CME available online: www.kp.org/permanentejournal

REVIEW ARTICLE

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

Patricia deSa, MS, (left) is a Care Management Consultant for the Kaiser Permanente Care Management Institute. E-mail: patricia.desa@kp.org.
David W Price, MD, FAAFP, (right) is the Chairman of the American Board of Family Medicine; Associate Professor of Family Medicine at the University of Colorado Health Sciences Center; Colorado Permanente Medical Group Director of Education and Clinician Researcher; and Care Management Institute Continuing Education and Depression Guideline Lead. E-mail: david.price@kp.org.

Patients with current suicidal ideation should be asked about their intentions ("Do you think you will commit suicide?")

age or older may be cost-effective from a societal perspective.[20] In fact, in 2002, the United States Preventive Services Task Force recommended screening all adults for MDD, provided that services are available for treatment and follow-up.[21] However, screening of asymptomatic adults at low risk may result in many false-positive tests. Thus, clinicians should weigh the potential benefits of screening asymptomatic low-risk adults against other clinical and operational priorities (including depression screening of higher-risk patients).

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 PHQ9[29] 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.[22] 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.

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

Two-question screening:[22] • "During the past month, have you often been bothered by feeling down, depressed, or hopeless?" • "During the past month, have you often been bothered by little interest or pleasure in doing things?"
Beck Depression Inventory (BDI)[23]
Center for Epidemiologic Studies in Depression scale (CES-D)[24]
Depression Arkansas Scale (D-ARK)[25]
Geriatric Depression Scale (GDS)[26]
Outcomes Questionnaire 45 (OQ-45)[27]
Primary Care Evaluation of Mental Disorders (PrimeMD)[28]
Patient Health Questionnaire (PHQ-9)[29]
Quick Diagnostics Panel (QDP)[30]
Zung Self-Rating Depression (SDS)[31]

All positive screening results should be confirmed with careful attention to possible substance abuse, medical, and other psychological causes or comorbidity (Table 2). The patient in the above example denied using alcohol or drugs and denied current or past physical, sexual, or emotional abuse; in addition, the complete blood cell count (CBC) and thyroid-stimulating hormone (TSH) level were normal. (TSH is measured to rule out hypothyroidism, a common postpartum condition that can cause 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.[41-44] 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.[45]

Treatment of MDD

Medication vs Psychotherapy

For most mildly or moderately depressed adult primary care outpatients, medication and psychotherapy are equally effective,[46] 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 study[48] 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.[49-51] 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[52] found that patients of different cultural backgrounds often prefer psychotherapy to medication, while another study[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[54] and may respond better to the combination of medication and psychotherapy.[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,[56] the severity of depression,[57] or the presence of another severe medical illness.[56] 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).[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.[60-65] 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.[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[66] or an effect equal to SSRIs[67]), others[68,69] 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;[59]

Treatment recommendations should also be based on cultural considerations.

Table 2. Selected differential diagnosis of MDD

Concurrent psychiatric conditions	Concurrent medical conditions	Medication-related
Adjustment disorder Bipolar disorder Dysthymia Personality disorder Psychotic depression Posttraumatic stress disorder/abuse Seasonal affective disorder Somatization Substance abuse	Endocrine: hypothyroidism Cushing's disease Central nervous system: Parkinson's disease Alzheimer's disease multiple sclerosis brain tumors Cardiovascular system: stroke myocardial infarction congestive heart failure Miscellaneous: rheumatoid arthritis AIDS pernicious anemia carcinoma	Antihypertensive/ cardiovascular agents: reserpine clonidine methyldopa digitalis hydralazine prazosin procainamide Sedative hypnotic agents: barbiturates chloral hydrate benzodiazepines Anti-inflammatory agents: indomethacin pentazocine opiates Steroids: corticosteroids Interferon

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]

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.[70] 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 buspirone[8] or adding low dose desipramine to an SSRI[5] may also be attempted. Adding lithium[5,10] or T3[10] 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.

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."

