

# Recognition and Management of Depression



CALIFORNIA  
ACADEMY OF  
FAMILY  
PHYSICIANS



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Academy of Family Physicians

## EB-CME/Practice Recommendations

Recommendations	Evidence Strength	Website
The US Preventive Task Force (USPSTF) recommends screening adults for depression in clinical practices that have systems in place to assure accurate diagnosis, effective treatment, and follow up. <b>B Recommendation.</b>	<b>B Recommendation:</b> The USPSTF recommends that clinicians routinely provide [the service] to eligible patients. The USPSTF found at least fair evidence that [the service] improves important health outcomes and concludes that benefits outweigh harms.	<a href="http://www.guideline.gov/summary/summary.aspx?doc_id=3176&amp;nr=002402">www.guideline.gov/summary/summary.aspx?doc_id=3176&amp;nr=002402</a>
Patients started on antidepressants who are considered to present an increased suicide risk or are younger than 30 years (because of the potential increased risk of suicidal thoughts associated with the early stages of antidepressant treatment for this group) should normally be seen after 1 week and frequently thereafter as appropriate until the risk is no longer considered significant. <b>Grade C.</b>	<b>Grade C:</b> Expert committee reports or opinions and/or clinical experiences of respected authorities (evidence level IV). This grading indicates that directly applicable clinical studies or good quality are absent or not readily available.	<a href="http://www.guideline.gov/summary/summary.aspx?doc_id=6228&amp;nr=003999">www.guideline.gov/summary/summary.aspx?doc_id=6228&amp;nr=003999</a>
Antidepressants should be continued for at least 6 months after remission of an episode of depression, because this greatly reduces the risk of relapse. <b>Grade A.</b>	<b>Grade A:</b> At least one randomized, controlled trial as part of a body of literature of overall good quality specific recommendation consistency addressing the condition (evidence level-I) without extrapolation.	
When patients present initially with severe depression, a combination of antidepressants and individual Cognitive Behavioral Therapy should be considered as the combination is more cost-effective than either treatment on its own. <b>Grade B</b>	<b>Grade B:</b> Well-conducted clinical studies but no randomized clinical trials on the topic of recommendation (evidence levels II or III); or extrapolated from level-I evidence.	
Patients who have had two or more depressive episodes in the recent past, and who have experienced significant functional impairment during the episodes, should be advised to continue antidepressants for 2 years. <b>Grade B.</b>	<b>Grade B:</b> Well-conducted clinical studies but no randomized clinical trials on the topic of recommendation (evidence levels II or III); or extrapolated from level-I evidence.	
Patients of all ages with mild depression should be advised on the benefits of following a structured and supervised exercise program of typically up to 3 sessions per week of moderate duration (45 minutes to 1 hour) for between 10 and 12 weeks. <b>Grade C.</b>	<b>Grade C:</b> Expert committee reports or opinions and/or clinical experiences of respected authorities (evidence level IV). This grading indicates that directly applicable clinical studies or good quality are absent or not readily available.	
First-line treatment of major depressive disorder (MDD). For patients with mild to moderate MDD, use either antidepressant medication or psychotherapy at first-line treatment ( <b>Evidence-based</b> ). Given the lack of evidence on a clearly superior approach for mild to moderate MDD, treatment decisions should be based on patient and clinician preference, potential side effects, and cost ( <b>Consensus-based</b> ). For patients with severe or chronic MDD, combined treatment with antidepressants and psychotherapy is recommended as first-line treatment ( <b>Evidence-based</b> ). If antidepressants are to be used, any class of antidepressant (SSRI, TCA, SNRI, NRI, or DA) can be prescribed as first-line treatment of MDD ( <b>Evidence-based</b> ).	<b>Evidence-based:</b> Sufficient number of high-quality studies from which to draw a conclusion, and the recommended practice is consistent with the findings of the evidence.  <b>Consensus-based:</b> Insufficient evidence and a practice is recommended on the consensus or expert opinion of the Guideline Development Team	<a href="http://www.guideline.gov/summary/summary.aspx?doc_id=9632&amp;nr=005152">www.guideline.gov/summary/summary.aspx?doc_id=9632&amp;nr=005152</a>
Because patient preferences for treatment may vary based on their ethnicity and culture, asking patients from different ethnic groups about treatment preference is recommended when discussing treatment options for MDD. <b>Evidence-based.</b>	<b>Evidence-based:</b> Sufficient number of high-quality studies from which to draw a conclusion, and the recommended practice is consistent with the findings of the evidence.	
The Canadian Task Force on Preventive Health Care (CTFPHC) concludes that there is fair evidence to recommend screening adults in the general population for depression in primary care settings that have integrated programs for feedback to patients and access to case management or mental health care. <b>Grade B.</b>	<b>Grade B:</b> The CTF concludes that there is fair evidence to recommend the clinical preventive action.	<a href="http://www.guideline.gov/summary/summary.aspx?doc_id=6524&amp;nr=004090">www.guideline.gov/summary/summary.aspx?doc_id=6524&amp;nr=004090</a>
Depressed patients frequently present with somatic complaints to their primary care doctor rather than complaining of depressed mood. <b>Grade C.</b>	<b>Grade C:</b> Observational trials.	<a href="http://www.guideline.gov/summary/summary.aspx?doc_id=8330&amp;nr=004662">www.guideline.gov/summary/summary.aspx?doc_id=8330&amp;nr=004662</a>

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Dr Bent declares that during the past 12 months neither he, nor any member of his family, has had a financial arrangement or affiliation with any corporate organizations providing moneys to support this CME activity.

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Dr McCahill declares that during the past 12 months neither she, nor any member of her family, has had a financial arrangement or affiliation with any corporate organizations providing moneys to support this CME activity.

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## Needs Statement

More than 19 million Americans suffer from depression, costing society \$44 billion annually in lost productivity. Major depression is now the leading cause of disability in the United States. It behooves family physicians and other primary care physicians (PCPs) to be comfortable recognizing depression and to take advantage of effective pharmacologic and nonpharmacologic treatments by implementing guideline-based treatment recommendations. However, depression is often not recognized, with the diagnosis missed in up to 50% of primary care patients. Even when diagnosed, many patients remain undertreated, despite strong evidence that guideline-based treatments significantly improve patient outcomes.

This vital gap, when addressed by effective, focused, and case-based education – developed by primary care physicians for primary care physicians, can become a vital link to improving patient care in the United States.

- More than 19 million Americans suffer from depression, costing society \$44 billion annually in lost productivity. Major depression is now the leading cause of disability in the United States.
- There are multidimensional aspects of depression that can complicate the presentation and recognition of depression.
- Per the US Preventative Services Task Force, primary care physicians miss more than half of all patients with depression.
- Effective pharmacotherapy and psychotherapy options are available to manage patients with depression

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### **Learning Outcomes**

At the conclusion of this activity, participants should be able to:

- Diagnose patients with depression using screening questions and analyzing patient symptoms.
- Appropriately prescribe medications for depression, including medication augmentation and switching, and titration of medications.
- Delineate the uses of psychotherapy for treatment of depression.
- Manage the patient with depression from diagnosis, through treatment, to a goal of remission.


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### **Cultural/Linguistic Competency**

New CAFP policy and California state law require that each learning activity have elements of cultural and linguistic proficiency included in the content. This could include health disparities information based on cultural or ethnicity, language issues, research results based on ethnicity, resources for more information, etc.

# Introduction

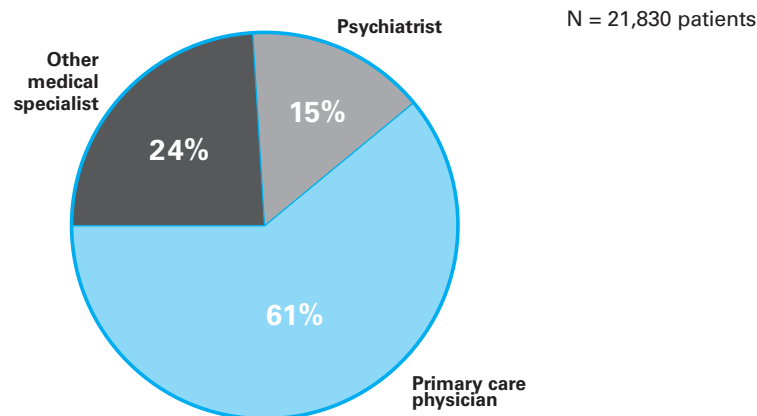
Depression is a chronic, serious, and costly mental illness, but can be effectively treated in more than 80% of people with medication, psychotherapy, or a combination of both.<sup>1</sup> It is commonly encountered in primary care settings, where the majority of patients seek help and are treated for depression (**FIGURE 1**).<sup>2-6</sup> It is the principal reason for 12.1 million office visits each year (primary care and specialist), and antidepressants are the therapeutic drug class most prescribed during office visits (81.2 million/year) (**TABLE 1**).<sup>6</sup> Yet many patients still fail to receive adequate treatment at an appropriate dose for sufficient duration.

**WEB RESULTS** by  (Showing Results 1-10 of 98,100,000 for depression) [[definition](#)].

Accessed: November 16, 2006.

Depression is associated with reduced quality of life (QOL).<sup>7</sup> The extent of patients' concern about depression is illustrated by 98.1 million results from a [www.Google.com](http://www.Google.com) search—sites where patients can acquire both information and misinformation on depression. Compare this to 33 million results for headache and 33.2 million results for hypertension, and to 5.8 million sites for depression in 2003. It behooves family physicians and other primary care physicians (PCPs) to be comfortable recognizing depression and to take advantage of effective pharmacologic and nonpharmacologic treatments by implementing guideline-based treatment recommendations.<sup>8-10</sup> However, depression is often not recognized, with the diagnosis missed in up to 50% of primary care patients.<sup>5,8,11</sup> Even when diagnosed, many patients remain undertreated, despite strong evidence that guideline-based treatments significantly improve patient outcomes.

**FIGURE 1 Prescription of SSRI by Medical Specialty**



# Epidemiology

Approximately 20.9 million American adults, or 9.5% of the US population aged 18 years and older, have a mood disorder (major depression, dysthymia, or bipolar disorder).<sup>12</sup> The lifetime prevalence of major depression in the general population is 13.2% to 17.1%, with a 12-month prevalence of 5.3% to 6.7%.<sup>8,12-15</sup>

The risk of depression is higher in individuals with serious medical illnesses (eg, heart disease, stroke, cancer, diabetes, asthma, chronic pain, HIV).<sup>1,13,16-24</sup> Alone, depression can be incapacitating, but co-morbid depression and medical illness worsen outcomes and are associated with greater distress, role-function impairments, poor self-care, less ability to follow lifestyle recommendations, and poor adherence to treatments for other medical conditions.<sup>1,13,25-27</sup> There is also evidence that depression can biologically affect the course of some medical illnesses and vice versa.<sup>28</sup> The association between depression and chronic diseases is discussed in the “*Understanding the Vital Link: Depression and Chronic Disease*” monograph, which is available at [www.familydocs.org](http://www.familydocs.org).<sup>29</sup>

## Economic Burden

Depression imposes a substantial burden on society as a leading cause of disability, lost work productivity, morbidity, mortality, and increased use of health services.<sup>14,30</sup> The World Health Organization Global Burden of Disease Survey estimates that by the year 2020, major depressive disorder (MDD) will be second only to heart disease in the amount of disability experienced by sufferers. Depression is costly because it is highly prevalent, often debilitating, and co-morbid with other psychiatric and medical illness, where it is associated with 50% to 100% higher medical costs.<sup>13,27,30-32</sup>

**TABLE 1** Top 10 Prescribed Therapeutic Classes at Office Visits: United States 2004

Therapeutic classification <sup>1</sup>	Number of occurrences in thousands	Percent of drug mentions <sup>2</sup>
1. Antidepressants	81,185	5.1
2. Nonsteroidal anti-inflammatory drugs	73,737	4.7
3. Antiasthmatics or bronchodilators	69,507	4.4
4. Antihypertensive agents	69,113	4.4
5. Hyperlipidemia	63,996	4.1
6. Antihistamines	58,163	3.7
7. Acid or peptic disorders	56,906	3.6
8. Antiarthritics	54,783	3.5
9. Blood glucose regulators	53,069	3.4
10. Non-narcotic analgesics	51,918	3.3

<sup>1</sup> Based on the standard 4-digit drug classification used in the *National Drug Code Directory*.

<sup>2</sup> Based on an estimated 1,577,208,000 drug mentions at office visits in 2004.

Hing E, et al. National Ambulatory Medical Care Survey: 2004 summary. Advance data from vital and health statistics; no 374. Hyattsville, MD: National Center for Health Statistics. 2006.

The economic burden of depression in the United States has been estimated at \$53 billion annually—the largest component derived from lost work productivity costs US employers between \$33 billion and \$44 billion annually.<sup>30,31</sup> Even when present at work, the performance of depressed workers can be significantly reduced (presenteeism).<sup>31</sup> One study found that major depression is associated with 27.2 lost workdays per ill worker per year (based on absenteeism and presenteeism) at a cost of \$4,426 per person annually.<sup>33,34</sup> Employed patients with depression experience greater deficits in managing mental-interpersonal, time management, output, and physical tasks.<sup>35</sup>

**Risk Factors**

There are many risk factors for depression, the presence of which can be ascertained by taking a thorough history (TABLE 2). The peak age of onset is 20 to 40 years, although the disorder may begin at any age, and it is up to twice as common in women as it is in men.<sup>15,36,37</sup> Women are also at increased risk for depression following childbirth, affecting approximately 10% of women, with the risk increasing in those with previous episodes of postpartum depression.<sup>37,38</sup> Patients’ marital status also has implications for developing depression, with unmarried males, married females, single mothers, and separated, divorced, or widowed persons reporting higher rates.<sup>5,15,37,39,40</sup>

The far-reaching consequences of depression also affect the children of depressed parents, who are at high risk for impairing psychiatric and medical problems that begin early and often continue through adulthood, which suggests that children of depressed parents should be evaluated.<sup>34,41-43</sup> Fortunately, remission of maternal depression has a positive impact on both mothers and their children, which emphasizes the importance of vigorously treating depressed parents.<sup>42</sup> A stressful early family environment is also significant in some individuals, particularly those with genetic polymorphisms that make them vulnerable to depression.<sup>44,45</sup> A first-degree relative with a history of major depression increases a patient’s risk by 1.5 to 3 times, compared with the general population.<sup>37,41,46</sup> Patients with a personal history of depression are also at higher risk for a subsequent episode—following one episode, patients face a 50% chance of another, with the risk increasing progressively with each episode.

