Major Depressive Disorder

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Learning Objectives

1. Using knowledge of therapeutic effects, adverse effects, and antidepressant drug interactions, devise an optimal pharmacotherapeutic treatment regimen for a patient with major depressive disorder.
2. Justify duration of pharmacotherapy for a patient with depression using available knowledge of relapse risk.
3. Analyze potential drug-drug and drug-food interactions with antidepressants and describe both their mechanism and clinical significance.
4. Develop augmentation strategies to add to pharmacologic regimens in patients with depression who have not responded to monotherapy.
5. Apply depression guidelines to a specific patient case.
6. Recommend treatments for depressive disorders in special populations such as children, adolescents, and the elderly.

Introduction

Epidemiology

Depression continues to be one of the most prevalent of all medical illnesses and remains a major concern worldwide. In the United States in 2005, the 12-month prevalence of major depressive disorder (MDD) in adults was 6.7%; of those adults, 30.4% had severe illness. It is estimated that 32–35 million American adults will experience MDD during their lifetime. Despite being recognized as a major health concern, depression is often overlooked in the clinical setting.

Factors associated with an increased risk of MDD include female sex, middle age, single marital status, white (non-Hispanic) race, low economic status, unemployment, and physical disability. Comorbidity with other psychiatric conditions is the rule rather than the exception; in one survey, two-thirds of those with MDD had at least one concurrent disorder recognized in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed., text revision (DSM-IV, TR). Depression is commonly associated with medical comorbidities and often is a predictor of increased morbidity and mortality.

Economic Impact

The estimated direct cost of depression in the United States is $26 billion annually. Workers with depression cost employers more than $30 billion per year in lost productivity. The World Health Organization has calculated adjusted life-years for the disorder in the United States and Canada; on the basis of these calculations, a diagnosis of depression is associated with greater disability than a diagnosis of ischemic heart disease.

Pathophysiology

The exact biologic mechanisms of depressive disorders remain unknown. Original theories were developed

Baseline Review Resources

The goal of PSAP is to provide only the most recent (past 3–5 years), updated information or topics. Chapters do not provide an overall review. Suggested resources for background information on this topic include:

- Gaynes BN, Rush AJ, Trivedi MH, Wisniewski SR, Spencer D, Fava M. The STAR*D study: Treating depression in the real world. Cleve Clin J Med 2008;75:57–66.
- Teter CJ, Kando JC, Wells BG. Major Depressive Disorder. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, et al, eds. Pharmacotherapy: A Pathophysiologic Approach, 8th ed. New York: McGraw-Hill, 2011.
- Diagnostic and Statistical Manual of Mental Disorders (4th ed., text revision). Chapter 6: Mood disorders. Arlington, VA: American Psychiatric Association, 2000.

Abbreviations in This Chapter

CBT	Cognitive behavior therapy
CO-MED	Combining Medications to Enhance Depression Outcomes
ECT	Electroconvulsive therapy
MAOI	Monoamine oxidase inhibitor
MDD	Major depressive disorder
NIMH	National Institute of Mental Health
QIDS-SR	Quick Inventory of Depressive Symptomatology – Self Report
SGA	Second-generation antipsychotic
SNRI	Serotonin norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
STAR*D	Sequenced Treatment Alternatives to Relieve Depression
TADS	Treatment for Adolescents with Depression Study
TCA	Tricyclic antidepressant
TMS	Transcranial magnetic stimulation

on the basis of physiologic responses to drug actions on neurotransmitter systems in the central nervous system. The monoamine hypothesis was developed after it was found that reserpine-induced monoamine depletion from neuronal synapses was associated with depressive symptoms, and repletion of these same neurotransmitters led to symptom resolution. All currently available antidepressant drugs act primarily by increasing synaptic neurotransmitter concentrations. Clinically, this increase in neurotransmitter concentrations occurs within hours after taking antidepressant drugs; however, the response time to antidepressant therapy is much longer.

Chronic stress is another proposed model for MDD. Stress leads to the increased secretion of glucocorticoids. These hormones, in turn, deplete neurons of brain-derived neurotrophic factor, which leads to a decrease in neurogenesis in the hippocampus. Animal models indicate that all antidepressant treatments lead to increased neuronal cell proliferation in the hippocampus. Future drug targets for depression will likely include corticotropin-releasing hormone, glucocorticoids, γ-aminobutyric acid, and glutamate.

Depression is heritable, as revealed by family studies, although the specific genes involved have yet to be definitively identified. However, environmental stressors also contribute to the development of the disorder. Depressive episodes may often be precluded by life stressors. Depression that occurs after significant events such as death of a family member may still benefit from pharmacotherapeutic interventions.

Diagnosis

Formal criteria for a major depressive episode have been outlined in the DSM-IV, TR. First, either depressed mood or loss of interest in almost all activities (anhedonia) must be present for the diagnosis. Second, at least four other symptoms must be present, or three if the patient has both anhedonia and depressed mood. These symptoms are 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 2 weeks and cannot be directly attributable to substance ingestion or other medical issues. Patients may also present with vague somatic complaints such as headaches, muscle pains, or gastrointestinal ailments. Symptoms such as these that do not respond to appropriate medical treatment suggest a possible depressive disorder and a need for evaluation for depression.

Major depressive disorder is characterized by one or more major depressive episodes with no history of manic, hypomanic, or mixed affective episodes. Major depressive disorder can be further classified by severity of illness and the presence or absence of clinical features of the current mood episode. Clinicians should carefully document these specifiers, which can alter treatment decisions. Severity of the current episode can help determine whether it can be treated with psychotherapy alone or whether pharmacotherapy is required. Features of the episode are likewise important; for example, depression with psychotic features must be treated with combination antidepressant and antipsychotic therapy.

Severity of MDD is determined by the number of symptom criteria met, the severity of the symptoms present, and the degree of functional impairment. Episodes with five or six depressive symptoms and minimal functional impairment are classified as mild, whereas severe episodes have almost all symptoms present with significant impairment in functioning. In contrast, dysthymic disorder is characterized by chronic depressed mood for at least 2 years without a symptom-free period 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 may only be given if no major depressive episodes occur during the initial 2-year period.

Major depressive disorder is considered in full remission when significant symptomatology has been absent for at least 2 months. Partial remission is defined as the continued presence of some depressive symptoms (i.e., either full criteria for MDD are not met or symptoms

are absent for less than 2 months). Response is defined as a 50% reduction in symptoms from baseline.

Course of Illness

The course of MDD varies from patient to patient. The typical age of onset is the late 20s, but depression can develop at any age. Of those who go through a depressive episode, 50% to 85% will suffer another bout of depression. This risk increases with each additional episode (i.e., 70% after two episodes, 90% after three). Between depressive episodes, functioning usually returns to baseline; however, in 20% to 35% of cases, residual symptoms remain, with persistent impairment in social and/or occupational functioning. Individuals with dysthymia and comorbid MDD are more likely to experience recurrence than are those with MDD whose symptoms remit. Other risk factors for MDD recurrence are concurrent chronic medical problems and additional psychiatric diagnoses.

Treatment and prevention of future depressive episodes is imperative because the lifetime risk of suicide is estimated to be 10% to 15% in those with mood disorders. Suicide is a lethal outcome of depression, and suicide risk should be assessed at every visit during treatment. Suicide was the 10th leading cause of death in 2007 in the United States, with almost 35,000 deaths; 90% of those had a diagnosis of depression or other mental disorder, including substance abuse. For every 11 suicide attempts, there is one completion.

Treatment Options

The patient presenting with depressive symptoms should be interviewed thoroughly to obtain a complete medical, family, and psychiatric history, including previous hospitalizations and suicide attempts. The pharmacist should obtain a list of current medications, including prescription, herbal, dietary, over-the-counter products, as well as previous and current psychotropic medications and response to each. Use of medications that may contribute to depressive symptoms should be determined. The patient should undergo physical examination and laboratory assessment including complete blood cell count, serum chemistries, and thyroid panel to rule out medical causes of depression. A psychiatric evaluation including a mental status examination should exclude other psychiatric disorders (e.g., bipolar disorder). The interview should also result in a detailed list of target symptoms and goals of therapy. A safety plan that consists of appropriate interventions for suicidal ideation or behaviors should be developed with the patient.

Once treatment is initiated, the patient should be reassessed weekly or biweekly for at least 8 weeks for adherence and medication tolerability and effectiveness. During the first week of therapy, sleep, appetite disturbances, and executive functioning begin to improve. 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 weeks or longer. The clinician should carefully monitor and address treatment-emergent adverse effects such as anxiety, restlessness, and jitteriness that may increase the risk of suicidal behavior.

