INTRODUCTION

Here we review the presentation and treatment of major depressive disorder (MDD) among adults in the primary care setting. To build on prior reviews of epidemiology,¹

KEY POINTS

- MDD has a lifetime prevalence of 16% in the United States and 25% in those with chronic diseases. Though the natural history of MDD is to eventually remit, 30% or more have refractory or treatment resistant depression and even in those whose depression remits, there is a high rate of recurrence.
- The Patient Health Questionnaire 2 (PHQ2) and PHQ9 are validated and reasonably sensitive screening tools for MDD. The PHQ9 can also be used to monitor symptoms and direct adjustment of treatment.
- Medical conditions, substance abuse, grief, sleep disorders, and other psychiatric conditions can both co-occur and mimic the symptoms of MDD. Providers should assess for the presence of these conditions when diagnosing MDD and consider co-morbid conditions in order to tailor management interventions.
- Of the lifestyle interventions for depression, exercise, and relaxation therapy have the best evidence.
- Psychotherapy effectively treats MDD. While no one type of psychotherapy is thought to be superior to others, there are important differences in the philosophy and approach to different types of therapy that should be considered when recommending psychotherapy for patients.
- Most antidepressants are similar in efficacy, though escitalopram and sertraline may confer a slight advantage. Clinicians should consider patient preferences, cost, side effects, and medication interactions when recommending pharmacotherapy interventions.
pharmacotherapy, and other facets of MDD in primary care, we focus on the clinical application of research evidence and treatment guidelines, the identification and differential diagnosis of major depression, and resultant treatment strategies. Other work more specifically addresses depression among children and the elderly.

THE SYNDROME OF MAJOR DEPRESSION AND ITS PRESENTATION

For research and clinical purposes, MDD is most commonly diagnosed by criteria in the Diagnostic and Statistical Manual (DSM). Largely unchanged in the new DSM 5th edition (DSM-5), the criteria specify that 5 of 9 symptoms be present for a 2-week period and represent a change in functioning. Box 1 summarizes the DSM-5 criteria for MDD. The most significant differences in DSM-5 include new emphasis on hopelessness as a feature of depression and the removal of the “bereavement exclusion,” described in more detail later.

Through type and severity specifiers, the DSM-5 allows for 14 categorizations of depression. Although the clinical value of this subtyping remains uncertain, it does illustrate the varying clinical symptomatology of MDD and highlights diagnostic challenges. As an example, Box 2 describes the “with anxious distress” specifier for depressive disorders in DSM-5.

DEPRESSION SUBTYPES

Other DSM-5 depressive disorder specifiers include atypical features of mood reactivity—significant weight gain or increased appetite, hypersomnia, leaden paralysis, and longstanding patterns of interpersonal rejection sensitivity. This symptom cluster can occur in up to one-third of patients with major depression. In clinical trials and community samples, atypical depression has been correlated with female sex.
younger age of onset, family history of depression, greater anxiety including specific phobias, somatoform disorders, substance abuse, personality disorders, and suicide attempts.\textsuperscript{12,14–18} It may be difficult for primary care providers to recognize atypical depression, as patients can often improve when circumstances are favorable and show a reactive, not depressed, affect. The epidemiology of atypical depression, along with the new DSM-5 specifier for MDD “with anxious distress,” reminds clinicians that anxiety symptoms are often comorbid with MDD. Melancholic features include pronounced anhedonia, early morning awakening, and depression that is worse in the morning.\textsuperscript{10} Psychotic symptoms often include mood-congruent themes of personal inadequacy, guilt, disease, punishment, or death.\textsuperscript{10}

### DETERMINATION OF DEGREE OF IMPAIRMENT

Although culture may influence the predominant symptom presentation of depression, there is no strong underlying epidemiologic evidence to support a predictable cultural pattern.\textsuperscript{19,20} A World Health Organization survey of primary care patients suggests a wide variation in prevalence of major depression across 14 countries (from 1.6% to 26.3%).\textsuperscript{21} This variation likely reflects differences in the threshold of functional impairment used to make the diagnosis rather than varying symptomatology.

The presence of “clinically significant distress or impairment” is crucial for the diagnosis of depression. However, there is marked variability and subjectivity in both the individual clinician’s determination and the patient’s manifestations of impairment and distress. In practice, the patient’s report of subjective distress is often considered sufficient for fulfilling this criterion, but there is ongoing debate and research seeking to constitute an appropriate diagnostic threshold for MDD.\textsuperscript{22–24} Patients in studies of major depression describe impairment as less satisfaction at work, at leisure, and among family members.\textsuperscript{25–28} Additional markers of function and impairment recognized in patients with MDD include changes in sexual drive and decline in physical function and

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**Box 2**

<table>
<thead>
<tr>
<th>DSM-5 “with anxious distress” specifier for depressive disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>With anxious distress: presence of at least 2 the following symptoms during most days of depressive episode</td>
</tr>
<tr>
<td>1. Feeling tense or keyed up</td>
</tr>
<tr>
<td>2. Feeling unusually restless</td>
</tr>
<tr>
<td>3. Difficulty concentrating because of worry</td>
</tr>
<tr>
<td>4. Fear that something awful might happen</td>
</tr>
<tr>
<td>5. Feeling that individual may lose control of him/herself</td>
</tr>
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</table>

Note: anxious distress is a prominent feature of bipolar disorder and MDD. High levels associated with higher suicide risk, longer duration of illness, greater likelihood of poor treatment response. Specification of severity is useful for treatment planning and monitoring.

Mild: 2 symptoms
Moderate: 3 symptoms
Moderate-Severe: 4 or 5 symptoms
Severe: 4 or 5 symptoms with motor agitation

physical health. Patients may say, “Things seem dark,” “more difficult,” or that they are “just not interested.” Patients describe their distress or impairment as cognitive dysfunction causing difficulty keeping track of things or focusing on work. However, distress and functional impairment, although sensitive for MDD, are not specific and do not differentiate depression from other diagnoses.

