

## Authors and Disclosures

Andrea A. Riley, Mindy L. McEntee, Linda Gerson, and Cheryl R. Dennison

Andrea A. Riley, MSN, MS, CNP, RD, is a family nurse practitioner at Hidalgo Medical Services in Lordsburg, NM. Mindy L. McEntee, MA, is a research assistant, Linda D. Gerson, PhD, RN, PMHCNS-BC, is an assistant professor, and Cheryl R. Dennison, RN, ANP, PhD, FAHA is an associate professor in the Department of Health Systems and Outcomes at Johns Hopkins University School of Nursing in Baltimore, MD. Dennison can be reached at [cdennison@jhmi.edu](mailto:cdennison@jhmi.edu). In compliance with national ethical guidelines, the authors report no relationships with business or industry that would pose a conflict of interest.

## From Journal for Nurse Practitioners

# Depression as a Comorbidity to Diabetes: Implications for Management

Andrea A. Riley; Mindy L. McEntee; Linda Gerson; Cheryl R. Dennison

Posted: 09/25/2009; Journal for Nurse Practitioners. 2009;5(7):523-535. © 2009 Elsevier Inc.

## Abstract and Introduction

### Abstract

Research has established a link between depression and diabetes, even though the underlying mechanisms in this relationship remain unclear. Primary care providers are often responsible for managing these conditions and are well positioned to provide integrated care improving patients' physical and mental health outcomes, yet they face a number of barriers contributing to the inadequate management of depression in primary care. All diabetic patients should be routinely screened for depression; management of these concomitant conditions should use a comprehensive approach that may include medication or referral for psychotherapy. This paper explores the relationship between depression and diabetes and implications for practice in the areas of screening, diagnosis, and management of depression in diabetic patients.

### Introduction

The odds of having depression among individuals with type 1 or 2 diabetes are more than twice that of non-diabetics,<sup>[1]</sup> with an estimated 33% of diabetics experiencing depressive symptoms severe enough to warrant treatment at any single point in time.<sup>[2]</sup> The course of depression in these individuals is often chronic<sup>[3]</sup> and may adversely affect the course of coexisting medical conditions.<sup>[4-6]</sup> A number of studies have found depression to be associated with poor self-care in people with diabetes.<sup>[7-13]</sup> Decreased adherence to medication,<sup>[7,10,13-15]</sup> diet,<sup>[7,8,13,14]</sup> exercise,<sup>[8,11,13]</sup> and blood glucose monitoring<sup>[13]</sup> may contribute to increased diabetic symptoms,<sup>[8,16]</sup> glucose dysregulation,<sup>[17-19]</sup> diabetic complications,<sup>[18,20,21]</sup> mortality,<sup>[22-24]</sup> decreased physical<sup>[7,8,25]</sup> and mental functioning,<sup>[7,26]</sup> lower quality of life,<sup>[7,27]</sup> and increased healthcare utilization<sup>[7,26,28]</sup> associated with comorbid diabetes and depression.

Because primary care providers (PCPs) are frequently charged with the management of type 2 diabetes and uncomplicated unipolar depression, they are well positioned to provide integrated care for these concomitant disorders.<sup>[29]</sup> While the co-occurrence of these conditions is a widely known clinical phenomenon, depression remains under-recognized and inadequately treated in primary care.<sup>[2,13,29-32]</sup> To provide high-quality care optimizing physical and mental health outcomes for their patients, it is important that PCPs understand the relationship between depression and diabetes. This paper examines the etiologies of these comorbid conditions and discusses implications for practice in the areas of screening, diagnosis, and management of depression in the diabetic population.

## Relationship between Diabetes and Depression

The high prevalence of comorbid depression and diabetes suggests that these disorders may be related.<sup>[33]</sup> Depression has been proposed as both a result of and precursor to diabetes, with this relationship attributed to a variety of mechanisms. Studies have examined a number of psychosocial and biological correlates of depression and diabetes, yet the causal relationship between these disorders, its direction, and underlying mechanisms remain unclear.<sup>[31,34]</sup>

## Depression as a Result of Diabetes

Some authors have proposed that depression may stem from the psychosocial burden and/or biochemical changes related to diabetes and its treatment.<sup>[1,17,18]</sup> This hypothesis may help explain why depression is more prevalent in diabetics than in the general population and is supported by the temporal finding among type 1 diabetics, in which diabetes typically precedes the onset of major depressive disorder (MDD).<sup>[34]</sup> While there is little empirical data on the psychosocial facet of this theory, there is some evidence that emotional distress is mediated by perceived threat of illness,<sup>[35,36]</sup> self-esteem,<sup>[37,38]</sup> self-efficacy,<sup>[35]</sup> coping skills,<sup>[39]</sup> and social support.<sup>[35,37]</sup>

Sociodemographic factors including younger age,<sup>[21,26,40]</sup> female gender,<sup>[1,21,26,40–44]</sup> low socioeconomic status,<sup>[26,43,45]</sup> ethnic minority status,<sup>[21,31,41,46]</sup> chronic stressors, and negative life events<sup>[47]</sup> have also been identified as predictors of depression among individuals with diabetes, although a causal relationship has not been established.

