Psychiatry I

UNIPOLAR DEPRESSION

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Learning Objectives

1. Distinguish major depressive disorder (MDD) from other unipolar disorders based on clinical presentation and course of illness.
2. Devise optimal pharmacotherapeutic treatment regimens for patients with depressive disorders using knowledge of therapeutic effects, adverse effects, and interactions of antidepressant drugs.
3. Given a patient case, justify duration of pharmacotherapy for depression based on individual patient characteristics and relapse risk.
4. Analyze potential drug-drug and drug-food interactions with antidepressant drugs and describe both their mechanism and clinical significance.
5. Create a strategy to augment pharmacological regimens in patients with depression who have not responded to monotherapy.
6. Recommend treatments for depressive disorders in special populations, including pregnant or lactating women, those with chronic pain, children, adolescents, and the elderly.

Overview of Depression

Depression is one of the most prevalent of not just mental disorders, but all medical illnesses. In 2002, more than 4% of the total global disease burden was attributable to major depressive disorder (MDD), similar to that of ischemic heart disease. In the United States, the prevalence rates of MDD range between 5.4% and 8.9%, affecting about 18.8 million Americans in any given year. Lifetime prevalence ranges from 10% to 25% for women and 5% to 12% for men. About 32–35 million American adults will suffer from MDD in their lifetime. Despite its recognition as a major health concern, depression is often overlooked in the clinical setting.

In 2004, unipolar depressive disorders were a leading source of disability in the United States, surpassed only by malignancy and cardiovascular disease. The estimated direct cost of depression in the United States is $26 million annually. Workers with depression cost employers in excess of $30 billion per year in lost productivity. By the year 2020, depression is projected to reach second place on disability adjusted life-years calculated for all ages by the World Health Organization.

Etiology and Pathophysiology

The exact biological mechanism of depressive disorders is unknown, and theories have originated based on the mechanism of effective antidepressant drugs. The original monoamine hypothesis related depression to a deficiency in norepinephrine (NE) and serotonin (5-HT). This theory developed from the discovery that depletion of these neurotransmitters led to depression, and drugs that increased monoamine availability improved depressive symptoms. The theory did not account for time to antidepressant response, which can take weeks to months, while neurotransmitter availability in the synapse is significantly increased after the first dose of drug. Stress effects on the hypothalamic-pituitary-adrenal axis lead to the secretion of glucocorticoids and cortisol. These hormones in turn deplete neurons of brain-derived neurotrophic factors, which leads to a decrease in neurogenesis in the hippocampus. Animal models have shown that all antidepressant treatments increase neuronal cell proliferation in the hippocampus. The role of substance P, also released during stress, is also being investigated in depression. These proposed theories have led to a plethora of novel drug targets to improve neuronal resilience, including corticotrophin-releasing hormone, glucocorticoids, gamma-aminobutyric acid, and glutamate.

Of imaging studies detecting anatomical abnormalities in unipolar depression, most consistent is enlargement of the lateral ventricles. Other findings include hyperdensities in the subcortical white matter and decreased size of the

Abbreviations in This Chapter

5-HT	Serotonin
H_1	Histamine-1 receptor
HAM-D	Hamilton Rating Scale for Depression
MAO	Monoamine oxidase
MAOI	Monoamine oxidase inhibitor
MDD	Major depressive disorder
NE	Norepinephrine
SSRI	Selective serotonin reuptake inhibitor
STAR*D	Sequenced Treatment Alternatives to Relieve Depression
TCA	Tricyclic antidepressant

putamen and caudate. Although no specific gene has been identified, depression is heritable as revealed by family studies. The development of depression is likely related to a combination of genetic predisposition and environmental stressors. Life stressors may precede a depressive episode. Depression subsequent to substantial adverse life events, including loss of a loved one, may still benefit from pharmacotherapeutic treatment.

Diagnosis

Formal criteria for a major depressive episode have been outlined in the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision. First and foremost, either depressed mood or loss of interest in nearly all activities must be present for the diagnosis. In addition, at least four other symptoms must be present. These include sleep disturbances (either insomnia or hypersomnia); changes in appetite or weight; alterations in psychomotor activity (either increased or decreased); fatigue or decreased energy; excessive feelings of guilt or worthlessness; indecisiveness or impaired concentration; and thoughts of death or suicide. The symptoms must have been present for at least a 2-week period and cannot be directly attributable to substance ingestion or medical issues.

Health care providers must be cognizant of nonspecific signs and symptoms, including vague somatic complaints, which may be related to depression. Symptoms such as headaches, gastrointestinal ailments, or bone or muscle aches that do not respond to appropriate medical treatment suggest a possible depressive disorder. Patients with persisting conditions despite adequate treatment should be evaluated for depression.

Major Depressive Disorder

Major depressive disorder is characterized by one or more major depressive episodes with no history of manic, hypomanic, or mixed episodes. Major depressive disorder can be further classified according to clinical status and the presence or absence of clinical features of the current mood episode. Clinicians should carefully document these specifiers, as these can alter treatment decisions.

Mild, Moderate, and Severe Without Psychotic Features

Severity of MDD is determined by the number of symptom criteria met, the severity of those symptoms present, and the degree of functional impairment. Episodes with five or six depressive symptoms and minimal functional impairment are classified as mild while severe episodes consist of the presence of nearly all nine symptoms with significant impairment in functioning.

Severe With Psychotic Features

Episodes classified as severe with psychotic features are characterized by delusions or hallucinations, usually auditory. In most cases, the psychotic symptoms match the depressive themes and are classified as mood-congruent psychotic features (e.g., delusions of guilt, and derogatory auditory hallucinations). In rarer circumstances, the psychosis does not have an apparent relationship to the depressed mood and is considered mood-incongruent. This is associated with a poorer prognosis.

Remission

Major depressive disorder is considered in full remission after the absence of significant symptoms for at least 2 months. Partial remission is defined as either continued presence of some depressive symptoms, but full criteria for MDD are not met or symptoms are no longer present but the duration is less than 2 months.

Chronic

A depressive episode is specified as chronic if full criteria for a major depressive episode have been met for at least 2 years. About 1 in 5 patients presenting in an acute depressive episode progress to chronic depression, and 12% have continued symptoms after 5 years.

With Catatonic Features

Catatonic features describe episodes with profound psychomotor changes such as immobility or increased motor activity, mutism, or echopraxia (involuntary imitation of another person's movements). The excessive activity is purposeless and not affected by external stimuli. The catatonic specifier may be applied if the patient exhibits at least two of the following: motoric immobility (cataplexy or stupor), excessive purposeless motor activity, extreme negativism characterized by resistance, opposition, and refusal to cooperate with requests, peculiar voluntary movements such as walking on tiptoes, and echopraxia or echolalia (immediate and involuntary repetition of words or phrases spoken by others). Electroconvulsive therapy is particularly useful in treating this form of depression.

With Melancholic Features

To merit the melancholic features specifier, there should be either a loss of pleasure in all or nearly all activities or an absence of reactivity to pleasurable stimuli. In addition, three or more additional criteria must be met: distinct

depressed mood, increased morning severity that improves as the day progresses, early awakenings, extreme loss of appetite or weight loss, and excessive guilt. This subtype is considered a severe form of depression.

With Atypical Features

Although the name implies otherwise, atypical features are not uncommon. They are more common in females than males. Individuals who suffer from this type of depression typically have an earlier age of onset and a more chronic course of illness. For a formal diagnosis, mood reactivity must be present, plus at least two of the following symptoms: significant weight gain or increased appetite, increased sleep, leaden paralysis, and a long history of sensitivity to interpersonal rejection.

With Seasonal Pattern

Recurrent MDD can be specified with seasonal pattern if the mood episodes occur repeatedly at specific times of the year. Most commonly the depressive episodes begin in the fall and remit in the spring, but may occur at any point during the year, including summer.

With Postpartum Onset

This specifier is used if the onset of the depressive symptoms occurs within 4 weeks after childbirth. The episode may or may not be accompanied by psychotic features.