EPIDEMIOLOGY AND COURSE OF MDD

Depression is a common and complicated illness. The lifetime prevalence of MDD in the United States is about 16% in a given year; about 7% of the population will experience an episode of MDD, half of which are moderate in severity. A Finnish study of primary care patients endorsing at least 2 current symptoms of depression found that current MDD was present in 66% of cases. The annual prevalence rate is up to 25% in patients with chronic medical illness. Risk factors are multifactorial and include genetic, medical, social, and environmental factors.

The course of MDD reflects this complexity: initial presentation can include a variety of physical symptoms including pain (headache, musculoskeletal, abdominal/pelvic), neurovegetative mood symptoms (see Box 1), and cognitive changes. The course of MDD is variable with some patients rarely experiencing a remission (>2 months with no or only a few mild symptoms) and others with having many years with few or no symptoms between discrete depressive episodes. Distinguishing patients who present during an exacerbation of chronic depressive symptoms from those with recent onset of symptoms is important in anticipating illness trajectory. Recent onset of symptoms is a strong determinant of near-term recovery. Many patients who have only been depressed for a few months may be expected to recover spontaneously. Chronicity of symptoms decreases the likelihood that full remission will follow treatment. Lower recovery rates are also associated with psychotic features, symptom severity, prominent anxiety, and personality disorders.

Most patients with symptoms of MDD do eventually improve. Recovery typically begins within 3 months of symptoms onset for about 40% of patients with MDD and within 1 year for approximately 80%. A prospective, observational study of 174 outpatients with MDD found that more than 70% achieved remission: 43% remitted by 6 months and maintained remission over 3 years, 40% fluctuated between periods of depression and remission, and a significant minority (17%) remained depressed without periods of improvement. These data are similar in proportion to the 33% of subjects who did not to respond after 4 treatment steps in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial but lower than seen in the Finnish cohort. Residual depressive symptoms—fatigue, cognitive impairment, and insomnia—may persist even after successful treatment. Persistence of symptoms after treatment heightens the risk for recurrence of a major depressive episode.

Unfortunately, depression is highly recurrent. In a prospective study of greater than 300 patients who had recovered from an episode of MDD, 64% experienced at least 1 additional episode of MDD with the greatest risk of recurrence in the first months after recovery. The probability of recurrence decreased as the period of remission progressed. A history of recurrent depressive episodes is the most predictive risk factor for additional episodes of MDD, and each recurrence increases the risk of experiencing another episode by 16%.

SCREENING

Depression is common and frequently goes undetected in primary care settings without screening. The US Preventive Services Task Force and other agencies
recommend the use of standardized screening instruments for the diagnosis of MDD in outpatient practice, screening all patients at routine visits.\textsuperscript{40,41} The Department of Veterans Affairs recommends screening for MDD annually.\textsuperscript{42} Factors in the choice of screening instruments include the diagnostic accuracy for the target population and pragmatic constraints such as the ease of administration/interpretation, such as number of questions and reading level requirements. Short screens that can be completed by patients while waiting for their visits or administered by staff during check-in for vital signs are practical and efficient.

The use of the Patient Health Questionnaire-2 (PHQ-2), a 2-item screener, is frequently suggested. It can be administered either written or verbally with yes/no or scaled responses. The PHQ-2 is based on the stem, “Over the last 2 weeks, how often have you been bothered by any of the following problems… (1) Little interest or pleasure in doing things…and (2) Feeling down, depressed, or hopeless.”\textsuperscript{43} Patients answer from 0 (not at all) to 3 (nearly every day) to for both questions, and a score of 3 or greater (out of 6) has a sensitivity of more than 80\% for MDD. A yes on either portion also indicates possible depression. A positive screening result should be followed up with further evaluation to diagnose depression. Box 3 summarizes risk factors for MDD. Patients with multiple risk factors on by history may be a higher prevalence population worthy of attention when targeting depression screening efforts.

The longer PHQ-9 (Table 1) is slightly more sensitive and allows clinicians to track depressive symptoms over time. It can also be used to educate patients as to the various symptoms of depression.\textsuperscript{44,45} Depression severity is scored 0, 1, 2, and 3, to the response categories of not at all, several days, more than half the days, and nearly every day, respectively, with total scores in a range of 0 to 27. Scores of 10 or higher indicate a possible depressive disorder. The question of whether depressive symptoms are impairing function is important in establishing a DSM-based diagnosis. However, like other screening tools, the PHQ-9 is not sufficiently accurate to establish a definitive diagnosis for depression. Scores indicating a positive screening result should prompt a thoughtful assessment of treatment considerations.

### Box 3

Selected risk factors for depression

- Prior depressive episode
- Family history
- Gender (female)
- Age (younger)
- Race (white)
- Childhood (ie, postpartum depression)
- Childhood trauma/adversity
- Stressful life events
- Poor social support
- Serious medical illness
- Cognitive impairment/dementia
- Substance use (illicit, prescription)

### Table 1
Use of PHQ9 in Initial Depression Management

<table>
<thead>
<tr>
<th>Name:</th>
<th>Date:</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Over the last 2 wk, how often have you been bothered by any of the following problems?</th>
<th>Not at all</th>
<th>Several days</th>
<th>More than half the days</th>
<th>Nearly every day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Little interest or pleasure in doing things</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Feeling down, depressed, or hopeless</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Trouble falling or staying asleep, or sleeping too much</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Feeling tired or having little energy</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Poor appetite or overeating</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Feeling bad about yourself, or that you are a failure, or have let yourself or your family down</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Trouble concentrating on things, such as reading the newspaper or watching television</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Moving or speaking so slowly that other people could have noticed? Or the opposite, being so fidgety or restless that you have been moving around a lot more than usual</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Thoughts that you would be better off dead or of hurting yourself in some way</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Total ___ = ___ + ___ + ___ + ___</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**PHQ-9 Score ≥10: Likely major depression.**