The biological component of this hypothesis speculates that the metabolic consequences of diabetes lead to structural and functional changes in the brain that increase susceptibility to stress and depression,<sup>[48]</sup> although data thus far have been inconclusive. The relationship between depression and glycemic control remains subject to debate; a meta-analysis of 26 studies found a significant relationship with comparable effect sizes in both type 1 and type 2 diabetes,<sup>[17]</sup> yet other research did not find this correlation,<sup>[42,49,50]</sup> or found it significant only for individuals with type 1 diabetes.<sup>[51,52]</sup> The connection between diabetic complications and depression has also produced mixed results;<sup>[18,31,44,53–57]</sup> these discrepancies may suggest that biochemical mechanisms have greater influence on the duration of depression rather than its initial onset.<sup>[34]</sup>

## Depression as a Precursor to Diabetes

An alternative hypothesis in which depression precedes and predisposes individuals to diabetes may explain the development of type 2 diabetes among patients diagnosed with depression several years earlier.<sup>[58]</sup> This theory proposes that diabetes may develop via the psychosocial effects of depression, including adiposity and negative health behaviors like poor diet, physical activity, smoking, and medication adherence; and/or as a result of biological mechanisms such as activation of the HPA axis<sup>[45,59–62]</sup> and inflammatory responses<sup>[63–66]</sup> that contribute to insulin resistance and decreased glucose uptake. A meta-analysis of 9 longitudinal studies showed that adults who were depressed were 37% more likely to develop type 2 diabetes than their non-depressed counterparts.<sup>[67]</sup> Other studies have shown that this increased risk remains significant after controlling for known demographic and clinical risk factors.<sup>[57,68–75]</sup> Adults receiving treatment for depression were still prone to developing diabetes,<sup>[75,76]</sup> with those taking a tricyclic antidepressant (TCA) and a selective serotonin reuptake inhibitor (SSRI) concurrently at greater risk (60%) than those prescribed either a TCA (44%) or SSRI (37%) alone.<sup>[77]</sup>

While research supports a trend in which depression precedes type 2 diabetes, causal mechanisms for this association remain speculative. A recent meta-analysis of 13 prospective studies found that while adverse psychosocial factors were associated with poor diabetes control in both type 1 and type 2 diabetes, they were not related to incidence of diabetes.<sup>[78]</sup> Variations in the extent to which depression increased the risk of type 2 diabetes after accounting for known risk factors suggest that additional factors affect this relationship.<sup>[44,57,70]</sup> Inflammatory markers interleukin-6 and C-reactive protein were elevated in depressed individuals and have been identified as risk factors for developing type 2 diabetes, yet models accounting for these variables were still unable to explain the association between depression and the incidence of type 2 diabetes in Golden et al.<sup>[44]</sup> Knol et al found that insulin resistance was not related to depressive symptoms, further challenging the proposed mechanisms underlying this relationship.<sup>[79]</sup>

## A Bidirectional Relationship

Contradictory research findings suggest the relationship between depression and diabetes is complex and may differ for type 1 and type 2 diabetes. The factors underlying this relationship may be bidirectional and consist of multiple mechanisms and/or indirect causation. Golden et al found evidence for a bidirectional relationship within the same cohort; adults with treated type 2 diabetes who were depression-free at baseline were 52% more likely to experience depressive symptoms than non-diabetics, while adults with elevated depression scores were 21% more likely than those with low or normal symptoms to develop type 2 diabetes after adjusting for clinical, demographic, and lifestyle risk factors.<sup>[44]</sup>

## Screening and Diagnosis

Although the link between depression and diabetes remains elusive, adverse effects can be minimized by adequate recognition and treatment. Because both conditions can produce similar somatic symptoms, concern has been raised that current diagnostic criteria

for depression are not appropriate for the diabetic population.<sup>[80]</sup> While rates of sympathetic arousal, gastrointestinal complaints, and fatigue are higher in depressed individuals with co-occurring medical conditions, the differences are modest and did not significantly affect the diagnostic process.<sup>[81,82]</sup> Depressed diabetics experienced a similar course of depression and were just as likely to respond to treatment as depressed individuals without diabetes, even though they reported lower levels of somatic well-being and contentment.<sup>[83]</sup> Moreover, mean scores and symptom profiles on the Beck Depression Inventory (BDI) did not significantly differ between depressed individuals with diabetes and those without.<sup>[80]</sup> These findings suggest that diagnostic criteria and screening methods currently accepted for use in the general population are also suitable for diabetic patients.

Current research suggests only 25% to 50% of diabetic patients with depression are identified in primary care.<sup>[32,84,85]</sup> The American Diabetes Association (2008) advises regular screening throughout the course of diabetes management: at diagnosis, routine management visits, hospitalizations, when complications develop, or when problems with glucose control, quality of life, or adherence to self-care are identified.<sup>[86]</sup> Administration of a brief depression screening tool should be included with annual screening for diabetes-related parameters.

