

# Diagnosis and Treatment of Depression in Adults With Comorbid Medical Conditions

## A 52-Year-Old Man With Depression

Mary A. Whooley, MD, Discussant

**DR LIBMAN:** Mr J is a 52-year-old man who reports a several-month history of depressive symptoms, including sadness, anhedonia, difficulty sleeping, and occasional suicidal thoughts. He was originally diagnosed as having depression during college and has received counseling and psychotropic drug therapy intermittently throughout his life. He feels that both have been somewhat helpful, but his symptoms never completely resolve. He is not currently seeing a mental health care professional. Mr J reports no past suicide attempts and has not been hospitalized for the condition. He states that his depression has prevented him from maintaining a job for an extended time and has made it difficult for him to develop a career. His family lives in the area but he has few friends and feels socially isolated. He has not been in a romantic relationship for many years. There is no family medical history of depression or other major psychiatric disorders. Mr J works as a chauffeur. He is single and lives alone. He does not smoke cigarettes and has no history of substance abuse. He drinks beer infrequently.

His medical history is otherwise noteworthy for borderline hypertension, esophageal reflux disease, cervical spondylosis, chronic intermittent low back pain, sleep apnea (managed with continuous positive airway pressure), non-alcoholic fatty liver disease, obesity, and hyperlipidemia. He denies other chronic medical problems. His medications include esomeprazole, fish oil, ibuprofen, pravastatin, and sucralfate. He has no known drug allergies.

Mr J appears well, alert, and oriented; his physical examination results are normal. He is able to engage readily in conversation. His affect is somewhat constricted. His mood appears moderately sad and he seems tearful on occasion. There is no evidence of thought disorder or cognitive impairment. He denies current suicidal ideation. His

**Approximately 1 in 10 primary care patients has major depressive disorder, and its presence is associated with poor health outcomes in numerous medical conditions. Using the case of Mr J, a 52-year-old man with depressive symptoms and several comorbid medical conditions, diagnosis and treatment of depression are discussed. Specific topics include evidence regarding appropriate depression screening and diagnosis, the importance of team-based care, patient self-management, exercise, structured psychotherapy, pharmacotherapy, monitoring of therapy, and indications for referral.**

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judgment appears to be intact. He has insight into his diagnosis and is interested in improving his condition but feels embarrassed and frustrated by it. He has no evidence of metabolic abnormalities or hypothyroidism on laboratory testing.

### MR J: HIS VIEW

I know I was suffering from really severe depression. In general, it felt like I was living in a fog and was always sleepy. In high school, in fact, a lot of people thought I was on drugs or something because I was really out of it. I know when I'm really depressed because it feels like a sort of membrane, almost like gelatin, enclosing me.

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When I'm depressed, there is very little I can do that I get pleasure or satisfaction from. Some of the things that I will do seem more like grunt work. I very much remember the first therapist I went to. I think she was more depressed than I was, and we would just sit there and stare at each other for 2 or 3 sessions.

When I was using Wellbutrin [bupropion], the symptoms got better. I don't recall being really suicidal when I was on that medication. I've been on several other medicines, which I can't recall. All the medications seemed to have the same benefit; they got me to a certain level but not quite to the finish line.

I've never tried to commit suicide. I was close when I was young. I was in a bathroom and I had a knife against my wrist. I was getting ready to do it, but I stood there for hours. I didn't go through with it. I never had to be hospitalized for depression. Maybe I should have, I don't know, but nobody's ever had to send me away. I think I've hidden it fairly well.

My depression over the last 20 years seems to get worse in the wintertime. My symptoms were much worse this December. In the past, I've lost a job because of it or I will just quit jobs. I don't have a college degree. I honestly can't decide what I want to do with my life, and I think that really has to do with depression.

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### AT THE CROSSROADS: QUESTIONS FOR DR WHOOLEY

Should primary care patients be routinely screened for depression, and, if so, what instrument should be used? How is depression diagnosed, and what other conditions may be confused with or contribute to it? How should primary care physicians deal with the stigma associated with depression if it interferes with a patient's willingness to be treated? What are the available treatment options and how should they be monitored? What is the role of primary care physicians in the management of depression, and what are the indications for referral to a mental health care professional? What would you recommend for Mr J?