Because depression is more common in patients with chronic medical illness, such as heart disease, stroke, diabetes, asthma, HIV, cancer, and chronic pain, the presence of such illness should prompt a careful evaluation for depression.<sup>1,13,16-24</sup>

**TABLE 2 Risk Factors for Major Depression**

<b>Risk factor</b>	<b>Association</b>
Female sex	2-fold higher risk
Age	Peak age at onset is 20 to 40 years
Family history of depression	1.5- to 3-fold higher risk
Personal history of depression	50% after 1 episode; 75% after 2 episodes; 90% after 3 episodes
Postpartum	Up to 1 in 10
Marital status	Separated, divorced, and widowed persons; unmarried males and married females; single mothers
Concomitant chronic conditions	Increased risk
Stressful early family environment	Increased risk

# Biologic Basis of Depression

The monoamine neurotransmitter deficiency hypothesis was one of the earliest theories proposed for the biologic basis of depression.<sup>37</sup> It postulated that depression was the result of a deficiency of one or more of the monoamine neurotransmitters in the central nervous system (CNS)—serotonin (5HT), norepinephrine (NE), and dopamine (DA)—and that antidepressants worked by increasing synaptic monoamine concentrations. However, this model failed to explain why antidepressants required three to four weeks for an initial effect, despite increasing monoamine concentrations in a shorter time.

The neurotransmitter receptor theory that evolved to explain this therapeutic latency postulated that depression was the result of an upregulation of monoamine receptors and that antidepressants downregulated receptors after the latency period.<sup>37</sup> The actions of monoamine receptors are determined by their subtype and their location. Multiple receptor subtypes have been identified for each of the three monoamine neurotransmitters—currently five for DA, 10 for NE, and 14 for 5HT.<sup>37,47</sup> Neurotransmitter projections in the brain mediate physiologic functions, which are regulated by multiple influences of a variety of neurotransmitters (TABLE 3).<sup>37</sup> Antidepressant agents have distinct effects on receptors and transporters thought to relate to the therapeutic and adverse effects of these agents.

A recently proposed explanation for monoamine loss in depression is through elevated monoamine oxidase A (MAO-A) levels, an enzyme that metabolizes monoamines such as 5-HT, NE, and DA.<sup>48</sup> Positron emission tomography has shown that the density of MAO-A is significantly elevated, on average by 34%, throughout the brain during major depression.<sup>48</sup> An advanced monoamine theory that has been proposed is that elevated MAO-A levels increase the metabolism of monoamines; thereafter, individual monoamine transporter densities have a secondary influence on specific monoamine levels.<sup>48</sup> If the transporter density for a particular monoamine is low, the effect of greater metabolism on that monoamine level is somewhat attenuated, resulting in moderate monoamine loss and in the moderate severity of particular symptoms.<sup>48</sup> If the transporter density for a particular monoamine is not low during a major depressive episode, the severely reduced extracellular concentration of the monoamine is associated with long-term regional loss of that particular monoamine and severe symptoms.<sup>48</sup> In this theory, elevated MAO-A levels are a general monoamine-lowering process, while the regional density of monoamine transporters has a selective influence on particular monoamines, with a strong relationship to particular symptoms.<sup>48</sup> This model is consistent with long-standing treatments that increase monoamine levels through inhibition of MAO-A or inhibition of monoamine transporters.<sup>48</sup>

**TABLE 3** Physiologic Effects of Monoamine Projections

Serotonin projections		Noradrenergic projections	
• Frontal cortex	• Mood	• Frontal cortex	• Mood, attention
• Basal ganglia	• Akathisia/agitation, obsessive-compulsive disorder	• Limbic area	• Energy, agitation, emotions
• Limbic area	• Anxiety, panic	• Brainstem	• Blood pressure
• Hypothalamus	• Appetite, eating behavior	Dopaminergic projections	
• Sleep center	• Insomnia	• Limbic area	• Ability to experience pleasure, cognitive processes
• Spinal column	• Sexual response	• Striatum	• Motor movements
• Brainstem vomiting center	• Nausea and vomiting		
• Gut	• GI cramps, diarrhea		

# Recognition of Depression

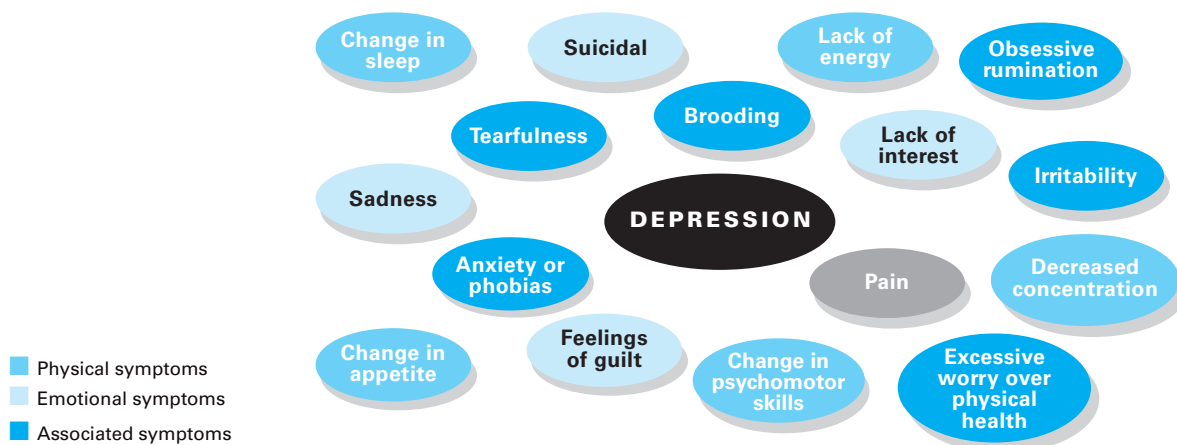
## Presenting Complaints

There are multidimensional aspects of depression, which include physical, emotional, and associated symptoms (FIGURE 2).<sup>49,50</sup> Common presentations for depressed patients are shown in TABLE 4.<sup>11</sup> The majority of patients who seek care for depression present with physical symptoms (somatizations) as the primary or sole complaint, in lieu of mentioning their psychologic symptoms.<sup>5,51-54</sup> Somatization may reflect the stigma associated with mental illness or patients' inability or unwillingness to acknowledge or express psychosocial distress. Some patients may hesitate introducing the subject of depression with their physicians because they may feel depression is an emotional weakness, moral failing, or cannot be treated, and that reporting somatic symptoms is a more acceptable route for seeking help.<sup>5,55,56</sup> If patients expect that their PCP will not directly address emotional issues but will send them to a psychiatrist, they may also avoid emotional issues or may express them in physical terms.<sup>55</sup> Behaviors such as showing empathy, listening attentively, being attuned to nonverbal clues, and asking questions about emotional issues are associated with increased willingness by patients to share concerns.<sup>55</sup>



Somatic complaints include fatigue or the “blahs,” constant tiredness, malaise, frequent headaches, vague abdominal pain, or joint aches. Other patients may complain of being “stressed out,” being unable to cope, having sleep problems, sexual dysfunction, or gastrointestinal (GI) complaints. Physicians should be alert to patients' remarks and find out what is behind the office visit for: “My husband thinks I need hormones,” “I’m only here because my wife/daughter made the appointment,” or, particularly from a younger male, “I need a checkup.”

**FIGURE 2** Multidimensional Aspects of Depression



APA. *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR)*. Washington, DC: APA;2000:352. Ohayon MM, et al. *Arch Gen Psychiatry*. 2003;60:39-47.

**TABLE 4** Common Presentations for Major Depression

- Multiple somatic complaints, weight gain/loss, mild dementia
- Multiple (>5/year) medical visits; problems in more than 1 organ system, with the absence of or insufficient physical findings to explain the complaints
- Fatigue
- Work or relationship dysfunction/changes in interpersonal relationships
- Sleep disturbances

Institute for Clinical Systems Improvement. *Major depression in adults in primary care*. 2006.

As the number of unexplained physical complaints increases, so too does the likelihood of a potentially treatable mood disorder (**FIGURE 3**).<sup>53,57</sup> However, because somatization can mask depression, without specific questioning and a careful evaluation for depression, physicians may not recognize depression in patients who present with somatic complaints.<sup>53,54</sup> This can lead to overutilization of physical and laboratory tests, unnecessary consultation, and repeated office visits.<sup>5,56</sup> Many patients will acknowledge depression as a cause of their illness when asked.

Whether a depressed patient presents with a somatic or psychiatric complaint may vary with his or her culture. For example, an international study found that the range of depressed patients in various countries who reported only physical symptoms was 45% to 95%. Patients from Turkey were most likely to present with a somatic complaint, while French patients were more likely to present with a psychiatric complaint.<sup>56</sup> Although one might interpret this to mean that certain groups are more comfortable discussing a psychiatric complaint, differences in the care setting (eg, continuity clinic vs urgent care setting), nature of the health care delivery (eg, duration of visit, degree of privacy), characteristics of the physicians, and patients' comfort with providers might also explain the differences. Regardless of the presenting complaint, this study found that most patients of all nationalities acknowledged depression as a possible cause of their complaint when specifically questioned.

## Screening



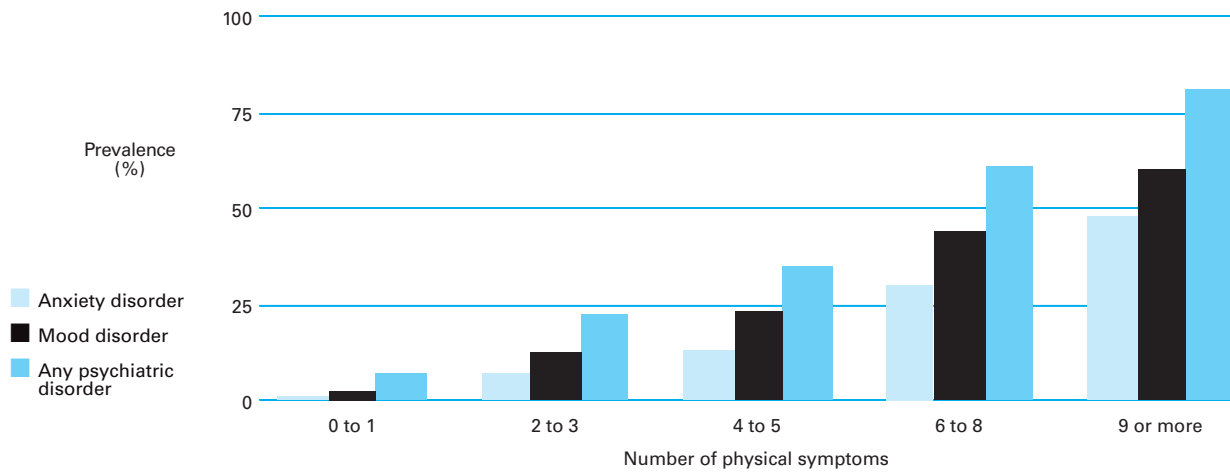
The US Preventive Services Task Force (USPSTF) recommends screening adults for depression in primary care settings that have effective resources to manage identified cases.<sup>8</sup> Identifying patients with depression can be difficult when time is limited, but several short screening instruments can be administered in less than five minutes (**TABLE 5**).<sup>8</sup> Most instruments have good sensitivity (80% to 90%), but only fair specificity (70% to 85%), and there is little evidence to recommend one over another.<sup>8</sup> The USPSTF found that asking the following two simple questions (sensitivity: 96%; specificity: 57%) about the presence of mood and anhedonia may be as effective for screening (but not case finding) as using more involved instruments:

1. Over the past two weeks, have you felt down, depressed, or hopeless?
2. Over the past two weeks, have you felt little interest or pleasure in doing things?

Other questions to ask patients are:

- How are things at work?
- How are things at home?
- We all have stresses in our lives. Has your stress level increased lately?
  - How are you handling it?
- How much are you drinking?
  - Is that more than usual?
- What medicines are you taking?
- What OTCs and herbal remedies are you taking?
- Has anyone in your family suffered emotional or stress-related problems?
  - Have you had problems like this before?
- Who do you have to talk to?
- HOW ARE YOU?

**FIGURE 3** Physical Symptoms as Predictors of Mood Disorders



Kroenke K. *Arch Fam Med.* 1994;3:774-9.

**TABLE 5** Case-Finding Instruments to Detect Depression in Adults in Primary Care Settings

Instrument	Items (n)	Time frame	Score range	Usual cut-point	Literacy level	Administration time (min)
Beck Depression Inventory	21	Today	0-63	Mild, 10; moderate, 20; severe, 30	Easy	2-5
Center for Epidemiologic Study Depression Screen	20	Past week	0-60	16	Easy	2-5
General Health Questionnaire	28	Past few weeks	0-28	4	Easy	5-10
Medical Outcomes Study Depression Screen	8	Past week	0-1	0.06	Average	<2
Primary Care Evaluation of Mental Disorders	2	Past month	0-2	1	Average	<2
Symptom-Driven Diagnostic System-Primary Care	5	Past month	0-4	2	Easy	<2
Zung Self-Depression Scale	20	Recently	25-100	Mild, 50; moderate, 60; severe, 70	Easy	2-5

Pignone MP, et al. *Ann Intern Med.* 2002;136:765-6.

Most importantly, have the wisdom to remain silent and listen to the patients' answers. Once probed, the psychologic problems of some patients may seem overwhelming to deal with in a short encounter; however, the PCP should still intervene, which may require scheduling the patient to return for a longer visit.