Dysthymic Disorder

Dysthymic disorder is characterized by chronic depressed mood for at least 2 years, and the duration of any symptom-free period is no greater than 2 months. In addition, at least two additional depressive symptoms (e.g., appetite disturbances, sleep disturbances, impaired concentration) must be present. The diagnosis can be given only if no major depressive episodes occur during the initial 2-year period. Depressive episodes may be superimposed on dysthymia after 2 years, referred to as double depression. As with MDD, a dysthymia diagnosis is not accurate if the patient experienced prior manic, mixed, or hypomanic episodes. In children, the required duration of symptoms is 1 year, and mood disturbances may involve irritability rather than sadness.

Dysthymic disorder is less common than MDD, with a lifetime prevalence of 6%. In adults, women are 2–3 times more likely to be diagnosed with dysthymia compared to men. The disorder frequently begins at an early age and maintains a chronic course throughout life. Some estimates are that nearly 75% of patients with dysthymia will develop MDD within 5 years. Spontaneous remission rates of dysthymia are low, but outcomes are significantly improved with treatment.

Depressive Disorder, Not Otherwise Specified

Disorders with depressive features that do not meet criteria for MDD, dysthymia, or adjustment disorders (symptoms resulting from an identifiable stressor) fall under the category of depressive disorder, not otherwise specified. Included are minor depressive disorder, premenstrual dysphoric disorder, and a situation that is deemed a depressive disorder, but its etiology (e.g., primary, secondary to a medical condition or substance) is undetermined.

Course of Illness

The course of illness with MDD varies from patient to patient. The typical age of onset is late 20s, but depression can develop at any age. Of those who go through a depressive episode, 50%–85% will suffer another bout of depression. The risk increases with each additional episode: after two episodes the risk increases to 70%, and after three, 90%. Between depressive episodes, functioning usually returns to baseline; however, residual symptoms remain with persistent impairment in social and/or occupational functioning in 20%–35% of cases.

Individuals with dysthymia and comorbid MDD are more likely to experience recurrence compared with those with MDD whose symptoms remit. Other risk factors for recurrence of MDD are concurrent chronic medical problems and additional psychiatric diagnoses. Treatment and prevention of future depressive episodes are imperative as the lifetime risk of suicide is estimated between 10% and 15% in those with mood disorders.

Depression is frequently associated with medical comorbidities and often is a predictor of increased morbidity and mortality. The rates of depression associated with a malignancy range from 10% to 50%. Similarly, MDD is common in patients with neurologic disorders. Depression is the most frequent psychiatric comorbidity in Parkinson's disease while about 50% of all patients with Alzheimer's disease meet criteria for MDD. Estimated depression rates post-stroke range from 8% to 75%. About 30% of patients who experience myocardial infarction develop depression.

Patient Assessment

Patients presenting with depressive symptoms should be interviewed thoroughly to obtain a complete medical, psychiatric, and family history. The pharmacist should obtain a list of current medications, including prescription, herbal, dietary supplements, and over-the-counter products, as well as previous and current psychotropic medications and the patient's response to each. The patient should undergo a physical examination and mental status examination, and laboratory testing should be performed that includes a complete blood cell count, serum chemistries, and thyroid panel. Less specific laboratory tests diagnostic for depression are not available. The interview should also result in a detailed list of target symptoms and therapy goals.

Care should be taken to rule out bipolar disorder, as treatment of a bipolar depressive episode is different than that of a unipolar depressive episode. In bipolar depression, antidepressant monotherapy is not recommended due to increased risk of cycling. Simple screening instruments such as the Mood Disorder Questionnaire can assist in identifying bipolar disorder.

Table 1-1. Antidepressant Drugs

Drugs	Dosage Forms	Dosage Range	Monitoring/ Counseling Points	Generic Available?
Selective Serotonin Reuptake Inhibitors				
Citalopram	Tablet, oral solution	20–60 mg/day		Yes
Escitalopram	Tablet, oral solution	10–20 mg/day		No
Fluoxetine	Tablet, capsule, oral solution	20–80 mg/day	Avoid use in hepatic impairment (long $t_{1/2}$)	Yes
Paroxetine	Tablet, controlled-release tablet, oral suspension	10–60 mg/day	Avoid abrupt discontinuation due to withdrawal syndrome	Yes
Sertraline	Tablet, oral solution	25–200 mg/day		Yes
Dual Reuptake Inhibitors				
Bupropion	Immediate-release tablet	300–450 mg/day (divided)	Contraindicated if seizure disorder or eating disorders	Yes
	Sustained-release tablet	150–400 mg/day (divided)		
	Extended-release tablet	150–300 mg/day		
Duloxetine	Delayed-release capsule	20–60 mg/day	May cause urinary hesitation Avoid in hepatic impairment Avoid with creatinine clearance less than 30 mL/minute	No
Venlafaxine	Tablet, extended-release capsule	75–300 mg/day	Monitor blood pressure; avoid abrupt discontinuation due to withdrawal syndrome	Yes
Novel Mechanism Agents				
Mirtazapine	Tablet, oral disintegrating tablet	15–45 mg/day	Give at bedtime; causes sedation	Yes
Nefazodone	Tablet	300–600 mg/day	Monitor liver function, signs of hepatic failure	Yes
Trazodone	Tablet	150–600 mg/day	Give at bedtime; causes sedation May cause priapism	Yes
Tricyclic Antidepressants				
Amitriptyline	Tablet	10–300 mg/day	May cause blue-green urine	Yes
Clomipramine	Capsule	25–300 mg		Yes
Desipramine	Tablet	10–300 mg/day	May cause blue-green urine	Yes
Imipramine	Tablet, capsule	10–300 mg/day		Yes
Nortriptyline	Capsule; oral solution	30–150 mg/day		Yes
Monoamine Oxidase Inhibitors				
Phenelzine	Tablet	60–90 mg/day divided		Yes
Selegiline	Transdermal patch	6–12 mg/day	Dietary restrictions for 9 mg and 12 mg patches	No
Tranylcypromine	Tablet	10–60 mg/day divided	More rapid onset than tricyclics	Yes

Once treatment is initiated, patients should be reassessed at weekly to biweekly intervals for at least 8 weeks to assess adherence, tolerability, and effectiveness. During the first week of therapy, sleep and appetite disturbances begin to improve, as well as executive functioning. By week 3, positive changes in energy, memory, and self-care appear. However, depressed mood and suicidality usually do not improve for at least 4 or more weeks. Clinicians should carefully monitor and address treatment-emergent adverse effects, such as anxiety, restlessness, and jitteriness, that may increase the risk of suicidal behavior.

Rating scales can be useful to assess the level of depressive symptoms or to measure change over time. Ratings used in clinical trials such as the Hamilton Rating Scale for Depression (HAM-D) and the Montgomery-Åsberg Depression Rating Scale are administered by trained personnel and require anywhere from 15 minutes to 30 minutes, limiting usefulness in routine care. Scales dependent on patient self-report such as the Beck Depression Inventory and the Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR) are easy to use and require minimal time commitment for clinicians. Patients may be given the rating scale upon check-in to the clinic, and have it completed before visiting with the clinician. Higher scores indicate increased severity of depressive symptoms. Treatment response requires at least a 50% reduction in score while remission is achieved with a QIDS-SR score of 5 or less, or a score of 10 or less on the Beck Depression Inventory.

Treatment for Depression

Antidepressant Drugs

Selective Serotonin Reuptake Inhibitors

Selective serotonin reuptake inhibitors (SSRIs) are the mainstay of antidepressant pharmacotherapy (Table 1-1). This is primarily due to their proven efficacy, as well as improved tolerability and general safety in overdose (i.e., minimal lethality) compared with older drugs. In addition, many drugs are available as a generic product, which are cheaper for patients. Although potentially anxiogenic during initiation of therapy, SSRIs are effective for anxiety symptoms. In patients with MDD and anxiety, doses should be initiated at 50% the typical starting dose to minimize the initial increased anxiety associated with SSRI therapy.

