THE AMERICAN JOURNAL of MEDICINE®

Introduction: Chronic Medical Conditions and Depression—the View from Primary Care

Martin Hickman maneuvered his way into the office and pulled up his sleeve as the medical assistant put the brake on his wheelchair and fastened the blood pressure cuff around his oversized upper arm. A bulky 56-year-old man with a heavy shock of gray hair teetering on the edge of his forehead, his problem list included type 2 diabetes mellitus, chronic obstructive pulmonary disease, hypertension, obesity, and hyperlipidemia. For the past 15 years he had used a wheelchair because of T4 paraplegia from a gunshot wound. He suffered from bouts of major depression that responded to sertraline but never fully remitted. As the medical assistant inflated the cuff, Mr. Hickman smiled weakly and maintained a cheerful façade even after she informed him that his blood pressure was 164/88 mm Hg and his glucose was 267 mg/dL (14.82 mmol/L)—both well above goal. Later, after more careful questioning by his primary care physician, Hickman admitted that he was feeling "more down than usual" and that he sometimes neglected to take his diabetes medicine and blood pressure pills. Thinking back over the years he had cared for this patient, the physician recalled that December tended to be a particularly bad month. Social isolation, tolerable for most of the year, became painful around the holidays. December also happened to mark the anniversary of Hickman's spinal cord injury.

The clock was running, the waiting room was full, and the physician realized he was already falling behind. . . .

[patient name is fictitious]

The role of primary care and of the roughly 220,000 primary care physicians in the United States is still being worked out as part of an ongoing national dialogue.[1] Shrinking resources, tight reimbursement policies, diminished interest among medical students, and poor clinician morale have created what some have called a "crisis in primary care."[2–4] Nevertheless, primary care remains the setting in which most Americans receive most of their medical care most of the time.[5] Perhaps nowhere is primary care more central than in the care of patients like Mr. Hickman who have coexisting chronic medical illness and depression.

Depending on the setting, primary care physicians are responsible for monitoring population health, delivering preventive services, diagnosing and treating acute disease, recognizing and stabilizing emergencies, performing minor procedures, providing end-of-life care, and acting as gatekeepers to specialty and high-tech services. Arguably, the most important role of the primary care physician is to coordinate the care of the 90 million Americans with ≥1 chronic medical condition.[6] Although considerable progress has been made in expanding the biomedical armamentarium, less attention has been paid to ensuring that effective treatments are delivered reliably to real patients in real-world settings.[7] Of equal importance, systems for helping physicians and patients manage complex coexisting conditions are incompletely developed and poorly disseminated. As a consequence, patients like Mr. Hickman suffer.

Depression is common and disabling, with an estimated lifetime prevalence of 16%[1] and a huge impact on disability-adjusted life-years.[2] Chronic medical conditions and depressive disorders frequently co-occur; a large worldwide population-based study found that people with chronic physical conditions were significantly more likely to have depression than were those without chronic conditions ($P < 0.0001$).[8] Depression alone impaired health to a greater degree than the 4 common chronic physical diseases studied (i.e., angina, arthritis, asthma, and diabetes). Additionally, depression occurring concomitantly with other chronic diseases incrementally worsened health compared with depression alone, with any of the chronic diseases alone, and with any combination of chronic diseases without depression.

Chronic illness raises the risk for depression, with depressive disorders roughly 2-fold more prevalent among patients with diabetes, coronary artery disease, human immunodeficiency virus infection, and stroke than among patients free of chronic illness.[9] Conversely, depression appears to raise the risk for developing various chronic

Statement of author disclosure: Please see the Author Disclosures section at the end of this article.

Dr. Kravitz is supported by Midcareer Research and Mentoring Award No. K24-MH072756 from the National Institute of Mental Health. Dr. Ford has received grants from the National Institute of Mental Health and the Robert Wood Johnson Foundation for research on the management of depression in primary care.

Requests for reprints should be addressed to Richard L. Kravitz, MD, MSPH, Department of Internal Medicine, University of California–Davis, 2103 Stockton Boulevard, Grange Building, Suite 2224, Sacramento, California 95817.