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### SCREENING FOR DEPRESSION

**DR WHOOLEY:** By 2030, major depressive disorder (MDD) is projected to be the number one cause of disability in developed nations and the second leading cause of disability in the world after human immunodeficiency virus and AIDS.<sup>1,2</sup> Like Mr J, many patients with depression do not seek specialty care for their illness and, thus, may not receive treatment unless it is provided by the primary care clinician. The US Preventive Services Task Force recommends screening adults for depression when collaborative care management (also referred to as team care, interdisciplinary stepped care, staff-assisted care, or the 3-component model) is in place to ensure accurate diagnosis, effective treatment, and follow-up (GRADE level of evidence B).<sup>3,4</sup>

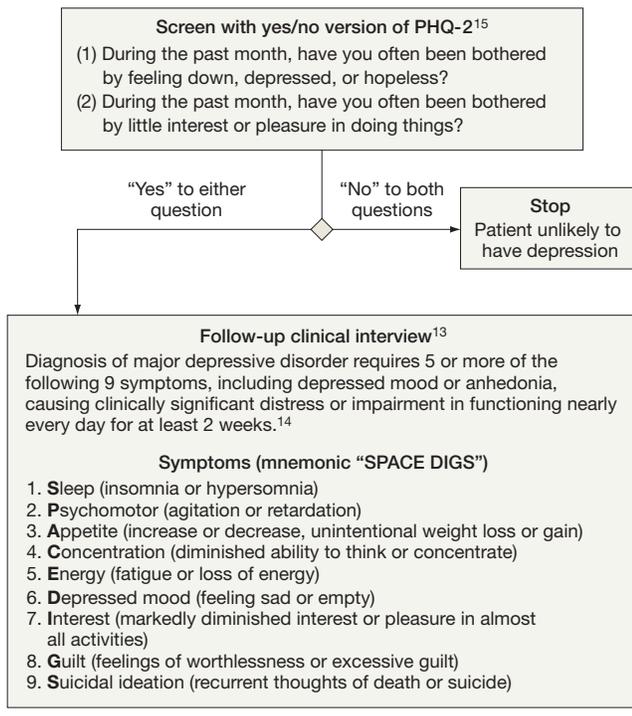
These recommendations are based on numerous randomized trials that have demonstrated greater recovery from depression when screening is combined with collaborative (vs usual) care management.<sup>5,6</sup>

Collaborative care is a team-based approach for managing depression that has 3 key components: the primary care physician, a depression care manager, and a consulting psychiatrist.<sup>7</sup> The care manager (a trained nurse or psychologist) provides patient education for behavioral activation and self-management, close telephone follow-up (to encourage adherence and remind patients that they should not expect immediate improvement), symptom monitoring, and timely stepped care for nonresponders (such as increasing the medication dosage by phone rather than waiting until the next visit). The consulting psychiatrist helps the care manager by supervising and assisting with patient management, including medication adjustment and augmentation of therapy ("treating to target"). Collaborative care includes many of the key components of the chronic care model of Wagner et al<sup>8</sup> and is currently being implemented in numerous health care organizations throughout the world.<sup>7</sup> Several online training programs with free downloadable training materials are available to help organizations adapt these programs to individual health care settings (Resources; available at <http://www.jama.com>).

Without collaborative care programs in place, primary care patients do not benefit from depression screening. Unfortunately, the increased recognition and treatment of depression that result from screening alone do not translate into clinical improvement (GRADE level C).<sup>3,4</sup> In a comprehensive review of the literature, the Cochrane Collaboration concluded that "there is substantial evidence that routinely administered screening questionnaires for depression have minimal impact on the outcome of depression. Practice guidelines and recommendations to adopt this strategy in isolation should be resisted."<sup>9,10</sup> Several reasons exist for why routine screening does not improve depression in the absence of collaborative care management. Patients must take antidepressant medications for 2 to 4 weeks before noticing improvement in symptoms, adherence to mental health referrals is poor, and medications are often not prescribed in adequate dosages. In addition stigma and embarrassment are major impediments to patients receiving and agreeing to take antidepressant therapy.

Interestingly, although there is no benefit from routine screening in the absence of collaborative care management, patients with depression identified through case-finding can still benefit from treatment by primary care physicians alone (without a care manager or consulting psychiatrist). It is unclear why depression treatment is more efficacious in patients identified through case-finding (testing of individuals with signs or symptoms of disease) than in those identified through screening (testing of individuals without overt signs or symptoms of disease).<sup>11</sup> It is possible that patients seeking care may have more severe symp-

**Figure.** Recommended Algorithm for Diagnosing Depression in Primary Care Patients



Adapted from Whooley.<sup>12</sup>

toms or be more likely to follow through with treatment recommendations than those identified through routine screening.

