reversible on drug discontinuation
	Sweating	Frequency and severity	May require change in therapy
SNRI-specific			
Desvenlafaxine	Dose-related hyperlipidemia	Lipid profile	Elevations in total cholesterol, low-density lipoproteins, and triglycerides
Duloxetine	Liver toxicity	Liver function tests	May be transient upon initiation or sustained
Mixed serotonergic effects (mixed 5-HT)			
Nefazodone	Liver toxicity	Liver function tests	Nefazodone black box warning in the United States for hepatotoxicity
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 (ie, >4 hours)
Vilazodone and vortioxetine	Nausea	Frequency and severity	Most common dose-limiting side effect
Serotonin and α_2-adrenergic antagonist			

Mirtazapine	Weight gain	Body weight	Frequently occurring and significant (>7% over baseline) weight gain among adults; diet mediated
Norepinephrine and dopamine reuptake inhibitor (NDRI)			
Bupropion	Seizure activity	Electroencephalogram if indicated	See Table 68-2 for proper dosing, which can help decrease seizure risk; caution use in patients with eating disorders or alcohol use disorders

Selective Serotonin Reuptake Inhibitors

- 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 (**Figure 68-1**).
- 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. The pharmacokinetics of the antidepressants is summarized in **Table 68-5**.
- 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.
- The primary adverse effects for SSRIs are nausea, vomiting, diarrhea, headache, insomnia, fatigue, and sexual dysfunction and have a reduced incidence of sedative, anticholinergic, and cardiovascular adverse effects or weight gain.
- A few patients have anxiety symptoms early in treatment which may be reduced by starting with lower doses and slowly titrating up.
- Citalopram and escitalopram may to an increase in QT interval at doses above 40 mg/day.
- Potentially fatal reactions may occur when any SSRI and MAOI are coadministered. A 5-week washout after fluoxetine discontinuation is critical before starting an MAOI.
- If an SSRI is added to a regimen which includes drugs known to interact with SSRIs, the SSRI starting dose should be low and slowly titrated.
- **Table 68-6** compares second- and third-generation antidepressants for their effects on CYP450 enzymes. 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.

TABLE 68-5

Pharmacokinetic Properties of Antidepressants

Generic Name	Elimination Half-Life[a]	Plasma Protein Binding (%)	Clinically Important Metabolites
Selective serotonin reuptake inhibitors (SSRIs)			
Citalopram	33 hours	80	None
Escitalopram	27–32 hours	56	None
Fluoxetine	4–6 days[b]	94	Norfluoxetine[c]
Fluvoxamine	15–26 hours	77	None

Paroxetine	24–31 hours	95	None
Sertraline	27 hours	99[d]	None
Serotonin–norepinephrine reuptake inhibitors (SNRIs)			
Desvenlafaxine	11 hours	30	None
Duloxetine	12 hours	90	None
Levomilnacipran	12 hours	22	None
Venlafaxine	5 hours	27–30	*O*-Desmethyl-venlafaxine
Tricyclic Antidepressants (TCAs)			
Amitriptyline	9–46 hours	90–97	Nortriptyline
Desipramine	11–46 hours	73–92	2-Hydroxy-desipramine
Doxepin	8–36 hours	68–82	Desmethyl-doxepin
Imipramine	6–34 hours	63–96	Desipramine
Nortriptyline	16–88 hours	87–95	10-Hydroxy-nortriptyline
Mixed serotonergic (mixed 5-HT)			
Nefazodone	2–4 hours	99	*meta*-Chlorophenyl-piperazine
Trazodone	6–11 hours	92	*meta*-Chlorophenyl-piperazine
Vilazodone	25 hours	>95	
Vortioxetine	66 hours	98	
Norepinephrine/Dopamine reuptake inhibitor (NDRI)			
Bupropion	10–21 hours	82–88	Hydroxy-bupropion
			Threohydro-bupropion
			Erythrohydro-bupropion
Serotonin and α_2-adrenergic antagonists			
Mirtazapine	20–40 hours	85	None

[a]Biologic half-life in slowest phase of elimination.