Pharmacotherapy

Antidepressant Drugs

Although other treatment modalities are available, antidepressant pharmacotherapy remains the mainstay of treatment. A wide range of classes of antidepressant drugs exists from which to choose (Table 1-1). Because of their improved safety and tolerability, newer antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) are preferred as initial therapy to older agents such as tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs). The MAOIs are associated with potentially fatal drug-food and drug-drug interactions and should not be used with serotonergic or sympathomimetic agents. Moreover, MAOIs cannot be used in combination with other antidepressants for treatment-refractory MDD.

In 2008, two new antidepressants were approved as monotherapy. Desvenlafaxine, the active *O*-desmethyl metabolite of venlafaxine, received U.S. Food and Drug Administration (FDA) label approval for the treatment of MDD. Similar to the parent compound venlafaxine, desvenlafaxine exerts greater affinity for the serotonin transporter than the norepinephrine transporter, though the clinical significance of this is unknown. The recommended daily dosage is 50 mg, but it may be increased to a maximum of 400 mg. Of note, daily dosages above 50 mg led to increased adverse effects and early termination of therapy in subjects in clinical trials but did not confer additional therapeutic benefit. Dosages should be reduced in patients with reduced kidney function or hepatic impairment. Common adverse effects include nausea, dizziness, hyperhidrosis, constipation, decreased appetite, anxiety, and sexual dysfunction in men (specifically, erectile dysfunction, delayed ejaculation, and anorgasmia). Desvenlafaxine differs from venlafaxine in its minimal dependence on cytochrome P450 (CYP) 2D6 for metabolism; increased concentrations of venlafaxine and decreased concentrations of metabolite were found in 2D6 poor metabolizers. The clinical significance of this is also unknown.

Vilazodone, a serotonin reuptake inhibitor and serotonin 1A partial agonist, received FDA-approved labeling in 2011 for the treatment of MDD. Registration trials show efficacy equal to SSRIs. The concept for the dual-action antidepressant was based on a theoretical faster onset of therapeutic response through modulation of the serotonin 1A receptor. More research is required to test this theory. A 2-week titration period is required to

Table 1-1. Antidepressant Medications

Medication	Dosage Forms	Usual Dosage Range (mg/day)	Monitoring/Counseling Points	Generic Available?
Selective Serotonin Reuptake Inhibitors				
Citalopram	Tablet, oral solution	20–40	ECG. Mg+ and K+ depletion causes QTc prolongation	Yes
Escitalopram	Tablet, oral solution	10–20		No
Fluoxetine	Tablet, capsule, oral solution	20–80	Avoid use in hepatic impairment (long t1/2)	Yes
Paroxetine	Tablet, controlled-release tablet, oral suspension	10–60	Avoid abrupt discontinuation because of withdrawal syndrome	Yes
Sertraline	Tablet, oral solution	25–200		Yes
Dual Reuptake Inhibitors				
Bupropion	Immediate-release tablet	300–450 (divided)	Contraindicated in seizure disorder or eating disorders	Yes
	Sustained-release tablet	150–400 (divided)		Yes
	Extended-release tablet	150–300		
Duloxetine	Delayed-release capsule	20–60	May cause urinary hesitation Avoid in hepatic impairment Avoid with chronic alcohol use Avoid with creatinine clearance less than 30 mL/minute	No
Venlafaxine	Tablet, extended-release capsule, sustained-release tablet	75–300	Monitor blood pressure Avoid abrupt discontinuation because of withdrawal syndrome Sustained release is ghost tablet	Yes
Desvenlafaxine	Tablet, extended release	50–400	Avoid abrupt discontinuation because of withdrawal syndrome	No
Novel Mechanism Agents				
Mirtazapine	Tablet, orally disintegrating	15–45	Causes significant sedation May increase triglycerides Monitor weight	Yes
Nefazodone	Tablet	300–600	Monitor liver function, signs of hepatic failure	Yes
Trazodone	Tablet	150–600	Give at bedtime; causes sedation May cause priapism	Yes
Vilazodone	Tablet	20–40	Must take with food for adequate absorption	No
Common Tricyclic Antidepressants				
Amitriptyline	Tablet	10–300	May cause blue-green urine	Yes
Desipramine	Tablet	10–300	May cause blue-green urine	Yes
Imipramine	Tablet, capsule	10–300		Yes
Nortriptyline	Capsule; oral solution	30–150		Yes
Monoamine Oxidase Inhibitors				
Phenelzine	Tablet	60–90 (divided)	Required medication and dietary restrictions	Yes
Selegiline	Transdermal patch	6–12	Dietary restrictions for 9-mg and 12-mg patches Medication restrictions	No
Tranylcypromine	Tablet	10–60 (divided)	More rapid onset than tricyclics Required medication and dietary restrictions	Yes
Isocarboxazid	Tablet	20–60 (divided)	Required medication and dietary restrictions	Yes

ECG = electrocardiography.

achieve the target 40-mg daily dosage. The agent must be taken with food for adequate absorption. No dosage adjustments are required for patients with hepatic or kidney function impairment. The effects of severe hepatic impairment on drug dosing have not been evaluated. The most common adverse effects are diarrhea, nausea, vomiting, and insomnia. The incidence of sexual dysfunction was not significantly different from placebo. Vilazodone is metabolized by CYP3A4, and dosage adjustments are required in the presence of CYP3A4 inhibitors.

In addition to pharmacokinetic interactions (Table 1-2), serotonergic antidepressants in general are implicated in serotonin syndrome, a potentially life-threatening condition related to excess serotonin. The condition occurs when several serotonergic agents are combined in one regimen. The syndrome is characterized by autonomic dysregulation, cognitive or mental status changes, and neuromuscular effects. Patients should be cautioned to look for symptoms of this syndrome when taking concomitant serotonergic agents, including triptans for abortive migraine therapy. Box 1-1 lists non-antidepressant drugs associated with serotonin syndrome.

Serotonergic antidepressants (specifically, TCAs and SSRIs) have also been associated with increased risk of gastrointestinal hemorrhage. The risk is further increased with the concomitant use of aspirin, nonsteroidal anti-inflammatory drugs, and anticoagulants. This phenomenon is believed to be related to activity at the serotonin transporters on circulating platelets, which leads to impaired platelet aggregation. Prolonged exposure to serotonergic antidepressants has also been associated with decreased bone mineral density and increased fracture rate, although causality cannot be determined. It is unclear whether the effect is related to depression, the drugs, or a combination of both. These issues should be considered when prescribing antidepressant therapy, especially for a prolonged duration.

A recent study found that the SSRI citalopram was associated with prolonged QTc interval in a dose-dependent fashion, with a daily dosage of 60 mg associated with

Box 1-1. Non-antidepressant Medications Associated with Serotonin Syndrome

- Antiemetics (metoclopramide, ondansetron, granisetron)
- Dextromethorphan
- Fentanyl
- Linezolid
- Meperidine
- Ritonavir
- Serotonin 1D agonists (sumatriptan and others)
- Sibutramine
- Tramadol
- Valproic acid

Table 1-2. Antidepressant Effects on the CYP 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 (e.g., metoprolol)
	Paroxetine	Potent	
	Duloxetine	Weak-moderate	
	Bupropion	Moderate	
	Amitripyline	Moderate	
	Escitalopram	Moderate	
	Citalopram	Weak-moderate	
	Sertraline	Weak-moderate (> 150 mg/day) Weak (< 100 mg/day)	
	Venlafaxine	Weak	
3A4	Nefazodone	Potent	Avoid statins metabolized through CYP3A4
	Norfluoxetine[a]	Weak-moderate	Unknown

[a]Norfluoxetine is a metabolite of fluoxetine.
CYP = cytochrome P450.

significant changes compared with placebo. Patients with preexisting cardiac disease or those with low serum concentrations of magnesium or potassium are at increased risk. Because of this study and postmarketing reports, the FDA decreased citalopram's maximum-labeled daily dosage to 40 mg in August 2011.

Second-Generation Antipsychotics

The use of second-generation antipsychotics (SGAs) for conditions other than psychotic disorders has increased dramatically during the past 10 years, with more than 70% now prescribed for conditions other than schizophrenia. Second-generation antipsychotics in combination with antidepressants are necessary for MDD with psychotic features. However, SGA use in nonpsychotic depression has only more recently been investigated.

Second-generation antipsychotics exhibit serotonin 2A receptor antagonism, and many are partial serotonin 1A receptor agonists as well; both mechanisms are associated with antidepressant action. In addition, indirect effects on norepinephrine transmission with low-dose SGAs may explain the rapid improvement in symptoms seen in some patients with MDD treated with SGA augmentation therapy.

The SGAs aripiprazole and extended-release quetiapine have FDA-approved labeling as adjunctive therapy in MDD. Risperidone and olanzapine also may effectively augment antidepressant therapy. Second-generation antipsychotics may be used to reduce the acute severity of depression, although data are limited on their efficacy in preventing relapse. Although these agents may be effective, patients are more likely to discontinue therapy because of adverse effects such as sedation, akathisia, and weight gain. When considering augmenting antidepressant therapy with SGAs, patients must be warned of the potential adverse effects associated with these agents.