## DIAGNOSIS OF DEPRESSION

The yes/no version of the 2-item Patient Health Questionnaire (PHQ-2) is the most effective screening tool for identifying MDD in primary care patients and takes less than 1 minute to complete (FIGURE).<sup>15</sup> A “yes” response to one or both questions (a positive screen) is 96% sensitive and 57% specific for MDD. A “no” response to both questions effectively rules out depression and no further screening is necessary. The yes/no version of the PHQ-2 is sometimes confused with the multiple-choice version of the PHQ-2 (score range, 0-6), which asks about the frequency of depressed mood and anhedonia (not at all=0; several days=1; more than half the days=2; nearly every day=3) and can also be used for depression screening.<sup>16</sup> The multiple-choice version of the PHQ-2 asks about depressive symptoms during the last 2 weeks, whereas the yes/no version asks about depressive symptoms during the past month. Both instruments have similar test characteristics, with excellent sensitivity and relatively low specificity, but the yes/no version is easier to administer and interpret.<sup>17</sup>

The low specificity and positive predictive value of the PHQ-2 (either version) means that fewer than half of pa-

tients with a positive screen ultimately meet criteria for MDD. Thus, any positive screen must be followed by a clinical interview to confirm the diagnosis (Figure). Mr J said, “When I’m depressed [depressed mood], there is very little I can do that I get pleasure or satisfaction from [lack of interest/anhedonia].” He described a general sleepiness [lack of energy/fatigue] and said he was “living in a fog . . . really out of it [psychomotor retardation].” He also said, “. . . [W]hen I’m really depressed . . . it feels like a sort of membrane, almost like gelatin, enclosing me . . . I honestly can’t decide what I want to do with my life [poor concentration].” Patients with MDD often feel that they cannot get enough clarity to make important decisions in their lives. Based on these 5 symptoms and their associated impairment in functioning (“In the past, I’ve lost a job because of it”), Mr J meets diagnostic criteria for MDD.

As an alternative to a clinical interview, some practitioners administer the 9-item Patient Health Questionnaire (PHQ-9).<sup>18</sup> The PHQ-9 is a self-report instrument that measures the frequency with which a patient has experienced each of the 9 depressive symptoms from the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) during the last 2 weeks (not at all=0; several days=1; more than half the days=2; nearly every day=3). Total scores range from 0 to 27 based on number and frequency of depressive symptoms. As another alternative to the clinical interview, some clinicians administer the 8-item Patient Health Questionnaire (PHQ-8), which omits the question regarding “thoughts that you would be better off dead or hurting yourself in some way.” Total scores on the PHQ-8 range from 0 to 24.

It is reasonable to make a diagnosis and start therapy for MDD based on a PHQ-8 or PHQ-9 score of 10 or higher if 1 of the 2 core symptoms (depressed mood and anhedonia) is present and the symptoms are associated with functional impairment. However, it must be kept in mind that the PHQ-9 was developed as a depression severity measure rather than a diagnostic instrument, and a cut point of 10 or higher misses some cases of MDD that would be detected by the clinical interview. In addition, administering the full PHQ-9 to all patients only marginally improves sensitivity over the PHQ-2 and requires more than half of patients to complete the PHQ-9 unnecessarily.<sup>19</sup> The advantage of using the yes/no PHQ-2 is that it rules out depression in more than half of patients using only 2 questions that take less than 1 minute to complete.

The differential diagnosis of MDD includes metabolic disorders, bipolar disorder, normal grief reaction, problem drinking, substance abuse, and medication toxicity. Hypothyroidism should be ruled out in all patients with MDD. To screen for bipolar disorder, it is important to ask whether the patient has any history of unusually elevated mood or times with markedly increased energy or impulsivity when others might think they are acting different than usual. A normal grief reaction can result in depressive symptoms, but even if symptoms are initially sparked by a significant loss,

**Table 1.** General Approach to Treatment of Major Depressive Disorder in Patients With Comorbid Medical Conditions Based on PHQ-8 or PHQ-9 Score and Degree of Functional Impairment<sup>a</sup>

PHQ-8 or -9 Score	Functional Impairment	Treatment		
		Self-Management	Psychotherapy	Pharmacotherapy
<10	Minimal	Yes		
10-14	Mild	Yes	Yes	
15-19	Moderate	Yes	Yes	Yes
≥20	Severe	Yes	Yes	Yes

Abbreviation: PHQ, Patient Health Questionnaire (8 or 9 item).  
<sup>a</sup>Optimal therapy for individual patients may differ.

patients with depressive symptoms lasting longer than 2 months may benefit from antidepressant therapy. Problem drinking and substance abuse are important considerations in the differential. However, the presence of these comorbid conditions should not preclude antidepressant therapy because stabilizing mood symptoms can be helpful for preventing relapse.<sup>20,21</sup> Some medications, such as interferon alfa, corticosteroids, and benzodiazepines, are associated with depression.<sup>22,23</sup> The anecdotal belief that  $\beta$ -blocker therapy causes depressive symptoms is not supported by data from clinical trials.<sup>24</sup>