### Diagnosis

Positive screening results should trigger full diagnostic interviews that use standard diagnostic criteria from the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) to determine the presence or absence of major depression (TABLE 6).<sup>49</sup> Five of nine symptoms for at least two weeks are required, which must include depressed mood or anhedonia, causing significant impairment in social, occupational, or other important areas of

**TABLE 6**      **DSM-IV Criteria for Major Depression\***

<b>Symptom</b>	<b>DSM-IV diagnostic criteria</b>
Depressed mood	Depressed mood most of the day, nearly every day
Anhedonia	Markedly diminished interest or pleasure in almost all activities most of the day, nearly every day
Sleep disturbance	Insomnia or hypersomnia nearly every day
Appetite or weight change	Substantial change in appetite nearly every day or unintentional weight loss or gain (eg, $\geq 5\%$ of body weight in 1 month)
Decreased energy	Fatigue or loss of energy nearly every day
Increased or decreased psychomotor activity	Psychomotor agitation or retardation nearly every day
Decreased concentration	Diminished ability to think or concentrate, or indecisiveness nearly every day
Guilt or feelings of worthlessness	Feelings of worthlessness or excessive guilt nearly every day
Suicidal ideation	Recurrent thoughts of death or suicide

\*Diagnosis of major depression requires 5 or more symptoms, including depressed mood and anhedonia, which have been present during the same 2-week period and cause clinically significant distress or impairment in social, occupational, or other important areas of functioning. APA. *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR)*. Washington, DC: APA; 2000:352.

functioning. PCPs should consider using a standardized instrument to document baseline depressive symptoms and severity to assist in evaluating progress.<sup>11</sup> The **A SAD FACE(S)** mnemonic can guide a rapid interview by reminding physicians of important symptoms to discuss with patients (**TABLE 7**).<sup>5</sup> A vertical notation on the side of the progress sheet can be used to monitor patients' progress.

Stigma associated with medical illness and patient denial can be obstacles when trying to discuss a diagnosis of depression with a patient.<sup>5</sup> Physicians should explore the patient's understanding and acceptance of the diagnosis, emphasize the neurochemical basis of depression, and reassure the patient that depression is a treatable disorder.

### *Differential Diagnoses*

In addition to major depression, differential diagnoses of patients with depressed mood include:

- Dysthymia (characterized by fewer symptoms or milder symptoms, and a chronic course lasting more than two years).
- Minor depression (a patient with insufficient number of symptoms to qualify for the diagnosis of major depression and who has not had symptoms long enough to qualify for dysthymia).
- Adjustment disorder (dysphoria which can usually be linked to an identifiable psychosocial stressor; eg, bereavement, marital discord, work conflict).
- Seasonal depression (minimum two-year pattern of depression in winter with spontaneous resolution in summer).
- Substance abuse.
- Medications (eg, benzodiazepines, opioids, interferon, reserpine, corticosteroids).
- Dementia syndrome and other comorbid psychiatric disorders.
- Medical conditions etiologic for depression (eg, hypothyroidism, Cushing's disease).

**TABLE 7** Guided Interview Using A SAD FACE(S) Mnemonic

+ - <b>A</b> ppetite	Causing weight gain or loss
+ - <b>S</b> leep	Insomnia or hypersomnia nearly every day
+ - <b>A</b> nhedonia	Diminished interest or pleasure in almost all activities
+ - <b>D</b> ysphoria	Depressed mood
+ - <b>F</b> atigue	Loss of energy nearly every day
+ - <b>A</b> gitation	Psychomotor agitation or retardation
+ - <b>C</b> oncentration	Difficulty concentrating
+ - <b>E</b> steem	Low self-esteem with feelings of worthlessness or guilt
+ - <b>S</b> uicidal ideation	Recurrent thoughts of death or suicide

Adapted from: Montano CB. *J Clin Psychiatry*. 1994;55(suppl):18-34.

### *Treatment Considerations Following Diagnosis*

Once the diagnosis of major depression is made, additional history should be elicited about factors that may affect treatment.<sup>58</sup> These include assessment for suicide, such as level of hopelessness, prior attempts or gestures, and whether the means and/or a plan exist. The risk of suicide is increased in patients with depression, and one retrospective study found that half of patients diagnosed with an affective disorder who completed suicide had sought care for their depression in the previous month.<sup>5</sup>

Assessing for co-morbid psychiatric disorders is important. Alcohol or substance abuse are common in primary care settings and often occur with depression. The combination can be difficult to treat and may require specialty mental health care, as may other concomitant psychiatric illnesses (eg, bipolar disorder, anxiety, obsessive-compulsive disorder, personality disorder, psychosis).<sup>59-67</sup> More than 1% of US adults suffer from bipolar disorder, but it is frequently misdiagnosed as unipolar depression.<sup>59;60;67</sup> In the absence of a mood-stabilizing agent, initiating antidepressants in patients with bipolar disorder risks precipitating acute mania, mixed states, or rapid-cycling states.<sup>67</sup> It is essential to screen for bipolar disorder in patients with depression, which can usually be accomplished by asking two questions:<sup>38</sup>

1. Have you ever had four continuous days when you were feeling so good, high, or "hyper" that other people thought you were not your normal self or you got into trouble?
2. Have you experienced four continuous days that you were so irritable that you found yourself shouting at people or starting fights or arguments?

If the patient answers affirmative to either of these questions, psychiatric consultation should be considered, as the patient may need a mood stabilizer prior to the initiation of antidepressant medication.

# Response: Management of Depression

The natural history of depression reveals that without treatment, 65% of patients will spontaneously recover within two years (40% in the first year), 20% to 25% will show slight improvement and become dysthymic, and 5% to 10% of patients will remain unchanged.<sup>68,69</sup> The impact of treatment on the natural history of major depression is shown in **FIGURE 4**.<sup>69</sup> Following recovery, the risk of recurrence in patients who have experienced one episode is 50%, increasing to 75% after two episodes, and to 90% after three episodes.<sup>37</sup>

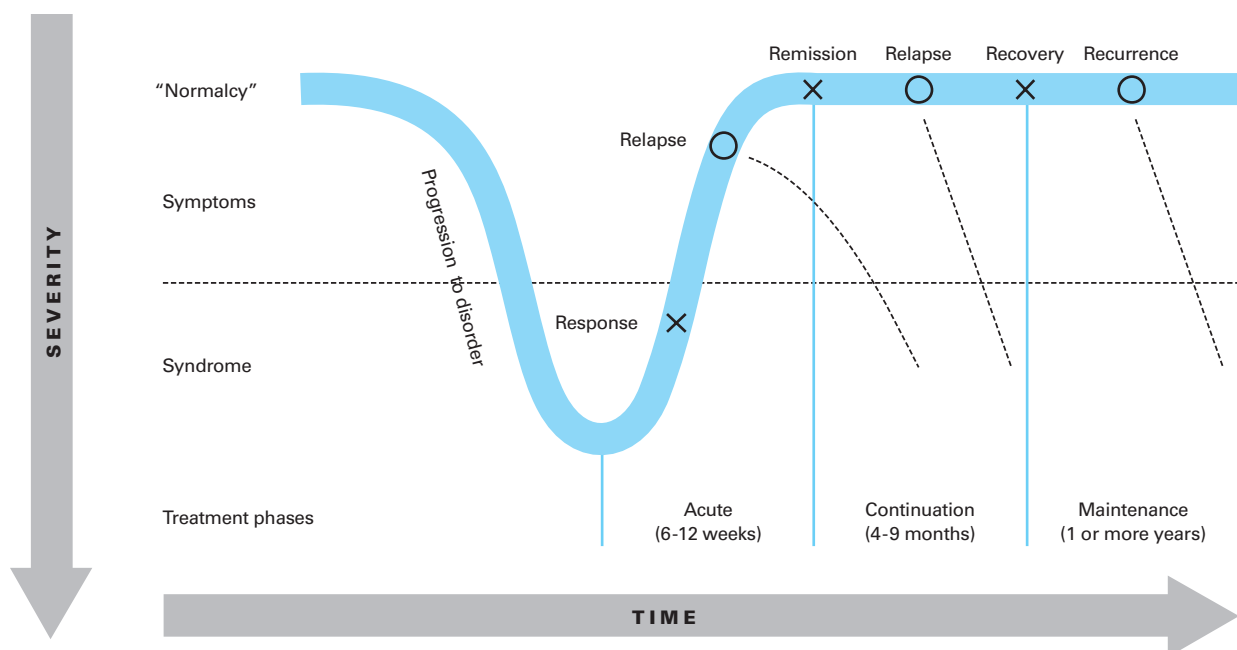
## Management Goals

The management goals for major depression can be broken down into three phases:

1. *Achieve remission of symptoms.*<sup>11</sup>

The acute phase of treatment begins when the patient first presents with an episode of depression and includes the six to 12 weeks required to achieve remission.<sup>70</sup> However, only about one-third of patients achieve full remission, and about 40% achieve partial remission after the acute phase.<sup>71,72</sup> The American College of Neuropsychopharmacology (ACNP) recommends that remission be ascribed after three consecutive weeks during which minimal symptom status (absence of both sadness and reduced interest/pleasure along with the presence of fewer than three of the remaining seven DSM-IV-TR diagnostic criterion symptoms) is maintained.<sup>73</sup>

**FIGURE 4** Phases and Effect of Treatment on Natural History of Major Depression



## 2. *Prevent relapse.*<sup>11</sup>

The continuation phase represents the six to 12 months during which one continues the antidepressant agent to prevent relapse (a return of major depressive symptoms). The ACNP recommends that recovery be ascribed after at least four months following the onset of remission, during which a relapse has not occurred. However, about one-third of patients who achieve recovery or remission suffer relapse or recurrence despite antidepressant treatment.<sup>74,75</sup>

## 3. *Maintain remission and prevent recurrence.*<sup>11</sup>

During maintenance treatment the goal is to maintain previous levels of occupational and psychosocial function and prevent recurrence by ensuring sustained remission. Strong consideration should be given to maintaining long-term antidepressant therapy in patients with a history of multiple episodes, recurrence within one year of stopping treatment, double depression (chronic dysthymia with additional more severe and pervasive episodes of major depression), onset after age 60 years, co-morbid anxiety or substance abuse, or a chronic medical condition worsened by depression.<sup>76,77</sup>




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## Pharmacotherapy

Pharmacotherapy is the cornerstone of managing patients with depression. Classes of antidepressant agents include the monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and novel agents (ie, bupropion, duloxetine, mirtazapine, nefazodone\*, trazodone, venlafaxine). The mechanisms of action of some of these agents are shown in **TABLE 8**. The TCAs block: 1) the reuptake of NE and/or 5HT, 2) histamine and acetylcholine receptors (responsible for their well-characterized side effects), and 3) sodium channels in the heart and brain at high doses (responsible for cardiac arrhythmias and seizures in the event of overdose).<sup>37,78</sup> SSRIs work primarily by inhibiting reuptake of 5HT. Among the novel antidepressant agents, bupropion increases catecholamines such as NE and DA through reuptake and other mechanisms, the dual-action serotonin and norepinephrine reuptake inhibitors (SNRIs) venlafaxine and duloxetine inhibit reuptake of 5HT and NE. Mirtazapine exerts its antidepressant effect by blocking the 5HT-2A and alpha-2 NE receptors, which augments the release of both 5HT and NE into the synapse. Trazodone acts by potent blockade of the 5HT-2A receptor, combined with less potent 5HT reuptake inhibitor actions, while nefazodone also has weak NE reuptake inhibition.<sup>37</sup>

### *Selection Factors*

Independent of the agent or class used, a 50% to 70% response rate can be expected for any of the available antidepressants.<sup>79,80</sup> Therefore, selection of an antidepressant is influenced by factors such as co-incident general medical conditions of the patient, anticipated side effects, safety and tolerability, patient preference, prior response, cost, and convenience of dosing.<sup>81,82</sup> Agents that have been successful for past depressive episodes are likely to be effective and well tolerated for subsequent episodes. Family history of response is another important factor to consider. Genetic variation is emerging as one of the reasons that patients whose treatment is unsuccessful with one antidepressant often respond to a different agent.<sup>83</sup> In addition, this may explain some disparities in response to




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**\*A note about nefazodone:** Nefazodone is mentioned here several times in the context of treatment-resistant depression, switching medications, and augmentation of antidepressant medication. It is mentioned for completeness in these clinical situations, but if used, it should be with great caution. The brand name version of nefazodone has been discontinued, and while the generic version is still available in the United States, the drug has been removed from the market altogether in several other countries because of the onset of life-threatening liver failure resulting in death or the need for liver transplant in some patients. Although this is relatively rare, it can occur without warning and sometimes after some weeks or months of apparently good tolerance to the drug. Nefazodone should not be used if baseline liver function tests (LFTs) are elevated, or if there is a history of liver disease (eg, hepatitis C). LFTs should be monitored for the entire time that the patient is on the medication, and nefazodone should be stopped if there are any clinical symptoms or signs of liver disease, or if there is a significant increase in baseline LFTs. Nefazodone should not be re-started if it is stopped because of liver problems. Physicians should consult the FDA's "Black Box Warning" and current prescribing information before prescribing nefazodone for a patient.

**TABLE 8 Therapeutic Action of Select Antidepressant Agents**

Action	TCA*	Bupropion	SSRI†	fluvoxamine	sertraline	paroxetine	SNRI	Trazadone	Mirtazapine
NE reuptake inhibition	1-2+	1+	0	1+	0	1+	2+	1+	0
5HT reuptake inhibition	0-2+	0	3+	3+	3+	3+	2+	0	0
Dopamine reuptake inhibition	0	1+	0	0	1+	0	0	0	0
Alpha-2 NE receptor blockade	0	0	0	0	0	0	0	0	0
5HT-2A receptor blockade	1+	0	0	1+	0	0	0	2+	2+

\*Some TCAs have more potency for inhibition of 5HT (eg, clomipramine), while others are more selective for NE over 5HT (eg, desipramine)

†In general; see individual agents for differences

TCA = tricyclic antidepressant; SNRI = serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor;

NE = norepinephrine; 5HT = serotonin

Adapted from: Stahl SM. *Essential Psychopharmacology of Depression and Bipolar Disorder*. New York, NY: Cambridge University Press, 2000.