Selectively screening individuals based on the presence of known risk factors alone is not recommended, as presence of these factors is not as reliable as use of brief screening tools in detecting depression.<sup>[87]</sup> Providers should, however, be mindful of certain triggers in patients' medical history that may warrant additional screening, including unexplained psychosomatic symptoms, history of depression, comorbid psychological illnesses, chronic pain, substance abuse,<sup>[87]</sup> or reported diabetes symptoms disproportionately high with respect to the course of diabetes.<sup>[16]</sup> Patients with a personal history of depression or current anxiety disorder are significantly more likely to have depression and may warrant a diagnostic interview instead of initial screening.<sup>[87]</sup>

### Depression Screening Tools

While guidelines agree routine screening for depression is necessary, they provide little guidance on selecting the best measure(s) to do so.<sup>[86,87]</sup> Several self-report questionnaires have been validated to assess depressive symptoms in primary care patients, although their use in diabetic populations has received considerably less study. Nevertheless, several screening tools have demonstrated sound psychometric properties detecting depression in samples of primary care patients with diabetes ( Table 1 ). In spite of differences in length, wording, and scoring criteria, each of these measures can be completed and scored within 5 to 10 minutes, allowing providers to follow up on the results of screening during the same visit.

**Table 1. Depression Screening Tools for Use in Primary Care**

Screening Tool	Public Domain	No. of Items	Time to Administer	Score Range	Usual Cut-point	Reliability & Validity in Primary Care Patients	Reliability & Validity in Diabetic Patients
Beck Depression Inventory II (BDI-II)	No	21	2–5 minutes	0–63	14–19 = Mild 20–28 = Moderate 29–63 = Severe	Arnau 2001 – cutoff 18 Sensitivity 94% Specificity 92% AUC = 0.96	Lustman 1997** – cutoff 13 Sensitivity 85% Specificity 88% AUC 0.94
Beck et al 1996						Dutton 2004 – cutoff 14 Cronbach $\alpha$ = 0.90 Sensitivity 88% Specificity 84% AUC = 0.91	**only original BDI validated in this population
Beck Depression Inventory for Primary Care (BDI-PC)	No	7	<2 minutes	0–21	$\geq 4$	Steer 1999 – cutoff 4 Cronbach $\alpha$ = 0.85 Sensitivity 97% Specificity 99% AUC = 0.99	n/a

Beck et al 1997						Beck 1997 outpatient – cutoff 6 Cronbach $\alpha$ = 0.88 Sensitivity 83% Specificity 95%	
Center for Epidemiological Studies Depression Scale (CES-D)	Yes	20	2–5 minutes	0–60	$\geq 16$	Whooley 1997 – cutoff 16 Sensitivity 88% Specificity 74% AUC = 0.89	Hermanns 2006 – cutoff 14 Sensitivity 79% Specificity 89% AUC = 0.80
Radloff et al 1977							McHale 2000 – cutoff 16 Sensitivity 71% Specificity 71% AUC = 0.81 Zauszniewski 2008 cutoff 16 Cronbach $\alpha$ = 0.87
Patient Health Questionnaire – 9 (PHQ-9)	Yes	9	<2 minutes	0–27	5–9 = Mild 10–14 = Moderate $\geq 15$ = Severe	Kroenke 2001 – cutoff $\geq 10$ Cronbach $\alpha$ = 0.89 Sensitivity 88% Specificity 88% AUC = 0.95	Kahn 2008 – cutoff $\geq 10$ Sensitivity 66% Specificity 52%
Kroenke 2001						Lowe 2002 – cutoff $\geq 10$ Cronbach $\alpha$ = 0.88 Sensitivity 81% Specificity 82% AUC = 0.95	Lamers 2008 – cutoff $\geq 7$ Sensitivity 92% Specificity 81%
Patient Health Questionnaire – 2 (PHQ-2)	Yes	2	<1 minute	0–6	$\geq 3$	Kroenke 2003 – cutoff $\geq 3$ Sensitivity 83% Specificity 92% AUC = 0.93	Daly 2007 – cutoff $\geq 3$ Sensitivity 83% Specificity 92%
Kroenke 2003						Brody 1998 – cutoff $\geq 3$ Sensitivity 65% Specificity 99%	
WHO-Five Well-being Index (WHO-5)	Yes	5	<2 minutes	0–25	<13	Henkel 2004 – cutoff <13 Sensitivity 94% Specificity 63% AUC = 0.91	De Wit 2007 – cutoff <13 Cronbach $\alpha$ = 0.82 Sensitivity 89% Specificity 86%
World Health Organization 1998						Lowe 2002 – cutoff <13 Cronbach $\alpha$ = 0.91 Sensitivity 94% Specificity 78% AUC = 0.91	Awata 2007 – cutoff <13 Cronbach $\alpha$ = 0.89 Sensitivity 100% Specificity 78% AUC = 0.92

Zung Self-Rating Depression Scale (SDS)	Yes	20	2–5 minutes	0–100	50–59 = Mild 60–69 = Moderate ≥70 = Severe	Okimoto 1982 – cutoff ≥ 60 Sensitivity 82% Specificity 87%	Rajala 1997 – cutoff > 55 Sensitivity 72% Specificity 83%
---	-----	----	-------------	-------	--	--	---

AUC Area under the curve index for receiver operating characteristics (ROC) curve.