Selective serotonin reuptake inhibitors are generally well-tolerated as a drug class. Common adverse effects include nausea, headache, insomnia, hypersomnia, increased sweating, and sexual adverse effects, including decreased libido, anorgasmia, and delayed ejaculation. Depression can result in a decrease in sexual desire and potency, but is less commonly associated with anorgasmia. Changes in baseline sexual functioning can assist the clinician in determining causality. Although gastrointestinal distress and headache typically abate after a few weeks of therapy, other adverse effects may persist. Treatment-emergent sexual dysfunction may be relieved with 5-phosphodiesterase inhibitors. Alternative augmentation strategies include immediate-release bupropion dosed later in the day and the α_2-antagonist yohimbine. Drug holidays may also be considered; however, this strategy works best with drugs with a short elimination half-life. Drug holidays also put the patient at risk for discontinuation of symptoms. Switching to antidepressants with less propensity to cause sexual dysfunction (e.g., bupropion, nefazodone, and mirtazapine) should also be considered.

In addition to pharmacokinetic interactions (Table 1-2), SSRIs are also implicated in serotonin syndrome (Table 1-3), a potentially life-threatening condition related to excess 5-HT. The condition occurs when multiple serotonergic agents are combined in one regimen and is characterized by autonomic dysregulation, cognitive or mental status changes, and neuromuscular effects. It is

Table 1-2. Antidepressant Effects on the Cytochrome P450 Enzyme System

Isoform	Medication	Degree of Inhibition	Clinical Relevance
1A2	Fluvoxamine	Potent	Avoid concomitant administration with clozapine, warfarin, and methylxanthines
2C19	Fluoxetine	Moderate	Caution with concomitant warfarin because of increased risk of bleeding
	Fluvoxamine	Moderate	
2D6	Fluoxetine	Potent	Avoid or use with caution with concomitant medications solely metabolized by 2D6 (metoprolol)
	Paroxetine	Potent	
	Duloxetine	Moderate-potent	
	Bupropion	Moderate	
	Amitriptyline	Moderate	
	Escitalopram	Moderate	
	Citalopram	Weak-moderate	
	Sertraline	Weak-moderate (> 150 mg/day) Weak (< 100 mg/day)	
	Venlafaxine	Weak	
3A4	Nefazodone	Potent	Avoid HMG CoA reductase inhibitors except fluvastatin
	Norfluoxetine[a]	Weak-moderate	Unknown

[a]Norfluoxetine is a metabolite of fluoxetine.
HMG CoA = hydroxymethyl glutaryl coenzyme A.

Table 1-3. Drugs Associated with Serotonin Syndrome in Combination with Selective Serotonin Reuptake Inhibitors

Valproic acid
Meperidine
Fentanyl
Tramadol
Antiemetics (metoclopramide, ondansetron, and granisetron)
5-HT_{1D} agonists
Linezolid
Ritonavir
Dextromethorphan

5-HT = serotonin.

impossible to predict who will develop serotonin syndrome, as many patients are able to tolerate multiple serotonergic drugs. Pharmacists should instruct patients to discontinue serotonergic drugs and seek medical attention immediately should they develop symptoms of serotonin syndrome, including sweating, severe gastrointestinal distress, confusion, or muscle spasms.

Dual Reuptake Inhibitors

Available dual reuptake inhibitors have varying affinities for NE and 5-HT transporters. Because of their broader spectrum of activity, some believe these drugs are superior to SSRIs in efficacy. Although meta-analyses indicate that venlafaxine may be superior to SSRIs in both pooled response and remission rates in depression, this has not been demonstrated consistently in randomized, controlled trials.

Venlafaxine has preferential affinity for 5-HT transporters and only inhibits NE reuptake at doses of 150 mg/day or greater. Venlafaxine can cause a sustained increase in blood pressure, so vital signs should be monitored weekly at the beginning of therapy and after dosage increases. This risk of blood pressure elevation is dose-dependent and is more likely to occur at doses in excess of 300 mg/day. Because its elimination half-life is short, patients may experience withdrawal symptoms, including nausea, headache, vertigo, and electric shock sensations, if the drug is abruptly discontinued. There is a risk of serotonin syndrome when venlafaxine is combined with other serotonergic drugs.

Duloxetine has similar affinity for NE transporter and 5-HT transporter. The clinical relevance of this is unknown. This drug has been associated with increased liver enzymes and is not recommended in patients with hepatic insufficiency. Liver function tests should be monitored at baseline and periodically after initiation of therapy with duloxetine.

Bupropion is unique among antidepressants in that it has no direct effect on 5-HT. Instead, the medication inhibits dopamine and NE reuptake. In addition to depression, bupropion is useful in smoking cessation. Bupropion has minimal sexual adverse effects and is a reasonable alternative if sexual dysfunction is a concern. The drug is contraindicated in patients with eating disorders or a seizure disorder because of its propensity to lower the seizure threshold.

Tricyclic Antidepressants

Although tricyclic antidepressants (TCAs) are effective, they are not first-line antidepressant drug therapy because of their adverse effects and the potential to cause fatal overdoses. These drugs have a narrow therapeutic window, and signs of toxicity are fairly predictable based on the plasma concentration. Plasma concentrations may also be obtained to help guide therapy; nortriptyline especially has a well-characterized curvilinear dose-response, with response documented at plasma concentrations of 50–150 ng/mL. Because of their effects on cardiac conduction, TCAs should not be used in patients with severe cardiac disease or in those who have previously experienced a myocardial infarction.

Tricyclic antidepressants inhibit NE and 5-HT reuptake in the synaptic cleft in varying degrees. In general, tertiary amine compounds such as amitriptyline and imipramine preferentially affect serotonergic transmission; however, clomipramine is relatively selective for 5-HT and has minimal effect on NE transporter. Secondary amines such as desipramine are selective for NE reuptake. Although sedation, orthostasis, and anticholinergic effects occur, in general these are milder with the secondary amines.

Antidepressive Drugs with Novel Mechanisms

Mirtazapine is unique among antidepressants available in the United States. It exerts its antidepressant effects by inhibiting post synaptic 5-HT_{2A}, 5-HT_{2C}, and 5-HT_3 receptors. It also indirectly increases serotonergic transmission through antagonism of α_2-heteroreceptors. Mirtazapine is a potent histamine-1 (H_1) receptor antagonist, which accounts for its most common adverse effects of increased appetite, weight gain, and excessive sedation. Because of its effects at the 5-HT_2 receptor, mirtazapine is less likely to induce sexual dysfunction.

The phenylpiperazine nefazodone is an inhibitor of 5-HT transporter and may weakly block 5-HT_{1A} presynaptic auto-receptors, thus increasing 5-HT transmission both directly and indirectly. Nefazodone has potent inhibitory actions on 5-HT_{2A} receptors, which minimizes effects on sexual functioning and also provides antianxiety properties. Its primary adverse effects are sedation and orthostasis and are related to antagonism of H_1-receptors and α_1-receptors. Nefazodone is used as a second-line or third-line drug because of its association with hepatotoxicity and fulminant liver failure (1 per 250,000–300,000 patient-years). Liver function tests should be monitored at baseline and bimonthly for at least 1 year of therapy. Patients should be counseled on the signs and symptoms of liver toxicity, including abdominal pain, dark urine, and jaundice.

Trazodone has similar pharmacology to nefazodone; however, due to extreme sedation at antidepressant doses of 300 mg/day or greater, it is rarely used to treat depression. It is commonly used as a sleep agent at lower doses. Although rare, priapism has been associated with trazodone. Patients should be counseled on the risk of this adverse effect and instructed to stop the drug and either call their physician or go to the emergency department if experiencing a prolonged, painful erection.

Table 1-4. Potential Drug and Food Interactions with Monoamine Oxidase Inhibitors[a]

Drugs to Avoid	Foods and Beverages to Avoid
Over-the-counter products	Food Products
Any product containing pseudoephedrine or phenylephrine (nasal decongestants, cold, sinus, and allergy medications may contain these sympathomimetics)	Aged cheeses
	Air-dried, aged, or fermented meats, sausages or salamis
	Pickled herring
	Sauerkraut
Dextromethorphan	Fava beans and other broad bean pods
Herbal Products	Soy sauce
Diet pills containing stimulants	Tofu
Ephedra	Concentrated yeast extract
Ginseng	Any food that has spoiled or is improperly stored
Kava Kava	Beverages
SAMe	Tap beers
St. John's Wort	Non-pasteurized beer
Valerian	Chianti
Yohimbine	Vermouth
Prescription Products	
All sympathomimetics and stimulants	
Other antidepressant drugs[a]	
Fluoxetine[b]	
Local anesthetics containing ephedrine or cocaine	
Atomoxetine	
Buspirone	
Carbamazepine	
Cyclobenzaprine	
Levodopa and dopamine	
Meperidine	
5-HT_1 agonists (buspirone)	

[a]Should be avoided while taking monoamine oxidase inhibitors (MAOIs) and for 2 weeks after discontinuation of therapy.
[b]Should be avoided while taking MAOIs and for 5 weeks after discontinuation of therapy.
5-HT = serotonin; SAMe = 5-adenosylmethionine

Monoamine Oxidase Inhibitors

Monoamine oxidase inhibitors (MAOIs) act by blocking the actions of the enzyme monoamine oxidase (MAO), which is responsible for the breakdown of NE, 5-HT, dopamine, and epinephrine intracellularly.