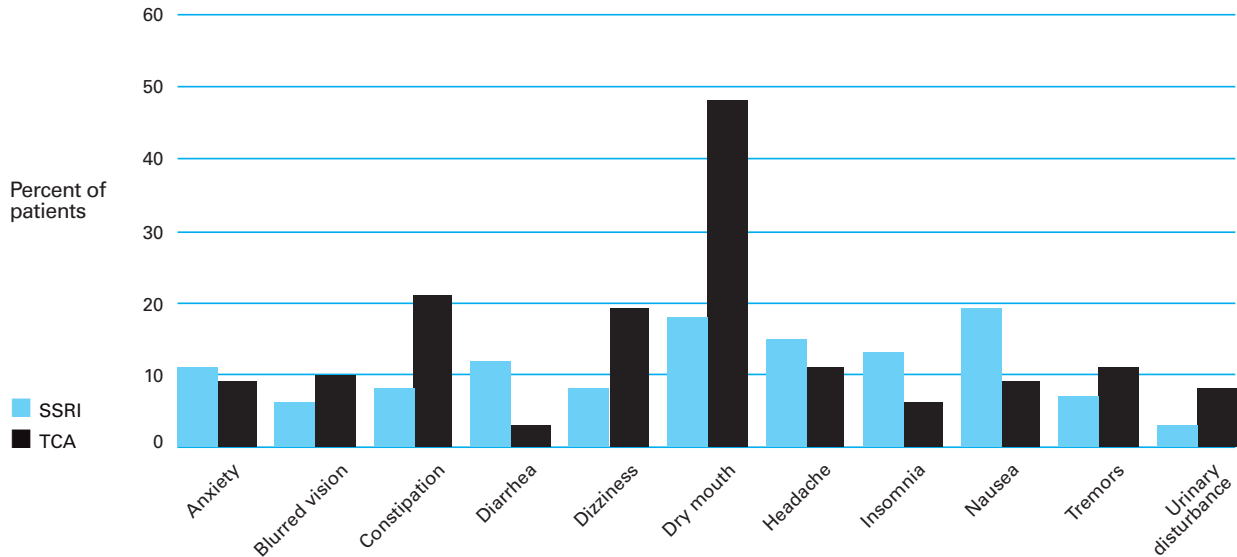
treatment by race—in one study, an allele that is associated with better treatment outcomes from SSRIs was six times more frequent in white than African American patients, who had a less favorable treatment outcome.<sup>83,84</sup> Different ethnic populations may have a number of different polymorphisms in monoamine transporters that explain some of the observed ethnic variation in response to antidepressants.<sup>85</sup> However, the ethical and practical questions concerning possible genetic screening for antidepressant drug response have not yet been addressed.<sup>86</sup>

MAOIs are effective antidepressants but are less commonly prescribed in primary care for a number of reasons, including the risk for potentially dangerous drug interactions, major side effects, and the need for strict dietary restrictions. Regardless of whether they prescribe them, PCPs should be aware of the side effects and potential drug interactions of MAOIs in order to safely manage other conditions in their patients who are prescribed these agents by psychiatrists. Efforts to address the safety concerns around MAOIs are leading to the development of more selective and reversible MAOIs, as well as novel drug delivery systems that bypass the GI and hepatic systems, thereby reducing the risk of interactions with tyramine-rich foods.<sup>87</sup> Selegiline is a selective monoamine oxidase B inhibitor approved for the adjunctive treatment of Parkinson's disease at low doses; at higher doses, oral selegiline is effective in major depression, but loses its selectivity and has the potential for tyramine interactions. To overcome these problems, a transdermal formulation of selegiline has been developed to preserve the GI barrier to ingested tyramine while maintaining an antidepressant effect at CNS sites.<sup>87-89</sup>

Antidepressants are associated with a variety of anticipated side effects, which are particularly important in the elderly and in patients with chronic medical conditions.<sup>59</sup> Although effective, the first-generation TCAs have generally been relegated to second-line therapy. Reasons include their narrow therapeutic index requiring therapeutic drug monitoring, risk for lethality with overdose, and their less favorable side-effect profile compared with SSRI agents (**FIGURE 5**).<sup>80,82,90</sup> Common side effects of TCAs include dry mouth, blurred vision, dizziness, constipation, orthostatic hypotension, sedation, and urinary disturbance, although desipramine and nortriptyline have improved side-effect profiles compared with other TCAs.

By virtue primarily of their ease in prescribing and their more favorable side-effect profiles, SSRIs have emerged as the first-line therapy for depression. Their most common short-term side effects are GI related (eg, nausea, vomiting, diarrhea) or associated with CNS stimulation (eg, insomnia, tremor, agitation). SSRIs may also cause sexual dysfunction and an increase in body weight during long-term treatment.<sup>91</sup>

**FIGURE 5 Comparison of Side Effects With SSRI and TCA Treatment**



TCA = tricyclic antidepressant; SSRI = selective serotonin reuptake inhibitor  
 Williams JW, et al. *Ann Intern Med.* 2000;132:743-56.

The novel antidepressant agents also possess some unique side effects. Bupropion has a dose-dependent risk for seizure, which is low in patients without seizure disorder provided no single dose exceeds 150 mg and the total daily dose remains less than 450 mg. The sustained-release preparation of bupropion also helps to minimize the risk of seizure. Although mirtazapine is associated with sedation and weight gain due to blockade of histamine receptors, it is without the SSRI-associated GI side effects and nausea.<sup>37</sup> Venlafaxine is associated with a dose-dependent elevation of blood pressure in some patients, which is uncommon until the dosage range is above 300 mg per day. Pre-existing treated hypertension is not a contraindication for venlafaxine, but patients receiving venlafaxine should have their blood pressure monitored regularly. Duloxetine treatment is also associated with small increases in blood pressure, which should be measured prior to initiating treatment and periodically throughout treatment.

**Drug Interactions:** A potentially important characteristic of antidepressants is their impact on the inhibition of the cytochrome P450 (CYP) system of enzymes responsible for the metabolism of a number of commonly used medications (**TABLE 9**).<sup>92,93</sup> The inhibitory effect of various antidepressants on the CYP systems are listed in **TABLE 10**.<sup>82</sup> Fluoxetine and fluvoxamine inhibit several enzyme systems and therefore hold the greatest potential risk for drug interactions. Although this is not usually a problem for patients not being treated with other medications, it is a factor to consider in an older patient on other medications. Venlafaxine, citalopram, and mirtazapine have low risk, with interactions less likely to occur. In addition, many antidepressant agents are metabolized by CYP enzymes, so there is also potential for interactions when they are given with other drugs that affect these enzymes. This is also true if it becomes necessary to change from one SSRI to another, when both antidepressants are metabolized by the same CYP system.

**TABLE 9 Medications Metabolized by Cytochrome P450 Enzymes**

CYP enzyme	Medications
CYP 1A2	Amitriptyline, imipramine, clozapine, olanzapine, thioridazine, propranolol, tacrine, theophylline, warfarin
CYP 2C9/10	Phenytoin, warfarin, tolbutamide
CYP 2C19	Citalopram, clomipramine, imipramine, mephenytoin, propranolol, diazepam
CYP 2D6	Antiarrhythmics (ie, encainide, mexiletine, propafenone), antipsychotics (ie, haloperidol, risperidone, thioridazine, clozapine), beta-blockers, opiates, SSRIs (ie, paroxetine, fluoxetine), bupropion, TCAs (ie, desipramine, imipramine, maprotiline, amitriptyline, nortriptyline), venlafaxine, nefazodone
CYP 3A3/4	Acetaminophen, antiarrhythmics (ie, propafenone, quinidine), anticonvulsants (ie, carbamazepine), antihistamines (ie, hismanal, loratadine), antipsychotics, benzodiazepines (ie, alprazolam, diazepam, etc), calcium-channel-blockers, macrolide antibiotics, steroids (ie, estrogen, testosterone, cortisol), tamoxifen, omeprazole, lovastatin, antidepressants, (ie, nefazodone, sertraline, venlafaxine, bupropion, TCAs)

CYP=cytochrome P450; TCA=tricyclic antidepressant; SSRI=selective serotonin reuptake inhibitor

Adapted from: Preskorn SH. *Clin Cornerstone*. 1999;1:31-55. Goldberg RJ. *Arch Fam Med*. 1996;5:406-12. Richelson E. *J Clin Psychiatry*. 1998;59(suppl 10):22-6.

**TABLE 10 Cytochrome P450 Profiles of Antidepressant Agents**

	CYP 1A2	CYP 2C9/10	CYP 2C19	CYP 2D6	CYP 3A3/4
Bupropion	-	-	-	+	-
Citalopram	-	-	-	-	-
Duloxetine	-	-	-	+	-
Escitalopram	-	-	-	+	-
Fluoxetine	-	++	++	++	-
Fluvoxamine	++	-	++	-	++
Mirtazapine	-	-	-	-	-
Nefazodone	-	-	-	-	++
Paroxetine	-	-	-	++	-
Sertraline	-	-	-	+	-
Trazodone	-	-	-	-	-
Venlafaxine	-	-	-	-	-

Adapted from: Preskorn SH. *Clin Cornerstone*. 1999;1:31-55.

## Guide to Use of Antidepressants

### Titration

Once an antidepressant has been selected, a trial can be initiated at doses suggested in **TABLE 11**, which also includes the target dose for titration after five to 10 days as well as the step-up dose (the maximum dose recommended above which no further beneficial effect is anticipated). For elderly patients, the dose should be reduced, generally to one-half of the initial dose, and slowly titrated to the initial recommended dose over five days and then to the target dose over the following five to seven days. Patients should be carefully monitored to assess their response to therapy and the emergence of side effects. However, in one study, during the first four weeks of treatment with antidepressants, 55% of patients saw a health care provider for any purpose, and only 18% saw a provider for mental health care.<sup>94</sup>

**TABLE 11** Guide to Using Selected Antidepressants

Generic	Brand	Initial Dose	Target Dose	Step-up Dose
<b>SSRI</b>				
Citalopram	Celexa®	20 mg/d	20 mg/d	40 mg/d
Escitalopram	Lexapro®	10 mg/d	10 mg/d	20 mg/d max
Fluoxetine	Prozac®	20 mg q am	20 mg q am	40-60 mg q am
Fluvoxamine	Luvox®	50 mg qhs	100-150 mg/d	200-300 mg/d
Paroxetine	Paxil®	20 mg/d	20 mg/d	50 mg/d
Sertraline	Zoloft®	50 mg/d	100 mg q am	150-200mg q am
<b>TCA</b>				
Amitriptyline	Elavil®, Endep®	25 mg qhs	100 mg qhs	150 mg qhs
Doxepin	Sinequan®	25 mg qhs	100 mg qhs	150-200 mg qhs
Imipramine	Tofranil®	25 mg qhs	100 mg qhs	150-200 mg qhs
Nortriptyline	Aventyl®, Pamelor®	10-25 mg/d	50-150 mg/d	monitor levels
<b>Miscellaneous</b>				
Bupropion	Wellbutrin®	75-100 mg BID	150 mg BID	150 mg TID
Duloxetine	Cymbalta®	20-30 mg/d	30 mg BID	60 mg/d max for depression
Mirtazapine	Remeron®	15 mg qhs	30 mg qhs	45 mg qhs
Trazodone	Desyrel®	50 mg qhs	200 mg qhs	200 mg BID
Venlafaxine	Effexor®	37.5 mg BID	75 mg BID	375 mg/d max.

TCA = tricyclic antidepressant; SSRI = selective serotonin reuptake inhibitor

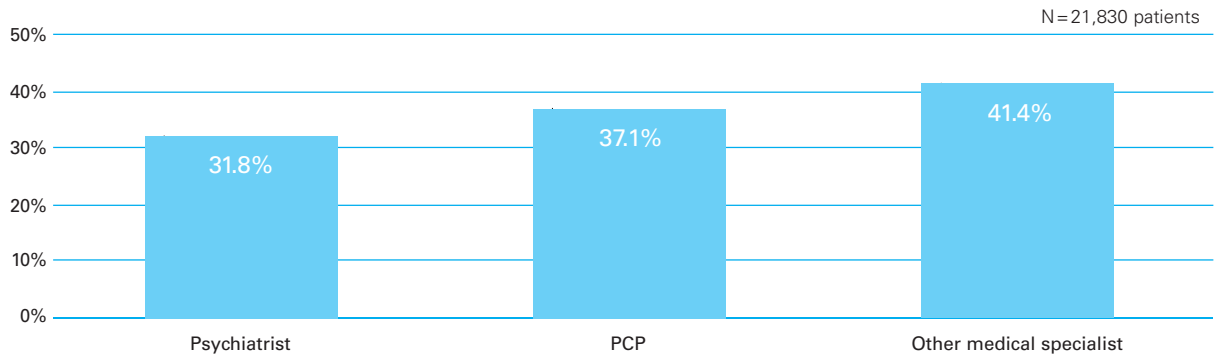
The full therapeutic effect of an agent may not be achieved until after four to six weeks of use, at which time the PCP should decide whether to maintain the target dose, increase it to the step-up dose, or change treatment (switching or augmenting). However, 30% to 40% of patients fail to continue antidepressant treatment over this acute phase (FIGURE 6).<sup>3,95</sup> Patients should be informed that it takes six weeks to determine the full effectiveness of the agent, although some patients may see some improvement in depression symptoms by the end of the first week of SSRI use.<sup>96</sup> Managing patients' expectations at treatment initiation rather than midway through a trial may increase adherence (TABLE 12).<sup>97</sup>



For patients who respond to therapy, it is recommended to continue treatment for a minimum of six to nine months after recovery, with follow-up visits every one to three months. However, about 50% of depression patients terminate pharmacotherapy prematurely, before completion of the continuation phase or in the early maintenance phase, which is associated with worse outcomes.<sup>98</sup> This may be due in part to discrepancies that exist between instructions physicians report they communicate to patients and what patients remember being told.<sup>99</sup> In one study, 72% of physicians reported that they usually ask patients to continue using antidepressants for at least six months, but only 34% of patients reported that their physicians asked them to continue using antidepressants for this duration.<sup>99</sup> Patients who remembered being told to take their medication for less than six months were three times more likely to discontinue therapy than patients who said they were told to take therapy for longer.<sup>99</sup>

**Managing Side Effects**

Managing side effects associated with antidepressants is essential for patient well-being and adherence. In addition, intolerance to one antidepressant does not necessarily mean intolerance to another, even within the same class.<sup>97</sup>

**FIGURE 6 Patient's Early Discontinuation of Antidepressants by Medical Specialty**

Lewis E, et al. *Psychiatr Serv.* 2004;55:494.

**TABLE 12 Increasing Adherence**

**To increase adherence to prescribed medication, advise the patient of the following:**

- Most people need to be on medication for at least 6 months.
- It may take from 2-6 weeks before the patient sees improvement.
- Take the medication as prescribed, even after the patient starts feeling better.
- Do not stop taking the medication without calling the provider. Side effects can be managed by changes in the dosage or dose schedule.