**Depression score ranges:**

- 5 to 9: mild
- 10 to 14: moderate
- 15 to 19: moderately severe
- ≥20: severe

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

<table>
<thead>
<tr>
<th>PHQ-9 Score</th>
<th>Depression Severity</th>
<th>Initial Treatment Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–4</td>
<td>None-minimal</td>
<td>None</td>
</tr>
<tr>
<td>5–9</td>
<td>Mild</td>
<td>Monitor/repeat PHQ-9 at follow up</td>
</tr>
<tr>
<td>10–14</td>
<td>Moderate</td>
<td>Consider counseling, +/- pharmacotherapy, follow-up 4–6 wk</td>
</tr>
<tr>
<td>15–19</td>
<td>Moderately Severe</td>
<td>Active treatment with pharmacotherapy +/- psychotherapy, close follow-up 2–4 wk</td>
</tr>
<tr>
<td>20–27</td>
<td>Severe</td>
<td>Address acute safety concerns. Immediate initiation of pharmacotherapy, follow-up 1 wk or sooner. Consider expedited referral to a mental health specialist for psychotherapy and/or collaborative management</td>
</tr>
</tbody>
</table>

Attention to screening is variably supported in the literature. Screening is recommended by the US Preventive Services Task Force for patients if there is adequate availability of appropriate treatment and staff assistance, such as having a nurse highlight a patient’s depression screener to the provider.\textsuperscript{40,46} The psychometric properties of available screening tools are detailed elsewhere.\textsuperscript{47}

**PATHOPHYSIOLOGY**

Although the diagnosis is made through clinical examination, major depression correlates with numerous biological measures signifying the MDD’s complex pathophysiology. The classic monoamine hypothesis of depression posits a relative deficiency of monoamine neurotransmitter activity, particularly serotonin, in the synaptic cleft. Several excellent reviews describe emerging, more complex neurobiological models involving multiple neurotransmitter systems.\textsuperscript{48–50} Depression correlates with hypersensitization of $\alpha$ adrenergic receptors (with resulting decrease in serotonin), and antidepressant treatment results in $\beta$ adrenergic receptor downregulation along with desensitization of inhibitory serotonin receptors.\textsuperscript{48–50} These changes affect longer-term adaptive neuronal changes that correlate with the therapeutic response time for antidepressants; reduced brain-derived neurotropic factor activity may account for morphologic changes and impaired neuroplasticity in depressed patients. The hypothalamic-pituitary-adrenal axis has also been implicated; depressed patients have elevated cortisol levels, fail to respond to dexamethasone suppression tests, and have enlarged pituitary and adrenal glands. Depressed patients have less rapid eye movement, stage 3, and stage 4 sleep perhaps resulting from the observed increase in proinflammatory cytokines (interleukin-1, interleukin-6, and tumor necrosis factor). Family and twin studies suggest some genetic contribution to major depression—the effect appears stronger for recurrent or early-occurring depression—but the mechanism of this effect remains unclear, and genetic effects are not likely stronger than environmental stressors.\textsuperscript{51–53} This increasingly sophisticated biological understanding may soon—but not yet—guide depression treatment selection and predict response.\textsuperscript{54}

**IDENTIFICATION, COMORBIDITY, AND DIFFERENTIAL DIAGNOSIS**

Many symptoms of major depression are shared by other medical and psychiatric illnesses, complicating diagnosis.\textsuperscript{32} Alternative diagnostic schemes have been proposed that substitute or ignore the somatic symptoms of depression in the presence of medical illness.\textsuperscript{55,56} But, the more traditional criteria remain widely used even under such circumstances. It is better to err on the side of sensitivity given the implications of missing major depression, and major depression often manifests as multiple somatic complaints in the primary care setting.

**Substance Use Disorder**

Anyone in whom depression is suspected must be screened for substance dependence including marijuana, prescription drug diversion, and especially alcohol. Substance dependence is common among patients with depression, may induce or exacerbate depressed mood and associated symptoms, and is an additional risk factor for suicide.\textsuperscript{57–59} In a telephone survey of the general population comparing short screeners for alcohol use disorders, the Rapid Alcohol Problems Screen 4 was the most sensitive (0.86 for alcohol dependence) and had high specificity (0.95 for dependence).\textsuperscript{60} The Rapid Alcohol Problems Screen 4 is positive if the patient answers yes to 1 of 4 questions: Have you felt guilt or remorse after drinking? Has a friend or family member ever told you about things you said or did while drinking
that you did not remember? Have you failed to do what was normally expected of you because of drinking? Do you sometimes take a drink when you first get up in the morning?

**General Medical Conditions**

Many medical conditions cause depressive symptoms like fatigue, changes in eating and sleeping pattern, and even hyper/hypoactivity, but these medical illnesses are less likely to induce cognitive distortions typical of major depression (low mood, anhedonia, feelings of guilt). Hence, these medical conditions can mimic symptoms of depression, but with careful history taking and use of screening tools like the PHQ9, as well as appropriate medical work-up, these conditions should be distinguished as independent from MDD. Complicating matters, is the strong co-morbid association between depression and some medical conditions such as COPD, acute MI, and chronic kidney disease. Delirium can induce depressive episodes, and a thorough medical investigation is warranted for patients with disorientation, difficulty maintaining consciousness or wakefulness, abnormal vital signs or physical examination, or a new psychiatric diagnosis after age 40. Initial testing for depression might include a complete blood count (testing for anemia and infection), basic metabolic panel (hyponatremia, renal failure, dehydration), liver function tests (hepatic encephalopathy), thyroid-stimulating hormone (hypothyroidism), and a pregnancy test (as changes related to pregnancy maybe misattributed to somatic manifestations of MDD, ie, fatigue, weight gain, changes in appetite, and sleep).

**Prescription Medications**

Medications associated with MDD include steroids, anticonvulsants, benzodiazepines, nonsteroidal anti-inflammatory drugs, dopamine, and clonidine. Polypharmacy can also contribute to depressive spectrum symptoms.

**Adjustment Disorders and Demoralization**

Adjustment disorders occur when patients experience significant distress in the presence of an identifiable life stressor but do not exhibit the range of symptoms necessary for the diagnosis of depression. Similarly, a syndrome of demoralization has been recognized among medically ill patients struggling with feelings of hopelessness, helplessness, and incompetence. As opposed to those with depression, demorlized patients are not usually anhedonic and quickly recover with abatement of the stressor. Patients who initially have an adjustment or demoralization disorder may progress to depression; patients who fulfill criteria for MDD merit the formal diagnosis and appropriate treatment.