Although MAOIs are effective, they have generally been relegated to patients with refractory depression because of required dietary restrictions (Table 1-4) as well as their potential to interact with a plethora of medications (both prescription and over-the-counter). There are two isoforms of MAO: MAO-A breaks down 5-HT, NE, and epinephrine, whereas MAO-B is selective for phenylalanine and benzylamine. Dopamine and tyramine are metabolized by both isoforms of MAO. The MAO-A that is located in the intestinal epithelium is responsible for the breakdown of tyramine and prevents its absorption. Inhibition of MAO-A allows for absorption of exogenous tyramine. Although the mechanism is not fully understood, it is widely believed that this absorbed tyramine displaces NE from storage vesicles in noradrenergic neurons. This may lead to excessive amounts of NE release and cause overstimulation of noradrenergic receptors, which in turn can trigger a hypertensive crisis and ultimately death.

Available oral drugs non-selectively inhibit both MAO-A and MAO-B. Tranylcypromine inhibits MAO reversibly, whereas phenelzine and isocarboxazid are irreversible inhibitors. Selegiline, which is used in the treatment of Parkinson's disease, irreversibly disables MAO-B at doses up to 10 mg/day. Selegiline is now available as a transdermal patch approved to treat MDD. Transdermal delivery allows for the bypass of first-pass metabolism as well as avoiding significant inhibition of the intestinal mucosal MAO. Transdermal selegiline allows for inactivation of both MAO-A and MAO-B in the central nervous system without increasing sensitivity to dietary tyramine.

Transdermal selegiline is available as 6, 9, and 12 mg/24-hour patches. Patches are replaced daily in accordance with standard transdermal patch etiquette. Dietary restrictions are not required for the 6 mg/24-hour dose, but there are dietary restrictions when the 9 mg and 12 mg/24-hour patches are being used. The risk for drug-drug interactions is similar to that of oral MAOIs, and precautions should still be followed. In clinical trials, the selegiline transdermal system demonstrated efficacy reflected by significantly higher rates of response compared with placebo in patients with MDD. However, its use in refractory depression has not been explored in the published literature.

Alternative Drugs

Over-the-counter products, most notably St. John's Wort (*Hypericum perforatum*), are available for treating depression. St. John's Wort is a dietary supplement with weak MAOI and serotonergic properties. Its efficacy in clinical trials has not been consistently demonstrated. In addition, its effects on cytochrome P450 3A4, 1A2, 2C9, and p-glycoprotein can lead to drug interactions. Significant interactions have been reported with digoxin, cyclosporine, and warfarin.

Other prescription drugs have been used in depression. Stimulants have been investigated as monotherapy, with both methylphenidate and dextroamphetamine demonstrating mixed results in open-label trials of medically ill patients. Pramipexole, a dopamine receptor agonist, showed significant improvement in depressive symptoms compared with placebo but not fluoxetine in a small, randomized, controlled trial; however, the results of that trial are limited by the small sample size. Aprepitant, a neurokinin-1 receptor antagonist approved for use as an antiemetic, was similar to paroxetine in effecacy in a randomized, controlled trial, but subsequent studies were unable to replicate these findings.

Nonpharmacological Alternatives

Vagal Nerve Stimulation

Chronic or recurrent depression not responding to antidepressant therapy can be treated with vagal nerve stimulation. The vagus nerve stimulator was approved in July 2005 as adjunctive long-term treatment of chronic or recurrent depression that has not responded to four adequate antidepressant drug trials. The device is not approved for use in patients under age 18.

The device is surgically implanted under the skin, and an electrical lead is connected from the device to the left vagus nerve. The vagus nerve receives mild electrical pulses in the neck, which are then sent to the brain. Implantation can be performed under general anesthesia in an outpatient setting. Ten or more weeks of treatment may be necessary for improvement in depressive symptoms. Other treatments, including pharmacotherapy and electroconvulsive therapy, should be continued while the patient is receiving vagal nerve stimulation.

Psychotherapy

Although treatment of depression primarily follows a drug model because of cost and time constraints, psychotherapy is still considered useful. Many studies confirmed the effectiveness of cognitive behavioral therapy. Other psychotherapeutic approaches, such as interpersonal therapy and group psychoeducation, can be beneficial. Combining psychotherapy with pharmacotherapy has not conclusively been shown to improve response rates in patients with depression, although a two-pronged approach may improve adherence or be useful in targeting specific symptoms.

Electroconvulsive Therapy

Electroconvulsive therapy is recommended for patients who have severe depression with psychosis or catatonia. In addition, electroconvulsive therapy is considered the treatment of choice in patients with severe suicidal ideation or those who refuse food. The procedure is considered safe, with risks similar to those of anesthesia. Adverse effects include confusion during the post-ictal period and anterograde amnesia. The therapeutic course typically consists of 6–12 treatments, followed by maintenance antidepressant or lithium therapy. Maintenance electroconvulsive therapy may be required.

Choosing an Antidepressant Drug

A multitude of pharmacotherapeutic options are available to treat depressive disorders, so selecting an initial antidepressant can be a daunting task. Several treatment guidelines are available to assist clinicians in choosing a drug, as well as in addressing a therapeutic failure or an incomplete response. The American Psychiatric Association and the Texas Department of State Health Services (Texas Medication Algorithm Project) have both published guidelines for the treatment of depression. These guidelines have not been updated since 2000, so newer drugs are not included.

Clinical trials have not shown one antidepressive drug to be more efficacious than another. In the National Institute of Mental Health-funded Sequenced Treatment Alternatives to Relieve Depression (STAR*D) effectiveness trial of depression in a real-world setting, those who failed or were intolerant to initial SSRI therapy had an equal likelihood of remission when switched to another SSRI compared with those who were given venlafaxine or bupropion. Thus, rather than superior efficacy in MDD, drugs are chosen based on differences in pharmacokinetics, drug-drug interactions (Tables 1-2 and 1-3), adverse effects, cost, available formulations, and patient preference. For patients previously treated for depression who suffer a recurrence, prior response to a drug is also an important factor.

Episodic Specifiers

Episodic specifiers can help direct clinicians to an appropriate drug regimen. Patients with psychotic features respond best to a combination of an antidepressant drug plus an atypical antipsychotic drug; monotherapy with either drug results in improvement in 30% of patients while the combination is effective in 70% of cases. Those with catatonic features will likely require adjunctive benzodiazepines to target motor disturbances. Patients with melancholic depression may respond better to TCAs than MAOIs and SSRIs. The opposite is true in patients who have depressive episodes with atypical features. These patients respond better to MAOIs versus TCAs. Selective serotonin reuptake inhibitors may also be more effective than TCAs in treating atypical symptoms. Selective serotonin reuptake inhibitors are still first-line treatment in both melancholic and atypical depression because of their improved safety and tolerability.

Pharmacokinetics

Fluoxetine can be used in patients with medication compliance issues because of its long elimination half-life. Its active metabolite, norfluoxetine, has a half-life of 7–9 days, and missed doses typically do not induce withdrawal symptoms. Partial adherence to therapy with

short half-life drugs such as paroxetine or venlafaxine can precipitate withdrawal symptoms, including nausea, headache, and jitteriness.

Drug Interactions

Many SSRIs, bupropion, and nefazodone have direct inhibitory effects on one or more enzymes of the cytochrome P450 system (Table 1-2). Venlafaxine, sertraline, and citalopram have minimal inhibitory actions on these enzymes and are reasonable alternatives when P450 substrates are present on a patient's medication profile. Pharmacodynamic drug-drug interactions at the 5-HT transporter can result in serotonin syndrome. Care should be given when adding drugs that block the 5-HT reuptake transporter to a regimen already containing proserotonergic drugs (Table 1-3).