Aripiprazole

Adjunctive aripiprazole has shown increased response and remission rates in patients with MDD without psychotic features who did not adequately respond to antidepressant monotherapy. Initial doses of 2 mg or 5 mg/day are recommended, with titration to a target dose of 5–10 mg/day. The maximal recommended dose for depression is 15 mg. The most common adverse effects associated with aripiprazole are akathisia, restlessness, insomnia, constipation, and fatigue. Because most patients find the drug activating, it is best to initiate dosing in the morning. As with all SGAs, there is a risk of metabolic adverse effects such as weight gain, glucose dysregulation, and lipid abnormalities, although the risk is less with aripiprazole than with other SGAs.

Extended-Release Quetiapine

In patients with MDD without psychotic features, extended-release quetiapine is effective as an adjunct when the disorder fails to respond adequately to antidepressant monotherapy. The drug must be titrated from 50 mg/day to an initial target dose of 150 mg/day over 2 days to minimize adverse effects, including orthostatic hypotension. If necessary, the dose may be increased to 300 mg/day to further target symptoms. Reported adverse effects include somnolence, dry mouth, fatigue, constipation, and weight gain. Because of the significant risk of sedation, the drug is typically administered at bedtime. Quetiapine has also shown efficacy as monotherapy at doses of 300 mg/day. However, because of the risks of metabolic abnormalities and tardive dyskinesia associated with long-term use in non-depression populations (e.g., schizophenia, bipolar disorder), quetiapine's FDA-approved labeling does not include the indication of monotherapy for depression.

Other SGAs

Olanzapine combined with fluoxetine in treatment-resistant depression may be effective in increasing remission rates; however, when the combination was compared with antidepressant monotherapy in clinical trials, the initial improvement was no longer significant by week 6. In addition, because olanzapine is associated with significant metabolic effects (e.g., hyperglycemia, hyperlipidemia, weight gain), extreme caution should be exercised when prescribing this agent.

Risperidone dosages of 1–2 mg/day, together with an SSRI or SNRI, result in higher remission rates in patients with MDD compared with antidepressant therapy alone. However, risperidone's FDA-approved labeling does not include the indication of adjunctive treatment in MDD. The most common adverse effects reported when risperidone is used in MDD are sedation and weight gain.

Folate

Although data are contradictory, a correlation appears to exist between depression and decreased serum folate concentrations, especially in women and the elderly. Patients with low folate status, as indicated by elevated homocysteine concentrations (greater than 15 micromoles/L), may take longer to respond to antidepressant therapy. Likewise, those with higher baseline folate concentrations respond better to antidepressant treatment. Folate itself is inactive and must be converted to bioactive l-methylfolate by methylene tetrahydrofolate reductase; it then can cross the blood-brain barrier and modulate the formation of the serotonin, norepinephrine, and dopamine neurotransmitters. Augmentation with folate after partial response to antidepressant therapy is generally considered a low-risk intervention, although efficacy data are extremely limited. It is unknown how long augmentation therapy should be continued, and the clinical utility of observing homocysteine concentrations has not been studied.

About 5% to 10% of the white population carries the C677T polymorphism of methylene tetrahydrofolate reductase (specifically the T/T genotype), which prevents the conversion of folate to its active form.. These people may be more likely to experience depression. L-Methylfolate is available by prescription as a medical food, intended as an adjunct to antidepressant therapy for those with decreased folate concentrations who do not respond fully to antidepressant monotherapy. It is unclear whether this product is superior to folic acid supplementation because head-to-head trials are lacking. However, it may be considered in patients who have depression and low folate concentrations and are homozygous for the T allele.

Other Augmentation Strategies

Buspirone, triiodothyronine, and lithium were studied in euthyroid patients in the National Institute of Mental Health (NIMH)-funded Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial; all three agents were found to be effective for the treatment of depression that had not responded to antidepressant monotherapy. Augmenting with an antidepressant with a different mechanism of action, called combination antidepressant therapy, may also be useful. Combinations studied in STAR*D included bupropion and SSRI and mirtazapine and SNRI. To date, there are no data to support combining agents with the same or similar mechanisms of action. Agents used to augment SSRIs and SNRIs may be found in Table 1-3.

Table 1-3. Agents Commonly Used to Augment SSRIs or SNRIs

Medication	Total Daily Dosage	Time to Response (weeks)
Atypical Antipsychotics		
Aripiprazole	5–15 mg	1–4
Quetiapine extended release	150–300 mg	1–4
Olanzapine	5–15 mg	4–8
Risperidone	0.5–2 mg	1–12
Other		
Bupropion	300 mg	1–6
Buspirone	30–45 mg	2–6
Lithium	600–900 mg	1–4
Mirtazapine	15–30 mg	4
Methylphenidate	10–40 mg	1–2
Liothyronine	25–50 mcg	1–6

SNRI = serotonin norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

Nonpharmacologic Therapies

Electroconvulsive Therapy

Although its use was previously limited because of stigma associated with the procedure, electroconvulsive therapy (ECT) remains a safe and effective treatment option, with no absolute contraindications to its use. Electroconvulsive therapy may be particularly useful in treating severe depression after many antidepressant trial failures, depression with psychotic features, and severe depression during pregnancy and in the elderly. It is considered first-line treatment when a rapid antidepressant response is needed (e.g., increased suicide risk, refusal to eat).

The primary risk associated with the treatment is related to the general anesthesia used during the procedure. Adverse effects include confusion during the postictal period and anterograde amnesia. Electroconvulsive therapy is typically administered two or three times/week for 6–12 sessions, but this may be extended until the patient's symptoms have remitted, because the risk of relapse is high with premature discontinuation. Maintenance ECT, administered as one session per month, may be required for those who experience relapse after completing acute ECT treatment. After 6 months, 40% to 50% of patients relapse if no maintenance ECT is provided.

Transcranial Magnetic Stimulation

Transcranial magnetic stimulation (TMS) involves placing a magnetic coil in contact with the head; this generates strong magnetic fields that produce electrical stimulation of superficial cortical neurons. Transcranial magnetic stimulation is approved for use when there is no response to initial antidepressant therapy. The procedure can be performed in an office or as an outpatient in about 40 minutes and, unlike ECT, does not require general anesthesia. Adverse effects are generally mild and include scalp discomfort and headache; rare but serious adverse effects include seizures, mania, and hearing loss (if not wearing adequate ear protection). Treatment is recommended 5 days/week for 4–6 weeks. Results in clinical trials have been mixed, and patients with lesser degrees of treatment resistance may have a more favorable response to TMS. Trials comparing TMS with ECT have not been published. Likewise, there are no published studies of TMS focused on the geriatric population. Choice of this treatment modality rests largely on patient preference. Current data are insufficient to recommend TMS as first-line therapy.

Psychotherapy

Although treatment of depression often follows a medication model because of cost and time constraints, psychotherapy is also clinically useful. Psychotherapy may be used alone or in combination with pharmacotherapy, depending on the severity of depression. Mild to moderate depressive episodes may be

treated with psychotherapy alone. Psychotherapy is especially helpful in addressing psychosocial stressors and psychological factors associated with mood episodes. These factors include comorbid personality disorders, which are patterns of abnormal inner experiences often leading to dysfunctional behaviors. Psychotherapy may also be preferred as initial treatment during pregnancy and lactation.

Although pharmacotherapy usually has a faster onset of symptom relief, psychotherapy has a longer duration of effect once treatment is completed. Cognitive behavior therapy (CBT), interpersonal psychotherapy, and behavioral psychotherapies have been the most studied. Psychotherapy is not without potential adverse effects (e.g., anxiety, increased emotions, patient distress).

Other Treatments

Over-the-counter therapies and somatic treatments are other treatment alternatives for depression. Over-the-counter treatments include St. John's wort, S-adenosylmethionine, and omega-3 fatty acids. St. John's wort may be useful for mild depressive symptoms, but its effectiveness may be limited in more severe depression. It has induction effects on the CYP3A4 isoenzyme, so caution must be used when combining St. John's wort with CYP3A4 metabolism-mediated agents. S-adenosylmethionine has been studied both as monotherapy and as adjunctive treatment to antidepressants, but data are preliminary at best and insufficient to recommend the drug as treatment. Omega-3 fatty acids have primarily been studied as adjunctive therapy, and their usefulness has not been clearly established. However, this is a low-risk treatment option with other potential benefits including increased cardiovascular health. Somatic treatments that may be considered include light therapy, which may be useful for seasonal affective disorder, and vagal nerve stimulation.

