Clinical Evidence Review: Best Practice

Diagnosis and Treatment of Major Depression 2007

By Patricia deSa, MS
David W Price, MD, FAAFP

Introduction

Depressive syndromes are commonly seen in the primary care setting. The National Institute of Mental Health estimates that 9.5% of adult Americans (about 19 million people) suffer from Major Depressive Disorder (MDD).\(^1\) Within Kaiser Permanente (KP), the overall prevalence of depression is about 8.4%,\(^2\) and direct medical costs to care for members with depression exceeds $2 billion annually.\(^3\)

In the primary care setting, treatment of depression usually includes evaluation by a physician, brief patient education, and either antidepressant therapy, referral to a behavioral health specialist or, in severe, resistant, or chronic cases, both a prescription and a referral. Although most depressed patients can be successfully treated by primary care clinicians, depression remains unrecognized or undertreated in many patients.

The first Major Depression Clinical Vignette, based on the 2002 CMI guideline, was published in the Winter 2002 issue of The Permanente Journal.\(^4\) This article discusses updated MDD diagnostic and treatment recommendations, based on the 2006 CMI Guideline for the Treatment of Major Depression in Adult Primary Care patients,\(^5\) and new evidence from the Sequenced Treatment Alternatives for Resistant Depression (STAR*D) trial.\(^6-10\)

Case Example

A 28-year-old married, employed female computer programmer with two young children is seen for a four-week history of fatigue, insomnia, headache, abdominal discomfort, and difficulty concentrating at work. She denies signs and symptoms of an acute infectious process and did not have headache or abdominal pain before the previous month. She has obtained intermittent relief from headache by using acetaminophen, and she takes a multivitamin regularly. She is appropriately and professionally dressed, and her children accompany her in the examination room. She appears tired but in no acute distress. Results of physical examination, including neurologic screening, are normal.

How should you proceed toward making a diagnosis? What treatment options are available? How should you follow this patient over time?

Definition of Major Depressive Disorder

MDD is characterized by at least two weeks of either depressed mood or loss of interest in previously pleasurable activities\(^11\) along with four or more additional symptoms, including:
- guilt
- sleep disturbance
- psychomotor retardation or agitation
- appetite disturbance
- difficulty concentrating
- decreased energy
- suicidal ideation, intention, or plan.\(^5\)

The mnemonic device DIGSPACES (Depression, loss of Interest, Guilt, Sleep disturbance, Psychomotor agitation/retardation, Appetite changes, loss of Energy, Suicidal thoughts) is a helpful way to remember these key symptoms of MDD. Diagnosis and treatment of other types of depression (eg, adjustment disorder with depressed mood; dysthymia; minor depressive disorders; depression with psychotic features; and bipolar disorder) are beyond the scope of this article.

Who Should be Screened for Depression?

Patients with cancer,\(^12\) chronic pain,\(^13\) heart failure,\(^14\) diabetes,\(^15\) recent stroke,\(^16\) or a recent acute cardiac event\(^17\) have higher rates of depression than the general population. Elderly patients with multiple medical comorbidity may also be at increased risk for depression.\(^18\) Patients with a prior history of MDD are at risk for recurrence.\(^19\) Other patients—those with multiple somatic complaints without known cause, women in the antenatal and postpartum periods, victims of domestic abuse, and HIV-positive patients—may also be candidates for screening.

Some evidence indicates that one-time screening of adults 40 years of age...
During the past month, have you often been bothered by...?"

All depressed patients, regardless of illness severity, should be screened for suicidal ideation. Many patients with depression have thoughts of suicide; asking “Have you thought about taking your life?” does not make patients more prone to attempt suicide. Patients with current suicidal ideation should be asked about their intentions (“Do you think you will commit suicide?”) and if they have a plan (“Have you thought about how you would kill yourself?” “Do you plan to kill yourself? If so, when?”). Clinicians should elicit a promise from actively suicidal patients not to harm themselves and should assess adequacy and availability of patient support systems (family, friends, and clergy). A behavioral health specialist should be contacted immediately in these cases. Risk factors for suicide include: recent loss; medical hospitalization within the past year; history of psychiatric hospitalization or suicide attempts; living alone; severe vegetative symptoms; severe hopelessness; comorbid substance abuse; and other comorbid psychiatric conditions. Patients with these risk factors should be closely monitored.