Institute for Clinical Systems Improvement. Major depression in adults in primary care. 2006.

Patients treated with SSRIs should be informed that nausea, insomnia, and anxiety/agitation are expected to spontaneously resolve within 10 to 14 days. When management is necessary for insomnia, interventions include dosing the antidepressant earlier in the day or decreasing the dosage.<sup>100</sup> Other potential options include adding trazodone or mirtazapine (which have sedative as well as antidepressant properties), adding a sedative/hypnotic (eg, zolpidem, zaleplon), or switching the antidepressant to one that is more sedating if these interventions are ineffective.

**Sexual Dysfunction:** Sexual dysfunction is a common side effect associated with antidepressant use, particularly SSRIs and SNRIs, which can negatively affect patients' satisfaction with treatment. Types of antidepressant-related sexual dysfunction are:<sup>101;102</sup>

- Altered sexual desire (loss or lack of desire).
- Orgasmic and ejaculatory dysfunction (anorgasmia, hyperorgasmia, painful orgasm, inhibited ejaculation).
- Erectile problems (erectile dysfunction, priapism, painful erection).
- Other problems (sexual arousal, reduced satisfaction, lubrication, dyspareunia, vaginismus).

The typical rate of sexual dysfunction reported with SSRIs is about 30%.<sup>103;104</sup> However, some studies have reported rates of sexual dysfunction up to 65% with SSRI use when they did not control for other contributing factors, such as possible age-associated sexual dysfunction, comorbid illnesses, other medications that might affect sexual function, and substance use disorders.<sup>102</sup> Therefore it is important to establish the patient's baseline sexual functioning before antidepressants are implicated.<sup>103;105</sup> Antidepressants such as bupropion that do not directly effect serotonin function have the lowest prevalence of dysfunction (7%).<sup>103;104</sup>

Sexual dysfunction attributed to antidepressant medication may reduce adherence to medications, particularly once patients achieve remission. Approximately one-third of patients find antidepressant-induced sexual dysfunction to be an unacceptable side effect of treatment, constituting possible grounds for treatment discontinuation.<sup>103</sup> Patients often find it difficult to discuss this subject and are not likely to spontaneously report sexual dysfunction to their physician, so careful inquiry is necessary.<sup>103</sup> Conservative approaches that may resolve the problem include:<sup>102;103</sup>

- **Watchful waiting**
  - Generally spontaneous remission occurs in only 5% to 10% of patients.
- **Dose reduction**
  - Gradual dose reduction may be useful in some patients, especially those experiencing other side effects. This should only be used in patients who have responded to the medication.
- **Drug holiday**
  - Patient is advised to skip the antidepressant for one or two days; this can be effective but can also undermine adherence.
  - This is only effective with an antidepressant that has a short half-life, such as the atypical antidepressant venlafaxine or the SSRI paroxetine.
  - For example, advise patient to skip one daily dose of SSRI (eg, Friday) when planning sexual activity for the next day, and take the SSRI immediately after the sexual activity (in this case Saturday). With a short half-life medication, the amount of drug present at the time of sexual activity is minimal and the patient only misses one dose per week of medication (eg, Friday).
  - This is only helpful for a patient in full remission who is willing to make specific plans for sexual activity in advance and to have sexual activity no more than about once a week; for some patients the compromise in spontaneity is acceptable, given that the medication has so greatly improved the rest of their QOL or, in some cases, has saved their life.

A switch to a different class of agent that works through a different mechanism of action with less potential for causing sexual dysfunction (eg, mirtazapine, bupropion) is another strategy.<sup>102;103;106-108</sup> Augmentation with bupropion is commonly used to improve SSRI-associated sexual side effects in both men and women, with most improvements occurring within the first two weeks.<sup>109;110</sup> Adding the phosphodiesterase inhibitors sildenafil and tadalafil have been shown to improve erectile function and other aspects of sexual dysfunction in men with SSRI-associated erectile dysfunction.<sup>102;111-114</sup> Buspirone augmentation has also shown some improvement in SSRI-induced sexual dysfunction.<sup>108;115</sup>

Anecdotal evidence exists for adding other agents that have been tested in open-label nonrandomized studies, case series, and case reports, but the results must be interpreted with caution. These agents include cyproheptadine (an antihistamine and 5HT<sub>2A</sub> antagonist), yohimbine (an alpha-2 adrenoceptor antagonist), amantadine (a dopamine agonist), and ginkgo biloba (a herbal medication).<sup>102;108</sup>

**Weight Gain:** Long-term antidepressant-induced weight gain can be a reason for drug discontinuation.<sup>116;117</sup> Weight gain is also a risk factor for medical complications such as diabetes, hypertension, and heart disease.<sup>118</sup> Knowing which antidepressant drugs are more likely to cause short- and long-term weight gain is important when selecting a drug for a patient in order to enhance adherence and prevent the metabolic sequelae of weight gain (**TABLE 13**).<sup>118;119</sup>

All TCAs and MAOIs are associated with weight gain.<sup>116;117</sup> The SSRIs were originally hypothesized to promote weight loss, but this antidepressant class has variable effects on weight gain.<sup>116</sup> Paroxetine may be more likely to produce the greatest long-term increase in weight than the other SSRIs, while fluoxetine and sertraline, for example, produce modest degrees of weight gain in some studies.<sup>116;120</sup> Among the atypical antidepressants, venlafaxine has been shown to be weight-neutral, duloxetine may induce a small weight gain over long-term treatment, and mirtazapine produces the greatest increase in both short- and long-term weight.<sup>116</sup> Bupropion has the least amount of associated weight gain and may induce long-term weight loss.<sup>116;121</sup>

**TABLE 13** Effect of Antidepressants on Weight

Drug/drug class	Effect on weight
MAOIs (irreversible)	Short- & long-term weight gain likely
TCA's	Short- & long-term weight gain likely
Mirtazapine	Short-term weight gain possible
SSRIs other than paroxetine	Short-term weight gain less likely; long-term weight gain possible, but evidence is varied
Paroxetine	Short- & long-term weight gain more likely than for other SSRIs
Nefazodone	Likely to have no effect on weight
Venlafaxine	Likely to have no effect on weight
Bupropion	May cause weight loss

Adapted from: Deshmukh R, Franco K. Cleve. *Clin J Med*. 2003;70:614-23.

When treatment-resistant depression is managed by augmentation with antipsychotic medications, the metabolic side effects (weight gain, dyslipidemia, increased susceptibility to diabetes) are particularly worrisome.<sup>122</sup> Their effects on body weight range from modest to large increases.<sup>123</sup>

### Risk of Suicide

Severe depression is also a major risk factor for suicide, and up to 15% of those hospitalized for depression eventually succumb to suicide.<sup>124</sup> Suicide is the third leading cause of death in adolescents and young adults in the United States, the majority of whom have a psychiatric illness, most commonly a mood disorder.<sup>125;126</sup> Suicide is still rare in youth, however, although suicidal ideation or attempts are relatively common.<sup>125</sup> Ever year, 19% of teenagers have suicidal ideation, 9% make a suicide attempt, but fewer than 0.1% actually complete suicide.<sup>125</sup> Among youth receiving care for depression the risks are higher: 35% to 50% have made, or will make, a suicide attempt, and 2% to 8% will die by suicide in a decade.<sup>125</sup>

Concerns about the effect of SSRIs on the risk of suicide arose from the higher frequency of suicide attempts reported with antidepressants relative to placebo among children and adolescents in randomized controlled trials (RCTs).<sup>125-129</sup> A study in older patients also found a substantial increase in relative risk of suicide following the initiation of SSRI treatment, but this was confined to the initial month of therapy and the absolute risk of suicide during the first month of treatment with SSRIs was still very low.<sup>124</sup> Several anecdotal reports also described the emergence of intense suicidality during the initial period of SSRI therapy, but it is difficult to separate the role of depression from a possible adverse effect of treatment.<sup>124</sup>

Several mechanisms are proposed to underlie the association between SSRIs and suicide.<sup>124</sup> During initial therapy, the risk of suicide ideation may increase as some aspects of depression resolve (eg, psychomotor retardation), thereby energizing the patient to suicide.<sup>124</sup> A study of psychotherapy for adolescent depression found that the incidence of emergent suicidality in depressed adolescents not receiving antidepressants was 12.5%, similar to rates observed in antidepressant trials.<sup>130</sup> Patients may also develop akathisia-like symptoms during treatment with SSRIs, which may increase the risk of suicide.<sup>124</sup> An alternative explanation is that physicians preferentially prescribe SSRI antidepressants to patients who are at higher risk of suicide because this class is safer in overdose.<sup>124</sup>

To examine the question of whether antidepressant drug treatment may induce suicidal behavior and ideation, the Food and Drug Administration (FDA) evaluated clinical data from manufacturer-sponsored short-term RCTs of nine commonly used antidepressants.<sup>131</sup> They found insufficient evidence that antidepressants were associated with an increased risk of completed suicide among patients with major depression, although they did not definitively exclude the association.<sup>131</sup> The FDA decided to require a black-box warning regarding clinical worsening and suicide risk among

children and adolescents for all antidepressants.<sup>126,129</sup> This decision sparked a debate over the relative risk of antidepressants compared with no antidepressants in suicidal youth.<sup>126,129</sup> An unintended consequence of the change in labeling may be a reduction in antidepressant prescriptions, particularly for youth, which may lead to an increase in youth suicide.<sup>126</sup>

In a national observational study, US counties with higher rates of SSRI use had lower suicide completion rates in children and young adolescents.<sup>125</sup> This is consistent with other observational studies that found increasing rates of adolescent antidepressant use were accompanied by stable or declining suicide rates.<sup>132-135</sup> However, although most seek professional help within one month before death, mostly with PCPs, only 2% of youth suicides are receiving medication at the time of suicide.<sup>125,136,137</sup> In addition, poor adherence among youth who are receiving antidepressant treatment may aggravate the problem; for example, in a study of 49 suicides in Utah, 24% had been prescribed antidepressants, but none tested positive for SSRIs at the time of death.<sup>125,138</sup> In the study among older patients, more than two-thirds of cases completed suicide while **not** receiving an antidepressant.<sup>124</sup> These findings suggest that lack of treatment contributes to suicide risk, and that more widespread antidepressant treatment may reduce suicide rates.<sup>125,126</sup>

The ACNP recommends clinicians treating depressed youth ask about suicide and suicidal thinking and perform ongoing monitoring, but that patients should continue to receive appropriate medications when indicated.<sup>126</sup> A suggested response to patients or families concerned about the risk of suicide with SSRIs is:<sup>132</sup>

The FDA requires a warning that antidepressants can sometimes cause or increase thoughts of suicide. Studies in children and adolescents have shown that antidepressants can increase suicidal thoughts. However, other studies have shown that the overall risk of attempting suicide goes down after starting antidepressant medication. Even if antidepressants help most people who take them, some people may have negative reactions. Thus it is important that we have regular contact over the next few weeks. If you have thoughts about suicide or harming yourself, please contact me right away.

The FDA warning label recommended pattern of follow-up care for pediatric patients prescribed antidepressants is:<sup>139</sup>

- At least weekly face-to-face visits during the first four weeks of treatment.
- Visits every other week during the next four weeks.
- A visit at 12 weeks of treatment.
- Visits as clinically indicated beyond that point.

Additional contacts by telephone as needed are encouraged between face-to-face visits.<sup>139</sup> While the impetus for the formation of these recommendations was the need for close follow-up in pediatric patients, they are also helpful minimum recommendations for adults at risk for suicidal ideation. The actual follow-up schedule for any given patient is decided by the physician based on many clinical variables, and the above are merely general recommendations.

### *Discontinuing Therapy*

In patients in whom you choose to discontinue serotonergic antidepressant therapy upon reaching the maintenance phase (eg, low-risk patients who have remained well during the continuation phase), it is advisable to taper by approximately 20% every one to two weeks for most agents, to avoid precipitating a serotonin reuptake inhibition discontinuation syndrome. This syndrome is not an issue for fluoxetine because its half-life is considerably longer than the other agents (one to four days), as is the half-life of its major metabolite norfluoxetine (seven to nine days) (**TABLE 14**). When discontinuing treatment, inform the patient of the possibility of recurrence.



**TABLE 14** Half-Lives of SSRIs and Select Novel Agents

Agent	Half-life
Bupropion	21 hours
Citalopram	35 hours
Duloxetine	12 hours
Escitalopram	27-32 hours
Fluoxetine	1-4 days
Norfluoxetine	7-9 days
Fluvoxamine	16 hours
Paroxetine	21 hours
Sertraline	26 hours
Venlafaxine	5 hours
O-desmethylvenlafaxine	11 hours

SSRI = selective serotonin reuptake inhibitor

Adapted from: Prescribing information for individual agents

## Psychotherapy

Psychotherapy can be as effective as medication in the acute treatment of mild to moderate depression, appears to be cost effective, and also yields enduring effects in preventing relapse of symptoms that extend beyond the end of treatment.<sup>140-147</sup> **TABLE 15** illustrates some brief psychotherapy techniques and **TABLE 16** describes the basic principles of cognitive restructuring. Benefits for PCPs from understanding the basic principles of pharmacotherapy in the treatment of depression and the formats (individual, family, marital/couple, group) in which psychotherapy is typically delivered include:

- Better use of referral resources for patients who can benefit from psychotherapy.
- Select appropriate technique (eg, cognitive behavioral therapy [CBT] to improve maladaptive thoughts / behaviors; interpersonal therapy so they can relate to others more effectively and become less isolated).
- Answer patient questions and overcome barriers to mental health care.
- Assist and communicate with mental health specialists.
- Solo practice in isolated areas.