The pharmacist plays an important role in providing education to prescribers on drug-drug interactions (including those that are clinically significant). Pharmacists can frequently advise the prescriber on appropriate drug choices to avoid significant interactions. If these drug choices are not viable options, the pharmacist can then help develop strategies to monitor for potential interactions, such as providing patient education on signs and symptoms to monitor.

Adverse Effects

The adverse effect profile of an antidepressant drug is essential to consider when developing a treatment regimen. Patients with a severe anxiety component to their illness may experience a worsening in their anxiety if they are given bupropion, which is generally more activating. Mirtazapine would not be an appropriate choice in individuals who are overweight or obese because of its appetite-stimulating properties. Hypersomnia and excessive fatigue can worsen when taking sedating antidepressant drugs, such as mirtazapine, nefazodone, or paroxetine. Drugs with prominent anticholinergic effects such as tertiary amine tricyclic drugs would not be ideal in those with narrow angle glaucoma, benign prostatic hypertrophy, chronic constipation, or cognitive impairment.

Duration of Treatment

Acute Phase

The acute phase begins at the start of therapy until the time symptoms remit, and usually lasts a minimum of 6–8 weeks. The acute phase should continue in patients with residual symptoms because of risk of relapse. Rather, these residual symptoms should be targeted aggressively to achieve resolution. Antidepressant drugs need to be taken for at least 4 weeks, but preferably 8 weeks, at an adequate dose before considering the drug a therapeutic failure and changing treatment.

More evidence is emerging to support waiting at least 8 weeks before deciding to switch or augment current therapy. In the STAR*D trial, more than 50% of the subjects who remitted upon receiving the first antidepressant drug did so after receiving antidepressant drugs for at least 8 weeks.

Continuation Phase

Antidepressant drugs should be continued at the same dose for an additional 16–20 weeks once remission is achieved to prevent relapse. Clinic visits may be further apart; some patients may be seen every 2–3 months during this therapy period based on patient and provider discretion. If symptoms recur, the patient's drug dosage should be maximized as tolerated before augmenting or switching to an alternative drug.

Maintenance Phase

Discontinuation of treatment can be considered in patients who complete the continuation phase. However, patients at risk for recurrence of symptoms should be considered for maintenance therapy, as well as those with a history of severe depressive episodes, including those with prior suicide attempts. Risk factors for recurrence include multiple prior episodes, residual depressive symptoms or dysthymia, comorbid psychiatric conditions, and chronic medical illness. Antidepressant drugs should be continued at the same dose used in the acute and continuation phase. Follow-up visits should occur every 2–3 months, depending on the clinical status of the patient. The required duration of maintenance therapy has not been well-studied. In general, maintenance therapy should be continued for at least 1 year, and potentially life-long, depending on the severity of the episode and risk factors for recurrence.

Definition of Response to Treatment

Response to antidepressant therapy is defined as a 50% reduction in symptoms from baseline and is the usual outcome measure in clinical trials of depression. However, response does not address the impact of residual symptoms and impaired functioning. Remission, which indicates complete resolution of depressive symptoms and return to premorbid functioning, should be the goal of treatment. Remission rates in 2-month clinical trials of SSRIs ranged from 25% to 40% and dropped to 22%–30% in studies of chronic depression. In STAR*D, only 28% of patients achieved remission after 12 weeks of initial antidepressant drug therapy. More and more studies are revealing that symptom remission often requires more than a single drug trial.

Results of the STAR*D trial revealed that in a generalizable population, predictors of remission of depressive symptoms included female gender, Caucasian race, having employment, and higher levels of education or income. Patients who failed to achieve remission typically had a longer duration of depressive episodes, comorbid psychiatric or medical disorders, and a lower functional status. Of note, treatment setting (psychiatric or primary care clinic) did not appear to affect response rates.

Strategies for Partial or Failure to Achieve Remission

Switching

After failure to achieve symptom remission with an antidepressive drug, clinicians may switch the patient to another antidepressant drug, frequently a drug with an alternative mechanism of action. However, clinical data indicate that staying within the same drug class may also be

effective. The STAR*D trial demonstrated that switching to drugs with alternate mechanisms of action did not result in higher remission rates than switching to a drug within the same drug class. Based on these findings, the choice of next antidepressant drug should be based on patient preference and the potential for drug interactions and adverse reactions, rather than alternate mechanism of action. Tapering of the initial drug may be required to minimize withdrawal symptoms.

Augmentation

An alternative to switching antidepressant drug therapies after failure to achieve remission is to initiate augmentation therapy. Augmentation involves adding an additional drug to improve the current therapy and it is typically recommended with a partial response to initial therapy. Traditionally, drugs with alternative mechanisms of action are combined with antidepressive drugs to improve symptom response. Lithium augmentation has been considered the gold standard for treating depression that fails to respond to monotherapies, but is limited by its narrow therapeutic index, adverse effects, and multiple drug interactions. Other drugs used to augment SSRIs include triiodothyronine, dopamine agonists, stimulants, atypical antipsychotics, mirtazapine, bupropion, and buspirone.

The STAR*D trial found that augmentation with bupropion or buspirone was equally effective, with nearly 30% of patients whose symptoms failed to respond to initial SSRI treatment achieving remission after an average of 5–6 weeks of augmentation therapy. Buspirone was not as well-tolerated as bupropion, but overall adverse effects were generally mild. The study also compared augmentation with triiodothyronine versus lithium in patients who failed to remit after two adequate antidepressant trials, with resulting similar remission rates. However, early discontinuation due to poor tolerability was higher with lithium.

Treatment in Special Populations

Depression During Pregnancy and Lactation

Pregnancy has traditionally been associated with a time of wellbeing, and has even been considered to provide a protective effect against psychiatric illness. Unfortunately, evidence to support these assumptions is lacking. Instead, women have been shown to be 1.7 times more likely than men to report a major depressive episode in their lifetime. Many of these depressive episodes will occur during the reproductive years, and proper antidepressant therapy to attenuate depressive symptoms and cause minimal harm to the fetus is essential.

Women may be reluctant to take antidepressant drugs during pregnancy, but there are risks of untreated depression during pregnancy. These risks include lower birth weights, lower Apgar scores, and preeclampsia. Infants born to mothers with depression have been shown to have lower cognitive skills and difficulty interacting as early as 2 months of age. Because of these potential risks associated with untreated depression, it is imperative to weigh the risks versus the benefits of drug therapy during pregnancy. Some instances where antidepressant therapy would be indicated include those where moderate to severe symptoms such as poor appetite or weight loss, inability to care for self, and suicidal ideations are present.

Because SSRIs are the foundation of antidepressant pharmacotherapy, understanding the risks associated with their use during pregnancy is essential (Table 1-5). As a drug class, SSRI use during late pregnancy has increased the risk of premature delivery, lower birth weight, and lower Apgar scores; however, maternal depression was not evaluated as a confounder. An FDA-issued public health advisory highlighted a 6-fold increased risk of neonatal persistent

Table 1-5. Antidepressant Drugs During Pregnancy and Lactation

Drug	Pregnancy Category	Findings in Pregnancy	Use During Lactation
Selective Serotonin Reuptake Inhibitors			
Fluoxetine	C	Higher rates of premature delivery	Present in breast milk
Paroxetine	D	Septal and atrial defects reported	Minimal/not present in breast milk
Sertraline	C	Least fetal exposure during maternal use	Low concentrations in breast milk
Citalopram	C	Greatest fetal exposure during maternal use	High concentrations in breast milk; not recommended
Escitalopram	C	Insufficient data	Insufficient data; not recommended
Novel Mechanism Agents			
Venlafaxine	C	Insufficient data	Low concentrations in breast milk
Duloxetine	C	Insufficient data	Insufficient data
Bupropion	C	Increased incidence of fetal malformations and skeletal variations in rabbits	Insufficient data
Mirtazapine	C	Insufficient data	Insufficient data
Nefazodone	C	Insufficient data	Present in breast milk; not recommended
Tricyclic Antidepressants (TCAs)			
Nortriptyline	C		Safest of TCAs during breastfeeding
Desipramine	C		Insufficient data
Amitriptyline	C	May cause infant cholinergic rebound	Risk of accumulation in the infant

pulmonary hypertension associated with SSRI use after the first 20 weeks of gestation. Finally, SSRI use during late pregnancy has been connected to a neonatal withdrawal syndrome characterized by convulsions, irritability, abnormal crying, and tremor.