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] 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.[12] 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 data[19,82] and consensus of the CMI Depression Guideline Development Team[5] 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);[84-88] 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.[5]

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 somewhat irritable with her husband. She was not suicidal and had no prior history of depression or other psychiatric illness, but she thought her mother may have been depressed. Other medical comorbidity was excluded, and she was diagnosed with MDD, first episode, with secondary anxiety (not meeting criteria for generalized anxiety disorder). After participating in a shared decision-making approach, she selected pharmacotherapy with an SSRI and started fluoxetine, 10 mg daily, the next morning. At two-week follow-up, her depressed mood and energy were "50% better," but she was still having trouble concentrating and sleeping and was still irritable. The dose of fluoxetine was increased to 20 mg in the morning, and 50 mg of trazodone was added at bedtime to help with sleep. At six-week follow-up, she was sleeping better, and her depressed mood and guilt about parenting were "almost gone." Her energy was "returning to normal," but she still worried about her work performance and reported having continued irritability with her husband. She elected not to change her medication regimen or to add psychotherapy and, at 12-week follow-up, reported total symptom resolution.

She remained on medication, without further symptoms, for one year (three months of acute-phase treatment plus nine months of continuation-phase treatment). She was then offered and elected a trial of medication discontinuation. She 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

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

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.[83]

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

Exercise is recommended as an adjunctive strategy (in addition to antidepressants or psychotherapy) for treating the symptoms of Major Depressive Disorder (MDD)
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 Therapy*[84]
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
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 (http://bluepages.anu.edu.au/)[86] Mood Gym (http://moodgym.anu.edu.au/),[86] and Overcoming Depression on the Internet (www.believebetter.org)[87]
Self-management strategies should be used as an adjunct to and not in lieu of other evidence-based treatments for MDD

Table 5. Consensus criteria for referral to a behavioral health specialist
Two months of treatment without desired clinical improvement
Active homicidal ideation
Active suicidal ideation
Bipolar or manic behavior
Counseling with or without medication
Difficulty adhering to treatment plans
Domestic violence
Failure to respond to second antidepressant
Lifelong/recurrent depressions
Partial response to medication
Psychotic symptoms
Significant alcohol/other substance abuse
Unclear diagnosis

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/pkc/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/pkc/national/cmi/programs/depression/guideline/bkgr_ackn.html (password protected).