Psychotherapy can be considered as monotherapy, especially in patients who prefer to avoid medication or who are resistant to antidepressant therapy. However, it is important that patients do not feel a referral means the physician is rejecting or “dumping” them or has dismissed the problem as “all in your head.”<sup>148</sup> In one trial, response rates to antidepressant (50%) and CBT (43%) groups at eight weeks were both superior to placebo (25%).<sup>140</sup> Many depressed patients in primary care, particularly older adults, indicate a preference for counseling or psychotherapy over antidepressant medication, but fewer than 10% had received such treatment in the previous three months in one study, and only 1% reported four or more counseling sessions.<sup>149</sup>



Psychotherapy is increasingly provided in conjunction with antidepressant drugs.<sup>150</sup> Combined therapy has proven to be more efficacious (85% response rate vs 55% and 52% in the antidepressant and psychotherapy monotherapy group by week 12) and patients who receive psychotherapy are significantly more likely to continue antidepressant

**TABLE 15** Brief Psychotherapy Techniques**Serenity pledge/prayer**

- I promise...to work as hard as I can to change the things I can change.
- I promise...to accept the things I cannot change.
- I promise...to work on the wisdom to know the difference.

**Two-column thought record**

- |                                   |   |
|-----------------------------------|---|
| ■ What if everyone hates my talk? | ■ That's never happened in 20 years' of presentations.      |
| ■ I'll never be invited back.     | ■ If it does today, unpleasant but not catastrophic.        |
| ■ I'll be a failure.              | ■ My self worth doesn't depend upon my performance/success. |

**0-100% mood/event rating**

1. I'm 90% mad about getting this ticket.
2. In the big picture, the ticket is worth a 2% rating.

**Tantrum time**

Schedule time (deliberately) to whine/pout/moan (safely), then release and go on.

treatment beyond 30 days.<sup>95,144</sup> Short-term CBT after successful antidepressant drug therapy can also have a substantial effect on relapse rate after discontinuation of antidepressants.<sup>151</sup> CBT may prevent relapse by training patients to change the way that they process depression-related cognitive material.<sup>152</sup>

Reasons for providing combined treatment include enhanced:<sup>141</sup>

- Magnitude of response (ie, more complete benefit in terms of symptom reduction or improved daily function from the combination than from either modality).<sup>141</sup>
- Probability of response.<sup>141</sup>
- Breadth of response (medications may work faster than some types of psychotherapy, but certain types of psychotherapy have broader or more enduring effects than medication).<sup>141</sup>
- Acceptability of treatment relative to the single modality (adding medication can make some patients more receptive to psychotherapy, whereas adding psychotherapy can make some patients more willing to accept medications or tolerate side effects).<sup>141</sup>

There are no side effects from psychotherapy and a long-lasting learning effect may be achieved. However, psychotherapy is time consuming, may take longer to show an effect, and may not be available or reimbursable. Psychotherapy can fail when patients have unrealistic expectations of immediate total relief, wait until they "feel like" working at therapy, or stop treatment or practice after quick initial relief. For example, CBT requires patients to actively participate in their own treatment by monitoring themselves and doing homework, which may not occur with unmotivated or resistant patients.<sup>148</sup>

Computer-assisted CBT for depression is emerging as a method to make treatment available to more patients.<sup>153</sup> One study demonstrated that computer-assisted CBT with 50% less therapist contact was as efficacious as standard CBT; however, its utility in the primary care setting has not yet been demonstrated.<sup>153</sup>

**TABLE 16 Basic Principles of Cognitive Restructuring**

<p><b>Step 1:</b> Identify the internal dialogue (thoughts) in a specific situation that leads to excessive or unwanted anxiety, anger, guilt, or depression. Identify:</p> <ol style="list-style-type: none"> <li>1. thoughts about yourself</li> <li>2. thoughts about others involved</li> <li>3. thoughts about the situation</li> </ol>
<p><b>Step 2:</b> Identify any of the irrational ideas that might be supporting the thinking in Step 1.</p>
<p><b>Step 3:</b> Challenge any irrational or rationalized thinking in Steps 1 and 2 by identifying:</p> <ol style="list-style-type: none"> <li>1. what is true that you are thinking</li> <li>2. what is not true that you are thinking</li> <li>3. identify any catastrophic (“what if...”), awfulized (“It would be awful...”), or absolutistic (“I must, I should...”) thinking</li> </ol>
<p><b>Step 4:</b> Substitute specific rational thoughts that when thought, lead to less anxiety, anger, guilt, or depression. These thoughts must be <b>true</b> and be directly counter to the thoughts that were disruptive.</p>

## Other Treatment Strategies

### Exercise

Exercise can be effective in reducing symptoms of depression and should be encouraged. Exercise has a physiologic effect on the patient by changing the endorphin and monoamine concentrations.<sup>154</sup> Depressed patients who exercise regularly may also receive positive feedback from others, exercise may act as a diversion from negative thoughts, and mastery of new skills may be seen as a notable accomplishment to patients.<sup>154</sup> Exercise used as an augmentation strategy to antidepressant therapy may further reduce depressive symptoms in partial responders to pharmacotherapy.<sup>155</sup> Aerobic exercise at a dose consistent with public health recommendations has been shown to be effective in treating mild to moderate depression, while a lower dose is comparable to placebo effect.<sup>156</sup> Patients of all ages with depression should be advised of the benefits of following a structured and supervised exercise program of typically up to three sessions per week at moderate duration (45 minutes to one hour) for 10 to 12 weeks.<sup>9</sup>

### Alternative Therapies

The use of St. John’s wort (*Hypericum perforatum*) for depression has remained popular in the United States and is the most commonly prescribed treatment for depression in Germany.<sup>157</sup> Its mechanism of action is thought to be inhibition of reuptake of 5HT, DA, and NE, as well as activation of gamma-amino-butyrate and glutamate receptors.<sup>157-159</sup> However, despite the popularity of St. John’s wort, its effectiveness in the treatment of depression is uncertain. Although several meta-analyses of RCTs have found St. John’s wort to be superior to placebo and equivalent to standard antidepressants for the treatment of mild to moderate depression, studies in major depression have had conflicting results.<sup>157;158;160;161</sup> In one trial where St. John’s wort was unsuccessful in patients with major depression, the investigators concluded that it should not be considered for such patients due to the risks associated with untreated major depression.<sup>162</sup>

St. John’s wort is considered to have few serious adverse effects and only the expected mild side effects (ie, GI upset, anxiety, minor palpitations, transient photosensitivity, fatigue, restlessness, dry mouth, headache, increased depression).<sup>158;163</sup> However, potentially dangerous drug-drug interactions can occur; for example, St. John’s wort taken with an SSRI could potentially cause a mild serotonin syndrome, and St. John’s wort can induce the activity of CYP 3A4, which plays a role in the metabolism of many medications, decreasing their blood drug levels.<sup>158;163;164</sup> St. John’s wort interacts with many commonly prescribed medications for general medical conditions. If a patient is taking St. John’s wort, a text or computer program on adverse drug-drug interactions should be consulted to assess the compatibility of St. John’s wort with the patient’s full medication list.

### *Omega-3 Fatty Acids*

Deficits in omega-3 fatty acids have been identified as a contributing factor to mood disorders.<sup>165</sup> Several studies have supported omega-3 supplementation as having a distinct antidepressant role, either directly or by augmenting standard antidepressants.<sup>165</sup> However, further research is required to verify this and to determine which omega-3 fatty acid is likely to have the greatest benefit and at what dose.<sup>165</sup>

### *Light Therapy*

An analysis of RCTs suggests that bright light treatment and dawn simulation for seasonal affective disorder and bright light for nonseasonal depression are efficacious, with effect sizes equivalent to those in most antidepressant pharmacotherapy trials.<sup>166</sup> However, the meta-analysis was restricted to a small number of studies that met the standard for inclusion.<sup>166</sup> Several side effects of bright light therapy have been described, including headache, eye strain, nausea, and agitation.<sup>166</sup> In addition, some psychotropic medications may increase photosensitivity, so further study of potential adverse effects of combined pharmacotherapy and light therapy is indicated.<sup>166</sup> Many questions of efficacy, safety, optimum dose, and the proper place of light therapy in the treatment of depressive disorders remain.<sup>166</sup>

# Remission

Full remission of symptoms is the optimal outcome of depression treatment, as opposed to settling for a significant but partial response.<sup>70;73;167</sup> The attainment of full remission is important because of the marked difference in relapse and recurrence rates seen in patients with a full response versus those with residual symptoms. Although relapse can occur after patients achieve full remission, the presence of residual symptoms increases the risk by four-to-five-fold (**FIGURE 7**).<sup>70;75;168-170</sup> Remission also has a beneficial economic impact — in one study, patients who achieved full remission averaged three fewer outpatient visits and 22 fewer sick-leave days during the six-month study period.<sup>171</sup> In another study, mental health and general medical service utilization costs were approximately 50% higher for patients with persistent depression than for patients who achieved full remission (**FIGURE 8**).<sup>71</sup>

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## Barriers to Remission

Although the majority of patients with depression will respond to antidepressant therapy, a significant portion of patients, even those receiving adequate therapy, achieve only partial remission.<sup>71;167</sup> A number of factors may be responsible for this. Some patients and physicians may be satisfied with partial improvement in symptoms and may not pursue full remission as the outcome of treatment.<sup>172</sup> Other patients may not tolerate or may be unwilling to accept side effects associated with the optimal dosages of medications, leading to nonadherence.<sup>167</sup> Underdosing is common by physicians who may be uncomfortable or unfamiliar with recommended optimal dosages. Other reasons for not achieving full remission include failure to recognize residual symptoms, inadequate follow-up, the presence of continued psychosocial stressors (eg, poverty, marital discord), and stigma.

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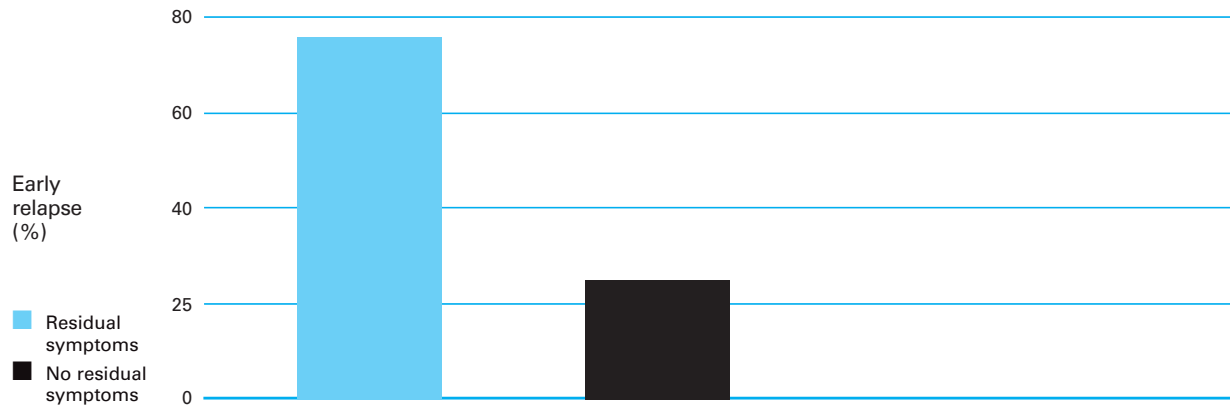
## Treatment-Resistant Depression

Treatment-resistant depression (TRD) is common, but a clear definition has not been established.<sup>173</sup> It is commonly defined as failure to respond to two or more adequate trials of different antidepressants.<sup>173</sup> However, the duration of the trials, whether different antidepressant classes should be involved, and how to measure response are not well defined. In addition, many patients who are considered treatment resistant are misdiagnosed or inadequately treated.<sup>173</sup>

Only 25% to 40% of depressed patients achieve full remission with the first course of therapy, and treatment resistance (including nonresponse and partial inadequate response) after multiple antidepressant trials is estimated to occur in 10% to 20% of patients.<sup>174;175</sup> When faced with a patient with TRD, it is important to consider problems with patients' medication adherence, whether the diagnosis of MDD is correct (bipolar depression is often overlooked), whether there are any comorbid medical or psychiatric diagnoses that are affecting the treatment outcome, and whether the patient has environmental stressors (eg, family, work, or financial difficulties).<sup>173;174;176</sup> Thyroid disorders, stroke, and HIV are examples of comorbid medical illnesses that may be associated with poor antidepressant response. Depressive subtypes that may require specific therapy include depression with psychotic features, depression with atypical features, and seasonal depression.<sup>175;1760</sup>

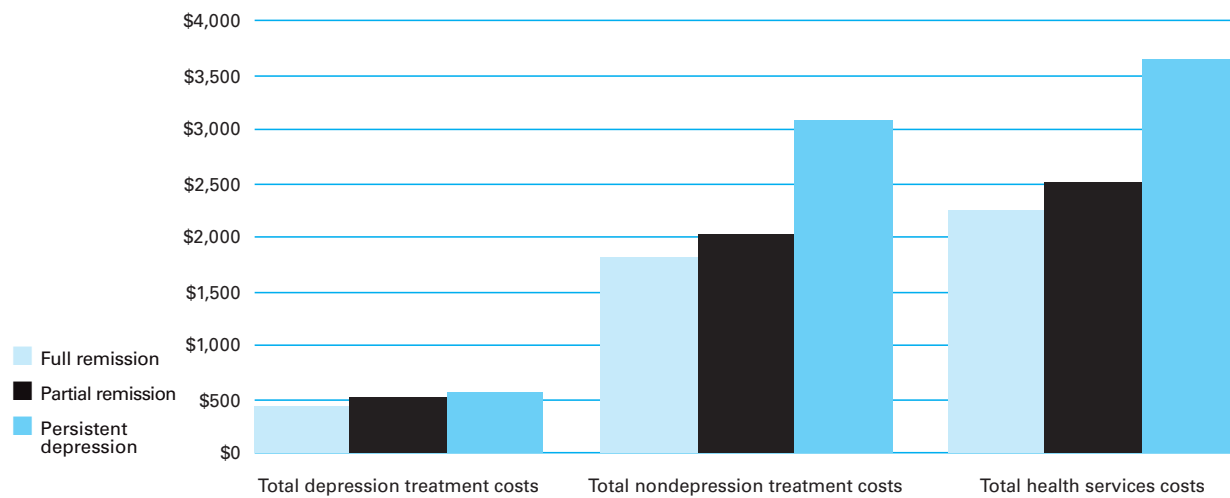
Lack of adequate dose is a major issue for the TCAs, with their narrow therapeutic index, but is less important for the SSRIs. Venlafaxine may have an ascending dose-response curve, with serotonergic effects seen at lower doses and higher doses required for the noradrenergic effects of this dual-mechanism agent.<sup>177</sup> The usual target dose of nefazodone

**FIGURE 7 Residual Symptoms as Predictors of Relapse**



Paykel ES, et al. *Psychol Med.* 1995;25:1171-80.