For every suicide death there are up to 25 nonfatal suicide attempts. Men and the elderly are more likely to have fatal suicide attempts than women and adolescents.

### Table 1. Instruments reviewed by the CMI Depression Guideline Group to screen for major depressive disorder (MDD) in adults

<table>
<thead>
<tr>
<th>Instrument</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two-question screening:22</td>
</tr>
<tr>
<td>Beck Depression Inventory (BDI)23</td>
</tr>
<tr>
<td>Center for Epidemiologic Studies in Depression scale (CES-D)24</td>
</tr>
<tr>
<td>Depression Arkansas Scale (D-ARK)25</td>
</tr>
<tr>
<td>Geriatric Depression Scale (GDS)26</td>
</tr>
<tr>
<td>Outcomes Questionnaire 45 (OQ-45)27</td>
</tr>
<tr>
<td>Primary Care Evaluation of Mental Disorders (PrimeMD)28</td>
</tr>
<tr>
<td>Patient Health Questionnaire (PHQ-9)29</td>
</tr>
<tr>
<td>Quick Diagnostics Panel (QDP)30</td>
</tr>
<tr>
<td>Zung Self-Rating Depression (SDS)31</td>
</tr>
</tbody>
</table>

### Diagnosis of MDD

Several screening tools are available to assist clinicians in screening for depression (Table 1).22-31 Many of these tools can be completed by the patient and easily scored by the clinician or by an assistant. These tools have similar sensitivity and specificity.28,30,32-40 One instrument, the PHQ929 is available as a questionnaire in KP HealthConnect.

A “yes” answer to one of the following two questions (see Table 1: Two-question Screening) is as sensitive a screen for MDD as most of these screening tools, but has a high false-positive rate.29 Therefore, a positive two-question screen needs to be confirmed with additional clinical history or a validated diagnostic instrument to determine if the patient meets criteria for major depression; a “no” answer to both questions will miss very few cases of major depression.

### Assessing Severity of Depressive Symptoms

Symptom severity is an important guide to selecting proper treatment for MDD. Many depression-screening instruments provide a range of scores corresponding to mild, moderate, and severe depression.22-40 Patients with five or six symptoms of MDD who have slightly impaired daily functioning are mildly depressed. Patients with six or seven MDD symptoms and moderately impaired daily functioning are moderately depressed. Patients with eight or nine MDD symptoms with profoundly impaired functioning in daily activities or suicidal intention or plans are severely depressed.

### Assessing Suicidal Ideation

All depressed patients, regardless of illness severity, should be screened for suicidal ideation. Many patients with depression have thoughts of suicide; asking “Have you thought about taking your life?” does not make patients more prone to attempt suicide. Patients with current suicidal ideation should be asked about their intentions (“Do you think you will commit suicide?”) and if they have a plan (“Have you thought about how you would kill yourself?” “Do you plan to kill yourself? If so, when?”). Clinicians should elicit a promise from actively suicidal patients not to harm themselves and should assess adequacy and availability of patient support systems (family, friends, and clergy). A behavioral health specialist should be contacted immediately in these cases. Risk factors for suicide include: recent loss; medical hospitalization within the past year; history of psychiatric hospitalization or suicide attempts; living alone; severe vegetative symptoms; severe hopelessness; comorbid substance abuse; and other comorbid psychiatric conditions. Patients with these risk factors should be closely monitored.

For every suicide death there are up to 25 nonfatal suicide attempts. Men and the elderly are more likely to have fatal suicide attempts than women and adolescents.

### Treatment of MDD

Medication vs Psychotherapy

For most mildly or moderately depressed adult primary care outpatients, medication and psychotherapy are equally effective, although psychotherapy might be slower to take effect.47 A shared decision-making approach describing the pros and cons of each option should be used with these patients to help them select initial treatment options consistent with their values and concerns. One study46 found that patients who select psychotherapy achieve better outcomes than patients who are “assigned” to it. A shared decision-
making approach in patients with other conditions has been shown to improve patient knowledge and to decrease patient uncertainty about type of treatment.\textsuperscript{9-11} This approach can also help instill a sense of control in depressed patients, who often feel “lost” as a result of their depression.