References

1. Real Men. Real Depression. Publication No. 03-5299. Bethesda (MD): National Institute of Mental Health. Printed March 2003, Reprinted December 2004.
2. KP Care Management Institute Clinical Outcomes of Evaluation (CORE) System; Adult Depression Prevalence, 2Q 2006.
3. KP Care Management Institute. Depression Care Management Business Case, 2005.
4. Price D. Evidence-based clinical vignettes from the Care Management Institute: major depression. Perm J 2002 Winter;6(1):34-42.
5. Kaiser Permanente Medical Care Program. Care Management Institute. Clinical practice guidelines for the management of depression in primary care [monograph on the Intranet]. Oakland (CA): Kaiser Permanente Medical Care Program, Care Management Institute; 2006 [cited 2007 Feb 28]. Available from: http://cl.kp.org/pkc/national/cmi/programs/depression/guideline/index.html. (Password protected.)
6. Trivedi MH, Rush AJ, Wisniewski SR, et al; STAR*D Study Team. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. Am J Psychiatry 2006 Jan;163(1):28-40.
7. Rush AJ, Trivedi MH, Wisniewski SR, et al; STAR*D Study Team. Bupropion-SR, sertraline, or venlafaxine-XR after failure of SSRIs for depression. N Engl J Med 2006 Mar 23;354(12):1231-42.
8. Trivedi MH, Fava M, Wisniewski SR, et al; STAR*D Study Team. Medication augmentation after the failure of SSRIs for depression. N Engl J Med 2006 Mar 23;354(12):1243-52.
9. Fava M, Rush AJ, Wisniewski SR, et al. A comparison of mirtazapine and nortriptyline following two consecutive failed medication treatments for depressed outpatients: a STAR*D report. Am J Psychiatry 2006 Jul;163(7):1161-72.
10. Nierenberg AA, Fava M, Trivedi MH, et al. A comparison of lithium and T(3) augmentation following two failed medication treatments for depression: a STAR*D report. Am J Psychiatry 2006 Sep;163(9):1519-30; quiz 1665.
11. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed, text revision. Washington (DC): American Psychiatric Association; 2000. p 349-56.
12. Minagawa H, Uchitomi Y, Yamawaki S, Ishitani K. Psychiatric morbidity of terminally ill cancer patients. A prospective study. Cancer 1996 Sep 1;78(5):1131-7.
13. Fishbain DA, Goldberg M, Meagher BR, Steele R, Rosomoff H. Male and female chronic pain patients categorized by DSM-III psychiatric diagnostic criteria. Pain 1986 Aug;26(2):181-97.
14. Havranek EP, Ware MG, Lowes BD. Prevalence of depression in congestive heart failure. Am J Cardiol 1999 Aug 1;84(3):348-50, A9.
15. Anderson RJ, Freedland KE, Clouse RE, Lustman PJ. The prevalence of comorbid depression in adults with diabetes: a meta-analysis. Diabetes Care 2001 Jun;24(6):1069-78.
16. Kotila M, Numminen H, Waltimo O, Kaste M. Depression after stroke: results of the FINNSTROKE Study. Stroke 1998 Feb;29(2):368-72.
17. Lehto S, Koukkunen H, Hintikka J, Viinamaki H, Laakso M, Pyorala K. Depression after coronary heart disease events. Scand Cardiovasc J 2000 Dec;34(6):580-3.
18. Lyness JM, King DA, Cox C, Yoediono Z, Caine ED. The importance of subsyndromal depression in older primary care patients: prevalence and associated functional disability. J Am Geriatr Soc 1999 Jun;47(6):647-52.
19. Viguera AC, Baldessarini RJ, Friedberg J. Discontinuing antidepressant treatment in major depression. Harv Rev Psychiatry 1998 Mar-Apr;5(6):293-306.
20. Schoenbaum M, Unutzer J, Sherbourne C, et al. Cost-effectiveness of practice-initiated quality improvement for depression: results of a randomized controlled trial. JAMA 2001 Sep 19;286(11):1325-30.
21. Screening for Depression [monograph on the Internet]. Rockville (MD): US Preventive Services Task Force: Agency for Healthcare Research and Quality 2002 May [cited 2007 Feb 28]. Available from: www.ahrq.gov/clinic/uspstf/uspsdepr.htm.
22. Whooley MA, Avins AL, Miranda J, Browner WS. Case-finding instrument for depression. Two questions are as good as many. J Gen Intern Med 1997 Jul;12(7):439-45.
23. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry 1961 Jun;4:561-71.
24. Irwin M, Artin KH, Oxman MN. Screen-