0002-9343/$ -see front matter
doi:10.1016/j.amjmed.2008.09.007

diseases. For example, depression has been associated with a doubling of the risk for type 2 diabetes[10,11] and a 64% increase in the risk for coronary artery disease.[12] In short, depression and chronic medical conditions have a reciprocal relationship; depression affects the prevalence, severity, and management of co-occurring chronic medical conditions and vice versa. With the aging of the US population, the prevalence of chronic illness will continue to increase. Addressing co-occurring depression and chronic medical illness is thus a critical challenge for primary care physicians, who are on the frontlines of caring for people with both mental and physical health conditions.

In the remainder of this Introduction, we discuss implications of chronic medical conditions for the treatment of depression and implications of depression for the treatment of chronic medical illness. We then explore opportunities to improve care for both physical and mental health conditions through an integrated chronic care model. We conclude by considering some of the many unanswered questions in need of further research.

CHARACTERISTICS OF PATIENTS WITH CHRONIC MEDICAL CONDITIONS THAT INFLUENCE DEPRESSION CARE

Treating depression in patients with chronic medical conditions presents ≥3 separate challenges. First, the physical and emotional burden of chronic illness can make depression more difficult to recognize, diagnose, and manage. Some diseases (particularly neurologic syndromes such as stroke or Parkinsonism) directly affect brain chemistry.[13] Others affect sleep, appetite, physical functioning, and ability to socialize, thereby exacerbating depressive symptoms while interfering with adjunctive interventions and social engagement. On an existential level, severe physical illness can rob patients of valued capabilities and impose a cap on hopefulness.

Second, patients with co-occurring depression and chronic medical conditions may tacitly collude with their physicians to "focus on the physical," putting off care of depression for weeks, months, or longer. While it may sometimes make sense to attend to physical symptoms before treating depression, undue delay not only complicates efforts to secure remission of depression but, paradoxically, makes treatment of the physical condition more difficult. Waiting to get the blood pressure below 130/80 mm Hg and the glycosylated hemoglobin under 7% before initiating or escalating treatment for depression may be the medical equivalent of "waiting for Godot." The good news is that depressed patients with medical comorbidities tend to be seen more frequently than medically ill patients without depression, which means that the physician has more opportunities to screen, monitor, adjust, and intensify depression-related therapy.

The third major challenge is that many chronic medical illnesses are increasingly treated with complex pharmacologic regimens. In the mid 1990s, about one third of community-dwelling elders were taking ≥5 medications[14]; adding pharmacologic treatment for depression increases the probability of drug–drug interactions in patients already medicated for comorbidities (Table 1).[15–23] Most antidepressants are metabolized in the liver; metabolism by the isoenzymes of the cytochrome P450 (CYP450) system, including CYP2D6, CYP3A3/4, and CYP2C19 are responsible for many drug-drug interactions in the clinical setting.[24] For instance, the metabolism of donepezil, a commonly prescribed treatment for Alzheimer disease, may be affected by antidepressants that inhibit CYP450.

Furthermore, some antidepressant agents may have specific properties potentially affecting antidepressant treatment choice in the presence of a comorbid chronic condition (Table 2).[17,25–41] For example, some selective serotonin reuptake inhibitors cause weight gain,[24] an effect that would be particularly deleterious for patients with diabetes, and venlafaxine has been associated with elevated blood pressure in elderly patients.[42] Conversely, tricyclic antidepressants, duloxetine, and venlafaxine have demonstrated efficacy in treating diabetic neuropathy,[39,40] and escitalopram or problem-solving therapy was associated with decreased 12-month incidence of poststroke depression.[31]

CHARACTERISTICS OF PATIENTS WITH DEPRESSION THAT INFLUENCE CARE OF CHRONIC MEDICAL CONDITIONS

Just as chronic medical conditions affect the treatment of depression, depressive symptoms can complicate treatment of chronic medical illness. Patients with depression share 2 characteristics that potentiate the challenges of chronic disease care. First, even without *Diagnostic and Statistical Manual of Mental Disorders–Fourth Edition*[43] classified somatization, depressed patients have a tendency to amplify somatic symptoms.[44] This tendency may manifest as a "positive review of symptoms," increased experience of and reporting of pain, excessive anxiety around disease susceptibility, or a tendency to "catastrophize" after experiencing setbacks in disease control. Such tendencies can disrupt effective chronic disease care by triggering testing cascades,[45] encouraging over-prescribing of potentially harmful medications (e.g., opiates, sedative-hypnotics), and interfering with self-care. The downstream result is greater healthcare utilization, higher costs, and worse health outcomes. Himelhoch and colleagues,[46] for example, have shown that emergency department visits are 2 to 3 times more common among patients with diabetes, hypertension, and heart disease who have depression than among similarly ill patients without depression.