Guidelines for the Treatment of MDD

The American Psychiatric Association (APA) published updated treatment guidelines for depression in 2010. These guidelines provide recommendations and levels of evidence for both pharmacologic and nonpharmacologic therapies. Changes from the previous guidelines include the use of psychotherapy, with or without pharmacotherapy, as initial treatment for mild to moderate depression; the use of ECT, MAOIs, and somatic therapies for severe and/or treatment-resistant depression; and the increased emphasis on maintenance therapy for those at risk of recurrence. Other updated recommendations involve the use of standardized rating scales to measure treatment response. Of particular interest to clinical pharmacists are the detailed sections describing the evidence for various pharmacotherapies and considerations for comorbid conditions.

Acute Phase

Patients with mild to moderate depression should receive pharmacotherapy, psychotherapy, or a combination of both. Those with more severe illness should receive pharmacotherapy, with or without adjunctive psychotherapy. Patients with psychotic features require either combination therapy with an antidepressant and antipsychotic or ECT. As described earlier, ECT is very effective in severe depressive illness, especially when a rapid antidepressant response is required; it is a useful treatment option for patients with less severe depressive illness as well. The goal of treatment, regardless of modality, is complete remission of depressive symptoms.

The choice of initial pharmacologic treatment of a depressive episode is based on several factors, including patient preference, prior response, safety, tolerability/adverse effects, comorbid disorders (Table 1-4), potential drug interactions, pharmacokinetic parameters, and cost. To date, no antidepressant agent has shown superior efficacy over another. Typically, TCAs and MAOIs are reserved for refractory MDD because of tolerability issues and a lower safety profile in overdose situations. Although a family history of response to antidepressant therapy may influence a patient's belief about certain drugs and antidepressant therapy in general, the direct impact of this factor on symptom response is unclear.

Initial therapy with combination antidepressants has shown mixed results in clinical trials. In a study of outpatients with depression, initial treatment with fluoxetine plus mirtazapine or venlafaxine plus mirtazapine produced significantly higher remission rates than fluoxetine monotherapy and combination therapy with mirtazapine and bupropion. However, the combination of escitalopram and bupropion or venlafaxine and mirtazapine did not result in higher remission rates than escitalopram monotherapy in patients who had moderate to severe depression in the larger, NIMH-funded, Combining Medications to Enhance Depression Outcomes (CO-MED) trial. The CO-MED trial was a follow-up to STAR*D that included 665 patients with depression, with the current episode lasting at least 2 months. There was no difference in response or remission rates between the three treatment arms, but there were significantly fewer adverse effects in the monotherapy arm than in the combination arms. Because data are inconclusive, antidepressant monotherapy is generally recommended over combination treatment as initial therapy.

Continuation Phase

Once there has been a clinically significant improvement in depressive symptoms (ideally, complete remission of symptoms), antidepressant therapy should continue at the same dosage for an additional 4–9 months to prevent relapse. Without this continuation phase, the risk of relapse may be as high as 85%, with the highest

Table 1-4. Clinical Comorbid Conditions Influencing Treatment of Depression

Condition	Recommended	Avoid/Caution	Comments
Benign prostatic hypertrophy		Amitriptyline Imipramine Paroxetine	Anticholinergic effects
Eating disorders	Fluoxetine	Bupropion	Risk of seizures with bupropion
Cardiovascular disease	Sertraline	TCAs Citalopram Mirtazapine	TCAs, citalopram can cause ECG changes
Cerebrovascular accident	SSRIs		Caution with antiplatelets and anticoagulants
Chronic pain/neuropathy	Duloxetine Venlafaxine Desvenlafaxine TCAs		
Diabetes mellitus		TCAs	May worsen glycemic control Low doses useful in diabetic neuropathy
Dementia	Citalopram Escitalopram Sertraline	TCAs	Anticholinergic effects
Hepatic insufficiency	Desvenlafaxine	Fluoxetine Duloxetine Nefazodone	Duloxetine and nefazodone associated with hepatotoxicity
Hypertension		TCAs Venlafaxine Desvenlafaxine Duloxetine	Increased sympathetic tone
Narrow angle glaucoma		Amitriptyline Imipramine Paroxetine	Anticholinergic effects
Obesity	Bupropion SSRIs (except paroxetine) SNRIs	Mirtazapine TCAs MAOIs	
Seizures	SSRIs SNRIs	Bupropion TCAs	
Tamoxifen therapy	Venlafaxine Desvenlafaxine Citalopram Escitalopram	Paroxetine Fluoxetine Bupropion	CYP2D6 inhibition prevents conversion to active compound
Tobacco use	Bupropion Nortriptyline		
Underweight	Mirtazapine	Bupropion	

CYP = cytochrome P450; ECG = electrocardiography; MAOI = monoamine oxidase inhibitor; SNRI = selective norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

risk in patients who did not achieve remission during the acute phase. Should relapse occur, potential causes (e.g., antidepressant dose reduction from the acute phase, decreased adherence, drug interactions, psychosocial stressors) should be addressed.

Maintenance Phase

Patients with chronic depressive symptoms or those with a history of three or more depressive episodes who successfully complete the continuation phase of treatment should progress to the maintenance phase to prevent the recurrence of a major depressive episode. Other risk factors to be considered when contemplating maintenance therapy include the presence of residual depressive symptoms, psychosocial stressors, family history, and severity of depressive episodes. For many patients, some form of maintenance antidepressant treatment will be required indefinitely.

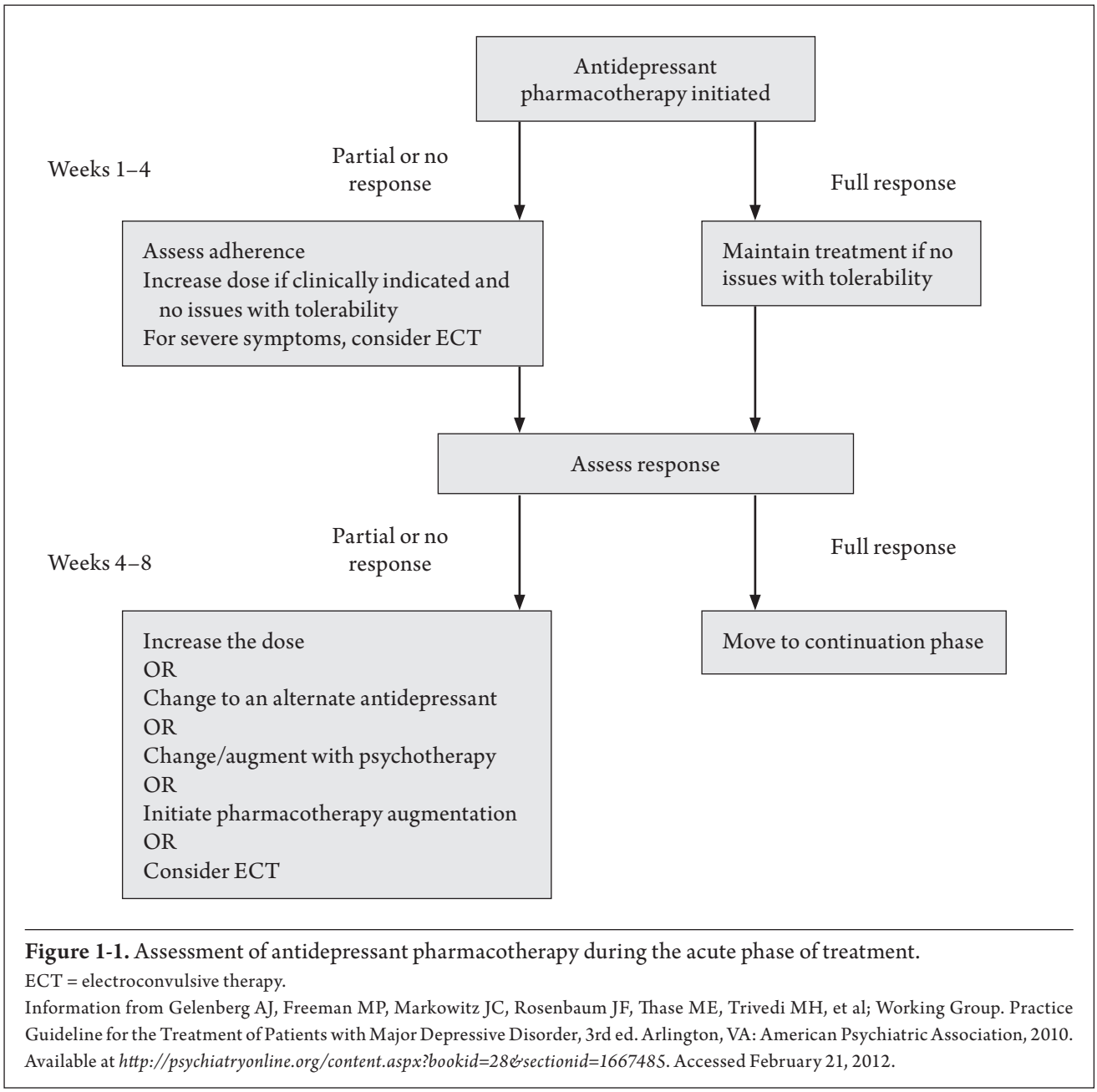

Figure 1-1. Assessment of antidepressant pharmacotherapy during the acute phase of treatment.
ECT = electroconvulsive therapy.
Information from Gelenberg AJ, Freeman MP, Markowitz JC, Rosenbaum JF, Thase ME, Trivedi MH, et al; Working Group. Practice Guideline for the Treatment of Patients with Major Depressive Disorder, 3rd ed. Arlington, VA: American Psychiatric Association, 2010. Available at *http://psychiatryonline.org/content.aspx?bookid=28&sectionid=1667485*. Accessed February 21, 2012.