ing for depression in the older adult: criterion validity of the ten-item Center for Epidemiological Studies Depression Scale (CES-D). Arch Intern Med 1999 Aug 9-23;159(15):1701-4.
25. A confidential, low-cost Internet solution for behavioral health outcomes assessment: Depression Outcomes Module [monograph on the Internet. NetOutcomes [cited 2007 Apr 3]. Available from: www.netoutcomes.net/body.asp?module=DOM&menu=contents.
26. Yesavage JA, Brink TL, Rose TL, et al. Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res 1982-1983;17(1):37-49.
27. Lambert MJ, Burlingame GM, Umphress V, et al. The reliability and validity of the Outcome Questionnaire. Clin Psychol Psychother 1996 Dec;3(4):249-58.
28. Spitzer RL, Williams JB, Kroenke K, et al. Utility of a new procedure for diagnosing mental disorders in primary care. The PRIME-MD 1000 study. JAMA 1994 Dec 14;272(22):1749-56.
29. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 2001 Sep;16(9):606-13.
30. Shedler J, Beck A, Bensen S. Practical mental health assessment in primary care. Validity and utility of the Quick PsychoDiagnostics Panel. J Fam Pract 2000 Jul;49(7):614-21.
31. Zung WW. A self-rating depression scale. Arch Gen Psychiatry 1965 Jan;12:63-70.
32. Mulrow CD, Williams JW Jr, Gerety MB, Ramirez G, Montiel OM, Kerber C. Case-finding instruments for depression in primary care settings. Ann Intern Med 1995 Jun 15;122(12):913-21. Erratum in: Ann Intern Med 1995 Dec 15;123(12):966.
33. Schein RL, Koenig HG. The Center for Epidemiological Studies-Depression (CES-D) Scale: assessment of depression in the medically ill elderly. Int J Geriatr Psychiatry 1997 Apr;12(4):436-46.
34. Agrell B, Dehlin O. Comparison of six depression rating scales in geriatric stroke patients. Stroke 1989 Sep;20(9):1190-4.
35. Cho MJ, Kim KH. Use of the Center for Epidemiologic Studies Depression (CES-D) Scale in Korea. J Nerv Ment Dis 1998 May;186(5):304-10.
36. Beekman AT, Deeg DJ, Van Limbeek J, Braam AW, DeVries MZ, Van Tiliburg W. Criterion validity of the Center for Epidemiologic Studies Depression scale (CES-D): results from a community-based sample of older adult subjects in The Netherlands. Psychol Med 1997 Jan;27(1):231-5.
37. Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire. JAMA 1999 Nov 10;282(18):1737-44.
38. Steer RA, Cavalieri TA, Leonard DM, Beck AT. Use of the Beck Depression Inventory for Primary Care to screen for major depressive disorders. Gen Hosp Psychiatry 1999 Mar-Apr;21(2):106-11.
39. Lasa L, Ayuso-Mateos JL, Vazquez-Barquero JL, et al; ODIN Group. The use of the Beck Depression Inventory to screen for depression in the general population: a preliminary analysis. J Affect Disord 2000 Jan-Mar;57(1-3):261-5.
40. Kramer TL, Smith GR. Tools to improve the detection and treatment of depression in primary care. In: Maruish ME, editor. Handbook of psychological assessment in primary care settings. Mahwah (NJ): Lawrence Erlbaum Associates; 2000. p 463-90.
41. Hirschfeld RM, Russell JM. Assessment and treatment of suicidal patients. N Engl J Med 1997 Sep 25;337(13):910-5.
42. Isacsson G, Bergman U, Rich CL. Antidepressants, depression and suicide: an analysis of the San Diego study. J Affect Disord 1994 Dec;32(4);277-86.
43. Cooper-Patrick L, Crum RM, Ford DE. Identifying suicidal ideation in general medical patients. JAMA 1994 Dec 14;272(22):1757-62.
44. Lin EH, Von Korff M, Wagner EH. Identifying suicide potential in primary care. J Gen Intern Med 1989 Jan-Feb;4(1):1-6.
45. National Institute of Mental Health. Suicide in the US: statistics and prevention [monograph on the Internet]. Bethesda (MD): National Institute of Mental Health, National Institutes of Health, US Department of Health and Human Services; 2001 Jan [Revised 2006 Dec; cited 2007 Apr 18]. (NIH Publication No. 03-4594). Available from: www.nimh.nih.gov/publicat/harmsway.cfm#risk.
46. Casacalenda N, Perry JC, Looper K. Remission in major depressive disorder: a comparison of pharmacotherapy, psychotherapy, and control conditions. Am J Psychiatry 2002; 159(8):1354-60.
47. Mynors-Wallis LM, Gath DH, Day A, Baker F. Randomised controlled trial of problem solving treatment, antidepressant medication, and combined treatment for major depression in primary care. BMJ 2000 Jan 1; 320(7226):26-30.
48. Chilvers C, Dewey M, Fielding K, et al; Counselling versus Antidepressants in Primary Care Study Group. Antidepressant drugs and generic counselling for treatment of major depression in primary care: randomized trial with patient preference arms. BMJ 2001 Mar 31;322(7289):772-5.
49. Morgan MW, Deber RB, Llewellyn-Thomas HA, et al. Randomized, controlled trial of an interactive videodisc decision aid for patients with ischemic heart disease. J Gen Intern Med 2000 Oct;15(10):685-93.
50. Murray E, Davis H, Tai SS, Coulter A, Gray A, Haines A. Randomized controlled trial of an interactive multimedia decision aid on benign prostatic hypertrophy in primary care. BMJ 2001 Sep 1;323(7311):493-6.
51. Murray E, Davis H, Tai SS, Coulter A, Gray A, Haines A. Randomized controlled trial of an interactive multimedia decision aid on hormone replacement therapy in primary care. BMJ 2001 Sep 1;323(7311):490-3.
52. Dwight-Johnson M, Sherbourne CD, Liao D, Wells KB. Treatment preferences among depressed primary care patients. J Gen Intern Med 2000 Aug;15(8):527-34.
53. Dwight-Johnson M, Lagomasino IT, Aisenberg E, Hay J. Using conjoint analysis to assess depression treatment preferences among low-income Latinos. Psychiatr Serv 2004 Aug;55(8):934-6
54. Keller MB, McCullough JP, Klein DN, et al. A comparison of nefazodone, the cognitive behavioral-analysis system of psychotherapy, and their combination for the treatment of chronic depression N Engl J Med 2000 May 18;342(20):1462-70. Erratum in: N Engl J Med 2001 Jul 19;345(3):232.
55. Thase ME, Greenhouse JB, Frank E,