**FIGURE 8 Health Services Costs Over the Subsequent 6 Months According to Acute Phase Depression Outcome**



Simon GE, et al. *J Clin Psychiatry* 2006; 67(8):1226-1231.

is 300 mg daily, but more than 400 mg daily may be needed for full response to this agent (however, please note the warning regarding nefazodone on page 15). Antidepressant plasma levels are sometimes useful to check for nonresponsive patients on nortriptyline, desipramine, or imipramine. For patients on SSRIs or other new antidepressants, there is no correlation between plasma drug levels and efficacy, although plasma levels may be useful to check for poor adherence.

An inadequate trial of treatment may also be responsible for TRD. Six weeks is usually considered an adequate trial, but this is not always the case. One study found a 31% to 41% remission rate at week 12 in patients with major depression who were nonresponsive to fluoxetine at six weeks.<sup>178</sup> However, another study found that nonresponse to fluoxetine as early as week two predicted an unfavorable outcome at eight weeks.<sup>179</sup> The proportion of patients who showed no improvement at weeks two, four, and six but who responded by week eight was 36%, 19%, and 6.5%, respectively.<sup>179</sup> More recently, a large prospective study of Sequenced Treatment Alternatives to Relieve Depression (STAR\*D) looked at 3,671 patients with depression at 41 sites, 18 of which were primary care facilities.<sup>72</sup> The four-step study design was based on the principle that an adequate dose of a given medication needs to be tried for an adequate period of time in order to determine the drug's effectiveness.<sup>72</sup> Rather than a typical four- or six-week clinical trial, patients remained in a treatment step for a range of 8.6 to 10.1 weeks, and the goal of treatment was remission.<sup>72</sup>

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### Options for Inadequate Response

For patients who do not respond to initial treatment, options include optimizing the initial medication treatment, switching to another antidepressant agent, combining antidepressants, augmenting antidepressant medications with other agents or psychotherapy, or electroconvulsive therapy (ECT).

The STAR\*D study confirms that about one-third of patients achieve remission with initial treatment and that remission rates decline with successive treatment failures.<sup>72;75;84</sup> Remission rates were 36.8%, 30.6%, 13.7%, and 13% after treatment steps one through four, which, although modest, does offer some hope to patients that successive treatments will increase their chance for remission.<sup>75</sup> Step one involved an SSRI agent, while level two provided seven possible treatments, including CBT.<sup>72</sup> Those who did not achieve remission or who were unable to tolerate treatment steps were encouraged to move to the next step, while those with an acceptable benefit, preferably remission, from any particular step could enter a 12-month naturalistic follow-up phase.<sup>72</sup> Patients who required more treatment steps tended to have greater depressive illness burden and more concurrent psychiatric and medical disorders.<sup>72</sup> For those who achieved remission at each step, the times to remission were 5.4 to 7.4 weeks across the four treatment steps.<sup>72</sup>

Consistent with prior data, patients who achieve remission are less likely to relapse than patients who have only responded (ie, persistent symptoms despite 50% or greater improvement in their rating).<sup>75</sup> In the STAR\*D study, rates of relapse increased with each treatment step; among those achieving remission, relapse rates were 33.5%, 47.4%, 42.9%, and 50.0% after the four treatment steps.<sup>75</sup> Relapse rates were even higher in patients who improved but did not achieve remission (range 59% to 83%).<sup>75</sup>

#### Switching

Potential advantages of switching to another antidepressant agent include improved adherence, reduced medication costs, and fewer drug interactions.<sup>180</sup> Preliminary data suggests equal efficacy when switching antidepressants within the same class or across classes.

Studies have generally shown about a 50% response when switching from one SSRI to another, although many clinicians estimate a lower response.<sup>181-183</sup> However, these studies were open label, uncontrolled, and some included SSRI-intolerant patients as well as patients who did not respond to the first SSRI. Because of their favorable side-effect profile, standard practice is to try one or two SSRI agents before switching classes. Patients who are intolerant to one SSRI may tolerate another because agents in this class are similar, but not identical.<sup>184</sup>

Investigators found that a treatment strategy of switching antidepressant class, from sertraline to imipramine and from imipramine to sertraline, resulted in clinically and statistically significant improvements in TRD.<sup>185</sup> Another trial compared switching to venlafaxine or paroxetine in patients who had failed two previous trials (most had received an SSRI).<sup>186</sup> The response rate was 52% for venlafaxine and 33% for paroxetine, and remission was achieved in 42% of venlafaxine-treated patients, compared with 20% of paroxetine-treated patients.<sup>186</sup> The results suggested

that such a switch outside of a class might offer an advantage, and that the dual action of venlafaxine might offer therapeutic advantages over an SSRI.<sup>186</sup>

The STAR\*D study demonstrated that after unsuccessful treatment for major depression with an SSRI, approximately one in four patients has a remission of symptoms after switching to another antidepressant: either sustained-release (SR) bupropion, sertraline, or extended-release (ER) venlafaxine.<sup>187</sup> These treatments did not differ significantly with respect to outcomes, tolerability, or adverse events.<sup>187</sup> For patients who failed two consecutive medications, switching to a third antidepressant monotherapy, mirtazapine or nortriptyline, resulted in similar remission rates (12.3% and 19.8%, respectively), tolerability, and adverse events.<sup>188</sup> STAR\*D also found that switching to the combination of ER venlafaxine plus mirtazapine in depressed adults who did not achieve remission from three failed antidepressant medication trials was as effective as the MAOI tranylcypromine, but with a lower side effect burden, lack of dietary restriction, and ease of use.<sup>189</sup> However, the remission rates were modest for both treatments (6.9% for tranylcypromine; 13.7% for venlafaxine/mirtazapine).<sup>189</sup>

When switching classes one must exhibit caution, especially if a MAOI is involved and observe the required wash-out times listed in **TABLE 17**. This is important to avoid precipitating a serotonin syndrome, which is manifested by changes in mental status, myoclonus, rigidity, autonomic instability, diarrhea, and rarely rhabdomyolysis and death. Fluoxetine requires the longest washout time because of its long half-life (**TABLE 14**).

A substantial proportion of patients treated for depression also do not respond to their initial trial of depression-targeted psychotherapy, after which there are numerous treatment options involving switching to or augmenting with a medication. However, few studies have evaluated the role of medication following nonresponse to psychotherapy and the efficacy of psychotherapy (switching to or augmenting with) following nonresponse to medication.<sup>190</sup> In a recent crossover study, a switch from an antidepressant medication to psychotherapy or vice versa appears to be useful for nonresponders to the initial treatment.<sup>190</sup>

**Augmentation**

Potential advantages of augmentation include minimizing relapses that can arise from discontinuing the first agent, boosting the function of a neurotransmitter system, and capacity to add a specific neurotransmitter effect. Disadvantages include increased risk for pharmacokinetic interactions, additive side effects, and regimen complexity leading to reduced adherence. Older patients are less likely to receive antidepressant augmentation than younger patients, perhaps due to concerns about adding medications to already complicated medical regimens or because of greater susceptibility to side effects.<sup>191</sup> First-line augmentation strategies have included lithium, thyroid hormones, and stimulants; more recent commonly used combinations are an SSRI with bupropion, and venlafaxine or mirtazapine with bupropion.<sup>192;193</sup> Any two agents may be combined, except an MAOI with a strongly serotonergic antidepressant. Any combination of an MAOI with another agent should be done in consultation with a psychiatrist.

Lithium augmentation of antidepressants is well studied as an effective strategy for treating patients who do not respond to SSRIs, TCAs, or MAOIs, although there are no consistent patient predictors for response.<sup>193;194</sup> In addition, lithium has been shown to be effective in the prevention of suicide, deliberate self-harm, and death from all causes in patients with mood disorders.<sup>195;196</sup> However, it is underutilized in clinical settings (used by just 0.5% of depressed

**TABLE 17 Required Washout Times When Switching Antidepressants**

Antidepressants	Required washout times
Fluoxetine to MAOI	5 weeks
Other SSRI to MAOI	2 weeks
SNRI to MAOI	1 week
MAOI to non-MAOI	2 weeks

MAOI=monoamine oxidase inhibitor; SSRI = selective serotonin reuptake inhibitor; SNRI=serotonin and norepinephrine reuptake inhibitor  
Adapted from: Prescribing information for individual agents

patients), possibly due to negative stigma for some patients and inconsistent acceptance by physicians due to side effects, risk of toxicity, and need for blood monitoring.<sup>191</sup> The time of onset of efficacy is variable, from two days to four weeks, and the optimal lithium plasma levels are not well defined. Discontinuation of lithium during continuation therapy can increase the risk of relapse. Responders to lithium augmentation should be maintained on the lithium-antidepressant combination for a minimum of 12 months.<sup>193</sup>

The addition of thyroid hormone can be effective among depressed patients refractory to antidepressants. In the STAR\*D study, remission rates with lithium and T(3) augmentation for participants who experienced unsatisfactory results with two prior medication treatments did not differ significantly (remission rates were 15.9% with lithium and 24.7% with T(3)).<sup>192</sup> The lower side-effect burden and ease of use of T(3) augmentation suggest that it has slight advantages over lithium for depressed patients who have experienced several failed medication trials.

Anecdotal clinical experience shows that augmenting any of the antidepressant classes with low-dose stimulants such as methylphenidate or dextroamphetamine is another approach, to which there is usually a rapid response (within days) when stimulants are effective.<sup>43,98,99</sup> Response to one stimulant may not predict response to another. Caution is warranted in stimulating severely depressed patients, who may be at increased risk for suicide. Stimulants may also worsen anxiety and irritability and may cause insomnia.<sup>97</sup>

Other augmentation strategies include adding a mood stabilizer (eg, lamotrigine), anxiolytic agent (eg, buspirone), or an antipsychotic agent. Psychiatry consultation should be considered when these combinations are utilized. In the STAR\*D study, augmenting SSRI therapy in patients who did not achieve remission after 12 weeks of therapy with either SR bupropion or buspirone achieved remission in approximately 30% of patients.<sup>197</sup> Augmentation with SR bupropion had fewer side effects and adverse events.<sup>197</sup>

### ECT

Electroconvulsive therapy is highly effective and can be life-saving for patients with major depression who are resistant to antidepressant medications and those diagnosed with chronic and disabling disorders (eg, psychosis, mania) or at high risk for suicide.<sup>198,199</sup> Patients typically receive ECT for acute episodes at a rate of three treatments per week until a positive clinical response occurs (six to 12 treatments).<sup>199</sup> However, relapses are common, exceeding 50% by six to 12 months following acute ECT. Continuation ECT along with long-term antidepressants is more effective in preventing relapse in chronically depressed patients who have responded to acute ECT treatment than treating patients with antidepressants alone after acute ECT.<sup>199</sup> A typical continuation ECT schedule would require therapy weekly for the first month, every two weeks for the following month, and monthly thereafter.

ECT may have a deleterious effect on various components of cognition and memory, most of which dissipates in the days after treatment, although persistent retrograde amnesia may persist.<sup>200</sup> These effects may be influenced by variables such as lead placement, voltage, and treatment frequency; and advancing age, lower premorbid intellectual function, and female gender may be associated with greater persistent cognitive deficits after ECT.<sup>200</sup>

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## When to Refer

The decision to consult with or refer to a mental health professional depends on the individual PCP's judgment of the severity of the problem and his or her own ability to manage it, the patient's preferences, and the availability and cost of mental health services. In the STAR\*D study, 40% of patients were managed by their PCPs.<sup>201</sup>

Many complicating factors render depressed patients difficult to treat.<sup>174</sup> Numerous medical illnesses and a large number of medications used to treat these illnesses can cause or exacerbate depression, or can interfere with the pharmacologic action of antidepressants. Comorbid psychiatric conditions may also complicate the treatment of depression. Many depressed patients have comorbid substance abuse disorders, and even moderate use of alcohol can interfere with the efficacy of antidepressants. Examples of patients who might benefit from referral to a psychiatrist, when such resources are available, are those with more severe symptoms, suicidal tendencies, bipolar disorder, atypical depression, history of mania, or psychotic depression (presence of delusions, hallucinations, or other psychotic symptoms); those who have experienced drug-drug interactions; or those who are treatment resistant.

# Cultural Barriers and Considerations

The Surgeon General's report *Race, Culture, Ethnicity and Mental Health* documented disparities in access to mental health treatment that leave many minority patients untreated or improperly treated.<sup>202</sup> African Americans and Asian Americans, for example, are more likely to obtain mental health care from a PCP than from a mental health specialist.<sup>202,203</sup> However, in primary care, minority patients are less likely than white patients to be identified as depressed and, even when identified, their depression is less likely to be actively managed.<sup>4;204-207</sup>

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## Barriers

There are a number of provider, patient, and practice-setting barriers to the detection and treatment of depression in minorities in primary care.<sup>205</sup> Hispanics and African Americans are underrepresented among mental health professionals, so ethnically matched care is unlikely for many ethnic minorities.<sup>208</sup> White physicians' communication styles have been found to minimize emotional expression by African Americans, relative to white patients, and African American patients are more likely to rate their visits with white physicians as less participatory and collaborative.<sup>205,208</sup> Bias, stereotyping, prejudice, and clinical uncertainty on the part of the provider, whether conscious or subconscious, may contribute to racial disparities.<sup>209</sup>

The concept of depression varies across cultures.<sup>11</sup> In many cultures, for depression to become a problem for which a person seeks medical help, symptoms may include psychosis, conversion disorders, or significant physical ailments.<sup>11;210</sup> During the primary care encounter, African Americans and Asian Americans are more likely to bring up somatic or physical symptoms of depression.<sup>205;211</sup> Minority patients also express more concerns about stigma and are less likely to find antidepressant medication or specialty mental health care acceptable.<sup>205;208;212</sup> Even when they accept antidepressant prescriptions from their providers, African Americans and Hispanics may be less likely to fill the prescription or take the medication.<sup>208</sup> Higher rates of nonadherence with medications among minority groups might be affected by expectations, communication problems, or cost.<sup>11;213</sup> In addition, African Americans tend to tolerate certain classes of psychotropic medications poorly (eg, more likely to be "poor metabolizers" of TCAs).<sup>205</sup> Physicians should consider these factors when negotiating treatment decisions for depression.<sup>212</sup> Patients who fail to take antidepressant medications could be encouraged to do so through supportive education about depression care. Use of the more patient-centered communication that elicits patients' concerns and preferences regarding treatment may improve uptake of depression care by ethnic minorities.<sup>208</sup>

Poverty and its associated psychosocial factors may contribute to lower quality mental health care among minority patients.<sup>205</sup> Because minorities are more likely to receive health care in outpatient hospitals and emergency departments, they are less likely to receive the continuity of primary care treatment that may allow better detection of depression.<sup>205</sup> Minority families may have fewer resources, such as transportation, child care, or availability of out-of-pocket funds to obtain depression care and lesser insurance benefits.<sup>208;214</sup> Research in low-income minority women demonstrates improved symptoms and social functioning with medication or psychotherapy when treatment was sufficiently accessible (availability of child care and transportation).<sup>11</sup>

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## Cultural Competency

Cultural competency is a set of academic and personal skills that allow physicians to increase their understanding and appreciation of cultural differences between groups. Culturally responsive care includes cultural awareness, knowledge, and skill that enables the PCP to seek out the patient's world view and understanding of health and illness, and to do so without stereotypes, and with respect for the individuality of each patient, within the context of his or her culture and life-way. Providing culturally competent and culturally responsive care is important to eliminate long-standing disparities in the health status of people with diverse racial, ethnic, and cultural backgrounds, and to improve the quality of care.