#### Beck Depression Inventory II

Beck AT, Steer RA, Brown GK. Beck Depression Inventory II Manual. San Antonio: The Psychological Corporation; 1996.

Arnau RC, Meagher MW, Norris MP, Bramson R. Psychometric evaluation of the Beck Depression Inventory-II with primary care medical patients. *Health Psychol* 2001;20:112–119.

Dutton GR, Grothe KB, Jones GN, Whitehead D, Kendra K, Brantley PJ. Use of the Beck Depression Inventory-II with African American primary care patients. *Gen Hosp Psychiat* 2004;26:437–442.

Lustman PJ, Clouse RE, Griffith LS, Carney RM, Freedland KE. Screening for depression in diabetes using the Beck Depression Inventory. *Psychosomatic Med* 1997;59:24–31.

#### Beck Depression Inventory for Primary Care (BDI-PC)

Beck AT, Guth D, Steer RA, Ball R. Screening for major depression disorders in medical inpatients with the Beck Depression Inventory for Primary Care. *Behav Res Ther* 1997;35:785–791.

Steer RA, Cavalieri TA, Leonard DM, Beck AT. Use of the Beck Depression Inventory for Primary Care to screen for major depression disorders. *Gen Hosp Psychiat* 1999;21(2):106–111.

Beck AT, Steer RA, Ball R, Ciervo CA, Kabat M. Use of the Beck Anxiety and Beck Depression Inventories for Primary Care with medical outpatients. *Assessment* 1997;4:211–219.

#### CES-D

Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. *Appl Psychol Measur* 1977;1:385–401.

Whooley MA, Avins AL, Miranda J, Browner WS. Case-finding instruments for depression: two questions are as good as many. *J Gen Intern Med* 1997;12:439–445.

Hermanns N, Kulzer B, Krichbaum M, Kubiak T, Haak T. How to screen for depression and emotional problems in patients with diabetes: comparison of screening characteristics of depression questionnaires, measurement of diabetes-specific emotional problems and standard clinical assessment. *Diabetologia* 2006;49:469–477.

McHale M, Hendrikz J, Dann F, Kenardy J. Screening for depression in patients with diabetes mellitus. *Psychosomatic Med* 2008;70:869–874.

Zauszniewski JA, Graham GC. Comparison of short scales to measure depressive symptoms in elders with diabetes. *West J Nurs Res* 2009;31(2):219–34.

#### PHQ-9

Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med* 2001;16(9):606–613.

Löwe B, Spitzer RL, Gräfe K, Kroenke K, Quenter A, Zipfel S, et al. Comparative validity of three screening questionnaires for DSM-IV depressive disorders and physicians' diagnoses. *J Affective Disorders* 2004;78:131–140.

Kahn LS, Fox CH, McIntyre RS, Tumiel-Berhalter L, Berdine DE, Lyle H. Assessing the prevalence of depression among individuals with diabetes in a Medicaid managed-care program. *Intern J Psychiat Med* 2008;38:13–29.

Lamers F, Jonkers CCM, Bosma H, Penninx BWJH, Knottnerus JA, van Eijk JTM. Summed score of the Patient Health Questionnaire-9 was a reliable and valid measure for depression screening in chronically ill elderly patients. *J Clin Epidemiol* 2008;61:679–687.

#### PHQ-2

Kroenke K, Spitzer RL, Williams JB. The Patient Health Questionnaire-2: validity of a two-item

depression screener. *Med Care* 2003;41:1284–1292.

Brody DS, Hahn SR, Spitzer RL, Kroenke K, Linzer M, deGruy FV et al. Identifying patients with depression in the primary care setting: a more efficient method. *Arch Intern Med* 1998;158:2469–2475.

Daly EJ, Trivedi MH, Raskin P, Grannemann BD. Screening for depression in a diabetic outpatient population. *Intern J Psychiatry Clin Pract* 2007;11:268–272.

WHO-5

World Health Organization: Regional Office for Europe. Well-being measures in primary healthcare: the DepCare Project. 1998. Stockholm, Consensus meeting.

Henkel V, Mergl R, Kohnen R. Identifying depression in primary care: a comparison of different methods in a prospective cohort study. *BMJ* 2003;326:200–201.

Löwe B, Spitzer RL, Gräfe K, Kroenke K, Quenter A, Zipfel S, et al. Comparative validity of three screening questionnaires for DSM-IV depressive disorders and physicians' diagnoses. *J Affective Disorders* 2004;78:131–140.

de Wit M, Pouwer F, Gemke RJJ, Delemarre-van de Waal HA, Snoek FJ. Validation of the WHO-5 Well-Being Index in adolescents with type 1 diabetes. *Diabetes Care* 2007;30:2003–2006.

Awata S, Bech P, Yoshida S, Hirai M, Suzuki S, Yamashita M et al. Reliability and validity of the Japanese version of the World Health Organization-Five Well-Being Index in the context of detecting depression in diabetic patients. *Psych Clin Neurosci* 2007;61(1):112–119.M

Zung (SDS)

Zung WW. A self-rating depression scale. *Arch Gen Psychiatry* 1965;12:63–70.