Monitoring Response to Antidepressant Therapy

Figure 1-1 presents an algorithm describing assessment points in antidepressant pharmacotherapy. The goal of treatment is remission of symptoms and a full return to normal functioning, defined as a minimum of 3 weeks with no depressed mood or anhedonia and three or fewer symptoms of the depressive episode. This is considered a score of 5 or less on the patient-administered Quick Inventory of Depressive Symptomatology – Self Report (QIDS-SR) or 7 or less on the clinician-administered Hamilton Rating Scale for Depression. Rating scales are particularly useful in systematically assessing symptom response. Scales can easily be administered; the patient may complete a self-reported scale while waiting to see the provider in clinic. Regardless of the assessment used, the risk of relapse with incomplete remission makes it vital to continue aggressive treatment until remission is achieved.

Predictors of Response

Predictors of remission of depressive symptoms include female sex, white race, employment, and higher levels of education or income. Patients who do not achieve remission typically have a longer duration of depressive episodes, comorbid psychiatric or medical disorders, and lower functional status.

Poor response to pharmacotherapy may be related to inadequate dose or duration of antidepressant. Treatment duration should be at least 4–6 weeks at an adequate dose before conclusions of nonresponse or partial response may be drawn. Other considerations in determining nonresponse to antidepressant therapy are listed in Box 1-2.

Box 1-2. Reasons for Nonresponse to Pharmacologic Treatment of Depression

- Comorbid disorders, including substance abuse
- Inadequate dose of medication
- Inadequate duration of therapy
- Incorrect diagnosis
- Nonadherence
- Persistent adverse effects
- Pharmacokinetic and pharmacodynamic factors
- Unaddressed psychosocial stressors or psychological issues

Strategies for Partial or Nonresponse

Unfortunately, only one-third of patients with MDD achieve remission with the initially prescribed antidepressant; therefore, most patients require significant modifications or changes to the initial treatment plan. If symptoms fail to respond to initial antidepressant therapy after 4–8 weeks at an adequate dose, the clinician may either switch to an alternate antidepressant or augment the current therapy with psychotherapy, another antidepressant (combination antidepressant therapy), or another medication as previously described (see Table 1-3). There is no evidence for the superiority of switching versus augmentation, and patient-specific factors guide the decision. Research funded by NIMH has shown that more than 30% of patients will not have a satisfactory response to four courses of therapies of adequate dose and duration. The clinician must be willing to work closely with the patient to develop a strong therapeutic relationship and find an effective treatment strategy.

Switching

If symptoms fail to respond to initial antidepressant therapy after 4–8 weeks at an adequate dose, the clinician may opt to switch to an alternate agent, especially if there has been no improvement at all. Few well-controlled trials have studied switching strategies, and the results have not shown a clear benefit of switching to an antidepressant in the same class or switching to an antidepressant with a different mechanism of action. However, switching to an antidepressant with a different mechanism is usual in clinical practice. Patient preference and potential for drug interactions and adverse reactions should be considered. Tapering of the initial agent during the switch may be required to minimize withdrawal symptoms, although cross-tapering usually helps relieve these symptoms.

Augmentation

An alternative to switching antidepressants after failure to achieve remission is to augment the current treatment with another antidepressant (combination therapy) or other agent. Augmentation, which involves adding an additional treatment to improve the current therapy, is typically used if there is a partial response to the initial therapy. Agents used to augment SSRIs and SNRIs include bupropion, mirtazapine, lithium, buspirone, triiodothyronine, dopamine agonists, and central nervous system stimulants. A growing body of evidence supports the use of SGAs as augmentation of antidepressant therapy, with aripiprazole and extended-release quetiapine both receiving FDA-approved labeling for these indications (see Table 1-3). Time to patient response may potentially be quicker with augmentation than with switching, when the initial antidepressant is discontinued and the baseline symptom burden resumes. The augmenting agent may have additional benefits in treating comorbid conditions such as insomnia or anxiety. However, disadvantages exist with using more than one agent, including increased risk of nonadherence, potential increased adverse effect burden from two treatments rather than one, and increased cost.

Augmentation with either buspirone or bupropion is generally the first choice because of safety issues. The STAR*D study included two augmentation trials. In the first, a buspirone and citalopram regimen was compared with a bupropion and citalopram regimen. Both treatments were similar in rates of response and remission, but the bupropion and citalopram regimen was better tolerated.

In the second STAR*D augmentation trial for more treatment-refractory patients, either lithium or liothyronine was added to the current antidepressant therapy. Lithium augmentation has long been considered the gold standard for depression that fails to respond to monotherapy; however, a narrow therapeutic index, adverse effects, and many drug interactions limit lithium use. Although sample size limited the results of this trial, thyroid augmentation had numerically higher remission rates than lithium. Liothyronine was also better tolerated, and significantly more patients in the lithium treatment arm withdrew early from the study because of adverse effects. On the basis of these data, triiodothyronine 50 mcg/day is at least as good as lithium as an option for acute augmentation with better short-term tolerability in depression that fails to respond to previous treatment. Of note, the long-term effects of triiodothyronine, including impact on bone density and cardiovascular health, have not been studied.

Treatment in Special Populations

Depression in the Elderly

Depression is common in older patients, with a prevalence of up to 25% in patients 60 years or older. The risk increases in patients residing in long-term care facilities, where MDD prevalence may be as high as 42%. Depression in older patients often manifests as irritability, neurovegetative symptoms, and cognitive impairment rather than overt sadness, and it can be easily overlooked and thus remain untreated. Accurate diagnosis and treatment is essential in this population because the elderly make up a disproportionate number of completed suicides.

Compared with younger patients, the elderly are less likely to achieve remission and more likely to relapse with antidepressant medications. Maintenance therapy should be strongly considered but is not required; treatment duration recommendations are the same as for the younger population. Careful selection of antidepressant treatment is required to minimize drug-drug and drug-disease state interactions.

Because of the risk of orthostasis and anticholinergic adverse effects, TCAs and MAOIs are not recommended first-line therapies. Although SSRIs are effective, caution should be taken with this class of antidepressant because the syndrome of inappropriate antidiuretic hormone secretion and resultant hyponatremia is more likely in the elderly population. Stimulants may be useful in older patients who have a primary target symptom of significant apathy. Electroconvulsive therapy can also be considered; it is effective in the geriatric population and produces higher response rates than in younger patients. Psychotherapy, specifically interpersonal therapy, results in comparable rates of decline in suicidal ideation in the depressed elderly. For episodes that do not fully respond to initial treatment, augmentation with additional medication is generally not favored over switching agents or adding psychotherapy because of the need to simplify medication regimens in this population.

Depression in Children and Adolescents

All antidepressants carry a boxed warning for increased risk of suicidal behaviors in individuals aged 24 years or younger. Much research in MDD has been performed in children and adolescents in recent years, partly because of concerns raised after the Treatment for Adolescents with Depression Study (TADS) found an increase in thoughts and behaviors related to self-harm with fluoxetine compared with no medication. Of note, there were no suicides in the TADS.

The relationship between antidepressants and suicidal thinking remains unclear. The current recommendation for children and adolescents with mild depression is to offer psychotherapy in lieu of antidepressant pharmacotherapy in most circumstances. If depressive symptoms fail to respond after 2–3 months of psychotherapy, medication should then be considered. For moderate to severe depression, pharmacotherapy should be considered earlier in the illness, in conjunction with psychotherapy. In adolescents whose initial antidepressant therapy fails within 6 weeks, medication switches are indicated, rather than a "wait-and-see" approach. Patients may be switched to an alternate antidepressant in the same class or switched to an alternate mechanism agent. Child and adolescent patients are likely to respond more favorably with a combination of CBT and pharmacotherapy.

Depression in Pregnancy

For pregnant women with depression, it is important to weigh the risks versus the benefits of drug therapy. Risks of untreated depression include maternal suicide, preeclampsia, lower birth weight, and lower Apgar score. Infants born to mothers with depression have lower cognitive skills and difficulty interacting as early as 2 months of age. However, antidepressant drugs have been associated with risks as well.