Tricyclic antidepressants were historically considered unsafe to use in pregnancy due to sporadic reports of limb anomalies. This has been disproven, and TCAs currently represent an antidepressant drug class that has no known teratogenic characteristics. Of all the TCAs, nortriptyline or desipramine is recommended during pregnancy because they are the least anticholinergic, which reduces the incidence of cholinergic rebound in the infant. Cholinergic rebound can present as a variety of symptoms, such as jitteriness or irritability, to urinary retention or even functional bowel obstruction. One strategy to avoid this neonatal withdrawal syndrome is to discontinue TCA therapy several days before delivery is expected and restart the antidepressant drug after birth.

For pregnant women already receiving antidepressant drug therapy, discontinuation is not recommended due to a high rate of relapse. In a recent study, 68% of women who discontinued antidepressant drug therapy during pregnancy relapsed compared with only 26% of women who continued drug treatment. In addition, discontinuation of an antidepressant drug after delivery is not recommended due to the high rate of postpartum depression.

Depression in the Elderly

Many psychosocial changes such as the loss of loved ones, increased illness, and a decline in activities of daily living contribute to depressive symptoms in the elderly. Depression in this population is frequently overlooked. A prevalence rate of 1%–9% has been reported; however, wide variations exist between population subsets. In the elderly who are hospitalized or in long-term care facilities, depression rates may be as high as 50%.

Depression in the elderly may not manifest as sadness. An elderly patient with MDD may present with cognitive changes, including confusion and problems with memory. Insomnia, loss of appetite, and increased irritability can also occur. Accurate diagnosis and treatment is essential, as the elderly have a disproportionately high rate of suicide. The Prevention of Suicide in Primary Care Elderly: Collaborative Trial demonstrated that both SSRI treatment and interpersonal therapy are effective and faster interventions to decrease suicidal ideations.

The same strategies for managing depression in the general population are applied to the elderly, although several considerations should be made. Elderly patients may take longer to respond to pharmacotherapy for depression compared with younger patients. In addition, antidepressant drug doses should be initiated at lower doses and titrated more slowly because of increased patient sensitivity to medications. Antidepressant drug therapy should be carefully chosen to minimize drug interactions and adverse effects. Because the elderly typically are taking medications for multiple medical problems, the pharmacist's input is important in identifying drug interactions.

As in the general population, SSRIs remain first-line therapy in the elderly. Tricyclic antidepressants should be avoided in the elderly due to anticholinergic adverse effects. Mirtazapine, venlafaxine, or bupropion are viable options if medication change is needed. Augmentation is generally not favored due to the need to simplify drug regimens.

Because recurrence of depression is problematic in the geriatric population, long-term antidepressant drug therapy may be appropriate. Prolongation of treatment for as long as 2 years has been shown to prevent recurrence.

Depression in Children and Adolescents

Treatment of depression in the pediatric population can consist of psychotherapy (specifically cognitive behavioral therapy), pharmacotherapy, or a combination of both. The combination of psychotherapy and drugs is ideal, but it is limited by cost and lack of trained therapists. Insurance carriers either do not cover or provide limited coverage for therapy visits. Drug management may be provided by a patient's primary care physician, which is typically covered by insurance plans.

Many drugs lack a pediatric indication because of minimal or no data from randomized, controlled trials. Fluoxetine is the only antidepressant drug with an approved indication for MDD in children and adolescents. Sertraline and fluvoxamine are approved for use in pediatric patients with obsessive-compulsive disorder.

Suicide rates in the adolescent population increased through the 1980s and early 1990s, but epidemiologic research reveals a decrease in suicides over the past 10 years. This may be due to the increased recognition and treatment of depression in children and adolescents. However, significant controversy surrounds the use of antidepressant drugs in adolesents. All antidepressant drugs carry a black box warning for increased suicidality in children and adolescents based on the FDA's review of available clinical trial data after the Treatment for Adolescents with Depression Study revealed an increase in self-harm in those who took fluoxetine compared with those who did not take fluoxetine. The relationship between antidepressant drugs and suicidal thinking is unclear, but clinicians are cautioned to use clinical judgment when using these drugs. Some clinicians have speculated that treatment leads to improved motivation and energy, allowing for a suicide attempt. Others suggest that the drugs may cause akathisia, an extrapyramidal adverse effect, leading to increased agitation. The FDA strongly recommends good communication and frequent contact with patients to minimize the risk of suicide (Table 1-6).

Depression and Chronic Pain

Individuals with depression who experience significant somatic symptoms are frequently misdiagnosed and their depression remains untreated. People who are depressed are more likely to experience unexplained fatigue and pain, and use more health resources than others. In studies, the prevalence of pain in individuals who are depressed ranges from 15% to 100%. Pain severity is correlated with severity of depression, unemployment, and doctor visits. Residual somatic symptoms can prevent remission of depressive symptoms. Of the antidepressant drugs, only duloxetine has received an FDA indication for pain, specifically diabetic peripheral neuropathic pain; however, venlafaxine and

Table 1-6. FDA Recommendations for Monitoring Suicidality in Children and Adolescents

Upon initiation of an antidepressant, face-to-face contact should be made:
Once weekly for 4 weeks
Once every other week for 4 weeks
As clinically indicated beyond 12 weeks
Telephone contact between visits as needed
Daily monitoring by family or caregiver
Warning Signs include:
Anxiety and/or panic attacks
Agitation
Akathisia
Hypomania or mania
Aggressiveness
Behavioral changes
Impulsivity
Insomnia
Worsening of depression
Suicidality

bupropion have published data available indicating efficacy in this population. Although some research suggests that simply improving depressive symptoms with SSRIs can also improve pain, dual-acting drugs should be considered in patients with significant pain issues.

Patient Counseling

A pharmacotherapy regimen that includes any antidepressant drug should include several key counseling points. First, patients and families must be aware of antidepressant drug onset of action and that it may take 2–4 weeks before beneficial effects are noticed. Patients need to understand that the drug does not work as needed, and that it must be taken exactly as prescribed to have the desired effect. Educating the patient on duration of therapy, typically at least 6–9 months, will enhance his or her expectations. Patients should be instructed to continue taking the drug, even if symptoms improve, and that the drug should not be discontinued without alerting the provider. Table 1-1 outlines key counseling points for each antidepressant drug class. Patients and their caregivers should watch for signs of increased suicidal thinking, restlessness, activation, and dysphoria, especially during the first few weeks of therapy. If these occur, the patients should contact their provider as soon as possible. Comprehensive patient counseling, provided by a pharmacist, is essential to ensuring good adherence.

Women of childbearing potential should be informed of the risks and benefits of receiving antidepressant drug therapy during pregnancy. Patients should be counseled on possible effects of antidepressant drugs on a developing fetus, and birth control issues should be discussed. Females considering pregnancy should be strongly encouraged to discuss the options with their prescriber.

Conclusion

Depression is a common and serious illness frequently requiring pharmacological intervention. Fortunately, many antidepressive drugs are available. Factors that should be considered when choosing an antidepressant drug include pharmacokinetics, adverse effect profile, drug interaction potential, cost, and patient preference. Patients and their families may be referred to their local National Alliance for the Mentally Ill chapter for more information on depression, treatments, and support groups.

Annotated Bibliography

1. Mann JJ. The medical management of depression. N Engl J Med 2005;353:1819–34.

   This paper provides a comprehensive review of depression and its treatments. The author focuses on pharmacotherapeutic strategies to treat depression, but also briefly discusses the role of nonpharmacologic treatment modalities. A basic treatment algorithm is provided. Special populations, including pregnancy, pediatrics, and comorbid bipolar disorder are briefly reviewed. The article includes two informative tables of antidepressant drugs and augmentation strategies that provide detailed information regarding doses, safety, and risk of common adverse effects. A limitation of the paper is the lack of mention of bupropion and buspirone as augmentation strategies.