### ADDRESSING STIGMA

The stigma of mental illness can be a barrier to patients engaging in treatment, but several approaches can help reduce stigma. First, the patient's feelings should be acknowledged and validated, and patients should be informed that they are not alone and that almost all patients feel embarrassed by a diagnosis of MDD. Additionally, patients should be informed that depressive symptoms are remarkably common. According to the National Health and Nutrition Examination Survey (2005-2008), 6.8% of US adults had moderate to severe depressive symptoms during the 2 weeks before the survey.<sup>25</sup> In the European Union, the 12-month prevalence of MDD was 6.9% for 2011.<sup>26</sup> In primary care patients, the prevalence is 10%.<sup>1</sup> Second, physicians should explain that depression is a medical disorder, not a problem of weakness or lack of will that patients can "snap out of." Third, it should be emphasized that MDD usually results from a combination of genetic predisposition and environmental factors. Emphasizing the biological etiology of depression can help patients feel more comfortable accepting medical therapy. Just as a patient with diabetes needs insulin to restore blood glucose levels to normal, a patient with depression may benefit from blocking reuptake of certain neurotransmitters in the brain. "Restoring something to normal" can be more acceptable to a patient than "fixing something that is broken."

Another approach to reducing the perceived stigma associated with depression is to point out that depression can lead to undesirable circumstances, including unemployment, loss of income, and decreased productivity in the workplace.<sup>27-29</sup> If patients are not willing to take antidepressant

medication for mental health reasons, they may be more willing to consider therapy to improve their job functioning. Likewise, some patients will be more open to depression treatment if they know that therapy can improve their other health conditions, such as diabetes, asthma, osteoarthritis, chronic obstructive pulmonary disease, inflammatory bowel disease, kidney disease, and cardiovascular disorders.<sup>30-33</sup> The final and perhaps most effective approach is to describe famous people with depression. Many celebrities have spoken out and some have written books about their struggles with depression.<sup>34,35</sup> This can help patients feel less embarrassed and more willing to consider therapy.

### TREATMENT OF DEPRESSION

For primary care practitioners, there are 4 evidence-based approaches to the treatment of depression: self-management, psychotherapy, pharmacotherapy or a combination (TABLE 1). Choice of therapy depends on severity of symptoms, patient preference, and degree of functional impairment (difficulty getting work done, taking care of things at home, and getting along with others). For patients with MDD and minimal symptoms (PHQ-9 score <10 with minimal impairment in functioning), a trial of self-management (described below) should be initiated, with reevaluation after 3 to 4 weeks of watchful waiting. For patients with mild symptoms (PHQ-9 score 10-14 and mild impairment in functioning), psychotherapy is considered first-line therapy.<sup>11,36</sup> For patients with moderate to severe symptoms (PHQ-9 score 15-19 and moderate impairment in functioning), pharmacotherapy is often necessary.<sup>37</sup> For patients with severe depressive symptoms (PHQ-9 score ≥20 and substantial impairment in functioning), psychotherapy may be beneficial, but a combination of pharmacotherapy and psychotherapy is more effective than either therapy alone.<sup>38,39</sup>

#### Self-management

Encouraging self-management through patient education, brief counseling, and prescribed exercise is an essential component of depression treatment.<sup>40,41</sup> First, clinicians should educate patients about the diagnosis of MDD and the range of treatments available. If available, written information on depression should be provided and patients should be in-

formed about local support groups and Internet resources. Brief counseling can incorporate several effective elements of structured psychotherapy, such as encouraging patients to schedule relaxing and pleasant activities, modifying negative self-perceptions, and breaking current life problems into smaller components that can be more easily addressed. Self-help books and online resources can augment treatment and help patients incorporate these cognitive and behavioral techniques into their daily lives. A downloadable “self-care action plan” is freely available from the MacArthur Initiative on Depression in Primary Care (see Online Resources).<sup>42</sup>

As part of self-management, it is critical for primary care clinicians to emphasize the importance of physical activity. Exercise not only improves depressive symptoms (effect size, 0.40; 95% CI, 0.14-0.66)<sup>43-45</sup> but has many other positive effects on physical health.<sup>46</sup> Regardless of depression, most adults should engage in moderate-intensity exercise for at least 150 minutes per week (eg, walking for 30 minutes 5 times per week), vigorous-intensity exercise for at least 75 minutes per week (eg, jogging or running for 25 minutes 3 times per week), or a combination of moderate- and vigorous-intensity exercise (GRADE<sup>3</sup> level A). However, adults who are unable to meet these targets can still benefit from engaging in less than the recommended amounts of exercise. Sedentary patients can start by finding a manageable activity (such as walking around the block once per day or swimming for 15 minutes 3 times per week), then increase as tolerated. When it comes to exercise, I always tell my patients that “some is better than none.”