et al. Treatment of major depression with psychotherapy or psychotherapy-pharmacotherapy combinations. Arch Gen Psychiatry 1997 Nov;54(11):1009-15.
56. Wilson K, Mottram P, Sivanranthan A, Nightingale A. Antidepressant versus placebo for depressed elderly (Cochrane Review). Cochrane Database Syst Rev 2001;2:CD000561.
57. Arroll B, Macgillivray S, Ogston S, et al. Efficacy and tolerability of tricyclic antidepressants and SSRIs compared with placebo for treatment of depression in primary care: a meta-analysis. Ann Fam Med 2005 Sep-Oct;3(5):449-56.
58. Geddes JR, Freemantle N, Mason J, Eccles MP, Boynton J. SSRIs versus other antidepressants for depressive disorder. Cochrane Database Syst Rev 2000;(2):CD001851.
59. Barbui C, Hotopf M, Freemantle N, et al. Selective serotonin reuptake inhibitors versus tricyclic and hetrocyclic antidepressants: comparison of drug adherence. Cochrane Database Syst Rev 2000;(4):CD002791.
60. Yerevanian BI, Koek RJ, Feusner JD, Hwang S, Mintz J. Antidepressants and suicidal behaviour in unipolar depression. Acta Psychiatr Scand 2004 Dec;110(6):452-8.
61. Martinez C, Rietbrock S, Wise L, et al. Antidepressant treatment and the risk of fatal and non-fatal self harm in first episode depression: nested case-control study. BMJ 2005 Feb 19; 330(7488):389.
62. Fergusson D, Doucette S, Glass KC, et al. Association between suicide attempts and selective serotonin reuptake inhibitors: systematic review of randomised controlled trials. BMJ 2005; 330(7488):396.
63. Gunnell D, Ho D, Murray V. Medical management of deliberate drug overdose: a neglected area for suicide prevention? Emerg Med J 2004 Jan;21(1):35-8. Erratum in: Emerg Med J 2004 Mar, 21(2):268.
64. Jick H, Kaye JA, Jick SS. Antidepressants and the risk of suicidal behaviors. JAMA 2004 Jul 21;292(3):338-43.
65. Jick SS, Dean AD, Jick H. Antidepressants and suicide. BMJ 1995; 310(6974):215-218.
66. Uebelhack R, Gruenwald J, Graubaum HJ, Busch R. Efficacy and tolerability of Hypericum extract STW 3-VI in patients with moderate depression: a double-blind, randomized, placebo-controlled clinical trial. Adv Ther 2004 Jul-Aug;21(4):265-75.
67. Szegedi A, Kohnen R, Dienel A, Kieser M. Acute treatment of moderate to severe depression with hypericum extract WS 5570 (St John's wort): randomised controlled double blind non-inferiority trial versus paroxetine. BMJ 2005 Mar 5;330(7490):503. Erratum in: BMJ 2005 Apr 2;330(7494):759. dosage error in text.
68. Linde K, Mulrow CD, Berner M, Egger M. St John's wort for depression. Cochrane Database Syst Rev 2005 Apr 18;(2):CD000448.
69. Geddes J, Butler R, Hatcher S. Depressive Disorders. In: Jones G, editor. Clinical Evidence. London: BMJ Publishing Group, 2006.
70. National Committee for Quality Assurance. HEDIS 2006. Volume 2. Technical specifications. Washington (DC): National Committee for Quality Assurance; 2005. p 146.
71. Unutzer J, Katon W, Callahan CM, et al; IMPACT Investigators. Improving Mood-Promoting Access to Collaborative Treatment. Collaborative care management of late-life depression in the primary care setting: a randomized controlled trial. JAMA 2002 Dec 11;288(22):2836-45.