**Sleep Disorders**

Insomnia or hypersomnia are cardinal symptoms of major depression; however, primary sleep disorders may mimic depression. Patients with obstructive sleep apnea describe difficulty with concentration, mood, and energy but are able to enjoy activities and lack the negative cognitive distortions of depression. Insomnia and parasomnia may underlie many symptoms of depression, and brief therapeutic interventions for insomnia may augment the efficacy of depression treatment.

**Posttraumatic Stress Disorder**

Patients with posttraumatic stress disorder (PTSD) complain of difficulty forming close relationships, envisioning a plan for their futures, poor sleep, and anhedonia. Focusing on these symptoms could lead a primary care physician (PCP) to diagnose MDD.
However, patients with PTSD will also report re-experiencing and hypervigilance symptoms (eg, startling easily). Appropriate treatment of PTSD requires different pharmacotherapeutic and psychotherapeutic approaches than for MDD.

**Grief and Bereavement**

Grief is “the mainly emotional response to bereavement,” “an almost universal life event.” In response to the loss of a loved one, it is natural for patients to experience sadness, guilt, and thoughts of joining the deceased. Psychotic experiences such as temporarily experiencing hallucinations in which the deceased is perceived as present (eg, seeing the deceased sitting in a favorite chair) may also occur. These symptoms can be associated with complicated grief particularly if out of proportion or inconsistent with religious, cultural, or age-appropriate norms. Clinicians should suspect pathologic major depression when feelings of sadness worsen rather than improve, or there is significant impairment in functioning, psychotic experiences unrelated to the deceased, or prominent feelings of worthlessness and anhedonia. Whereas the previous DSM-IV test revision specified that bereavement should not last longer than 2 months, DSM-5 does not specify a time period by which grief is expected to normally resolve and recognizes that “the exercise of clinical judgment” is necessary to distinguish normal grief from a major depressive disorder. Bereaved patients are at higher risk of new depression, substance use, suicide, and mortality.

**Minor and Persistent Depression**

Patients may describe long-standing depressive symptoms that do not fulfill criteria for MDD because of insufficient symptom duration, intensity, or impairment. With some variation in quality or duration, these states have been described as minor or subsyndromal depression, dysthymic disorder, and, now in DSM-5, persistent depressive disorder. Chronic dysthymia can be associated with significant impairment, and 4 in 5 patients also experience a major depressive episode. Moreover, these syndromes may be less amenable to traditional treatments. MDD merits treatment if present, and chronically depressed patients should be referred for psychotherapy.

**Personality**

Many patients report a depressive pattern in response to life circumstances but lack anhedonia or blunted affect. Asking these patients “When was the last time you felt good?” often evokes a response of “years.” The duration of depressive symptoms may be quite long, even lifelong, without a clear temporal course. These clues should raise suspicion for personality characteristics underlying the depressive symptoms. A combination of negative affect, somatization, and social inhibition has been described as Type D personality and subsequently associated with poor psychosocial and health outcomes. Type D personality can be a helpful psychological construct for clinicians to consider, although not a pathologic diagnosis in DSM-5.

Astute clinicians will appreciate that many of the above diagnoses can be comorbid with MDD—more than half of patients with MDD have another psychiatric diagnosis, most commonly an anxiety or personality disorder. Regardless of comorbidity, MDD should be treated. Comorbidity can impact treatment resistance and functional impairment and may manifest as new psychiatric symptoms in a patient whose depressed mood is otherwise improving. When multiple diagnoses are present, there is no evidence to guide which diagnosis should be treated first.
Depression is strongly associated with completed suicide, and suicide assessment is intrinsic to any evaluation of the depressed patient. In a prospective 5-year study of patients with major depressive disorder, nearly 15% of subjects attempted suicide at least once. This risk increased 21 times during periods of active depression compared with periods in remission. The lifetime risk of death by suicide among patients with major depression, cited to be as high as 6%, is comparable to the risk of those with schizophrenia or alcoholism. Primary care providers must be familiar with suicide risk assessment, as 23% to 45% of patients completing suicide are last seen by a nonpsychiatric provider.

Because completed suicide is a very rare event, predicting suicide completion is not possible. Rather, assessment centers on risk stratification, which begins with asking the patient about suicidal thoughts or ideation. In one analysis of data from a managed care system, outpatients who reported thoughts of death or self-harm nearly every day on the PHQ-9 screener were 10 times more likely to attempt suicide in the following year. The excellent review by McDowell and colleagues of suicide risk assessment in the primary care setting endorses a model based on low-,-medium-, and high-risk stratification. Low-risk patients have no prior suicide attempts or suicidal ideation or have suicidal ideation without a plan or intent; these patients require outpatient follow-up. Medium-risk patients endorse suicidal ideation and a plan but not rehearsals or intent. These patients should be referred to psychiatry, at least, or perhaps the emergency room if other pressing risk factors are present (eg, a lack of close social supports, impulsivity, philosophic reasons for dying, or active alcohol use disorder). High-risk patients have a suicide plan and the intent to complete suicide concurrent with agitation, psychosis, or recent suicide attempt. High-risk patients require constant observation in clinic while transportation to emergency treatment is arranged. Clinicians should document the reasoning underlying their risk assessment and interventions taken.

Several modalities have evidence for efficacy in the treatment of MDD. These include behavioral interventions/self-care strategies, psychotherapy in its many forms, and psychopharmacologic interventions.

The quantification of severity in MDD can help guide management strategies not only for initial therapy but also for ongoing management once the diagnosis has been made.

**Behavioral Interventions and Self-Care**

Many patients are opposed to treating depressive symptoms with psychotherapy or medications. Some patients have had adverse reactions to medications, and others may not have access to resources or the time necessary for traditional interventions. These patients seek to start with interventions they can initiate on their own or with alternative support.