Treatment recommendations should also be based on cultural considerations. One study\textsuperscript{52} found that patients of different cultural backgrounds often prefer psychotherapy to medication, while another study\textsuperscript{53} specific to low-income Latinos found that this population prefers combination therapy over medication or counseling alone.

Severely depressed patients may respond better to medication than psychotherapy\textsuperscript{54} and may respond better to the combination of medication and psychotherapy.\textsuperscript{54,55} Consultation with a psychiatrist or other behavioral health specialist is recommended for severely depressed patients seen in the primary care setting.

**Types of Antidepressant Medication**

All antidepressant classes appear to be equally effective in depressed patients regardless of their age,\textsuperscript{56} the severity of depression,\textsuperscript{57} or the presence of another severe medical illness.\textsuperscript{58} The CMI Depression Guideline Development Team did not find high-quality studies comparing the effectiveness of different antidepressants in patients of different ethnic groups.

In the first 6 to 12 weeks of therapy, selective serotonin reuptake inhibitors (SSRIs) are somewhat better tolerated than tricyclic agents (TCAs) (number needed to treat, 20-33).\textsuperscript{58,59} Risk of death by overdose is greater with TCAs than with SSRIs, although rate of suicide from all causes does not differ on the basis of type of antidepressant.\textsuperscript{58,59} However, given the lethality of TCAs when overdosed, the CMI Depression Guideline Development team strongly recommends that TCAs be avoided by patients who are suicidal.\textsuperscript{5} Antidepressant agents have different side effect profiles that clinicians should consider when prescribing for patients with other comorbidities; patients may express a preference for a type of medication on the basis of discussing class-specific side effects with the clinician. Given the generally equal effectiveness of antidepressants, cost is also a consideration, especially for patients with tiered or no prescription coverage. Patients successfully treated for depression with a particular antidepressant in the past should be offered that agent again.

Research examining the effectiveness of hypericum (St John’s wort) is equivocal. While some studies showed a benefit over placebos\textsuperscript{60} or an effect equal to SSRIs\textsuperscript{61}, others\textsuperscript{62,63} have suggested that the data on hypericum are “inconsistent and confusing” primarily because of the lack of standardized preparations across trials, variations in patient populations studied, and overall study design quality. The CMI Depression Guideline Development Team shares these concerns about the data regarding St John’s wort. The US Food and Drug Administration (FDA) does not regulate St John’s wort, and the amount of active ingredient may vary widely between and within brands. For these reasons, the CMI Depression Guideline Development Team recommends caution in prescribing St John’s wort for treatment of depression. Clinicians should consider discussing these concerns with patients who wish to use St John’s wort. This substance should not be used in combination with other antidepressant agents.

**Treatment Phases and Follow-up**

**Acute Phase**

The acute phase of treatment for MDD is defined as the period extending from the start of treatment that achieves symptom remission for a period of three months. The risk of patients discontinuing treatment is highest in the first months of treatment.\textsuperscript{59}
Because of higher risk of lifetime recurrence, the Depression Guideline Development Team recommends longer term treatment for patients with two or more lifetime episodes of major depression.5

Table 3. Script for explaining the diagnosis of depression to patients

"Depression isn’t all in your head, and it’s not a personal failing. It’s a real illness caused by imbalance of chemicals in your body—just like diabetes. In diabetes, your body chemicals get out of balance and can’t control your blood sugar. In depression, chemicals in your brain get out of balance, and it affects the way you think, act, and feel."