Use of SSRIs has been associated with neonatal persistent pulmonary hypertension, but data are inconclusive. In addition, use during late pregnancy may result in neonatal withdrawal symptoms, including jitteriness, poor feeding, and tremor. Although most SSRIs are FDA pregnancy category C, paroxetine has a category D rating because of the correlation between use during the first trimester and cardiac defects. Tricyclic antidepressants have no known teratogenic characteristics. Nortriptyline and desipramine are preferred to tertiary amine TCAs because of minimal anticholinergic effects on the fetus. Antidepressant therapy is generally recommended for pregnant patients with moderate to severe mood-related symptoms (e.g., poor appetite or weight loss, inability to care for self, suicidal ideation).

Pharmacogenomics

Considerable research has been directed at finding genes involved in response to antidepressant therapy, but to date, there is insufficient information to use genetic profiling to predict which antidepressant will work best in a specific patient. Unfortunately, this leaves patients and providers still dependent on trial and error to find the best antidepressant treatment for each individual. However, the pharmacogenomics of depression is a rapidly growing field of study.

Gene variants involved in the pharmacokinetics of antidepressant drugs are primarily single mutations in CYP enzymes. Polymorphisms of these enzymes (e.g., CYP2D6, CYP2C9, CYP2C19) can drastically alter plasma concentrations, and thus effectiveness and tolerability, of antidepressants. Fortunately, these are well-studied effects, and dosage adjustments can

be made for individual patients. To a degree, alterations in the transporter gene ABCB1, which encodes for the P-glycoprotein transporter protein found at the blood-brain barrier, can modify the concentrations of certain antidepressants in the central nervous system. However, the clinical implications of this mutation in the treatment of MDD have yet to be determined.

Many genes have been theorized to affect the pharmacodynamic effects of antidepressants, including response and remission, as well as adverse effects. These include genes that encode the serotonin and norepinephrine transporters, various serotonin receptors, tryptophan hydroxylase, brain-derived neurotrophic factor (BDNF), catechol-*O*-methyltransferase, glucocorticoids, and glutamate receptors. Unfortunately, sample sizes used in the published research are small, meta-analyses are limited by the heterogeneity of included studies, and research results are mixed. The best evidence supports polymorphisms in the serotonin transporter (short S or long L allele), tryptophan hydroxylase (C/C genotype), and the BDNF gene as being associated with response to antidepressant therapy. Even with stronger evidence, the effect sizes for these genes are modest at best.

Patient Counseling

A pharmacotherapy regimen that includes any antidepressant should include several key counseling points. Specific issues for each medication class are found in Table 1-1. In general, for any antidepressant pharmacotherapeutic agent, patients and families must be aware of the antidepressant's onset of action and of the 2–4 weeks it may take 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 achieve the desired effect.

Education on therapy duration (typically at least 6–9 months) will enhance patient expectation. Patients should be instructed to continue taking the drug even if symptoms improve, and they should be told that the drug should not be discontinued without alerting the provider. Patients should be educated on serotonin withdrawal symptoms that can occur with acute discontinuation or interruption of therapy (Box 1-3). Patients and their caregivers should also be alerted to signs of increased suicidal thinking, restlessness, activation, and dysphoria, especially during the first few weeks of therapy. If these occur, the patient should contact his or her provider or seek medical attention as soon as possible. Emergency contact phone numbers should be provided so that patients can reach qualified personnel 24 hours/day, 7 days/week. Comprehensive patient counseling, provided by a pharmacist, is essential to ensure good adherence.

Box 1-3. Symptoms of Serotonin Withdrawal Syndrome

- Electric shock sensations
- Headache
- Nausea
- Paresthesias
- Sweating
- Tremulousness
- Vomiting

Pharmacists can be especially helpful in educating providers and patients alike on the potential risks and benefits of antidepressant therapy during pregnancy and lactation. Women with depression or a history of depression who are considering pregnancy should be strongly encouraged to discuss the options with their prescriber and pharmacist before conceiving. Women of childbearing potential must be informed of the risks and benefits of receiving antidepressant therapy during pregnancy. Patients should be counseled about the possible effects of antidepressants on a developing fetus, and birth control issues must be discussed and documented.

Pharmacists can refer patients and their families to their local National Alliance for the Mentally Ill chapter to glean more information on depression, treatments, and support groups. Pharmacists can work closely with patients to ensure successful treatment outcomes.

Conclusion

Even though they are often overlooked in the clinical setting, depressive disorders are prevalent and are associated with significant economic burden. Despite a wide range of antidepressant drugs and options for augmentation, depression remains difficult to treat, with about one-third of patients achieving remission with initial therapy. Patients and health care providers must work closely together to create an effective treatment plan.

Annotated Bibliography

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   The APA guidelines, updated in 2010, are based on the best available data and clinical consensus. The guidelines are easy to link to DSM-IV because the APA developed both publications. The practice guidelines are extensive, detailing a multidisciplinary approach to the treatment of depressive disorders. These guidelines provide recommendations for patient assessment including suicide risk, psychotherapeutic approaches, and treatment settings in addition to pharmacotherapy.

Levels of confidence (though not levels of evidence) are documented for each recommendation. The first one-half of the text provides specific treatment recommendations, whereas the second one-half focuses on levels of evidence to support the guidance provided in the earlier section. References are cited and listed at the end, giving clinicians the opportunity to review specific articles if desired.

2. Rush AJ, Trivedi MH, Stewart JW, Nierenberg AA, Fava M, Kurian BT, et al. Combining Medications to Enhance Depression Outcomes (CO-MED): acute and long-term outcomes of a single-blind randomized study. Am J Psychiatry 2011;168:689–701..

   This NIMH-funded study compared remission rates in depressed outpatients treated at initiation with monotherapy with those treated with antidepressant combination therapy. The 675 patients with depression enrolled were randomized to receive escitalopram monotherapy, escitalopram plus bupropion, or mirtazapine plus venlafaxine for 7 months. Subjects were blinded to treatment, whereas investigators were not. Remission was defined as a score of 5 or less on the patient-rated QIDS-SR rating scale. At 12 weeks, there was no difference between groups in remission rates, nor was there a difference at 7 months. One strength of the study is its generalizability, because the investigators included patients with comorbid psychiatric and medical conditions. The primary limitations are the single-blind design and the total reliance on patient self-rated scales as outcome measures.

3. Chen J, Gao K, Kemp DE. Second-generation antipsychotics in major depressive disorder: update and clinical perspectives. Curr Opin Psychiatry 2011;2:10–17.

   This review article summarizes the latest findings on the use of SGAs in depression. The authors reviewed evidence of SGAs used as monotherapy and for augmentation; data on efficacy as well as tolerability and adverse effects were included. Randomized controlled trials are included, as are meta-analyses. Evidence tables are available in the text. The article is particularly helpful because the use of these agents for nonpsychotic disorders has increased significantly, and two SGAs have now received FDA-approved labeling as adjunctive treatment for MDD. The authors also provide opinions, based on available evidence, on the place of these agents in therapy.

4. Zobel A, Maier W. Pharmacogenetics of antidepressive treatment. Eur Arch Psychiatry Clin Neurosci 2010;260:407–17.

   The authors review the literature on the impact of genetics on the efficacy as well as the tolerability of antidepressant pharmacotherapy. Effects of CYP polymorphisms are not discussed; instead, the focus of the article is on the potential impact of genes on the pharmacodynamics, rather than pharmacokinetics, of antidepressant medications. Limitations of pharmacodynamic phenotypes are included. The authors review research of targets of interest, including various serotonin receptors, modulators, and the serotonin transporter. The limitations of available data are adequately discussed. Although pharmacogenetic profiles are not yet able to clinically predict antidepressant response or adverse effects (other than genes associated with altered pharmacokinetics), this is a subject area of exponential growth that will likely be clinically practical in the near future.

5. Preskorn SH. Treatment options for the patient who does not respond well to initial antidepressant therapy. J Psychiatr Pract 2009;15:202–10.

   Because less than one-third of patients experience remission of depression with initial drug therapy, and because 40% of patients do not experience symptom response even after four trials of antidepressant therapy, there is great interest in determining the next step after treatment failure. The STAR*D trials, funded by NIMH, provided some answers but also raised new questions. In this article, the author assembles evidence from the NIMH research, atypical antipsychotic data in depression, and other less-studied treatment alternatives. This article summarizes the available evidence and provides the clinician with guidance in choosing the next step for specific patients.

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   Combination antidepressant therapy at treatment initiation remains controversial. The large, single-blind CO-MED study found no benefit in response or remission rates with combination agents at treatment initiation versus SSRI monotherapy. In this 6-week, double-blind study, the authors compared fluoxetine monotherapy with bupropion/mirtazapine, venlafaxine/mirtazapine, and fluoxetine/mirtazapine in moderately depressed patients. Unlike in CO-MED, sample sizes were smaller, drug doses were fixed, and outcomes were measured using a clinician-administered rating scale rather than a patient self-report scale. The results showed significantly higher remission rates with the various combinations than with SSRI monotherapy, and no significant differences in tolerability were seen. This study's results conflict with outcomes found in CO-MED, possibly because of differences in study design.