[b]Four to 6 days with chronic dosing; norfluoxetine, 4–16 days.

[c]Take with food to increase area under the curve concentrations by greater than 60%.

[d]Increases 30%–40% when taken with food.

TABLE 68-6

Second- and Third-Generation Antidepressants and Cytochrome (CYP) P450 Enzyme Inhibitory Potential

	CYP Enzyme			
Drug	**1A2**	**2C**	**2D6**	**3A4**
Bupropion	0	0	+++	0
Citalopram	0	0	+	NA
Duloxetine	0	0	+++	0
Escitalopram	0	0	+	0
Fluoxetine	0	++	++++	++
Fluvoxamine	++++	++	0	+++
Mirtazapine	0	0	0	0
Nefazodone	0	0	0	++++
Paroxetine	0	0	++++	0
Sertraline	0	++	+	+
(des)-Venlafaxine	0	0	0/+	0

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

Serotonin–Norepinephrine Reuptake Inhibitors and Antidepressants with Mixed Serotonin Effects

- The serotonin–norepinephrine reuptake inhibitors 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. 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.
- Mirtazapine enhances central noradrenergic and serotonergic activity by antagonizing central presynaptic α_2-adrenergic autoreceptors and heteroreceptors. It also antagonizes 5-HT_2 and 5-HT_3 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.

- Levomilnacipran is a single-isomer, extended-release form of milnacipran which is FDA-approved to treat fibromyalgia which pharmacologically inhibits NE reuptake more than 5HT reuptake. This agent may increase blood pressure and heart rate and its place in therapy for MDD is unknown.
- Trazodone and nefazodone antagonize the 5-HT_2 receptor and inhibit the reuptake of 5-HT. They can also enhance 5-HT_{1A} neurotransmission. Trazodone blocks α_1-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. Common side effects with nefazodone are dizziness, orthostatic hypotension, and somnolence.

  ✔ Priapism occurs rarely with trazodone (1 in 6000 male patients). Surgical intervention may be required, and impotence may result.

  ✔ Nefazodone carries a black box warning for life-threatening liver failure. Do not initiate nefazodone in individuals with active liver disease or elevated serum transaminases.
- Vilazodone and vortioxetine are other antidepressants with mixed serotonin effects that are a combination SSRI and 5-HT_{1A} 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).

Bupropion

- **Bupropion** inhibits both the NE and DA reuptake that 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

- Tricyclic antidepressant (TCA) 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 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.
- 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. Dose-related kinetics cannot be ruled out in older patients. Factors reported to influence TCA plasma concentrations include renal or hepatic dysfunction, genetics, age, cigarette smoking, and concurrent drug

administration.

- In acutely depressed patients, there is a correlation between antidepressant effect and plasma concentrations for some TCAs (eg, **amitriptyline, nortriptyline, imipramine**, and **desipramine**). The best-established therapeutic range is for **nortriptyline**, and data suggest a therapeutic window (Table 68-2).
- 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. Plasma concentrations should be obtained at 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

- **Isocarboxazide**, **phenelzine,** and **tranylcypromine** increase the concentrations of NE, 5-HT, and DA within the neuronal synapse through inhibition of monoamine oxidase (MAO). They are nonselective inhibitors of MAO-A and MAO-B. **Selegiline**, available as a transdermal patch for treatment of major depression, inhibits brain MAO-A and MAO-B but has reduced effects on MAO-A in the gut.
- **Table 68-7** shows dietary and medication restrictions for patients taking phenelzine or tranylcypromine.
- 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 mildly to moderately sedating, but tranylcypromine is often stimulating, and the last dose of the day is administered in the early afternoon. Sexual dysfunction in both genders is common. 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 (see Table 68-7). Symptoms of 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. 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 coadministered with an MAOI. However, TCAs and MAOIs can be combined in refractory patients by experienced clinicians with careful monitoring.