Therefore, follow-up is needed to assess patient adherence to therapy, symptom remission, and, if medication is chosen, presence of worrisome or unacceptable side effects. No scientific evidence suggests an optimal frequency of follow-up during the acute phase, but Health Plan Employer Data Information Set (HEDIS) criteria require three follow-up contacts (including one face-to-face contact with a prescribing provider) in the first 12 weeks of treatment.76

On the basis of consensus and clinical judgment, the CMI Depression Guideline Development team believes that a minimum of two follow-up contacts should occur in the acute phase: one within the first month, and the other four to eight weeks after the first contact. On the basis of the experience of the team members other successful models of care for depressed patients,71,72 contacts may be in person, by phone or via e-mail.5

Several options are available for patients who do not achieve symptom remission within 6 to 12 weeks. The diagnosis should be reevaluated, and possible presence of other untreated comorbid conditions should be considered. Adherence to treatment regimen should be assessed and reinforced. Dosage of medication may be increased,6 the medication can be changed to a different antidepressant in the same or different class,5,7,9 or psychotherapy and medication can be combined. Augmentation with bupropion or buspirone9 or adding low dose desipramine to an SSRI5 may also be attempted. Adding lithium5,10 or T310 may also be attempted in refractory cases. Referral to a behavioral health specialist is also an available option for patients who do not respond to prescribed medication.

Continuation Phase

After the acute phase has ended, patients should continue treatment for at least an additional 6 to 12 months.73-76 Terminating treatment sooner is associated with early recurrence of symptoms.77 No available data exist to suggest an optimal frequency of patient follow-up during the continuation phase. The CMI Depression Guideline Development Team consensus opinion recommends at least one follow-up during the fifth or sixth month of treatment to assure continued remission of symptoms and patient adherence to treatment as well as to determine necessity of adjusting treatment.5

More frequent follow-up can be scheduled on the basis of clinical judgment and patient preference.

Discontinuation or Maintenance?

A single episode of MDD is associated with a 50% lifetime risk of recurrence; two episodes are associated with a 70% lifetime recurrence risk, and three or more episodes are associated with a 90% lifetime recurrence risk.78 After successfully completing acute and continuation phase treatment for a first episode of major depression, patients should be offered a trial of medication discontinuation.19 Fluoxetine at doses less than 20 mg daily can be discontinued without tapering with a relatively low risk of adverse effects;79,80 higher fluoxetine doses and other medications should be tapered over a two- to four-week period.79,81 Patients with MDD should be educated about this risk and instructed to call their clinician at the first signs or symptoms of recurrent MDD. Data suggest that risk of recurrence is highest during the first year after medication is discontinued.19 The CMI Depression Guideline Development Team suggests that patients be reassessed three months after discontinuing medication and again at 12 months.

Because of higher risk of lifetime recurrence, the Depression Guideline Development Team recommends longer term treatment for patients with two or more lifetime episodes of major depression.5 Available data19,82 and consensus of the CMI Depression Guideline Development Team83 suggest that a treatment duration of 15 months to 5 years or longer after the acute phase response demonstrates benefit. No available data exist to suggest an optimal frequency of patient follow-up during maintenance treatment. The CMI guideline recommends at least one annual contact with the patient to detect symptom relapse and to determine need for treatment adjustment.5 These patients should also receive patient education on the signs of depression relapse.

Patient Education

Despite a trend toward increasing acceptance, many patients still feel stigmatized by the diagnosis of MDD. Therefore, clinicians should explain to these patients that MDD is a real illness and is not “all in their head.” Comparison with diabetes may be helpful (Table 3). Patients choosing medication should be informed about side effects and given instructions designed to enhance compliance with prescribed medication regimens (Table 4).83 Patients should also be educated about the signs and symptoms of relapsing or worsening depression.
Patient Self-Management

Several self-management strategies may be helpful as adjunct treatments for MDD (Table 5); they help patients regain a sense of control. Studies have not compared self-management strategies to “traditional” first-line treatment for major depression; most studies have focused on patients with depressive symptoms, few of whom have a diagnosis of MDD. Due to these and other limitations, the CMI Depression Guideline Development Team could not recommend for or against these strategies as sole treatment for MDD; however, the consensus of the Guideline Team is to consider these self-management strategies as an adjunct to other evidence-based MDD treatments.

Specialty Referral

The CMI Depression Guideline workgroup recommends referral or consultation with a behavioral health specialist for the situations listed in Table 6.