Okimoto JT, Barnes RF, Veith RC, Raskind MA, Inui TS, Carter WB. Screening for depression in geriatric medical patients. *Am J Psych* 1982;139:799–802.

Rajala U, Keinänen-Kiukaanniemi S, Kivelä S-L. Non-insulin-dependent diabetes mellitus and depression in a middle-aged Finnish population. *Social Psychiatry Psychiatric Epidem* 1997;32:363–367.

Reliability and validity data for these instruments is also summarized in Table 1 . Cutoff scores optimizing the sensitivity and specificity of these measures were determined through receiving operator characteristics (ROC) analysis, while area under the ROC curve (area under the curve [AUC] index) assessed how well an instrument could discriminate between depressed and nondepressed individuals. Small variations in these statistics were reported across studies, though overall there was little difference between primary care (sensitivity 81–97%, specificity 63–99%, AUC 0.89–0.95) and diabetic patients (sensitivity 66–100%, specificity 52–92%, AUC 0.80–0.94). Because there is little evidence to suggest that any one of these measures is superior to the others, PCPs may wish to use the 2-item Patient Health Questionnaire (PHQ-2) as an initial screening tool for diabetic patients ( Table 2 ). For those who indicate they have been bothered in the last 2 weeks from either "little interest or pleasure in doing things" or "feeling down, depressed, or hopeless," providers can investigate further by administering the 9-item Patient Health Questionnaire-9 (PHQ-9) ( Table 3 ). This combination of tools, available in public domain, provides an effective method of screening for depression that also addresses time constraints frequently encountered by PCPs.

**Table 1. Depression Screening Tools for Use in Primary Care**

Screening Tool	Public Domain	No. of Items	Time to Administer	Score Range	Usual Cut-point	Reliability & Validity in Primary Care Patients	Reliability & Validity in Diabetic Patients
Beck Depression Inventory II (BDI-II)	No	21	2–5 minutes	0–63	14–19 = Mild 20–28 = Moderate 29–63 = Severe	Arnau 2001 – cutoff 18 Sensitivity 94% Specificity 92% AUC = 0.96	Lustman 1997** – cutoff 13 Sensitivity 85% Specificity 88% AUC 0.94

Beck et al 1996						Dutton 2004 – cutoff 14 Cronbach $\alpha$ = 0.90 Sensitivity 88% Specificity 84% AUC = 0.91	**only original BDI validated in this population
Beck Depression Inventory for Primary Care (BDI-PC)	No	7	<2 minutes	0–21	$\geq 4$	Steer 1999 – cutoff 4 Cronbach $\alpha$ = 0.85 Sensitivity 97% Specificity 99% AUC = 0.99	n/a
Beck et al 1997						Beck 1997 outpatient – cutoff 6 Cronbach $\alpha$ = 0.88 Sensitivity 83% Specificity 95%	
Center for Epidemiological Studies Depression Scale (CES-D)	Yes	20	2–5 minutes	0–60	$\geq 16$	Whooley 1997 – cutoff 16 Sensitivity 88% Specificity 74% AUC = 0.89	Hermanns 2006 – cutoff 14 Sensitivity 79% Specificity 89% AUC = 0.80
Radloff et al 1977							McHale 2000 – cutoff 16 Sensitivity 71% Specificity 71% AUC = 0.81 Zauszniewski 2008 cutoff 16 Cronbach $\alpha$ = 0.87
Patient Health Questionnaire – 9 (PHQ-9)	Yes	9	<2 minutes	0–27	5–9 = Mild 10–14 = Moderate $\geq 15$ = Severe	Kroenke 2001 – cutoff $\geq 10$ Cronbach $\alpha$ = 0.89 Sensitivity 88% Specificity 88% AUC = 0.95	Kahn 2008 – cutoff $\geq 10$ Sensitivity 66% Specificity 52%
Kroenke 2001						Lowy 2002 – cutoff $\geq 10$ Cronbach $\alpha$ = 0.88 Sensitivity 81% Specificity 82% AUC = 0.95	Lamers 2008 – cutoff $\geq 7$ Sensitivity 92% Specificity 81%
Patient Health Questionnaire – 2 (PHQ-2)	Yes	2	<1 minute	0–6	$\geq 3$	Kroenke 2003 – cutoff $\geq 3$ Sensitivity 83% Specificity 92% AUC = 0.93	Daly 2007 – cutoff $\geq 3$ Sensitivity 83% Specificity 92%
Kroenke 2003						Brody 1998 – cutoff $\geq 3$ Sensitivity 65% Specificity 99%	

WHO-Five Well-being Index (WHO-5)	Yes	5	<2 minutes	0–25	<13	Henkel 2004 – cutoff <13 Sensitivity 94% Specificity 63% AUC = 0.91	De Wit 2007 – cutoff <13 Cronbach $\alpha$ = 0.82 Sensitivity 89% Specificity 86%
World Health Organization 1998						Low 2002 – cutoff <13 Cronbach $\alpha$ = 0.91 Sensitivity 94% Specificity 78% AUC = 0.91	Awata 2007 – cutoff <13 Cronbach $\alpha$ = 0.89 Sensitivity 100% Specificity 78% AUC = 0.92
Zung Self-Rating Depression Scale (SDS)	Yes	20	2–5 minutes	0–100	50–59 = Mild 60–69 = Moderate ≥70 = Severe	Okimoto 1982 – cutoff ≥ 60 Sensitivity 82% Specificity 87%	Rajala 1997 – cutoff > 55 Sensitivity 72% Specificity 83%

AUC Area under the curve index for receiver operating characteristics (ROC) curve.