72. Meresman JF, Hunkeler EM, Hargreaves WA, et al. A case report: implementing a nurse telecare program for treating depression in primary care. Psychiatr Q. 2003 Spring;74(1):61-73.
73. Rapaport MH, Bose A, Zheng H. Escitalopram continuation treatment prevents relapse of depressive episodes. J Clin Psychiatry 2004 Jan;65(1):44-9.
74. Keller MB, Ruwe FJ, Janssens CJ, Sitsen JM, Jokinen R, Janczewski J. Relapse prevention with gepirone ER in outpatients with major depression. J Clin Psychopharmacol 2005 Feb;25(1):79-84.
75. Montgomery SA, Entsuah R, Hackett D, Kunz NR, Rudolph RL. Venlafaxine versus placebo in the preventive treatment of recurrent major depression. J Clin Psychiatry 2004 Mar;65(3):328-36.
76. National Collaborating Centre for Mental Health. Clinical Guideline 23: Depression: Management of depression in primary and secondary care [monograph on the Internet]. London: National Institute of Clinical Excellence (NICE); 2004 Dec [cited 2007 Apr 3]. Available from: www.nice.org.uk/pdf/CG023NICEguideline.pdf.
77. Geddes JR, Carney SM, Davies C, et al. Relapse prevention with antidepressant drug treatment in depressive disorders: a systematic review. Lancet 2003 Feb;361(9358):653-61.
78. Trivedi MH, Kleiber BA. Algorithm for the treatment of chronic depression. J Clin Psychiatry 2001;62 Suppl 6:22-9.
79. Zajecka J, Fawcett J, Amsterdam J, et al. Safety of abrupt discontinuation of fluoxetine: a randomized, placebo-controlled study. J Clin Psychopharmacol 1998 Jun;18(3):193-7.
80. Rosenbaum JF, Fava M, Hoog SL, Ascroft RC, Krebs WB. Selective serotonin reuptake inhibitor discontinuation syndrome: a randomized clinical trial. Biol Psychiatry 1998 Jul 15;44(2):77-87.
81. Sunder KR, Wisner KL, Hanusa BH, Perel JM. Postpartum depression recurrence versus discontinuation syndrome: observations from a randomized controlled trial. J Clin Psychiatry 2004 Sep;65(9):1266-8.
82. Kupfer DJ, Frank E, Perel JM, et al. Five-year outcome for maintenance therapies in recurrent depression. Arch Gen Psychiatry 1992 Oct;49(10):769-73.
83. Lin EH, Von Korff M, Katon W, et al. The role of the primary care physician in patients' adherence to antidepressant therapy. Med Care 1995 Jan;33(1):67-74.
84. Dunn AL, Trivedi MH, Kampert JB, Clark CG, Chambliss HO. Exercise treatment for depression: efficacy and dose response. Am J Prev Med 2005 Jan;28(1):1-8.
85. Burns D. Feeling Good. New York: Guilford Press; 1980.
86. McNeil JK, LeBlanc EM, Joyner M. The effect of exercise on depressive symptoms in the moderately depressed elderly. Psychol Aging 1991 Sep;6(3):487-8.
87. Christensen H, Griffiths KM, Jorm AF. Delivering interventions for depression by using the Internet: randomised controlled trial. BMJ 2004 Jan 31;328(7434):265.
88. Clarke G, Eubanks D, Reid E, et al. Overcoming Depression on the Internet (ODIN) (2): a randomized trial of a self-help depression skills program with reminders. J Med Internet Res 2005 Jun 21;7(2):e16.