Second, patients with depressive disorders exhibit reduced self-efficacy and "will to function." Self-efficacy, as defined by Bandura,[47] is confidence in the ability to carry out a behavior or accomplish a task. A growing body of evidence places self-efficacy as a central medi-

Table 1 Potential drug–drug interactions between antidepressants and medications commonly used to treat chronic comorbid illnesses

Comorbidity	Antidepressant Drug	Potential Interaction	Adverse Event Risk(s)
Cardiovascular conditions	SSRIs, SNRIs	Warfarin, NSAIDs, aspirin, and other drugs that affect coagulation	Increased bleeding
	Fluoxetine, paroxetine, sertraline, duloxetine, bupropion	Type 1C antiarrhythmics (e.g., propafenone, flecainide)	Increased antiarrhythmic plasma levels
	Paroxetine	Phenytoin	Reduced drug plasma concentrations of both drugs
	Citalopram, escitalopram, fluvoxamine, venlafaxine	Metoprolol	Increased metoprolol plasma levels; reduced cardioselectivity
Diabetes mellitus	Sertraline	Tolbutamide	Decreased clearance of tolbutamide
Neurologic disorders	SSRIs, SNRIs, bupropion	MAOIs	Serotonin syndrome
	SSRIs, SNRIs	Triptans	Serotonin syndrome
	Fluoxetine, fluvoxamine, sertraline	Diazepam	Increased diazepam plasma concentrations
	Fluoxetine, paroxetine, duloxetine	Phenothiazines	Increased phenothiazine plasma levels
	Fluoxetine, fluvoxamine, venlafaxine	Lithium	Increased lithium plasma concentrations; serotonin syndrome
Osteoarthritis	SSRIs, SNRIs	Tramadol	Increased risk of seizures and serotonin syndrome
	SSRIs, SNRIs	NSAIDs	Increased bleeding

NSAIDs = nonsteroidal anti-inflammatory drugs; SNRIs = serotonin–norepinephrine reuptake inhibitors; SSRIs = selective serotonin reuptake inhibitors.

ator of health-related behavior. It is influenced by past personal experience with the behavior or task at hand, observation of others (i.e., modeling), and verbal persuasion. Depressed mood and associated feelings of helplessness, hopelessness, and guilt tend to suppress self-efficacy across a broad spectrum of health-related behaviors, thereby disrupting effective chronic disease self-management. For example, all else equal, depressed patients will be less confident in their ability to count carbohydrates, monitor their own blood pressure, or take medications regularly. In addition, depression is associated with a diminution in will to function.[48] This concept was developed as an explanation for why patients with similar physiologic derangements function very differently. Depressed patients with impaired will to function manifest greater levels of disability or impairment at a given level of chronic condition severity.

In summary, chronic medical conditions affect depression care by altering brain function, contributing to disability, reinforcing collusive avoidance of depression treatment, and raising the prospect of drug–drug and drug–disease interactions. Depression affects chronic disease care by amplifying somatic symptoms and diminishing self-efficacy and the will to function. The challenges of managing coexisting depression and chronic medical illness are therefore considerable.

THE CHRONIC CARE MODEL: PROMISES AND LIMITATIONS

Prompted by studies showing large deficits in quality of care for patients with chronic physical and mental health conditions, Wagner and colleagues[49–51] promulgated the Chronic Care Model (CCM), a multipronged systems-based approach to care improvement. The CCM leverages community resources to improve healthcare organization through self-management support, delivery system redesign, decision support, and clinical information systems (Table 3). In various guises, the CCM has been successfully applied to numerous chronic conditions, including diabetes, hypertension, congestive heart failure, and depression. A 2005 meta-analysis of 33 studies evaluating the CCM in depression showed modest but statistically significant improvements in clinical outcomes, quality of life, and process of care.[52] However, for the most part, successful CCM programs have been implemented in organized systems of care (such as group-model health maintenance organizations) and have targeted 1 chronic condition at a time. These parameters are a nonstarter for the majority of primary care clinicians. After all, 50% of primary care physicians practice solo or in small groups, and most lack electronic medical records.[53] It is unrealistic to expect physicians practicing in such settings to establish separate disease management schemes for even the most common chronic medical and psychiatric condi-