#### Beck Depression Inventory II

Beck AT, Steer RA, Brown GK. Beck Depression Inventory II Manual. San Antonio: The Psychological Corporation; 1996.

Arnau RC, Meagher MW, Norris MP, Bramson R. Psychometric evaluation of the Beck Depression Inventory-II with primary care medical patients. *Health Psychol* 2001;20:112–119.

Dutton GR, Grothe KB, Jones GN, Whitehead D, Kendra K, Brantley PJ. Use of the Beck Depression Inventory-II with African American primary care patients. *Gen Hosp Psychiat* 2004;26:437–442.

Lustman PJ, Clouse RE, Griffith LS, Carney RM, Freedland KE. Screening for depression in diabetes using the Beck Depression Inventory. *Psychosomatic Med* 1997;59:24–31.

#### Beck Depression Inventory for Primary Care (BDI-PC)

Beck AT, Guth D, Steer RA, Ball R. Screening for major depression disorders in medical inpatients with the Beck Depression Inventory for Primary Care. *Behav Res Ther* 1997;35:785–791.

Steer RA, Cavalieri TA, Leonard DM, Beck AT. Use of the Beck Depression Inventory for Primary Care to screen for major depression disorders. *Gen Hosp Psychiat* 1999;21(2):106–111.

Beck AT, Steer RA, Ball R, Ciervo CA, Kabat M. Use of the Beck Anxiety and Beck Depression Inventories for Primary Care with medical outpatients. *Assessment* 1997;4:211–219.

#### CES-D

Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. *Appl Psychol Measur* 1977;1:385–401.

Whooley MA, Avins AL, Miranda J, Browner WS. Case-finding instruments for depression: two questions are as good as many. *J Gen Intern Med* 1997;12:439–445.

Hermanns N, Kulzer B, Krichbaum M, Kubiak T, Haak T. How to screen for depression and emotional problems in patients with diabetes: comparison of screening characteristics of depression questionnaires, measurement of diabetes-specific emotional problems and standard clinical assessment. *Diabetologia* 2006;49:469–477.

McHale M, Hendrikz J, Dann F, Kenardy J. Screening for depression in patients with diabetes mellitus. *Psychosomatic Med* 2008;70:869–874.

Zauszniewski JA, Graham GC. Comparison of short scales to measure depressive symptoms in elders with diabetes. *West J Nurs Res* 2009;31(2):219–34.

#### PHQ-9

Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure.

J Gen Intern Med 2001;16(9):606–613.

Löwe B, Spitzer RL, Gräfe K, Kroenke K, Quenter A, Zipfel S, et al. Comparative validity of three screening questionnaires for DSM-IV depressive disorders and physicians' diagnoses. J Affective Disorders 2004;78:131–140.

Kahn LS, Fox CH, McIntyre RS, Tumieli-Berhalter L, Berdine DE, Lyle H. Assessing the prevalence of depression among individuals with diabetes in a Medicaid managed-care program. Intern J Psychiat Med 2008;38:13–29.

Lamers F, Jonkers CCM, Bosma H, Penninx BWJH, Knottnerus JA, van Eijk JTM. Summed score of the Patient Health Questionnaire-9 was a reliable and valid measure for depression screening in chronically ill elderly patients. J Clin Epidemiol 2008;61:679–687.

PHQ-2

Kroenke K, Spitzer RL, Williams JB. The Patient Health Questionnaire-2: validity of a two-item depression screener. Med Care 2003;41:1284–1292.

Brody DS, Hahn SR, Spitzer RL, Kroenke K, Linzer M, deGruy FV et al. Identifying patients with depression in the primary care setting: a more efficient method. Arch Intern Med 1998;158:2469–2475.

Daly EJ, Trivedi MH, Raskin P, Grannemann BD. Screening for depression in a diabetic outpatient population. Intern J Psychiatry Clin Pract 2007;11:268–272.

WHO-5

World Health Organization: Regional Office for Europe. Well-being measures in primary healthcare: the DepCare Project. 1998. Stockholm, Consensus meeting.

Henkel V, Mergl R, Kohonen R. Identifying depression in primary care: a comparison of different methods in a prospective cohort study. BMJ 2003;326:200–201.

Löwe B, Spitzer RL, Gräfe K, Kroenke K, Quenter A, Zipfel S, et al. Comparative validity of three screening questionnaires for DSM-IV depressive disorders and physicians' diagnoses. J Affective Disorders 2004;78:131–140.

de Wit M, Pouwer F, Gemke RJJ, Delemarre-van de Waal HA, Snoek FJ. Validation of the WHO-5 Well-Being Index in adolescents with type 1 diabetes. Diabetes Care 2007;30:2003–2006.