Case Example Diagnostic and Treatment Approach

In addition to sleep disturbance, decreased energy, and difficulty concentrating, the patient in the above example admitted being sad and tearful as well as feeling guilty and worrying about her parenting skills, and she had lost interest in socializing. She also admitted to worrying about work performance and being some what irritable with her husband. She remained on medication, with symptoms had resolved, and the patient was re-educated on the symptoms of MDD and elected to monitor symptoms without resuming medication. At follow-up 3 months, 6 months, and 12 months later, the patient remained asymptomatic at three weeks and at three month follow-up calls. During a health maintenance visit one year after medication discontinuation, she reported slight decrease in appetite as well as increase in worry and irritability, which she attributed to job stress. Repeat screening was not diagnostic for recurrent MDD or anxiety. The patient was re-educated on the symptoms of MDD and elected to monitor symptoms without resuming medication. At follow-up 3 months, 6 months, and 12 months later, the symptoms had resolved, and the patient remained in remission.

Conclusion

This vignette illustrates how clinicians can apply current evidence,

Table 4. Patient instructions for taking medication

<table>
<thead>
<tr>
<th>Instruction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidepressants only work if taken every day (specific time/daily routine).</td>
</tr>
<tr>
<td>Antidepressants are not addicting or habit forming. Benefits appear slowly and may take two to six weeks.</td>
</tr>
<tr>
<td>Mild side effects are common and usually improve after a couple of weeks.</td>
</tr>
<tr>
<td>It’s important to continue the medication even after you feel better.</td>
</tr>
<tr>
<td>Antidepressants must be continued for a minimum of 7-12 weeks.</td>
</tr>
<tr>
<td>Call with any questions. If you feel you need to stop medication, please let us know.</td>
</tr>
</tbody>
</table>

Adapted and revised with the assistance and permission of the author from: Lin EW, Von Korff M, Katon W, et al. The role of the primary care physician in patients’ adherence to antidepressant therapy. Med Care 1995;33(1):67-74.51

Table 5. Depression self-management strategy recommendations from the 2006 CMI Depression Guideline5, 83-87

<table>
<thead>
<tr>
<th>Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise is recommended as an adjunctive strategy (in addition to antidepressants or psychotherapy) for treating the symptoms of Major Depressive Disorder (MDD)</td>
</tr>
<tr>
<td>Bibliotherapy is an optional adjunct strategy (in addition to antidepressants or psychotherapy) for treating the symptoms of MDD. Patients may be advised to read written material based on cognitive-behavioral approaches to depression, Feeling Good: The New Mood Therapy44</td>
</tr>
<tr>
<td>Befriending (which consists of designated befriender meeting the depressed person to talk and socialize for at least one hour per week) is an optional adjunct to antidepressants or psychotherapy for treating the symptoms of MDD</td>
</tr>
<tr>
<td>Patient self-help materials on the following Internet sites are an optional adjunct strategy (in addition to antidepressants or psychotherapy) for treating the symptoms of MDD: Blue Pages (<a href="http://bluepages.anu.edu.au)46">http://bluepages.anu.edu.au)46</a> Mood Gym (<a href="http://moogym.anu.edu.au),45">http://moogym.anu.edu.au),45</a> and Overcoming Depression on the Internet (<a href="http://www.believebetter.org)47">www.believebetter.org)47</a></td>
</tr>
<tr>
<td>Self-management strategies should be used as an adjunct to and not in lieu of other evidence-based treatments for MDD</td>
</tr>
</tbody>
</table>