Table 2 Relatively compelling indications and contraindications for use of specific depression treatments

Specific Treatment	Indication/Contraindication
Antidepressant treatments	
Tricyclic antidepressants	• Generally contraindicated in organic heart disease owing to proarrhythmic properties[25] • Contraindicated for severely depressed or suicidal patients owing to toxicity in overdose • Contraindicated in Parkinson disease due to anticholinergic side effects and aggravation of Parkinson disease–associated orthostatic hypotension[26] • Limited use in diabetes mellitus due to weight gain, cardiac exacerbation, and postural hypotension[27,28]
Nortriptyline	• Demonstrated efficacy in poststroke depression[29]
SSRIs	• Perception that SSRIs may worsen motor function in Parkinson disease[26] • Generally safe and well tolerated in patients with CHD when used with appropriate precautions[25,30]
Escitalopram	• Demonstrated efficacy in preventing poststroke depression[31]
Citalopram	• Reduced depression in patients with CHD[32] • Demonstrated efficacy in poststroke depression[29] • One of the most studied agents in comorbid depression and heart disease
Fluoxetine	• Some evidence for depression efficacy and glycemic control in diabetes[33,34] • Appeared safe and reasonably effective in stable CHD[35]
Sertraline	• Demonstrated efficacy in poststroke depression[29] • One of the most studied agents in comorbid depression and heart disease • Some evidence of antidepressive maintenance efficacy in diabetes[36] • Safe to use after an acute coronary syndrome but only modestly efficacious for depression[37]
Bupropion	• May be particularly useful in diabetes owing to lack of weight gain/weight loss and improved glycemic control[38] • Effective in the treatment of diabetic neuropathy[39]
Venlafaxine	• Care should be taken in patients with established hypertension or CHD owing to sustained increases in blood pressure, increased QT_c interval, and tachycardia[17] • Effective in the treatment of diabetic neuropathy[39]
Duloxetine	• Some evidence for efficacy in comorbid musculoskeletal pain[40] • Effective in the treatment of diabetic neuropathy[39]
Nonpharmacologic therapies	
Cognitive behavioral therapy	• CBT has benefits in treating depression in multiple sclerosis • CBT has demonstrated efficacy for depression and long-term glycemic control[41] • Problem-solving therapy was significantly superior to placebo in preventing poststroke depression for 1 year[31]
Interpersonal psychotherapy	• No additional improvement with psychotherapy added to citalopram in CHD

CBT = cognitive behavioral therapy; CHD = coronary heart disease; SSRIs = selective serotonin reuptake inhibitors.

tions (e.g., diabetes, hypertension, congestive heart failure, chronic obstructive pulmonary disease/asthma, and depression). Integrated approaches that play off commonalities among conditions are more promising.[54]

OPPORTUNITIES FOR PRACTICE IMPROVEMENT

Recognition of chronic medical condition and depression comorbidity represents an opportunity for primary care physicians to integrate and enhance services while becoming skilled at containing treatment costs and improving patient outcomes. In this supplement to *The American Journal of Medicine*, content experts review current evidence regarding treatment of co-occuring depression and other illnesses. In the first article, Dr. Wayne J. Katon discusses the under-recognition and undertreatment of depression, which is often chronic and severe, in the growing population with diabetes. Next, Dr. Elizabeth H. B. Lin explores the relation between depression and osteoarthritis, and explores the costs to individuals and society of these prevalent conditions. Drs. Ronald M. Carney and Kenneth E. Freedland then explore the association of depression and coronary heart disease, and provide information on treatments and screening techniques for use in primary care and cardiology settings. Dr. Murray A. Raskind follows with a look at the challenges to diagnosing and treating the frequent occurrence of depression in the context of neurologic disorders, such as Alzheimer and Parkinson disease and multiple sclerosis, where the frequent overlap of signs and symptoms and the lack of validated diagnostic guidelines for depression place an increased burden on the clinician. Finally, Dr. Daniel E. Ford evaluates the challenges and opportunities for providing care for depression in patients with chronic medical conditions in the primary care setting.