7. Beydoun, MA, Shroff MR, Beydoun HA, Zonderman AB. Serum folate, vitamin B-12, and homocysteine and their association with depressive symptoms among U.S. adults. Psychosom Med 2010;72:862–73.

   Many depressed patients and their families are interested in complimentary medicine alternatives and adjuncts. Folic acid and its active form L-methylfolate have been associated with antidepressant effects, and

low serum folate concentrations are associated with increases in depressive symptoms and poorer response to therapy. This cross-sectional study of National Health and Nutrition Examination Survey data found that depressive symptoms were associated with low folate concentrations, particularly among women, but not with abnormal homocysteine or vitamin B_{12}. However, in those older than 50, elevated homocysteine concentration was positively associated with elevated depressive symptoms. The major limitation of the study is its cross-sectional design, which allows multiple confounders and cannot determine causality.

8. National Institute for Health and Clinical Excellence. Depression in Children and Young People. February 2011: London. Available at *www.nice.org.uk/CG28*. Accessed February 22, 2012.

   The UK-based National Institute for Health and Clinical Excellence is an independent organization that provides national guidance on a variety of wellness topics and disease states, including mental health. These guidelines, published in 2005 and reviewed for updates in 2011, provide evidence-based treatment recommendations for depression in children aged 5–18 years. The key topics and questions addressed are specific psychotherapies and pharmacotherapies, diagnosis and screening, and the potential impact of the guidance on clinical practice. The guidance provides a detailed description of the development process and levels of evidence, as well as the findings acquired when the guidelines were reviewed for updates.

9. Emslie GJ, Mayes T, Giovanna P, Benedetto V, Greg C, Dineen WK, et al. Treatment of resistant depression in adolescents (TORDIA): week 24 outcomes. Am J Psychiatry 2010;167:782–91.

   This trial was conceived as a follow-up of TADS, which increased awareness of suicidal behaviors and the potentially harmful role of antidepressant drugs in adolescents. The TORDIA study investigated the effects of various treatment options after the failure of initial SSRI therapy in adolescents with depression, including switching to an alternative SSRI with or without CBT and venlafaxine with or without CBT. The study went out to 72 weeks; this article reviewed outcomes at the 24-week mark, finding no differences in remission rates between treatment arms. Although 40% of patients eventually achieved remission, most had done so by 6 weeks of treatment. On the basis of these findings, treatment should be modified at an earlier point rather than waiting for the currently recommended 8–12 weeks to see whether improvement occurs before changing therapy.

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    There has been much debate on the role of antidepressants during pregnancy. This article summarizes the risks of maternal depression on pregnancy, including miscarriage, fetal growth, and preterm delivery, as well as postnatal effects on the child. The authors then review the literature on adverse birth outcomes associated with antidepressant use. Specific antidepressant risk is associated with each potential negative outcome. Other treatment modalities, including ECT and psychotherapy, are included. This article is particularly useful when discussing the risks and benefits of treatment with depressed women who are pregnant or considering pregnancy.

11. Wu Q, Liu J, Gallegos-Orozco JF, Hentz JG. Depression, fracture risk, and bone loss: a meta-analysis of cohort studies. Osteoporos Int 2010;21:1627–35.

    Previous studies have found a correlation between antidepressant use and risk of bone loss and fracture. Unfortunately, this research does not address whether the bone loss is related to depression or to antidepressant drugs. This meta-analysis attempted to correlate fracture and bone loss with the presence of depressive disorders rather than with antidepressant use, as in previous research. The authors included 14 studies, with most reporting fracture as an outcome. Mean follow-up ranged from 1 to 23 years. The authors include a clear evidence table that summarizes each included study. Given their findings, it appears both depression and antidepressants have a negative impact on bone density and fracture risk.

12. Boyer EW, Shannon M. The serotonin syndrome. N Engl J Med 2005;352:1112–20.

    Every pharmacist should have a copy of or at least have read this review of serotonin syndrome. Patient counseling recommendations always include a warning about the risk of serotonin syndrome, but practitioners often have difficulty explaining what serotonin syndrome is and what symptoms patients should look for. In this article, the authors describe in detail the epidemiology, pathophysiology, patient presentation, differential diagnosis (with a decision tree), and management of serotonin syndrome. Differences between serotonin syndrome, anticholinergic toxicity, and neuroleptic malignant syndrome are reviewed in depth. Figures and tables accompany the article.

Self-Assessment Questions

Questions 1 and 2 pertain to the following case.
R.T. is a 35-year-old man brought to the emergency department with fever, tremors, gastrointestinal distress, and mental status changes for the past 24 hours. He has a history of depression, chronic back pain, and migraine headaches. His current drugs are fluoxetine 40 mg/day for depression, tramadol 50–100 mg four times/day as needed for pain, divalproex extended release 1000 mg at bedtime for migraine prophylaxis, and sumatriptan 100 mg by mouth as directed for migraine headache—may repeat x 1 in 2 hours. R.T.'s vital signs are oral temperature 101.2°F, blood pressure 157/96 mm Hg, and heart rate 102 beats/minute. Upon physical examination, he is found to have nystagmus, inducible clonus, and hyperactive bowel sounds. He is admitted to the intensive care unit, and his outpatient drugs are discontinued. Twelve hours later, he continues to experience agitation and altered mental status. His oral temperature is 101.5°F, blood pressure is 168/96 mm Hg, and heart rate is 101 beats/minute.

1. **Which one of the following drugs is most likely responsible for R.T.'s current presentation?**

   A. Fluoxetine.
   B. Tramadol.
   C. Divalproex.
   D. Sumatriptan.

2. After 3 days, R.T.'s condition stabilizes, and he is ready for discharge. Changes to his drug regimen include discontinuing divalproex and initiating verapamil for migraine prophylaxis, as well as discontinuing tramadol. The treatment team would like to change the antidepressant therapy to an agent less likely to be involved in another similar situation. **Which one of the following would be best to recommend for R.T.?**

   A. Nefazodone.
   B. Bupropion.
   C. Desipramine.
   D. Aripiprazole.

Questions 3 and 4 pertain to the following case.
S.M. is a 43-year-old man (height 71″, weight 102 kg) who is referred to the clinic from his primary care physician for treatment of depression. S.M.'s target symptoms for therapy are moderate depressed mood, difficulty falling asleep, fatigue, decreased appetite, and problems focusing. He denies excessive guilt, changes in psychomotor activity, and thoughts of self-harm. His Quick Inventory of Depressive Symptomatology – Self Report (QIDS-SR) score is 13. S.M.'s medical history is significant for type 2 diabetes mellitus, peripheral neuropathy, and coronary artery disease. His current drugs are simvastatin 40 mg at bedtime, lisinopril 10 mg/day, metoprolol 12.5 mg twice daily, and capsaicin cream topically to his feet twice daily. Current vital signs include blood pressure 128/78 mm Hg and heart rate 72 beats/minute. S.M. has never been treated for depression.

3. **Which one of the following would be the best initial antidepressant for S.M.?**

   A. Duloxetine.
   B. Mirtazapine.
   C. Phenelzine.
   D. Paroxetine.

4. After 6 weeks of treatment, S.M.'s QIDS-SR score is 4. He is concerned about the large number of drugs he takes daily and the risk of adverse effects. He asks how much longer he will have to take the antidepressant medication. **Given his current presentation as reflected by the QIDS-SR score, psychiatric history, and risk factors, which one of the following is the best estimate of how much longer S.M. should receive antidepressant pharmacotherapy?**

   A. 2–3 months.
   B. 4–9 months.
   C. 9 months after remission is achieved.
   D. 24 or more months after remission is achieved.

Questions 5–8 pertain to the following case.
A.J. is a 23-year-old woman who presents to the walk-in clinic with jitteriness, anxiety, nausea, increased sweating, and unusual tingling sensations in her head and extremities (described as electric shocks) intermittently for the past 3 weeks. Upon questioning, she says she was prescribed medication for depression 2 months ago. A.J. admits that she sometimes does not take her drugs as prescribed, sometimes taking more, sometimes less. She also occasionally takes her friends' medications when she is feeling bad.

5. **Which one of the following is the most likely explanation for A.J.'s symptoms?**

   A. Partial adherence.
   B. Excessive adherence.
   C. Drug interaction.
   D. Untreated symptoms.

6. A.J. agrees to take her medication (and only her own medication) as prescribed, but she asks to take

an alternate agent because she now has negative thoughts about her current medication. **From her description, which one of the following agents was most likely initially prescribed for A.J.?**

A. Paroxetine.
B. Fluoxetine.
C. Aripiprazole.
D. Bupropion.

7. A.J. is now prescribed sertraline, titrated to 100 mg/day over 1 week. **Which one of the following would be the optimal time for A.J. to receive follow-up?**

A. 1 week.
B. 2 weeks.
C. 4 weeks.
D. 6 weeks.

8. Six weeks later, A.J. reports a 60% improvement in her symptoms but continues to experience residual anergia, amotivation, hypersomnia, and difficulty concentrating. **Which one of the following would be the best next step in A.J.'s treatment?**

A. Switch her antidepressant to citalopram.
B. Add triiodothyronine to her current regimen.
C. Add mirtazapine to her current regimen.
D. Add bupropion to her current regimen.