Although the increase in the diagnosis of depression over the last several decades discussed above may be owing to improved screening and awareness by patients and providers, it may also reflect a true increase in the incidence and prevalence of MDD in society. Hidaka makes a case that compared with 40 to 50 years ago, Western societies eat more calorie-dense nutrition-poor foods and exercise less. The article evidenced the association between depression and a modern lifestyle to also include isolation from a family unit, less meaningful social interactions in a community,
sleep-wake disruption, inadequate exposure to sunlight, and high stress levels. In short, depression may be increasing because more people today are undernourished yet obese, isolated, lonely, stressed, and sedentary. It follows that attempts to reverse these possible drivers of depression may treat or prevent the condition.

**Diet**

An excellent review by Sarris and colleagues in 2014 summarizes the evidence for lifestyle medicine for depression. Cross-sectional and longitudinal studies conducted in multiple international sites evidence the association between the Western diet and the likelihood for depression development; unfortunately, insufficient studies assess if changing diet will treat depression. A randomized, controlled study is currently looking at this question, and those results are expected in 2015.

**Exercise**

Unlike dietary intervention, exercise has been studied more extensively as an intervention for MDD but yielded mixed outcomes. Fortunately, a 2013 Cochrane review looks at exercise interventions for the treatment of depression. For the purposes of the review, exercise is defined as “planned, structured repetitive bodily movement done to improve or maintain one or more components of physical fitness.” Pooled outcomes of 35 trials comparing exercise with no intervention show that exercise provides a moderate positive effect, but methodologic problems are noted for several trials. Looking only at the 6 high-quality trials in the review, the effect of exercise diminishes, and although positive, is no longer statistically significant. Interestingly, exercise was non-inferior to both psychotherapy (7 trials) and pharmacotherapy (4 trials) for MDD. Notably, the National Institute for Health and Clinical Excellence 2009 guidelines recommend a structured group-based physical activity program as low intensity intervention for mild-to-moderate MDD. Yoga, which combines exercise and mindfulness practices is also moderately effective. In practical terms, exercise is a low-cost, relatively low-risk intervention to recommend to patients, although clinicians should be mindful about the exercise capacity of those who suffer from other medical comorbidities.

**Sleep**

The relationship between MDD and sleep is complicated as illustrated by the manifestations of insomnia and hypersomnia in MDD. There is strong correlation with sleep disruption and mood disorders, and insomnia in one review predicts a 2-fold increased risk for MDD. The review by Sarris and colleagues notes that most studies on intervention for sleep disturbance in MDD are focused on sleep hygiene, cognitive behavioral therapy and pharmacotherapy interventions. A small randomized, controlled trial (RCT) shows cognitive behavioral therapy added to antidepressant therapy to address sleep disturbance increases remission rates from 33% in the control arm to 61% in the intervention arm. A small but interesting surgical study found that 75% of depressed patients receiving corrective surgical intervention for obstructive sleep apnea experienced remission of their MDD. So, although it is well evidenced that disruptions in sleep contribute to and are manifestations of MDD and other psychiatric disorders, the evidence remains sparse that treating sleep derangements primarily will effectively treat MDD. Currently, clinicians should consider treatment of sleep abnormalities an adjunctive approach to treating MDD and not a first- or even second-line measure.

**Alcohol and tobacco use**

Alcohol use disorder and MDD appear to have a reciprocal relationship—the presence of one doubles the risk of the other. The same review shows abstinence from alcohol
rapidly alleviates depressive symptoms. A 2014 systematic review and meta-analysis of 26 studies found that maintaining smoking cessation for greater than 6 weeks statistically reduces (measured in standard mean difference) depression (−0.25), anxiety (−0.37), and mixed anxiety and depression states (−0.31) and improves psychological quality of life (+0.22).98

Other lifestyle interventions
A systematic review (15 studies) and meta-analysis of 11 RCTs on relaxation techniques, including progressive muscle relaxation, relaxation imagery, and autogenic training, found relaxation therapy moderates self-reported depression ratings and trends toward a benefit in clinician-reported depression ratings (2 studies).99 Meditation,93 music therapy,100 and animal-assisted therapy101 have some evidence for benefit in the treatment of MDD. However, lifestyle interventions require more robust RCTs before most clinicians will recommend them with confidence.

Psychotherapy for MDD
Psychotherapy is a well-studied intervention for MDD. Many forms of psychotherapy including cognitive behavioral therapy, behavioral activation therapy, interpersonal psychotherapy, problem-solving therapy, nondirective counseling, and psychodynamic therapy show effectiveness in the treatment of MDD.102 No one type of psychotherapy is thought to be superior to another for MDD.

The efficacy of psychotherapy in the setting of high placebo response rates seen in studies calls into question the true clinical benefit of the intervention. Two recent meta-analyses attempted to determine if psychotherapy has meaningful effectiveness compared with placebo. Huhn and colleagues103 found acute phase psychotherapy had a moderate effect size (standard mean difference, 0.58) compared with placebo or no treatment. A 2014 meta-analysis looked at the absolute number of patients that no longer met the diagnosis of depression, response, and remission rates based on the Beck Depression Rating Scale and the Hamilton Depression Rating Scale (highly validated scales for depression severity and diagnosis). After psychotherapy interventions, 62% of study patients no longer met criteria for MDD compared with 43% of controls and 48% of patients receiving care as usual. The authors reported that psychotherapy added a 14% additional benefit for resolving depression over usual care.

PCPs can offer more direction to patients than a referral to psychotherapy. There are practical considerations and important differences among the forms of psychotherapy that should be considered before referral. First, patients should understand their insurance benefits. Some insurers will cover mental health benefits including psychotherapy but may preferentially cover a particular type of psychotherapy or therapist (preferred providers). Secondly, there are differences in the premise and approach of different types of psychotherapy (Table 2) that may confer certain advantages and disadvantages depending on the patient’s philosophy, level of insight, willingness to participate, and preferences.104 Lastly, other practical considerations like proximity to work and home, therapist reputation, and a patient’s prior experiences with psychotherapy may drive the selection of the type of therapy and the therapist.