Several overarching principles emerge from the information in these articles:

Table 3 The chronic care model: components and interventions

Components of Chronic Care	Interventions
Delivery system redesign	• Organize patient care teams that include the physician, nurses, and nonmedical staff • Train nonphysician staff to provide routine assessment, prevention tasks, and self-management support • Allocate tasks • Have ready access to specialist care (e.g., medical specialists, nutritionists, social workers) • Use specialist care support as needed • Assure regular patient contact through practice-initiated appointments and follow-up
Physician assisted patient self-management	• Assess patient knowledge • Provide patient education • Mutually agree on the definition of the problem • Set realistic goals to target issues of greatest importance to the physician and patient • Develop a personalized intervention plan with patient input • Provide self-management support tools (e.g., disease management instructions, behavioral support programs, exercise options) • Arrange for practice-initiated follow-up at regular intervals
Decision support	• Conventional referral or consultation • Increase expertise through continuing medical education • Access to recent textbooks and journals • Use of electronic evidence-based medicine resources • Use of PDA-based prescribing resource • Use of treatment algorithms • Use of measurement-based care • Use of electronic decision support systems with audits and reminders
Clinical information systems	• Use computerized patient registries to facilitate reminders for follow-up and preventive care • Provide patient-carried medical records and care plans • Use an information system to get patient feedback • Ensure access to longitudinal computerized patient information

DDA = personal data assistant.

- Treat depression and comorbid medical conditions simultaneously
- Set aggressive goals: remission of depression, reestablishment of near normal physiology, good functional status
- Monitor depression status (e.g., use the Patient Health Questionnaire [PHQ]–9[55] or other standardized instrument) along with blood pressure, body weight, or hemoglobin A_{1c}
- Fight clinical inertia[56]: if depression has not remitted or chronic disease parameters are not under control, switch or intensify treatment
- Get help: create real or virtual teams that may include primary care physicians, psychiatrists, medical subspecialists, nurses, therapists, health educators, and office personnel

Applying these principles will require effort, expertise, and resources. Primary care practices need materials and resources to implement an integrative CCM that cuts across disease states. The situation is both urgent and remediable. Researchers should focus on developing materials and methods for implementing the CCM in small practices, leaving policymakers to focus on finding the resources to turn academic innovation into practice-based reality. The ultimate goal—improved care for patients like Mr. Hickman—is within reach.

Richard L. Kravitz, MD, MSPH
Department of Internal Medicine
University of California–Davis
Sacramento, California, USA
E-mail address: rlkravitz@ucdavis.edu.

Daniel E. Ford, MD, MPH
Division of General Internal Medicine
Johns Hopkins School of Medicine
Baltimore, Maryland, USA

ACKNOWLEDGMENTS

We acknowledge the assistance of Carol Dyer, MS, Laurance Macke, MS, and Adam Ruth, PhD, of Prescott Medical Communications Group in identifying references, preparing tables, and facilitating the manuscript revision process.

AUTHOR DISCLOSURES

The authors who contributed to this article have disclosed the following industry relationships:

Richard L. Kravitz, MD, MSPH, has served as a consultant to Merck & Co. Inc.; has received unrestricted research grants from Pfizer Inc.; and has received an honorarium from Forest Laboratories, Inc.

Daniel E. Ford, MD, MPH, has served as a consultant to Pfizer Inc.; and has received an honorarium from Forest Laboratories, Inc.