2. Sandson NB, Armstrong SC, Cozza KL. An overview of psychotropic drug-drug interactions. Psychosomatics 2005;46:464–94.

   The authors provide a general introduction of drug-drug interactions, and then describe the role of metabolic enzymes and the P-glycoprotein transporter system. Although this article is not limited to antidepressive drugs, their interaction potentials are provided in detail. The text description is somewhat limited in that clinical significance is not discussed. However, the interaction tables in the appendix contain the mechanism of the interaction, pharmacokinetic results, and clinical consequences.

3. American Psychiatric Association. Practice Guideline for the Treatment of Patients with Major Depressive Disorder, 2nd ed. Arlington, VA: American Psychiatric Association, 2000.

   The American Psychiatric Association guidelines are based on the best available data and clinical consensus. The guidelines easily relate to Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, as they are both produced by the American Psychiatric Association. Levels of confidence (though not levels of evidence) are documented for each recommendation. The document is extensive and details a multidisciplinary approach to the treatment of depressive disorders. Rather than just pharmacotherapy, these guidelines provide recommendations for patient assessment, including suicide risk, psychotherapeutic approaches, and treatment settings. The first half of the text provides specific treatment recommendations while the second part focuses on levels of evidence to support the guidance provided in the earlier section. References are cited and listed, which gives clinicians the opportunity to pull specific articles if desired. Updates to

the guidelines are available on the American Psychiatric Association Web site (*www.psych.org*).

4. Fochtmann LJ, Gelenberg AJ. Guideline Watch: Practice Guideline for the Treatment of Patients with Major Depressive Disorder, 2nd ed. Arlington, VA: American Psychiatric Association, 2005.

   This watch was meant as an update to the current American Psychiatric Association guidelines for major depression. Recent information on medication toxicities including the risk of hepatotoxicity with nefazodone, as well as new antidepressant drugs are contained in the watch. In addition, recent data on depression treatment in the elderly are included. Although approved by the American Psychiatric Association's executive committee on practice guidelines, the update did not go through the same rigorous process as the full guidelines, and the information provided represents the expert opinion of the authors.

5. Trivedi MH, Shon S, Crismon ML, Key T. Texas Implementation of Medication Algorithms (TIMA)-Guidelines for Treating Major Depressive Disorder: TIMA Physician Procedural Manual. Texas Department of State Health Services [updated 12/2000]. Available at *http://www.dshs.state.tx.us/mhprograms/TIMA.shtm*. Accessed May 21, 2007.

   These guidelines are specific and address antidepressant drug treatment at each decision point, from the choice to initiate treatment, to switching to an alternative antidepressant, to consideration of electroconvulsive therapy, to treatment discontinuation. Each treatment is discussed in detail, and appropriate time frames for therapy are included. The algorithm diagrams are provided for both psychotic and non-psychotic depression and are easy to follow. Simple "algorithm at a glance" cards are also included and are extremely useful. Monographs for all antidepressant and augmentation drugs available at the time of publication are provided. Special populations such as women who are pregnant, pediatric patients, and elderly patients are not addressed in the guidelines. The biggest limitation of these guidelines is that the last update was in 2000, and newer data are not included.

6. Amsterdam JD. A double-blind, placebo-controlled trial of the safety and efficacy of selegiline transdermal system without dietary restrictions in patients with major depressive disorder. J Clin Psychiatry 2003;64:208–14.

   A transdermal system of selegiline was developed to bypass intestinal and hepatic monoamine oxidase and thus allow targeted MAO-A inhibition with minimal sensitivity to dietary tyramine. This study examined the safety and efficacy of transdermal selegiline without dietary restrictions. The investigators randomized 301 patients with moderate to severe depression to either a selegiline patch 20 mg/cm^2 or placebo and performed assessments for up to 8 weeks. Dietary restrictions were neither required nor advised. Patients receiving selegiline achieved lower HAM-D_{28} and Montgomery-Åsberg Depression Rating scores at end point, and more patients were considered responders in the selegiline arm. However, there was no significant difference in the primary outcome measure of HAM-D_{17} scores at end point. More patients receiving selegiline experienced localized skin reactions, but there were no differences in hypotensive episodes or sexual adverse effects. There were no reports of hypertensive reactions during the study. Although symptom response was modest at best compared to placebo, selegiline transdermal at 20 mg/cm^2 (6 mg/24 hours) appears to be safe without dietary restrictions.

7. Trivedi MH, Rush AJ, Wisniewski SR, Nierenberg AA, Warden D, Ritz L, et al; STAR*D Study Team. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. Am J Psychiatry 2006;163:28–40.

   The National Institute of Mental Health funded the STAR*D trial in an effort to determine what to do when depression fails to respond to a standard trial of treatment with an antidepressant medication. This publication details the first level of the study. Outpatients with a depressive disorder seeking medical care were recruited. Minimal exclusion criteria were used to maximize generalizability. Enrolled patients received open-label, flexible-dose citalopram, titrated to 60 mg/day for a maximum of 14 weeks, at 41 primary care and psychiatric centers. Clinician treatment was guided by a detailed procedural manual to improve consistency between sites. The end points were remission, intolerability, or failure to reach remission after 9 weeks at the maximally tolerated dose. Assessments were performed over the telephone by raters blinded to treatment. Out of 4790 patients screened, 2876 depressed outpatients were included in the analysis. The authors had predicted a 40% remission rate, but only 27.5% actually achieved this end point. Of patients with remission, 40.3% achieved remission after 8 weeks of therapy. A total of 1475 subjects moved to first level follow-up after achieving either response or remission, though responders were encouraged to enter level two rather than the continuation phase. The results demonstrate the difficulty of achieving remission in a real-world setting. The study also reveals the need to treat for an adequate duration before deeming therapy a failure. The study duration was longer than other depression trials, which were typically 6 weeks long. Because clinicians were not blinded to treatment assignment, they may have felt more comfortable increasing dosage rather than having subjects advance to the next level. The patient population was more indicative of real-world situations, as patients with comorbid conditions including personality disorders were included.

8. Rush AJ, Trivedi MH, Wisniewski SR, Stewart JW, Nierenberg AA, Thase ME; STAR*D Study Team. Bupropion-SR, sertraline, or venlafaxine-XR after failure of SSRIs for depression. N Engl J Med 2006;354:1231–42.

   Level two of the STAR*D trial consisted of two pathways: augmentation or switch. This article details the antidepressant switch arm. Of the 1439 patients who enrolled in level two, 727 were randomized to a switch alternative. Patients who did not achieve remission with (n=320; 44%) or were intolerant (n=407; 56%) to citalopram monotherapy were randomized to receive sustained-release bupropion 400 mg/day, extended-release venlafaxine 375 mg/day, or sertraline 200 mg/day for up to 14 weeks in an equipoise fashion: patients were allowed to choose which treatment arms were acceptable and which were not. For example, a subject could refuse to be randomized to another SSRI (sertraline) but agree to sustained-release bupropion or extended release venlafaxine. Similar to level one, treatments were flexible-dose and unblinded to the clinicians, but raters were blinded to treatment. Citalopram was stopped without tapering, but the alternative drugs were titrated up more than

6–9 weeks. At the end of the study, HAM-D_{17} remission rates did not differ between treatment groups, with venlafaxine at 24.8%, bupropion 21.3%, and sertraline 17.6%. Similarly, time to remission did not differ significantly (p=0.16). This study supports the use of switching to an alternate SSRI if a therapeutic failure occurs with the initial therapy, rather than immediately labeling an episode SSRI-resistant. A limitation of the study was the slow titration schedule used for initiating the second antidepressant. Therapeutic antidepressant doses were not achieved until 4 weeks into therapy, despite the fact that citalopram was not tapered.

9. Trivedi MH, Fava M, Wisniewski SR, Thase ME, Quitkin F, Warden D; STAR*D Study Team. Medication augmentation after the failure of SSRIs for depression. N Engl J Med 2006;354:1243–52.