Recommendations PCPs can follow to help address barriers to the detection and treatment of depression in minority patients include:

### ■ *Improve diagnosis*

- Inquire about somatic symptoms (eg, musculoskeletal pain, fatigue), since this is a common presentation of depression in some cultures.<sup>11</sup> Assess their relationship to psychosocial stressors, which may be more prevalent in minority populations (eg, housing, daycare, employment, finances, transportation, immigration status).<sup>11,205</sup>
- Assess stigma toward mental health in patients suspected to be depressed.<sup>205</sup>
- Some assessment tools may not be applicable for certain populations.<sup>11</sup>
- Acknowledge the impact of culture on physical and mental health.<sup>11,215,216</sup>
- Maintain a respectful, open stance in understanding patients' styles of coping with depressive symptoms, including use of spirituality.<sup>11,217</sup> Assess for other resources the patient may have used such as elders, native or spiritual advisers/healers.<sup>11</sup> Acknowledge their role and collaborate if possible/appropriate.

### ■ *Provide effective management*

- Ask patients about treatment preferences for psycho- or pharmacotherapy when discussing treatment options, and provide referrals for counseling if appropriate and as resources permit.<sup>10,205</sup>
- Educate patients about antidepressant medication onset of action and side effects.<sup>205</sup>
- At each visit after initiation of depression management, check for adherence to pharmacotherapy or to referred psychotherapy and discuss adherence factors.<sup>11,205</sup>
- Assist patients who cannot maintain regular visits for depression care to find strategies to overcome social or financial barriers.<sup>205</sup>



# Practice Changes to Improve Acceptability of Treatment

Many persons who might benefit from an intervention for depression never fully engage in the treatment recommended by their physicians.<sup>218</sup> Depressed patients are often fearful, suspicious, or disparaging about care, and higher perceived stigma predicts medication nonadherence, particularly among older adults.<sup>212;219-221</sup> Personal responsibility for the management of depression has emerged as a pervasive approach among older people to dealing with depression, which includes the idea that managing depression is a matter of “picking oneself up by the bootstraps” and that self-indulgence is a weakness.<sup>218</sup>

To reduce nonadherence and poor acceptance of mental health care for depression, new initiatives have been launched in primary care settings.<sup>221</sup> Depression fits into the “chronic disease management model” for many other common problems in primary care today, such as diabetes, heart disease, chronic lung disease, and arthritis.<sup>201</sup> This model incorporates practices such as developing a registry of all patients with a given condition, the use of a care manager, the consistent use of an evidence-based care plan or management algorithm, standardized monitoring, and access to an expert consultant for unanticipated problems and complicated patients.<sup>201</sup> Such a chronic-disease model that involves collaborative care management of depression in primary care has shown improved outcomes, although it is associated with increased cost.<sup>222</sup> In such interventions, trained on-site care managers (nurses or psychologists trained as depression clinical specialists) operationalize guidelines to provide recommendations to PCPs and help patients with treatment adherence.<sup>223;224</sup> Many of the care managers’ services are reimbursable under the existing Medicare codes.<sup>223</sup>

The Treatment Initiation Program (TIP) is an example of a brief, early intervention developed to target older adults’ attitudes about depression in order to increase treatment acceptance.<sup>221</sup> The intervention included three 30-minute meetings with the patient during the first six weeks of pharmacotherapy, followed by two follow-up telephone calls at eight and 10 weeks, administered by a care manager.<sup>221</sup> A “contact sheet” that list barriers in each domain and specific intervention techniques serves as the guide for sessions.<sup>221</sup> Patients who participated in the intervention experienced a greater decrease in depression severity and hopelessness and were more likely to remain in treatment compared with usual care.<sup>221</sup>

Another example is the Improving Mood-Promoting Access to Collaborative Treatment (IMPACT) study, where primary care patients received a 20-minute educational videotape and a booklet about late-life depression and were encouraged to schedule an initial visit with a depression care manager.<sup>225</sup> Care managers worked with the patient and PCP to establish a treatment plan according to a recommended treatment algorithm.<sup>225</sup> Care managers followed up with patients for 12 months, at which time 45% of intervention patients experienced a 50% or greater reduction in depressive symptoms from baseline compared with 19% of usual care patients.<sup>225</sup> Intervention patients had 107 more depression-free days over 24 months as well as improved physical function.<sup>226;227</sup> One year after IMPACT resources were withdrawn, enduring benefits in terms of less depression, better physical functioning, and enhanced QOL were maintained in intervention patients.<sup>228</sup>

Telephone-based depression care management programs using depression care managers supervised by mental health specialists to assist PCPs with patient management have also been developed.<sup>229</sup> One study showed that for

primary care patients beginning antidepressant treatment, a telephone program integrating care management and an eight-session structured CBT program delivered by telephone can significantly improve satisfaction and clinical outcomes compared with pharmacotherapy alone.<sup>230</sup> Although telephone programs are not ideal compared with in-person therapy, they address several barriers to dissemination of effective depression treatments.<sup>230</sup> Telephone outreach can engage patients who might not be reached by traditional in-person treatment; telephone sessions eliminate travel and waiting time and allow more flexible scheduling.<sup>230</sup> Care managers use detailed agendas and checklists during therapy sessions to improve treatment quality and consistency.<sup>230</sup> Advantages may be greater in rural settings where access to psychotherapists is more limited and the stigma attached to visiting a mental health provider may be greater.<sup>230</sup> However, such a program may not be supported by current fee-for-service reimbursement models.<sup>230</sup>

Group visits could be scheduled for interested patients so they can discuss self-managing their depression with others who are in similar situations.<sup>231;232</sup> This also allows physicians to deliver extensive education and self-management instruction while possibly increasing financial productivity.<sup>233</sup> Billing codes for group visits are not yet established—some recommend that group visits be billed as individual office visits using existing CPT codes.<sup>233</sup> CPT codes should be chosen based on the level of complexity for the individual visit and not on length of time spent with the patient in the group education session; time can be used as a controlling factor when counseling dominates individual visits but not when it is shared in a group context.<sup>233</sup> Physicians should inquire whether their insurance health plans and government health plans have group-visit billing policies.<sup>233</sup> Completing forms and reviewing charts prior to the group visits facilitate the documentation of complexity levels after the encounters.<sup>233</sup>

Several evidence-based programs to improve depression treatment in primary care may help efforts to incorporate depression management into disease management programs for chronic disease.<sup>13</sup> These include the Robert Wood Johnson Foundation's Depression in Primary Care Project ([www.wpic.pitt.edu/dppc/](http://www.wpic.pitt.edu/dppc/)), the IMPACT program developed by the John A. Hartford Foundation, the California Health Care Foundation, the RWJ Foundation, the Hogg Foundation ([www.impact.ucla.edu](http://www.impact.ucla.edu)), and the RESPECT model developed by the Mac Arthur Foundation ([www.depression-primarycare.org](http://www.depression-primarycare.org)).<sup>13</sup>

# Case Studies

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## Case 1

PL is a 32-year-old female business executive with a two-month history of feelings of sadness and a loss of interest in family and recreational activities. She has also had difficulty focusing her attention at work, an increased appetite with weight gain, and early morning awakening. This is her first episode of depression. She meets with DSM-IV criteria for MDD, with five of the nine symptoms, including depressed mood and anhedonia, for sufficient duration; you started her on the SSRI citalopram 20 mg per day.

She shows a marked improvement in mood, but is now experiencing difficulty getting to sleep. Insomnia is a potential side effect of citalopram and other SSRI agents, but may be transient. You encourage PL to follow good sleep hygiene (eg, refrain from napping during the day, use bed only for sexual activity and for sleeping, go to bed the same time every night) and direct her to take citalopram in the morning, which may decrease her symptoms dramatically enough to allow her to fall asleep.

Two weeks later, PL is still experiencing insomnia; you reduce the dose of citalopram, but her depressive symptoms begin to return. Options now include adding a more sedating antidepressant (eg, trazodone) or short-acting sedative/hypnotic (eg, zolpidem), or switching to a more sedating antidepressant. You add trazodone 50 mg qhs, and both her depressive symptoms and insomnia improve.

Three months into the treatment, PL reports sexual dysfunction with reduced libido and anorgasmia. SSRI-associated sexual dysfunction can be transient. You plan to “wait and see” for three weeks. If there is no improvement in PL’s sexual function; options include reducing the dose of citalopram, taking a drug holiday, adding buspirone or bupropion, or switching to an antidepressant that has less potential to cause sexual dysfunction (eg, mirtazapine, bupropion).

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## Case 2

JR is a 52-year-old stockbroker who has been taking amitriptyline 50 mg a day for prophylaxis of frequent chronic tension headaches for several months. You recently prescribed him fluoxetine 20 mg q am for dysthymia. He returns in three weeks complaining of excessive sedation, orthostatic dizziness, blurred vision, and a dry mouth. His blood levels of amitriptyline are elevated.

Fluoxetine is a potent inhibitor of CYP 2D6, which is involved in the metabolism of amitriptyline. Adding fluoxetine to JR’s regimen increased his blood concentration of amitriptyline to levels that triggered the common unpleasant side effects of a medication that he previously tolerated well. You discontinue fluoxetine (a taper is not necessary because of its long half-life) and select another antidepressant with a CYP 450 profile that will not affect amitriptyline, such as venlafaxine or mirtazapine, both of which have a much lower potential for interaction.

# Conclusions

Patients with depression frequently seek help in primary care settings, but often remain unidentified and continue to experience the significant morbidity associated with this disorder. Family physicians, with their deep knowledge of patients' lives and strong relationships, are ideally placed to identify those patients who are likely to benefit from treatment of depression. They are also the ideal physician to assess patients for medical conditions that may present as depression, and to manage the treatment of depression, because this can impact other co-existing medical problems that patients may have. Providing the best treatment options possible for this chronic and debilitating disorder will make a demonstrable difference in patients' lives.

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# Post-Test

In order to receive CME credit you **must** complete and submit the following post-test and evaluation.

Name: \_\_\_\_\_

Address: \_\_\_\_\_

City/State/Zip: \_\_\_\_\_

Phone: \_\_\_\_\_

Fax: \_\_\_\_\_

E-mail: \_\_\_\_\_

1. Patients with major depressive disorder who achieve full clinical remission on antidepressant therapy have the same relapse rate as patients who achieve partial remission.  
True/False
2. Following 1 episode of depression, patients have a chance of another:
  - a) 10%
  - b) 25%
  - c) 50%
  - d) 75%
  - e) 100%
3. The majority of patients who seek care for depression in primary care present with:
  - a) sadness
  - b) somatic complaints
  - c) anxiety
4. A response rate of 50% to 70% can be expected for:
  - a) Selective serotonin reuptake inhibitors
  - b) Tricyclic antidepressants
  - c) Dual-action antidepressants
  - d) Any available antidepressant
5. Psychotherapy plus antidepressant therapy has been shown to be more effective than either of these two interventions alone.  
True/False
6. For patients who respond to therapy, it is recommended to continue treatment for a minimum of:
  - a) 1 to 3 months
  - b) 3 to 6 months
  - c) 6 to 9 months
  - d) 9 to 12 months
7. A 56-year-old patient with advanced cirrhosis and esophageal varices is seen by you for depression. His current medications include propranolol. Which of the following antidepressants is least likely to interact with his beta-blocker?
  - a) Fluoxetine (Prozac)
  - b) Paroxetine (Paxil)
  - c) Venlafaxine (Effexor)
  - d) Fluvoxamine (Luvox)
  - e) None of the above
8. A 55-year-old male has developed depression following an anterior myocardial infarction and has been placed on warfarin. Which of the following antidepressants should be avoided in this setting?
  - a) Fluoxetine (Prozac)
  - b) Citalopram (Celexa)
  - c) Venlafaxine (Effexor)
  - d) Paroxetine (Paxil)
  - e) Mirazepine (Remeron)

# Evaluation

Rating Scale: **4** = fully addressed **3** = mostly addressed **2** = partially addressed **1** = not addressed

Please fill in the circles completely.

	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>
<b>Please rate the monograph as it met the objectives to:</b>				
Diagnose patients with depression	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Appropriately prescribe medications for depression including medications, augmentation and switching, and titration of medications	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Delineate the uses of psychotherapy and referral for the treatment of depression	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Manage the patient with depression from diagnosis, through treatment, to a goal of remission	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
<b>Please rate the monograph for:</b>				
It was understandable and easy to read	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
It presented information appropriate to the topic	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
It used examples and patient cases that were informative and appropriate	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
It presented useful information	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
It was well-organized	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
It was engaging and interesting	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

**Was the monograph free of promotion?** Yes No

If not, why not?

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## Final Question.

What do you anticipate you will do differently as a result of reading this monograph?

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## Return Post Test and Evaluation to:

California Academy of Family Physicians  
 1520 Pacific Avenue, San Francisco, CA 94109-2627  
 or fax to: 415.345.8668



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