Questions 9–11 pertain to the following case.
P.C. is a 78-year-old man brought to his primary care provider appointment by his daughter. P.C.'s medical history is significant for hypertension, hypercholesterolemia, and mild chronic obstructive pulmonary disease; he has no psychiatric history. The patient has no complaints during his visit. However, his daughter expresses concern to the provider that P.C. no longer wants to leave his house, preferring to stay in his room and sleep. He no longer is interested in reading the paper or watching the news. He has unintentionally lost 30 lb since his last visit 3 months ago because he "just has not felt like eating." When asked, P.C. denies feeling depressed but does admit he has problems concentrating. He denies active thoughts of killing himself but admits to frequent thoughts of death and endorses hopelessness. No medical issues that could cause his symptoms have been found.

9. **Given his history and current presentation, which one of the following is the best treatment option for P.C.?**

A. Citalopram monotherapy.
B. Paroxetine with cognitive behavior therapy (CBT).
C. Desvenlafaxine with transcranial magnetic imaging.
D. Sertraline with interpersonal therapy.

10. **Which one of the following would be the best length of time for P.C. to receive antidepressant medication after achieving remission?**

A. 3 months.
B. 5 months.
C. 9 months.
D. 24 or more months.

11. Four weeks later, P.C.'s depressive symptoms have not improved. He continues to verbalize passive suicidal ideation and has lost an additional 7 lb. The treating psychiatrist recommends electroconvulsive therapy (ECT) because of the severity of his symptoms and their failure to respond to treatment. P.C.'s daughter asks your opinion. **Which one of the following best supports ECT for P.C.?**

A. Safety and efficacy in the elderly.
B. Presence of psychotic features.
C. Severity of depressive illness.
D. No known contraindications to anesthesia.

Questions 12 and 13 pertain to the following case.
A.D., a 27-year-old man (height 68″, weight 102 kg) with a history of recurrent depression, comes to the clinic with depressed mood, anhedonia, insomnia, poor concentration, and psychomotor agitation. He has been off medications for the past 6 months. A.D. has no suicidal ideations currently but has had a past attempt (cut his wrists). He has no medical problems, takes no medications, smokes one-half pack of cigarettes per day, drinks 5 or 6 beers on 4 or 5 nights per week, and uses marijuana once a month. His vital signs are within normal limits. A.D. states his previous medications included fluoxetine (6 months) and sertraline (1 year); these never worked well by his report, and he would like to try a different antidepressant.

12. **Which one of the following antidepressant drugs would be best to recommend for A.D.?**

A. Duloxetine.
B. Citalopram.
C. Mirtazapine.
D. Nefazodone.

13. Six weeks later, A.D.'s symptoms have improved 50%, but he still has significant residual symptoms. The prescriber decides to augment with aripiprazole 5 mg/day. One week later, A.D. returns to the clinic with his girlfriend. His mood has continued to improve, with a 75% improvement in his QIDS-SR score from baseline. However, his girlfriend reports that A.D. was increasingly restless during the past week and now has difficulty sitting still for any length of time. His vital signs are within

normal limits, and he notes no other complaints. **Which one of the following adverse effects is A.D. most likely experiencing?**

A. Akathisia.
B. Serotonin syndrome.
C. Serotonin withdrawal.
D. Peripheral neuropathy.

14. A patient has received nefazodone therapy for the past 4 years with satisfactory results. Now, this patient has received a diagnosis of hyperlipidemia (low-density lipoprotein cholesterol 156 mg/dL, high-density lipoprotein cholesterol 41 mg/dL, triglycerides 127 mg/dL) and a second diagnosis of chronic depression. The physician enters a prescription for simvastatin 20 mg/day but is alerted to a potential drug interaction. **Which one of the following would be best to recommend for this patient?**

A. Change nefazodone to sertraline.
B. Order pravastatin instead of simvastatin.
C. Order simvastatin and have more frequent follow-up.
D. Order gemfibrozil instead of simvastatin.

15. A woman has been taking fluoxetine 60 mg/day for depression for the past 10 weeks. Her depressive symptoms have significantly improved from baseline, but she continues to feel sluggish and somewhat depressed. She also takes lamotrigine for seizures and hydrochlorothiazide for blood pressure. **Which one of the following augmentation strategies would be most appropriate for this patient?**

A. Bupropion 150 mg/day in the morning.
B. Lithium 300 mg twice daily.
C. Liothyronine 25 mcg/day in the morning.
D. Aripiprazole 15 mg/day in the morning.

16. A 28-year-old woman who is planning to start a family within the next 6 months is referred for counseling on antidepressant use during pregnancy. She has a history of three major depressive episodes, one requiring hospitalization after a suicide attempt. The patient has been stable on fluoxetine for 2 years, with residual symptoms of decreased motivation, mild depressed mood, and impaired concentration. Psychotherapy has been largely ineffective for her in the past. **Which one of the following is best to recommend for this patient?**

A. Continue fluoxetine therapy.
B. Discontinue antidepressant medication.
C. Switch treatment to psychotherapy.
D. Decrease dose of fluoxetine.

17. A 15-year-old adolescent boy received a diagnosis of moderate major depressive disorder (MDD) 2 months ago. At that time, paroxetine was initiated. Six weeks ago, the drug was titrated to his current dose of 40 mg/day. Since taking antidepressant medication, the patient's symptoms have improved by 40%, but he still experiences significant periods of depression and irritability. **Which one of the following is the best recommendation to give to his primary care physician?**

A. Continue current therapy for an additional 4 weeks and reassess response.
B. Discontinue current antidepressant treatment and initiate CBT.
C. Augment the current antidepressant regimen with quetiapine XR.
D. Switch to an alternate antidepressive agent and initiate CBT.

18. A 26-year-old man with a first episode of depression and moderate symptoms presents at the request of his new wife. He has a history of hypertriglyceridemia and onychomycosis of the toenails. His medications include fenofibrate 160 mg/day and itraconazole 200 mg/day. He denies using alcohol, tobacco products, and illicit substances. The patient has never been prescribed medications for depression, though he did engage in sessions with a therapist in the past. Both he and his wife have heard friends discuss problems with sexual functioning associated with antidepressant drugs. They would like to avoid this adverse effect if possible. **Which one of the following would be the best initial treatment for this patient?**

A. Vilazodone.
B. Desvenlafaxine.
C. Mirtazapine.
D. Bupropion.

Questions 19 and 20 pertain to the following case.
Y.J. is a 29-year-old woman who is referred to your clinic to discuss her antidepressant medication. She has no comorbid medical conditions and takes no medications. This is Y.J.'s first episode of depression. She admits to feeling hesitant about taking any drugs including antidepressants, but at this point, her depressive symptoms are interfering with her work as a legal secretary. Y.J. verbalizes she has no reason to feel down and feels guilty she cannot just "shake it off." She has been prescribed venlafaxine 37.5 mg twice daily for 3 weeks and has noticed no change in her symptoms. A review of her weight and vital signs reveals no change from baseline.

19. **Which one of the following is the most likely reason Y.J.'s symptoms have not responded?**

A. Venlafaxine lacks effectiveness for this patient.
B. Comorbid undiagnosed axis II disorder.
C Inadequate dosage and duration of treatment.
D. Psychosocial issues unaddressed.

20. Y.J. weighs her options with her provider and chooses to continue venlafaxine. The dose is increased to 75 mg three times/day. She returns in 2 weeks reporting significant improvement in symptoms. She denies adverse effects or tolerability issues and wishes to continue the medication. **In addition to her symptom response, which one of the following is most important to include in Y.J.'s routine monitoring plan?**

A. Blood pressure.
B. Body weight.
C. Liver function.
D. Electrocardiography.

21. A 31-year-old man was given a diagnosis of MDD 2 years ago and has been on several pharmacologic regimens. Despite this, he has not had a resolution of symptoms and remains moderately depressed, as indicated by a score of 13 on QIDS-SR. He agrees to a trial of phenelzine 10 mg three times/day. After 3 weeks of therapy, his QIDS-SR score decreases to 6, and the medication is continued at that dose. One month later, he develops a cold and presents to a local pharmacy for recommendations to treat his symptoms. **Which one of the following recommendations is most appropriate to give to the patient?**

A. Temporarily decrease the dose of phenelzine and begin dextromethorphan.
B. Continue phenelzine and begin diphenhydramine.
C. Temporarily discontinue phenelzine and begin pseudoephedrine.
D. Taper and discontinue phenelzine and begin phenylephrine.