## Psychotherapy

For patients with mild to moderate depression, structured psychotherapy along with self-management should be considered as first-line treatment.<sup>11,36</sup> Structured psychotherapy is most typically administered by a trained psychologist or masters-level therapist in 8 to 16 fifty-minute sessions over 3 to 6 months. However, therapy can be delivered individually, in groups, by telephone, via the Internet, or on a computer. Computerized cognitive behavioral therapy is considered at least as beneficial as traditional face-to-face therapy and has gained widespread endorsement.<sup>47-50</sup> The UK National Institute of Health and Clinical Excellence (NICE) recommends a specific computerized cognitive behavioral therapy program called “Beating the Blues” as an option for delivering computerized therapy for management of mild to moderate depression.<sup>47</sup>

Five different types of structured psychotherapy have proven efficacy (TABLE 2) (GRADE<sup>3</sup> level A).<sup>60</sup> Behavioral activation encourages patients to increase the frequency of and focus attention on pleasurable activities. Cognitive therapy works by helping patients identify and challenge pessimistic or self-critical thoughts that cause or perpetuate depression. Cognitive-behavioral therapy, the most commonly administered form of psychotherapy, helps patients increase positive experiences and focus on their accomplishments rather than dwelling on negative life experiences. Problem-solving therapy helps patients break larger problems into smaller pieces and identify specific steps to

**Table 2.** Evidence-Based Psychotherapies for Treatment of Depression in Patients With Comorbid Medical Conditions

Therapy	Goals	Specific Techniques	Effect Size (95% CI) <sup>a</sup>
Behavioral activation <sup>51,52</sup>	Increase and focus attention on positive life experiences	Increase frequency of pleasant activities Activate social networks Increase positive reinforcement Increase self efficacy and mastery Focus attention on accomplishments	0.87 (0.60-1.15)
Cognitive therapy <sup>53</sup>	Identify and modify dysfunctional ideas that contribute to depression	Recognize dysfunctional cognitions Modify negative thought processes Uncouple behaviors from negative thoughts Improve problem-solving skills	0.44 (0.08-0.80)
Cognitive-behavioral therapy <sup>54,55</sup>	Enhance positive life experiences and change dysfunctional cognitions	Combine techniques of cognitive and behavioral therapy (listed above) Individual, group, telephone, computer, and Internet-based applications available	0.67 (0.60-0.75)
Interpersonal therapy <sup>56</sup>	Improve management of interpersonal situations, such as relationship conflicts, grief, or major life events, that contribute to depression	Identify interpersonal challenges Improve existing relationships Increase social support Strengthen self-esteem Enhance communication skills	0.63 (0.36-0.90)
Problem-solving therapy <sup>57,58</sup>	Identify everyday life problems that contribute to depression and develop skills to manage them	Identify problems and break them into smaller pieces Generate alternative solutions Select the best solution Develop a plan Implement the plan Evaluate the efficacy of problem solving	0.34 (0.02-0.48)

<sup>a</sup>The standardized mean difference (effect size or Cohen *d*) is the difference in mean depression scores (after 6-16 sessions delivered over 3-6 months) between treatment and control groups divided by the pooled standard deviation of all study participants. Effect sizes can range from 0 to 3 SDs (0.2-0.5 is considered small, 0.5-0.8 is considered medium, and >0.8 is considered large).<sup>59</sup>

ward change.<sup>57,58</sup> Interpersonal therapy focuses on clarifying interpersonal conflicts and working to resolve them.

### Pharmacotherapy

During the past 15 years, there has been a marked broadening and expansion of antidepressant treatment in the United States,<sup>61</sup> with more than 75% of antidepressant medications now being prescribed by general medical practitioners.<sup>62</sup> Patients such as Mr J, who have moderate to severe depressive symptoms with substantial impairment in functioning, usually benefit from pharmacotherapy (effect size, 0.66; 95% CI, 0.38-0.94; GRADE<sup>3</sup> level A).<sup>63,64</sup> The decision about which antidepressant medication to prescribe should incorporate patients' preferences, adverse effects, and possible interactions with other medications. However, it can be overwhelming for primary care physicians to sort through all of the different types of antidepressant medications and their adverse effects.<sup>65</sup> Moreover, there are no grounds to recommend one antidepressant over another based on efficacy.<sup>64</sup> Therefore, my approach is to become familiar with 1 or 2 antidepressant medications and use these as first-line pharmacological agents for most patients (TABLE 3).