Pharmacotherapy
Nonpsychiatrists are responsible for 64% of psychotropic medication prescriptions to adults in the United States.105 PCPs are increasingly responsible for both diagnosing and pharmacologically managing conditions like depression with or without the help of mental health specialists.106 However, specific training during residency and
<table>
<thead>
<tr>
<th>Type of Psychotherapy</th>
<th>Description</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive behavioral therapy</td>
<td>Based on a premise that thoughts and behaviors are modifiable. Patients learn &quot;rational&quot; thoughts and &quot;adaptive&quot; behaviors. Homework is assigned 8–16 sessions</td>
<td>• Well validated and studied  • Insurers are more likely to pay for it because of measurable goals  • Short-term and interactive</td>
<td>• Patients struggling with motivation or resistance may struggle with the expectation of active participation  • Does not address psychic conflict  • Requires a skilled therapist</td>
</tr>
<tr>
<td>Interpersonal therapy</td>
<td>Based on the premise that current interpersonal conflicts drive psychiatric symptoms. The focus is on short-term, present-focused interpersonal skills, communication, and coping. Key areas are:  • Grief  • Role transition  • Interpersonal conflicts  • Interpersonal deficits</td>
<td>• Short-term  • Behaviorally specific treatment plans  • Measurable goals  • Patients learn strategies for effective living  • More likely to be covered by insurers</td>
<td>• Patients must actively participate  • Patients must implement change in behaviors  • Does not address intrapsychic conflict</td>
</tr>
<tr>
<td>Psychodynamic therapy</td>
<td>Freudian theory that difficulties are caused by internal and unconscious conflicts, often rooted in childhood experiences, repeating in the present and during the therapy relationship. Coming to terms with loss/grief is a major focus.</td>
<td>• Helpful in patients with unconscious or internal conflict  • Time-limited sessions are available</td>
<td>• Less helpful in people without unconscious conflict  • May not be helpful in severe psychopathology, psychotic symptoms, severe personality disorders</td>
</tr>
<tr>
<td>Client-centered therapy</td>
<td>Insight-oriented approach that focuses on the present not past. The therapist approach is nondirective, with empathetic active listening, rephrasing, and reflecting the patient’s emotions and statements.</td>
<td>• Accepted by patients because they feel unconditional acceptance  • Models healthy relationships</td>
<td>• Less scientifically based  • Unclear treatment endpoints  • May not be helpful in severe depression  • Does not address intrapsychic conflict</td>
</tr>
</tbody>
</table>

continuing medical education on the topic of psychopharmacology is highly variable among providers.

**General approach**

In general, first- and second-generation antidepressants have equal efficacy with 60% to 70% of patients responding (symptoms >50% improved) to therapy.\textsuperscript{107} Second-generation medications like selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), bupropion, and mirtazapine are preferred over first-generation medications (tricyclic antidepressants [TCAs] and monoamine oxidase inhibitors [MAOIs]) because of their less problematic side effects and reduced risk for fatality in overdose situations.\textsuperscript{108,109} Antidepressants are best evidenced for more severe depression\textsuperscript{77} and have been used as monotherapy or in combination with psychotherapy and other modalities of care (see Table 1).

After a systematic review found minimal differences in efficacy among the second-generation antidepressants,\textsuperscript{110} the American College of Physicians 2008 Guidelines recommended that providers consider side effects (to avoid or to harness for the benefit of the patient), cost, and patient preference in selecting a first-line antidepressant.\textsuperscript{111} This advice remains sound in general, but the specific pharmacodynamics of medications within and among classes help to explain both the effectiveness and tolerability of antidepressants. Understanding these differences can help guide providers to tailor medication management to the specific needs of patients.

Once an antidepressant has been initiated, the PHQ-9 should be tracked at follow-up and can be used to guide adjustments in dosages and changes to the overall regimen. Four to 6 weeks after medication initiation, if the PHQ-9 score decreases by 5 or more the current treatment should be continued. For score reduction between 2 and 4 increasing the dose of the medication should be considered, and for score reductions of less than 2, switching or augmenting the medication should be considered. A common pitfall for PCPs is not pushing antidepressant medication dosages to therapeutic levels before considering them a failure. Up to one-third of patients require 10 weeks at a therapeutic antidepressant level to experience a response.\textsuperscript{112}

As providers have many options of electronically based medication references specific medication dosing is not covered in this review. These tools should be employed to confirm starting doses, usual treatment doses, and maximum doses of antidepressants. Dose adjustments based on liver and kidney function, and safety in the setting of pregnancy or lactation should also be reviewed prior to selection of a medication.

The goal of treatment is for full remission of major depression. PCPs should familiarize themselves with terms commonly used in psychiatry, including partial response, response, remission, and recovery (Table 3).

<table>
<thead>
<tr>
<th>Table 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grading response to treatment</strong></td>
</tr>
<tr>
<td>Grade</td>
</tr>
<tr>
<td>No response</td>
</tr>
<tr>
<td>Partial response</td>
</tr>
<tr>
<td>Response</td>
</tr>
<tr>
<td>Remission</td>
</tr>
<tr>
<td>Recovery</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Reduction in the initial score from a validated instrument – Examples include PHQ9, Hamilton Depression Rating Scale, Beck Depression Inventory.
Mechanism of action, efficacy and tolerability

In 2009 a systematic review of 117 RCTs found that mirtazapine (highest efficacy), escitalopram, venlafaxine, and sertraline, were most efficacious statistically versus 12 antidepressants assessed (although not specifically based on head-to-head trials). The same review found escitalopram, sertraline, citalopram, and bupropion were the best tolerated medications based on having the lowest dropout rates in studies (in order with the lowest dropout rate first). The superiority of escitalopram and sertraline over comparator antidepressants was further substantiated in a pair of Cochrane Review articles, although the lead author was the same for all 3 reviews.113,114 Hence, all other considerations being equal, PCPs can consider escitalopram and sertraline statistically superior to other choices for first-line therapy based on a combination of high efficacy and tolerability in studies. However, as with many studies, the impact of these statistical differences in real life clinical differences for patients is unclear.