References

1. Family physicians and the primary care physicians workforce in 2004 [Graham Center One-Pager). *Am Fam Phys*. 2005;71:2260.
2. Bodenheimer T. Primary care—will it survive? *N Engl J Med*. 2006; 355:861-864.
3. Grumbach K. Primary care in the United States—the best of times, the worst of times. *N Engl J Med*. 1999;341:2008-2010.
4. Larson EB, Grumbach K, Roberts KB. The future of generalism in medicine. *Ann Intern Med*. 2005;142:689-690.
5. Green LA, Hames CG Sr, Nutting PA. Potential of practice-based research networks: experiences from ASPN [Ambulatory Sentinel Practice Network]. *J Fam Pract*. 1994;38:400-406.
6. Hoffman C, Rice D, Sung HY. Persons with chronic conditions: their prevalence and costs. *JAMA*. 1996;276:1473-1479.
7. Woolf SH, Johnson RE. The break-even point: when medical advances are less important than improving the fidelity with which they are delivered. *Ann Fam Med*. 2005;3:545-552.
8. Moussavi S, Chatterji S, Verdes E, Tandon A, Patel V, Ustun B. Depression, chronic diseases, and decrements in health: results from the World Health Surveys. *Lancet*. 2007;370:851-858.
9. Katon WJ. Clinical and health services relationships between major depression, depressive symptoms, and general medical illness. *Biol Psychiatry*. 2003;54:216-226.
10. Eaton WW, Armenian H, Gallo J, Pratt L, Ford DE. Depression and risk for onset of type II diabetes: a prospective population-based study. *Diabetes Care*. 1996;19:1097-1102.
11. Kawakami N, Takatsuka N, Shimizu H, Ishibashi H. Depressive symptoms and occurrence of type 2 diabetes among Japanese men. *Diabetes Care*. 1999;22:1071-1076.
12. Rugulies R. Depression as a predictor for coronary heart disease: a review and meta-analysis. *Am J Prev Med*. 2002;23:51-61.
13. Sobel RM, Lotkowski S, Mandel S. Update on depression in neurologic illness: stroke, epilepsy, and multiple sclerosis. *Curr Psychiatry Rep*. 2005;7:396-403.
14. Moxey E, O'Connor J, Novielli K, Teutsch S, Nash D. Prescription drug use in the elderly: a descriptive analysis. *Health Care Financ Rev*. 2003;24:127-141.
15. Celexa [package insert]. St. Louis, MO: Forest Pharmaceuticals, Inc.; 2007.
16. Cymbalta [package insert]. Indianapolis, IN: Eli Lilly and Company; 2007.
17. Effexor XR [package insert]. Philadelphia, PA: Wyeth Pharmaceuticals Inc.; 2008.
18. Fluvoxamine maleate tablets [package insert]. Elizabeth, NJ: Purepac Pharmaceutical Co.; 2000.
19. Lexapro [package insert]. St. Louis, MO: Forest Pharmaceuticals, Inc.; 2007.
20. Prozac [package insert]. Indianapolis, IN: Eli Lilly and Company; 2008.
21. Paxil [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2008.
22. Wellbutrin XL [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2007.
23. Zoloft [package insert]. New York, NY: Pfizer Inc.; 2008.
24. Schatzberg AF. Safety and tolerability of antidepressants: weighing the impact on treatment decisions. *J Clin Psychiatry*. 2007;68(suppl 8):26-34.
25. Davidson KW, Kupfer DJ, Bigger JT, et al. Assessment and treatment of depression in patients with cardiovascular disease: National Heart, Lung, and Blood Institute Working Group Report. *Ann Behav Med*. 2006;32:121-126.
26. McDonald WM, Richard IH, DeLong MR. Prevalence, etiology, and treatment of depression in Parkinson's disease. *Biol Psychiatry*. 2003; 54:363-375.
27. Williams MM, Clouse RE, Lustman PJ. Treating depression to prevent diabetes: understanding depression as a medical complication. *Clin Diabetes*. 2006;24:79-86.
28. Lustman PJ, Griffith LS, Clouse RE, et al. Effects of nortriptyline on depression and glycemic control in diabetes: results of a double-blind, placebo-controlled trial. *Psychosom Med*. 1997;59:241-250.
29. Starkstein SE, Mizrahi R, Power BD. Antidepressant therapy in poststroke depression. *Expert Opin Pharmacother*. 2008;9:1291-1298.
30. Sheline YI, Freedland KE, Carney RM. How safe are serotonin reuptake inhibitors for depression in patients with coronary heart disease? *Am J Med*. 1997;102:54-59.
31. Robinson R, Jorge R, Moser D, et al. Escitalopram and problem-solving therapy for prevention of poststroke depression. *JAMA*. 2008; 299:2391-2400.
32. Lesperance F, Frasure-Smith N, Koszycki D, et al, for the CREATE Investigators. Effects of citalopram and interpersonal psychotherapy on depression in patients with coronary artery disease: the Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE) trial. *JAMA*. 2007;297:367-379.
33. Breum L, Bjerre U, Bak JF, Jacobsen S, Astrup A. Long-term effects of fluoxetine on glycemic control in obese patients with non-insulin-dependent diabetes mellitus or glucose intolerance: influence on muscle glycogen synthase and insulin receptor kinase activity. *Metabolism*. 1995;44:1570-1576.
34. Lustman PJ, Freedland KE, Griffith LS, Clouse RE. Fluoxetine for depression in diabetes: a randomized double-blind placebo-controlled trial. *Diabetes Care*. 2000;23:618-623.
35. Strik JJ, Honig A, Lousberg R, et al. Efficacy and safety of fluoxetine in the treatment of patients with major depression after first myocardial infarction: findings from a double-blind, placebo-controlled trial. *Psychosom Med*. 2000;62:783-789.
36. Lustman PJ, Clouse RE, Nix BD, et al. Sertraline for prevention of depression recurrence in diabetes mellitus: a randomized, double-blind, placebo-controlled trial. *Arch Gen Psychiatry*. 2006;63:521-529.
37. Glassman AH, O'Connor CM, Califf RM, et al. Sertraline treatment of major depression in patients with acute MI or unstable angina. *JAMA*. 2002;288:701-709.
38. Lustman PJ, Williams MM, Sayuk GS, Nix BD, Clouse RE. Factors influencing glycemic control in type 2 diabetes during acute- and maintenance-phase treatment of major depressive disorder with bupropion. *Diabetes Care*. 2007;30:459-466.
39. Duby JJ, Campbell RK, Setter SM, White JR, Rasmussen KA. Diabetic neuropathy: an intensive review. *Am J Health Syst Pharm*. 2004;61:160-173; quiz 175–176.
40. Jann MW, Slade JH. Antidepressant agents for the treatment of chronic pain and depression. *Pharmacotherapy*. 2007;27:1571-1587.
41. Lustman PJ, Griffith LS, Freedland KE, Kissel SS, Clouse RE. Cognitive behavior therapy for depression in type 2 diabetes mellitus: a randomized, controlled trial. *Ann Intern Med*. 1998;129:613-621.
42. Johnson EM, Whyte E, Mulsant BH, et al. Cardiovascular changes associated with venlafaxine in the treatment of late-life depression. *Am J Geriatr Psychiatry*. 2006;14:796-802.
43. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders–Fourth Edition, Text Revision (DSM-IV-TR)*. Washington, DC: American Psychiatric Association, 2000.
44. Sayar K, Kirmayer LJ, Taillefer SS. Predictors of somatic symptoms in depressive disorder. *Gen Hosp Psychiatry*. 2003;25:108-114.
45. Mold JW, Stein HF. The cascade effect in the clinical care of patients. *N Engl J Med*. 1986;314:512-514.