For patients with depression and comorbid medical conditions, selective serotonin reuptake inhibitors (SSRIs) are the antidepressants of first choice given their demonstrable effect on quality of life and their apparent safety in cardiovascular disease.<sup>67</sup> Of the SSRIs available, sertraline, citalopram, and escitalopram are the best tolerated.<sup>65,68-70</sup> Fluoxetine inhibits the cytochrome p450 system and has a very long half-life, so it has more likelihood of interacting with other medications in patients being treated for comorbid medical conditions. Paroxetine is associated with more sedation and weight gain than other SSRIs.<sup>71</sup> The most problematic adverse effect of SSRIs is sexual dysfunction (decreased libido, impotence, or difficulty having an orgasm), which can occur in up to 40% of patients.<sup>72</sup> Uncommon but important adverse effects include extrapyramidal symptoms such as akathisia (restless legs syndrome),<sup>73,74</sup> hyponatremia,<sup>75</sup> and gastrointestinal bleeding, especially with concurrent use of nonsteroidal anti-inflammatory medication.<sup>76,77</sup>

The other medication with which primary care physicians should be familiar, particularly for younger patients who may be more concerned about the sexual adverse ef-

**Table 3.** Selected Antidepressant Medications Currently Available in Generic Form for Treatment of Depression in Patients With Comorbid Medical Conditions<sup>a</sup>

Medications	Initial Dosage <sup>b</sup>	Usual Effective Dosage	Maximum Dosage	Monthly Cost, \$ <sup>c</sup>	Most Common Adverse Effects
Selective serotonin reuptake inhibitors					
Citalopram	20 mg/d	20-40 mg/d	40 mg/d <sup>d</sup>	31-38	Sexual dysfunction (decreased libido, impotence, difficulty having orgasm), insomnia or somnolence, weight gain or loss, constipation or diarrhea, nausea, xerostomia
Escitalopram	10 mg/d	10-20 mg/d	20 mg/d <sup>d</sup>	41-58	
Fluoxetine	20 mg/d	20-40 mg/d	80 mg/d	22-56	
Paroxetine	20 mg/d	20-40 mg/d	50 mg/d	22-37	
Sertraline	50 mg/d	100-200 mg/d	200 mg/d	28-56	
Norepinephrine and dopamine reuptake inhibitors					
Bupropion	75 mg 2 times per d	100 mg 3 times per d	150 mg 3 times per d	62	Insomnia, nausea, xerostomia, headache Lowest rate of sexual adverse effects
Bupropion SR (sustained release)	150 mg/d	150 mg 2 times per d	200 mg 2 times per d	62	
Bupropion XL (sustained release)	150 mg/d	300 mg/d	450 mg/d	120	
Second-line agents					
Mirtazapine	15 mg at bedtime	30 mg at bedtime	45 mg at bedtime	44	Sedation, weight gain, postural hypotension
Venlafaxine	37.5 mg 2 times per d	75-100 mg 2 times per d	125 mg 3 times per d	89-99	Nausea, increased blood pressure and heart rate
Venlafaxine XR (extended release)	37.5 mg/d	75-150 mg/d	225 mg/d	115-129	

<sup>a</sup>The information provided in this table is intended as a guide. Clinicians should refer to the package inserts or consult with a pharmacist for individual dosage recommendations, precautions, and drug interactions.

<sup>b</sup>Start with half of this dose in frail or elderly patients and in patients with hepatic or renal disease.

<sup>c</sup>From Consumer Reports Health Best Buy Drugs.<sup>70</sup> Prices reflect US nationwide retail average (in US dollars) for generic form of drug.

<sup>d</sup>Doses higher than 40 mg of citalopram (20 mg in patients aged >60 y) or 20 mg of escitalopram (10 mg in patients aged >60 y) should be avoided due to prolongation of QT interval.<sup>66</sup>

fects of the SSRIs, is bupropion. Bupropion has efficacy similar to the SSRIs.<sup>78,79</sup> It has also been approved for smoking cessation, which is an added benefit for some patients. Unlike the SSRIs, which can be started at their usual effective dose, bupropion should be started at a lower dose and increased after 1 week if adverse effects are tolerable. Bupropion can be used in combination with SSRIs to augment therapy for nonresponders. However, bupropion should be avoided in pregnancy and does have a very small (<1%) risk of seizures. A comprehensive review of depression management during pregnancy has recently been published.<sup>80</sup>

Three additional classes of antidepressant medications deserve mention. The serotonin and norepinephrine reuptake inhibitors (venlafaxine and duloxetine) are not first-choice agents for treating depression because they can cause an increase in blood pressure and may not be as well tolerated in patients with comorbid medical conditions.<sup>81</sup> However, in patients for whom SSRIs and bupropion have been ineffective, venlafaxine is a reasonable choice.<sup>82,83</sup> The serotonin antagonist mirtazapine can be useful in elderly patients because increased appetite and sedation are sometimes beneficial side effects.<sup>67</sup> However, mirtazapine is associated with weight gain,<sup>84</sup> can cause hypertensive urgency when administered with clonidine,<sup>85</sup> and in rare cases has been associated with agranulocytosis. Tricyclic antidepressants (eg, nortriptyline, desipramine) should not be used as first-line agents for treatment of depression in patients with comorbid medical conditions because of their adverse effects (eg, postural hypotension, dry mouth, dry eyes, urinary retention, constipation) and association with adverse cardiovascular events.<sup>86</sup>