TABLE 68-7

Dietary and Medication Restrictions for Patients Taking Monoamine Oxidase Inhibitors[a]

Foods to Avoid Completely	Approximate Tyramine Content (mg) Per Ounce
Aged cheeses (eg, cheddar, blue, Swiss, Camembert)	25–45
Chicken liver	60
Dry aged meats (eg, mortadella, salami, prosciutto)	2–45
Fava beans	Unknown
Kim chee	Unknown
Red wine	Variable
Sauerkraut	1–3
Smoked or pickled fish (eg, lox, caviar, pickled herring)	0–80
Soy sauce, fermented soy, miso	Varies
Tap beer	20–40
Yeast extract	2–60
Foods to Eat in Moderation	
American cheese, Parmesan cheese	<2
Canned, filtered beer	<2 per 12 oz (355 mL)
Havarti, brie	Thought to be low
Pepperoni	<2
Pizza (large commercial chains generally safe; avoid gourmet with aged cheeses and meats)	2 slices
White wine	<1 per 4 oz (120 mL)
Foods Without Restrictions	
Fresh dairy products (cottage cheese, cream cheese, fresh milk, ice cream, ricotta, sour cream, yogurt)	
Fresh meats (including fresh sausage)	
Processed meats (eg, lunch meat, hot dogs, ham)	
Spirits (eg, bourbon, gin, rum, vodka)	
Yeast bread products	

Medications to Avoid Completely		
Antidepressants[a]	Dopamine	Methylphenidate
Amphetamines	Ephedrine	Reserpine
Appetite suppressants	Epinephrine	Sympathomimetics
Asthma inhalants	Guanethidine	Tryptophan
Buspirone	Levodopa	
Carbamazepine	Local anesthetics[b]	
Decongestants	Meperidine	
Dextromethorphan	Methyldopa	

[a]Tricyclic antidepressants may be used with caution by experienced clinicians in treatment-refractory populations.

[b]Those containing sympathomimetic vasoconstrictors.

Ketamine

- **Ketamine** is an older anesthetic agent, which modulates glutamate activity via extrasynaptic *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 treatment refractory MDD.
- **Esketamine** is the single *s*-isomer of ketamine that has a higher affinity for the NMDA receptor than the *r*-isomer. Intranasal esketamine is FDA-approved and requires supervised, in-clinic self-administration (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 antidepressant effect by allosteric modulation of GABAA receptors, which may increase 5HT and NE transmission and is FDA-approved for postpartum depression. Administration involves a 60-hour stepped dose, intravenous infusion.
- 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 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.

Pediatric Patients

- Symptoms of depression in childhood include boredom, anxiety, failing adjustment, and sleep disturbance.
- Data supporting efficacy of antidepressants in children and adolescents are sparse. Fluoxetine and escitalopram are 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 baseline electrocardiogram (ECG) is recommended.

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.
- The absolute risk of antidepressant use in pregnancy is unknown.
- Risks reported with SSRIs use in pregnancy include low birth weight, respiratory distress, and congenital heart defects.
- The risks and benefits of drug therapy during pregnancy must be weighed, including concerns about untreated depression.
- 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 different agent (eg, mirtazapine or nortriptyline).
- Alternatively, the current antidepressant may be augmented by addition of another agent (eg, lithium or triiodothyronine [T_3]), 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. Figure 68-1 is an algorithm for treatment of depression including refractory patients.

EVALUATION OF THERAPEUTIC OUTCOMES

- Several monitoring parameters, in addition to plasma concentrations, are useful. Monitor regularly for adverse effects (**Table 68-4**), remission of target symptoms, and changes in social or occupational functioning. Assure regular monitoring for several months after discontinuation of antidepressants.
- Regularly monitor blood pressure of patients given serotonin–norepinephrine reuptake inhibitors.
- a pretreatment ECG is recommended before starting TCA therapy in children, adolescents, and patients over 40 years of age, and perform follow-up ECGs periodically.
- Monitor for suicidal ideation after initiation of any antidepressant, especially in the first few weeks of treatment and up to 30 days after treatment discontinuation.
- In addition to the clinical interview, use psychometric rating instruments to rapidly and reliably measure the nature and severity of depressive and associated symptoms.

See Chapter 85, Major Depressive Disorder, authored by Amy M. Vandenberg, for a more detailed discussion of this topic.