Awata S, Bech P, Yoshida S, Hirai M, Suzuki S, Yamashita M et al. Reliability and validity of the Japanese version of the World Health Organization-Five Well-Being Index in the context of detecting depression in diabetic patients. Psych Clin Neurosci 2007;61(1):112–119.

Zung (SDS)

Zung WW. A self-rating depression scale. Arch Gen Psychiatry 1965;12:63–70.

Okimoto JT, Barnes RF, Veith RC, Raskind MA, Inui TS, Carter WB. Screening for depression in geriatric medical patients. Am J Psych 1982;139:799–802.

Rajala U, Keinänen-Kiukaanniemi S, Kivelä S-L. Non-insulin-dependent diabetes mellitus and depression in a middle-aged Finnish population. Social Psychiatry Psychiatric Epidem 1997;32:363–367.

**Table 2. Patient Health Questionnaire-2 (PHQ-2)**

Over The Past 2 Weeks, How Often Have You Been Bothered By Any Of The Following Problems?				
	Not At All	Several Days	More Than Half The Days	Nearly Every Day
Little interest or pleasure in doing things	0	1	2	3
Feeling down, depressed, or hopeless	0	1	2	3

*Developed by Drs. Robert L. Spitzer, Janet B.W. Williams, and Kurt Kroenke and colleagues, with an educational grant from Pfizer Inc. For research information, contact Dr. Spitzer at [rls8@columbia.edu](mailto:rls8@columbia.edu).*

*Copyright © 2005 Pfizer, Inc. All rights reserved. Reproduced with permission.*

**Table 3. Patient Health Questionnaire-9 (PHQ-9)**

Over The Last 2 Weeks, How Often Have You Been Bothered By Any Of The Following Problems?								
	Not At All		Several Days		More Than Half The Days		Nearly Every Day	
1. Little interest or pleasure in doing things	0		1		2		3	
2. Feeling down, depressed, or hopeless	0		1		2		3	
3. Trouble falling or staying asleep, or sleeping too much	0		1		2		3	
4. Feeling tired or having little energy	0		1		2		3	
5. Poor appetite or overeating	0		1		2		3	
6. Feeling bad about yourself- or that you are a failure or have let yourself or your family down	0		1		2		3	
7. Trouble concentrating on things, such as reading the newspaper or watching television	0		1		2		3	
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0		1		2		3	
9. Thoughts that you would be better off dead or of hurting yourself in some way	0		1		2		3	
Office coding: Total Score _____ =	0	+	_____	+	_____	+	_____	
If you checked off <i>any</i> problems, how <i>difficult</i> have these problems made it for you to do your work, take care of things at home, or get along with other people?								
Not difficult at all		Somewhat difficult		Very difficult		Extremely difficult		

Developed by Drs. Robert L. Spitzer, Janet B.W. Williams, and Kurt Kroenke and colleagues, with an educational grant from Pfizer Inc. Copyright © 2005 Pfizer, Inc. All rights reserved. Reproduced with permission.

### Management of Depression in Diabetes

To optimize patient outcomes, PCPs should have a thorough understanding of research findings related to the treatment of depression in diabetes. While necessary, provider education and screening alone had little impact on patient outcomes and other barriers to management.<sup>[14,87,88]</sup> Depression remains inadequately treated in primary care,<sup>[2,13,31,89]</sup> with patients receiving inappropriately titrated doses of antidepressants<sup>[90]</sup> and up to 50% discontinuing use prior to achieving remission.<sup>[91]</sup> Both psychopharmacology<sup>[92–101]</sup> and psychotherapy<sup>[102–107]</sup> have been shown to effectively treat depression in diabetic patients, yet studies estimate only 33% to 52% of these patients were prescribed antidepressants,<sup>[2,32,108]</sup> while less than 20% completed 4 or more counseling sessions.<sup>[32]</sup>

Antidepressants are the most common pharmacological treatment option, although PCPs class selection must take into account a patient's presenting symptoms, comorbid medical conditions, drug interactions, and side effects. Because most antidepressants have little impact on the course of depression once discontinued and relapse following successful treatment is common,<sup>[89]</sup> a comprehensive treatment approach by the PCP should consider a referral for psychotherapy in addition to initial treatment and maintenance with medication. Both psychotherapy and medications are effective treating depression in diabetics, although the combination of these approaches has been shown to be more effective than either treatment alone in nondiabetic samples.<sup>[109]</sup> Monoamine oxidase inhibitors (MAOIs) are not recommended in diabetic patients due to associated dietary restrictions, weight gain,

and the potential for sudden, severe hypoglycemia.<sup>[97,99]</sup> Research findings and considerations for the use of TCAs, SSRIs, newer antidepressants, and cognitive behavior therapy (CBT) are summarized below.