Table 6. Depression self-management strategy recommendations

<table>
<thead>
<tr>
<th>Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise is recommended as an adjunctive strategy (in addition to antidepressants or psychotherapy) for treating the symptoms of Major Depressive Disorder (MDD)</td>
</tr>
<tr>
<td>Bibliotherapy is an optional adjunct strategy (in addition to antidepressants or psychotherapy) for treating the symptoms of MDD. Patients may be advised to read written material based on cognitive-behavioral approaches to depression, Feeling Good: The New Mood Therapy44</td>
</tr>
<tr>
<td>Befriending (which consists of designated befriender meeting the depressed person to talk and socialize for at least one hour per week) is an optional adjunct to antidepressants or psychotherapy for treating the symptoms of MDD</td>
</tr>
<tr>
<td>Patient self-help materials on the following Internet sites are an optional adjunct strategy (in addition to antidepressants or psychotherapy) for treating the symptoms of MDD: Blue Pages (<a href="http://bluepages.anu.edu.au)46">http://bluepages.anu.edu.au)46</a> Mood Gym (<a href="http://moogym.anu.edu.au),45">http://moogym.anu.edu.au),45</a> and Overcoming Depression on the Internet (<a href="http://www.believebetter.org)47">www.believebetter.org)47</a></td>
</tr>
<tr>
<td>Self-management strategies should be used as an adjunct to and not in lieu of other evidence-based treatments for MDD</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise is recommended as an adjunctive strategy (in addition to antidepressants or psychotherapy) for treating the symptoms of Major Depressive Disorder (MDD)</td>
</tr>
<tr>
<td>Bibliotherapy is an optional adjunct strategy (in addition to antidepressants or psychotherapy) for treating the symptoms of MDD. Patients may be advised to read written material based on cognitive-behavioral approaches to depression, Feeling Good: The New Mood Therapy44</td>
</tr>
<tr>
<td>Befriending (which consists of designated befriender meeting the depressed person to talk and socialize for at least one hour per week) is an optional adjunct to antidepressants or psychotherapy for treating the symptoms of MDD</td>
</tr>
<tr>
<td>Patient self-help materials on the following Internet sites are an optional adjunct strategy (in addition to antidepressants or psychotherapy) for treating the symptoms of MDD: Blue Pages (<a href="http://bluepages.anu.edu.au)46">http://bluepages.anu.edu.au)46</a> Mood Gym (<a href="http://moogym.anu.edu.au),45">http://moogym.anu.edu.au),45</a> and Overcoming Depression on the Internet (<a href="http://www.believebetter.org)47">www.believebetter.org)47</a></td>
</tr>
<tr>
<td>Self-management strategies should be used as an adjunct to and not in lieu of other evidence-based treatments for MDD</td>
</tr>
</tbody>
</table>

The Permanente Journal/ Summer 2007/ Volume 11 No. 3 39
Table 5. Consensus criteria for referral to a behavioral health specialist

<table>
<thead>
<tr>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two months of treatment without desired clinical improvement</td>
</tr>
<tr>
<td>Active homicidal ideation</td>
</tr>
<tr>
<td>Active suicidal ideation</td>
</tr>
<tr>
<td>Bipolar or manic behavior</td>
</tr>
<tr>
<td>Counseling with or without medication</td>
</tr>
<tr>
<td>Difficulty adhering to treatment plans</td>
</tr>
<tr>
<td>Domestic violence</td>
</tr>
<tr>
<td>Failure to respond to second antidepressant</td>
</tr>
<tr>
<td>Lifelong/recurrent depressions</td>
</tr>
<tr>
<td>Failure to respond to medication</td>
</tr>
<tr>
<td>Domestic violence</td>
</tr>
<tr>
<td>Failure to respond to second antidepressant</td>
</tr>
<tr>
<td>Lifelong/recurrent depressions</td>
</tr>
<tr>
<td>Partial response to medication</td>
</tr>
<tr>
<td>Psychotic symptoms</td>
</tr>
<tr>
<td>Significant alcohol/other substance abuse</td>
</tr>
<tr>
<td>Unclear diagnosis</td>
</tr>
</tbody>
</table>

including the 2006 CMI Guideline for Treatment of Major Depression in Primary Care Adult Patients, to patient care scenarios. The full guideline document is available on the Permanente Knowledge Connection Web site: http://cl kp.org/pck/national/cmi/programs/depression/guideline/files/CMI_Depression_Guidelines_2006.pdf. The adult depression guideline is updated every two years; the next revision is scheduled for early 2008. CMI has achieved depression disease management recognition from the National Center for Quality Assurance (NCQA).

Acknowledgments
The authors would like to thank Elizabeth HB Lin, MD, MPH, for sharing her more recent research and for her help in revising Table 4. The authors would also like to thank the members of the guideline development team for their hard work during the guideline development process. A complete list of guideline work group members can be found in the Depression Guideline, available online at: http://cl kp.org/pck/national/cmi/programs/depression/guideline/bkgd_ackn.html (password protected).

References
14. Irwin M, Arlin KH, Oxman MN. Screen-
Diagnosis and Treatment of Major Depression 2007


55. Thase ME, Greenhouse JB, Frank E,