46. Himelhoch S, Weller WE, Wu AW, Anderson GF, Cooper LA. Chronic medical illness, depression, and use of acute medical services among Medicare beneficiaries. *Med Care*. 2004;42:512-521.
47. Bandura A. Self-efficacy: toward a unifying theory of behavioral change. *Psychol Rev*. 1977;84:191-215.
48. Hays R, Cunningham W, Ettl M, Beck C, Shapiro M. Health-related quality of life in HIV disease. *Assessment*. 1995;2:363-380.
49. Wagner EH, Austin BT, Von Korff M. Organizing care for patients with chronic illness. *Milbank Q*. 1996;74:511-544.
50. Bodenheimer T, Wagner EH, Grumbach K. Improving primary care for patients with chronic illness: the chronic care model, part 2. *JAMA*. 2002;288:1909-1914.
51. Bodenheimer T, Wagner EH, Grumbach K. Improving primary care for patients with chronic illness. *JAMA*. 2002;288:1775-1779.
52. Tsai AC, Morton SC, Mangione CM, Keeler EB. A meta-analysis of interventions to improve care for chronic illnesses. *Am J Manag Care*. 2005;11:478-488.
53. Burt CW, Sisk JE. Which physicians and practices are using electronic medical records? *Health Aff (Millwood)*. 2005;24:1334-1343.
54. Dorr DA, Wilcox A, Burns L, Brunker CP, Narus SP, Clayton PD. Implementing a multidisease chronic care model in primary care using people and technology. *Dis Manag*. 2006;9:1-15.
55. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med*. 2001;16:606-613.
56. Trivedi MH, Lin EH, Katon WJ. Consensus recommendations for improving adherence, self-management, and outcomes in patients with depression. *CNS Spectr*. 2007;12(suppl 13):1-27.