This article details the alternate option for level two of STAR*D, in which patients were randomized in an equipoise fashion to receive augmentation to their current citalopram therapy. A total of 565 patients who received citalopram for a mean duration of 11 weeks but failed to achieve remission were randomized to either flexible-dose sustained-release bupropion (n=279) or buspirone (n= 86) in addition to citalopram therapy (mean dose 55 mg) for up to 14 weeks. Target doses for bupropion and buspirone were 400 mg and 60 mg, respectively, by week 6. Similar to level one, treatments were flexible-dose and unblinded to the clinicians, but raters were blinded to treatment. Remission rates using HAM-D17 were similar between bupropion and buspirone (29.7% vs. 30.1%; p=0.93). Significantly more patients receiving buspirone discontinued treatment due to adverse effects (p<0.0009). There has been much discussion comparing the results of the augmentation study to those of the switch study described above. Remission rates appear higher in the augmentation arm, and the question now posed is whether augmentation should be preferred over switching to an alternative agent. Caution should be used when comparing these studies. A key factor in the apparently higher rates of remission with the switch study may have been the immediate discontinuation of citalopram and slow titration of the second antidepressant. Further analysis should be completed before recommending one strategy over another.

10. Eberhard-Gran M, Eskild A, Opjordsmoen S. Treating mood disorders during pregnancy: safety considerations. Drug Safety 2005;28:695–706.

This article summarizes the safety concerns of treating mood disorders during pregnancy. Psychotropic drugs were evaluated according to teratogenicity, neonatal effects, and long-term neurobehavioral effects. The authors review pharmacokinetic changes during pregnancy that can affect efficacy and dosing. A highlight of the article is the review of principles of treatment during pregnancy and the importance of considering nonpharmacological treatment. Safety of antipsychotic drugs was discussed, a topic frequently overlooked in review articles examining treatment of maternal depression. General practitioners should use this resource as a brief, understandable article summarizing the safety considerations of treating mood disorders during pregnancy.

11. Chambers CD, Hernandez-Diaz S, Van Marter LJ, Werler MM, Louik C, Jones KL, et al. Selective serotonin-reuptake inhibitors and risk of persistent pulmonary hypertension of the newborn. N Engl J Med 2006;354:579–87.

This case-control study examined the association of SSRI use after the 20th week of gestation and persistent pulmonary hypertension in neonates. This study tested the hypothesis that maternal use of SSRIs was a risk factor for pulmonary hypertension in neonates. Data were collected from the Slone Epidemiology Center Birth Defects Study and infants with pulmonary hypertension in neonates between 1998 and 2003 were identified. Infants were defined as having pulmonary hypertension in neonates if gestational age was more than 34 weeks and they had a presentation of severe respiratory failure shortly after birth. A total of 337 infants with confirmed pulmonary hypertension in neonates were matched to 836 controls, according to hospital and date of birth. The results showed that infants exposed to SSRIs after the 20th gestational week were 6.1 times more likely to have pulmonary hypertension in neonates. A limitation of this study is recall bias. Mothers who give birth to infants with significant health problems are more likely to recall and report possible explanations for adverse outcomes. Finally, a higher proportion of males were included in the pulmonary hypertension in neonates group (63.4%) compared with the control group (49%); male sex has been identified as an independent risk factor for pulmonary hypertension in neonates.

12. Cohen LS, Altshuler LL, Harlow BL, Nonacs R, Newport DJ, Viguera AC, et al. Relapse of major depression in women who maintain or discontinue antidepressant treatment. JAMA 2006;295:499–507.

This prospective, longitudinal cohort study examined the risk of major depression relapse as defined by DSM-IV. Women less than 16 weeks pregnant were eligible if they had a history of major depression, were currently or recently on antidepressant therapy and were euthymic for 3 months before pregnancy. Subjects were characterized according to the following: maintaining antidepressant therapy for the entire pregnancy, antidepressant discontinuation lasting 1 week, a decrease from optimal dose, or an increase from optimal dose. The study results indicate women who increased or discontinued antidepressant therapy had a shorter time to relapse than those that maintained or decreased antidepressant doses. Women who discontinued their medication were 5 times more likely to relapse during pregnancy then women who continued drug therapy. A possible limitation is that participating sites specialized in psychiatric illness during pregnancy. This population may be more likely to relapse than women in a general, primary care setting, so results may be skewed.

13. Bruce ML, Ten Have TR, Reynolds CF 3rd, Katz II, Schulberg HC, Mulsant BH, et al. Reducing suicidal ideation and depressive symptoms in depressed older primary care patients: a randomized, controlled trial. JAMA 2004;291:1081–91.

The authors conducted a randomized, controlled trial that examined the effect of a primary care intervention (citalopram or interpersonal therapy) versus usual care on depression and suicidal ideation in the elderly. The author's main conclusion was that the patients who received the intervention got well sooner than those whom received the usual care. There was a significant reduction in suicidal ideation among those with major depression; however, this study did not show that an intervention, based on an algorithm that included

antidepressant therapy or psychotherapy, was effective in reducing suicidal ideation in minor depression. The clinical significance of the results should be considered as the difference of HAM-D scores between the usual care and intervention groups had a small effect size.

14. Hammad TA, Laughren T, Racoosin J. Suicidality in pediatric patients treated with antidepressant drugs. Arch Gen Psychiatry 2006;63:332–9.

    Increasing concern of the potential for increased suicidality with antidepressant use in children and adolescents led the FDA to review all placebo-controlled antidepressant trials in pediatric patients to examine the relationship between the medications and suicide-related events. The analysis included 4582 patients in 24 trials for depression, obsessive-compulsive disorder, generalized anxiety disorder, social phobia, and attention deficit/hyperactivity disorder. One hundred nine events were included in the analysis. When all trials were pooled together, the relative risk for suicidality was significantly higher with antidepressant therapy (risk ratio = 1.95; 95% confidence interval = 1.28–2.98). The only individual trial with an increased risk for suicidal behavior was the Treatment for Adolescents with Depression Study. The authors provide a thorough discussion of study limitations, including concern with post hoc analyses, the use of short-term data, the lack of fixed-dose trials, and the role of antidepressant drug discontinuation. In addition, clinical applicability of the results is presented as recommendations by the FDA. These results further reiterate the importance of weighing risks versus benefits of antidepressant therapy in each specific case as well as careful monitoring and close followup after initiation of treatment.

15. March J, Silva S, Petrycki S, Curry J, Wells K, Fairbank J, et al; Treatment for Adolescents With Depression Study (TADS) Team. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents with Depression Study (TADS) randomized, controlled trial. JAMA 2004;292:807–20.

    The objective of the National Institute of Mental Health-funded Treatment for Adolescents With Depression Study was to evaluate the effectiveness of fluoxetine and cognitive behavioral therapy, alone and in combination, in the treatment of MDD in adolescents. Four hundred thirty-nine adolescent outpatients diagnosed with MDD were randomized to receive fluoxetine, cognitive behavioral therapy, fluoxetine/cognitive behavioral therapy combined, or placebo for 12 weeks. The combination was more efficacious compared with either treatment modality alone as well as placebo. Although there was no difference in suicide-related adverse events, more harm-related events occurred with fluoxetine compared with no fluoxetine. This study sparked controversy over increased suicide risk with SSRIs in this population. What is often overlooked is that in this study suicidality overall improved with any treatment.

16. Bair MJ, Robinson RL, Katon W, Kroenke K. Depression and pain comorbidity: a literature review. Arch Intern Med 2003;163:2433–45.

    In this review, the authors searched for human studies using the search terms depression or depressive disorders and pain, limited to English language. Studies were excluded if they addressed pain related to a specific disease or syndrome. A meta-analysis was not performed on the data because of significant heterogeneity between studies. The researchers found a strong correlation between depression and pain, with 65% of those with depression also had pain complaints while 5%–85% of patients with pain had depression. The presence of pain also decreases the likelihood of providers recognizing depression and providing treatment. Pain worsens depression outcomes while depression decreases the likelihood of improvement of pain. Adequate treatment of depression may improve pain in some patients. The authors mention the theoretical benefit of antidepressive drugs acting on both NE and 5-HT in improving both depression and pain, although they do not discuss these studies in any detail. Eli Lilly, the pharmaceutical company that manufactures duloxetine marketed for depression with painful symptoms, served as a source of funding for this review. Although the majority of the authors had some affiliation with Eli Lilly, this review did not appear biased as specific medications were not discussed.