Escitalopram may be easier to tolerate because it binds in a highly selective way to 5-hydroxytryptamine (5-HT) serotonin reuptake receptors, whereas most SSRIs bind with varying degrees to both 5-HT and the noradrenaline (NA) receptor that modulates norepinephrine reuptake inhibition.115 In general, the more neurotransmitter effects an antidepressant causes, the more side effects it causes as well. For example, MAOIs, some of the most difficult to tolerate antidepressants, not only modulate serotonin and norepinephrine, they are also anticholinergic like TCAs, antihistaminic, and affect tyramine levels. Sertraline and escitalopram may be more efficacious than some because, except for paroxetine and duloxetine, they are the most potent in their binding to 5-HT.115 Interestingly, sertraline is also a significant dopamine reuptake inhibitor.

Table 4 summarizes the mechanisms of action of antidepressants and the implications for common side effects related to those mechanisms. Table 5 highlights common side effects and the antidepressants most likely to cause them. Notably, the primary reason for discontinuation of antidepressants cited in studies is nausea and vomiting.110 Fortunately, nausea and vomiting resolve within 2 weeks of initiation or a dose increase and can be mitigated with lower initial doses and taking medication with food.116 As the preliminary nausea resolves, many antidepressants including SSRIs, TCAs, MAOIs, and mirtazapine cause weight gain; the least likely to do so are bupropion and SNRIs.

If PCPs understand antidepressant side effects well they can counsel patients on the specific risks and benefits of classes and specific medications. Identification of deal-breaker side effects, like sexual dysfunction for some patients, can help to eliminate some choices. It is helpful to counsel patients that SSRI side effects like nausea, vomiting, diarrhea, and headache tend to resolve over time, but fatigue, weight gain, and sexual dysfunction can be more chronic.116 It is important to adequately prepare patients for nearly immediate experience of side effects and the delay in the experience of improved mood.

Serious side effects

Common side effects listed above are problematic for quality of life but rarely have significant clinical long-term harm. However, antidepressants are not innocuous, and there are several serious side effects worth highlighting.

SSRIs have been found in observational studies to cause upper gastrointestinal bleeding especially in combination with NSAIDs.117 This risk increases with the concurrent use of other substances that accelerate ulcer formation, such as alcohol and corticosteroids, and is reduced with acid suppression medications including proton pump inhibitors and H2 blockers.118
### Table 4
**Antidepressant side effects related to affected neuroamine**

<table>
<thead>
<tr>
<th>Neuroamine</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serotonin (5-HT reuptake inhibition)</td>
<td>Abdominal upset, diarrhea, Sexual dysfunction, Short-term anxiety, Sleep disturbances</td>
</tr>
<tr>
<td>Norepinephrine (Na reuptake inhibition)</td>
<td>Elevated blood pressure, Dry mouth, Constipation</td>
</tr>
<tr>
<td>Dopamine (DA reuptake inhibition)</td>
<td>Hyperprolactinemia, Extrapyramidal symptoms, Sexual dysfunction, Cognitive dysfunction, Galactorrhea, gynecomastia</td>
</tr>
<tr>
<td>Acetylcholine (Muscarinic receptor blockade)</td>
<td>Head, Eyes, Ears, Nose and Throat (HEENT): dry eyes, blurred vision, dry mouth, acute narrow angle glaucoma, Cardiovascular: sinus tachycardia, Gastrointestinal: constipation, Genitourinary: urinary retention, Neuro: memory dysfunction</td>
</tr>
<tr>
<td>Histamine (H1 receptor blockade)</td>
<td>Sedation, Weight gain</td>
</tr>
<tr>
<td>Alpha-1 adrenergic receptor (antagonism)</td>
<td>Orthostatic hypotension, Dizziness, Reflex tachycardia</td>
</tr>
</tbody>
</table>

### Table 5
**Antidepressants and common side effects**

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Medications</th>
<th>Clinical Pearl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea and vomiting</td>
<td>Venlafaxine highest. Common in multiple antidepressants.</td>
<td>Use extended release formulation of venlafaxine to reduce nausea.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Start at lower doses.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Take with food.</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Sertraline &gt; paroxetine</td>
<td>Consider using in patients with constipation.</td>
</tr>
<tr>
<td>Weight gain</td>
<td>TCAs/MAOIs, mirtazapine &gt; paroxetine</td>
<td>Consider using in patients with anorexia or unintentional weight loss.</td>
</tr>
<tr>
<td>Somnolence</td>
<td>Trazodone &gt; mirtazapine</td>
<td>Use in patients with concurrent insomnia. Dose at night.</td>
</tr>
<tr>
<td>Dizziness</td>
<td>Venlafaxine &gt; sertraline, duloxetine</td>
<td>Consider bedtime dosing.</td>
</tr>
<tr>
<td>Headache</td>
<td>Venlafaxine &gt; bupropion, paroxetine, sertraline, escitalopram</td>
<td></td>
</tr>
<tr>
<td>Sexual dysfunction</td>
<td>Sertraline &gt; venlafaxine &gt; citalopram &gt; paroxetine</td>
<td>May require dose reduction or medication switch.</td>
</tr>
<tr>
<td></td>
<td>Bupropion and mirtazapine do not have this effect</td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>Bupropion &gt; sertraline, fluoxetine, paroxetine, venlafax</td>
<td>Take in the morning.</td>
</tr>
</tbody>
</table>

*Data from Refs. 115,128–130*
Hyponatremia is most apt to occur around 2 weeks after initiation of an SSRI. The highest risk populations for hyponatremia are women older than 65, especially those taking diuretics or medications that interact with the liver metabolism of antidepressants. In US Food and Drug Administration case reports, fluoxetine was most frequently reported (70%). Clinicians should consider checking a chemistry panel 2 weeks after initiation in high-risk populations or any patient manifesting typical signs and symptoms of hyponatremia.