### Other Therapies

Complementary and alternative therapies for depression include bright light therapy and *Hypericum perforatum* (St John's wort). Bright light treatment (10 000 lux for 30 min/d, 5000 lux for 60 min/d, or 2500 lux for 120 min/d) for 7 days has been shown to improve depressive symptoms (effect size, 0.20; 95% CI, 0.01-0.38; GRADE<sup>3</sup> level B).<sup>87-89</sup> For patients with MDD and mild to moderate depressive symptoms (PHQ-9 score <15), St John's wort may be similarly effective and has fewer adverse effects than standard antidepressants (effect size, 0.47; 95% CI, 0.30-0.64; GRADE<sup>3</sup> level B).<sup>90</sup> However, the interactions of St John's wort with many other medications make this agent less useful in patients with comorbid medical conditions.<sup>91</sup> It is especially important to note that the combination of St John's wort and an SSRI can cause a life-threatening serotonin syndrome (eg, agitation, hyperthermia, diaphoresis, tachycardia, rigidity).

In treating Mr J, I would first educate him about the diagnosis of MDD and emphasize the importance of self-management, including regular exercise. I would also suggest he consider either in-person or computerized cognitive-behavioral therapy. He reports having responded to bupropion in the past but was also treated with several other medications. If there is a particular

antidepressant medication to which he has previously responded, I would restart that medication. Any medication from which he has experienced no response at maximum doses or intolerable adverse effects should obviously be avoided. For patients who are similar to Mr J but who have never taken antidepressant medications, I would prescribe either an SSRI (such as citalopram, 20 mg/d) or sustained-release bupropion (150 mg/d for 1 week, then 150 mg twice per day) and explain that it will take at least 4 weeks to see benefit. I would also encourage Mr J to use bright light therapy, especially during the winter, when he reported having worse symptoms.

### Monitoring of Therapy

Close monitoring during the first 3 months of therapy is critical to the effectiveness of depression treatment. It is important to educate patients that antidepressant medication must be taken for at least 4 weeks before symptom improvement should be expected. The clinical benefits of therapy may not be evident for 6 to 8 weeks, and recovery may take as long as 16 weeks.<sup>53</sup> Collaborative care management programs include telephone or in-person contact every 2 to 4 weeks, with patient education, monitoring of medication adherence, repeated assessment of symptoms using the PHQ-9, and psychiatric consultation as necessary.<sup>92-95</sup> If psychotherapy does not result in symptom improvement by 6 to 8 weeks or full remission by 16 weeks, the addition of a medication should be considered. If antidepressant medication does not improve symptoms by 4 weeks and adverse effects are tolerable, the initial medication dosage should be doubled. If symptoms have not improved by 8 weeks and adverse effects still remain tolerable, the dosage should again be increased to the maximum allowable. Only about half of patients with MDD respond to the first medication prescribed, so if no improvement has occurred by 12 weeks, the patient should be switched to a different medication.<sup>82</sup> Once the patient has responded to pharmacotherapy, it should be continued for at least 6 months to prevent relapse. Patients with a history of MDD should continue pharmacotherapy for at least 2 years, and possibly indefinitely.

### Role of the Primary Care Clinician and Indications for Referral

Most cases of depression can be managed by primary care practitioners. However, patients should be referred to a psychiatrist if they have a history of psychosis or mania, if they have a suicide plan, or if they have not responded to therapies initiated by the primary care clinician. When a diagnosis of MDD is made, the practitioner should ask, "Have you ever had thoughts about harming yourself or taking your own life?" If the answer is yes, suicidal thoughts can be further explored using the 4P mnemonic<sup>96</sup>: past history (Have you ever attempted to harm yourself or take your own life?), plan (Have you thought about how you would actually take your own life?), probability (How likely is it that you will act on these thoughts?), and prevention (Is there anything

that would prevent you from taking your own life)? Any patient with an active plan for self-harm should receive immediate psychiatric evaluation. If there is no active plan, then immediate referral is generally not necessary.

### Other Benefits to Depression Treatment

There are many other benefits of depression treatment, including improvements in chronic pain,<sup>97</sup> substance abuse,<sup>20,21</sup> sleep, and quality of life. The TEAMcare study found that integrating depression and chronic disease care among patients with diabetes mellitus and/or coronary heart disease resulted in greater overall 12-month improvement in glycosylated hemoglobin, low-density lipoprotein cholesterol, systolic blood pressure, depressive symptoms, and quality of life.<sup>30</sup> One trial found that collaborative care treatment for depression was associated with lower mortality compared with usual care in older primary care patients.<sup>31</sup> Both the COPES and SUPRIM trials found that treatment for depression was associated with a lower risk of secondary cardiovascular events among patients with coronary heart disease.<sup>32,33</sup>

### RECOMMENDATIONS FOR MR J

For Mr J, treatment would ideally involve a collaborative care management team to ensure close follow-up every 2 to 4 weeks, monitoring of medication adherence, repeated assessment of depressive symptoms, and timely adjustment of dosing. If he were to start citalopram, 20 mg/d, and show no or minimal response after 6 weeks, I would increase the dosage to 40 mg/d, assuming adverse effects were tolerable. I would also recommend cognitive-behavioral therapy if it had not already been initiated. If he achieved partial but not complete recovery after 12 weeks of citalopram, I would add bupropion, 150 mg/d for 1 week then 150 mg twice per day. If he had still not achieved complete recovery after 24 weeks of citalopram, 12 weeks of cognitive-behavioral therapy, and 12 weeks of bupropion, I would refer him to a psychiatrist. Once remission is achieved, I would educate Mr J that depression tends to be a chronic condition with cyclical ups and downs and that he may benefit from indefinite treatment with antidepressant medication.

### QUESTIONS AND DISCUSSION

**QUESTION:** Some staff here have put together a terrific proposal for collaborative care, but it's been very difficult to sell this to those who might pay for it as an intervention that's going to improve value by both reducing cost and improving quality. What do you think is going to drive more widespread dissemination of collaborative care management programs?

**DR WHOOLEY:** Lack of reimbursement remains the single greatest obstacle to more widespread adoption of collaborative care,<sup>98</sup> and we must continue to develop better funding mechanisms to capture its added value.<sup>99,100</sup> Although collaborative care management programs can be associated with increased cost in the short term,<sup>5</sup> they are cost-effective and probably cost-saving in the longer term.<sup>101-104</sup>

Moreover, recovery from depression predicts lower health services costs,<sup>105</sup> and collaborative care management can reduce adverse outcomes from other chronic medical conditions.<sup>30</sup> The Centers for Medicare & Medicaid Services has recently determined that annual screening for depression will be covered for Medicare beneficiaries in primary care settings that have staff-assisted depression care supports in place to ensure accurate diagnosis, effective treatment, and follow-up.

**QUESTION:** I've seen a lot more direct-to-consumer advertising for drugs that you didn't mention, such as Seroquel [quetiapine]. Do you have any comment on whether these are actually effective or useful or if they have any role in the treatment of patients with depression in primary care?

**DR WHOOLEY:** Primary care physicians should not prescribe atypical antipsychotic medications (eg, clozapine, olanzapine, risperidone, sertindole, aripiprazole, ziprasidone, quetiapine) unless they have been initiated by a psychiatrist. These medications are expensive<sup>106</sup> and can lead to obesity, dyslipidemia, metabolic syndrome, and increased cardiovascular risk.<sup>107-109</sup> In my opinion, they should never be initiated for depression treatment in the primary care setting.

**QUESTION:** I noticed one therapy avenue you didn't mention is electroconvulsive therapy. How effective is it for the treatment of depression and in what situations should it be considered?

**DR WHOOLEY:** Electroconvulsive therapy is a very safe and effective treatment for severe depression in patients who are refractory to antidepressant medication and psychotherapy.<sup>110</sup> It can induce remission much more quickly than pharmacotherapy and has remarkably few adverse effects other than the long-term memory decline that can occur with repeated treatments. Kitty Dukakis has written an excellent book about her experiences with electroconvulsive therapy that is very accessible to the public.<sup>34</sup>

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**Online-Only Material:** Resources are available at <http://www.jama.com>.

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## Online-Only Resources: Selected Internet Resources on Management of Depression

DIAMOND Initiative (search for “depression tools”)<sup>a</sup>

<http://www.icsi.org>

Evidence-Based Psychotherapies

<http://www.evidencebasedpsychotherapies.org>

Improving Mood Promoting Access to Collaborative Treatment (IMPACT)<sup>a</sup>

<http://impact-uw.org>

International Foundation for Research and Education on Depression

<http://www.depression.org>

MacArthur Initiative on Depression and Primary Care<sup>a</sup>

<http://www.depression-primarycare.org>

Mental Health America

<http://www.nmha.org/go/depression>

National Depressive and Manic-Depressive Association

<http://www.ndmda.org>

National Institute of Health and Clinical Excellence (search for “depression”)<sup>a</sup>

<http://www.nice.org.uk>

Psychology Information Online

<http://www.psychologyinfo.com/depression>

Society of Clinical Psychology

<http://www.psychologicaltreatments.org>

TEAMcare<sup>a</sup>

<http://www.teamcarehealth.org>

<sup>a</sup>These websites include downloadable training materials for collaborative care management of depression.