Falls and fractures have been reported with SSRI use. A 2014 Canadian prospective cohort study of 6600 postmenopausal women found that use of SSRIs or SNRIs increased the risk for fragility fractures (hazard ratio, 1.88) even after controlling for history of falls and bone mineral density in the spine and hip (hazard ratio, 1.68). Given the prevalence of antidepressant medication use and the morbidity and mortality associated with osteoporotic fractures (especially of the hip), clinicians should consider the risk/benefit ratio of antidepressant therapy in at risk populations for osteoporosis.

Serotonin syndrome is a rare but potentially fatal condition that arises from the use of multiple serotonergic medications. A seminal New England Journal of Medicine review in 2005 describes a clinical triad of mental status changes, autonomic hyperactivity, and neuromuscular abnormalities that characterize the syndrome. The review describes neuromuscular changes that start with symptoms of akathisia then progress to tremor, clonus, and finally rigidity; autonomic changes that include tachycardia, hypertension, diaphoresis and hyperthermia; and mental status changes that progress from agitation and hypervigilance to overt delirium. Recognizing the correlation between these symptoms and signs and interacting medications or recreational substance use is imperative, because the treatment only is supportive with the immediate discontinuation of the offending agents. Culprit medications include all antidepressants but also triptans, lithium, buspirone, antiemetics, drugs of abuse including ecstasy, and opiates (eg, methadone, fentanyl, meperidine). A good resource for determining the safety of medications use, including antidepressants, during lactation is the National Institute of Health sponsored site - LacMed- http://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm. The nuances of antidepressant safety during pregnancy are beyond the scope of this review. Clinicians need to weigh the risks of birth defects that have been reported in case-reports or cohort studies such as persistent pulmonary hypertension, and cardiac defects with the risks of untreated depression on the health of the mother and unborn fetus.

Medication interactions
Many antidepressants are metabolized through the hepatic cytochrome P450 system (TCAs, fluoxetine, paroxetine, venlafaxine) and are susceptible to medication interactions. Complicating matters, some antidepressants are cytochrome P450 inhibitors (fluoxetine, paroxetine, bupropion, duloxetine). Given the risks of these interactions, PCPs should check for medication interactions whenever initiating an antidepressant or adding a different medication to a medication regimen that already includes an antidepressant.

Treatment-resistant depression
Unfortunately, approximately 30% to 40% of patients will not respond to first-line antidepressant interventions. Treatment-resistant depression (TRD) by strict definition is the failure to respond to adequate doses and duration of therapy of 2 different antidepressants from 2 different classes. More liberal definitions have been used in studies and in practice. Taking a complete psychiatric history with detailed
information on number of prior episodes of major depression; comorbid psychiatric, medical, and substance use disorders; and history of antidepressant use including highest dose achieved, duration of therapy, and experience with efficacy and side effects is helpful for the ongoing treatment of patients with refractory depression. Many patients report a history of not responding to an antidepressant but never used the medication long enough or never achieved a therapeutic dose to determine efficacy.

The 2006 STAR*D trial is the best study on the medication management of TRD and suggests a reasonable approach. After failure to respond to citalopram, 25% of subjects experienced remission with switching medications to another SSRi or to a different class of medications (venlafaxine, bupropion). Alternatively, 30% of subjects experienced remission with augmentation of the SSRi with bupropion or buspirone (although buspirone had higher dropout rates). After failing to improve with the switch of medications, or augmentation, an additional 25% had remission of symptoms with augmentation with liothyronine (triiodothyronine) versus 16% with lithium. Switching antidepressants instead of augmenting at this stage had lower efficacy with 13% remission with mirtazapine and 20% with nortriptyline. By the fourth attempt at a medication change in the study, adding or changing medications to this highly refractory group had low remissions rates of 7% to 14%.

The take-home points for PCPs are to consider switching medications or using an augmenting agent if patients do not reach remission. However, if patients have refractory symptoms after 2 to 3 medication changes, they should be seen by a psychiatrist for assistance in the management of TRD.

A dose-equivalent, immediate medication switch can occur if medications are changed to one in the same class (eg, sertraline 150 mg to escitalopram 20 mg). If the new medication is of a different class, a cross-tapering strategy can be used (eg, sertraline 200 mg to venlafaxine XR 150 mg). During the first week, half the dose of the first antidepressant can be used at the same time as half the therapeutic equivalent dose of the second antidepressant (eg, sertraline 100 mg and venlafaxine XR 75 mg). After this crossover week, the first antidepressant is discontinued and the second antidepressant is increased to the full therapeutic equivalent dose (eg, discontinue sertraline, increase venlafaxine XR to 150 mg). If providers are unfamiliar with use of augmenting agents, they should seek the advice of a psychiatrist to discuss dose initiation, titration, and monitoring of medications like triiodothyronine and lithium.

SUMMARY

Depression is a common and morbid condition seen frequently in primary care settings. PCPs are increasingly responsible for the diagnosis and management of this condition. Well-validated and time-effective screening modalities exist and should be used in the ambulatory setting as long as adequate access to support and interventions is available. Although MDD is usually episodic, it confers significant harm, and the specific symptoms and degree of functional impairment experienced by patients is variable. Characterizing the severity of symptoms helps with determining an optimal management plan.

Lifestyle, psychotherapy, and pharmacotherapy interventions are effective for the treatment of MDD. Options should be discussed with patients so that an appropriate and acceptable strategy can be mutually determined. Adherence to psychotherapy and pharmacotherapy can be improved by engaging patients in the risks, benefits,
timing, and practical implications of each approach. Side effects are the most common reason for discontinuation of medication therapy, but providers can tailor the choice of medications to best fit the individual needs of patients. The goals of therapy are to reach remission, but approximately one-third of patients experience refractory symptoms. PCPs should be familiar with strategies to address TRD depression but also acknowledge when MDD symptoms are either too severe or refractory for primary management by a generalist.

There are many opportunities to improve the care of depressed patients in the primary care setting. Education and understanding by providers about the identification and management of MDD is just one step. Cultural and societal stigmas continue to hamper the care of many patients; ongoing public health campaigns and parity of access and coverage for mental health is necessary to meet the needs of patients. Improvements in drug design can address the delay in efficacy and the problematic side-effect profile of antidepressants to improve efficacy and tolerability of pharmacologic approaches to care.

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