### Tricyclic Antidepressants

TCAs are the oldest class of antidepressants and were commonly prescribed in primary care before the development of safer alternatives like SSRIs. Serious risks associated with the use of TCAs limit their current use, most notably due to cardiac effects<sup>[92,110–112]</sup> and lethality in overdose.<sup>[113]</sup> Weight gain,<sup>[92,97,110,114]</sup> hyperglycemia,<sup>[92,97]</sup> anticholinergic effects,<sup>[110]</sup> and impaired memory<sup>[97]</sup> also contribute to the limited use of these medications in patients with diabetes. In spite of their side effects, TCAs may aid in regulating sleep<sup>[110,112]</sup> and are well established as a treatment for diabetic neuropathy; both desipramine and amitriptyline were shown to be more effective treating neuropathy than the SSRI fluoxetine in a randomized, double-blind, placebo-controlled study.<sup>[115]</sup> While the TCA nortriptyline effectively reduced depressive symptoms among diabetics in a double-blind, placebo-controlled trial, it produced an adverse hyperglycemic effect unrelated to the drug's effect on weight. A similar increase in fasting blood glucose was found in nondiabetic patients following treatment with imipramine,<sup>[116]</sup> adding to the concern of TCAs in individuals with diabetes. Consequently, TCAs are not recommended as a first-line treatment for this population, and should only be considered when patients are unresponsive to trials of at least 2 newer antidepressants.

### Selective Serotonin Reuptake Inhibitors

SSRIs are frequently a first-line choice of antidepressants in primary care, treating depression as effectively as TCAs with fewer adverse effects.<sup>[112,117,118]</sup> SSRIs have received a significant amount of study in diabetic patients, examining the effect of these drugs on depression as well as diabetes outcomes and self-care. Fluoxetine,<sup>[93,100,116]</sup> sertraline,<sup>[95,98,119]</sup> and paroxetine<sup>[100,101,120]</sup> were all effective treating depression in this population; fluoxetine and paroxetine were also associated with improved quality of life.<sup>[100]</sup> There was little evidence for superior effectiveness of one SSRI over another in any study, although patients treated with fluoxetine experienced a reduction in depression severity 2 weeks earlier than those receiving paroxetine.<sup>[100]</sup> Fluoxetine has also been associated with moderate weight loss,<sup>[121]</sup> though the effect of other SSRIs on weight has been inconsistent.<sup>[114]</sup> While SSRIs are associated with substantially fewer anticholinergic and cardiovascular effects, side effects such as sexual dysfunction, gastrointestinal distress, and agitation remain fairly common in diabetics and should be taken into consideration.<sup>[110]</sup>

Several randomized controlled trials have demonstrated a trend toward improvement in HgbA1c levels with SSRI treatment,<sup>[93,95,100,120]</sup> with statistically significant change in 2 open-label studies.<sup>[95,98]</sup> Musselman et al noted that the metabolic effect of SSRIs on certain oral antihyperglycemic agents may increase the risk of hypoglycemia, yet no clinical interaction of these drugs have been reported.<sup>[68]</sup> While the majority of treatment studies ranged from 8 to 12 weeks, a year-long maintenance regimen of sertraline following successful treatment found patients taking the drug were less likely to experience recurring depression than those receiving placebo.<sup>[95]</sup> Moreover, the initial improvement in glycemic control during treatment was sustained throughout the maintenance phase.<sup>[95]</sup> Based on this research, PCPs can prescribe an SSRI to treat depression with reasonable confidence that the medication will not worsen the course of diabetes and may even contribute to better glycemic control.

Research examining the use of SSRIs in the treatment of diabetic neuropathy is limited. Randomized, double-blind, placebo-controlled trials have demonstrated the effectiveness of paroxetine<sup>[122]</sup> and citalopram,<sup>[123]</sup> although a number needed to treat analysis suggests they were less effective than TCAs.<sup>[124]</sup> Two 8-week open trials found sertraline improved neuropathic symptoms, yet its effectiveness has not been compared to other treatments.<sup>[125]</sup> Fluoxetine was the only SSRI studied in the treatment of depressed patients with neuropathy; although the drug was associated with improved neuropathic symptoms, its effects were no different than placebo.<sup>[115]</sup> Thus, while SSRIs are better tolerated than TCAs and have been well established to effectively treat depression, they are not deemed a sufficient choice for neuropathy.<sup>[126]</sup>

### Newer Antidepressants

Several other new antidepressants are widespread in use, including serotonin-norepinephrine reuptake inhibitors (SNRIs), norepinephrine-dopamine reuptake inhibitors (NDRIs), and noradrenergic and specific serotonergic antidepressants (NASSAs). Like SSRIs, antidepressants in these classes are generally considered safer alternatives to TCAs for the treatment of depression. Many of these newer drugs may have indications for use either as a first-line treatment or when patients do not respond to SSRIs, although research on their use in diabetic patients is extremely limited.

SNRIs have been shown to effectively treat diabetic neuropathy in addition to depression. Duloxetine was approved by the FDA for

this purpose in 2004 and is generally well-tolerated, with fewer adverse events than routine care.<sup>[127,128]</sup> While associated with a modest increase in fasting glucose and A1C, long-term studies have found no adverse effects of duloxetine on lipid profiles or weight.<sup>[127–129]</sup> The relative efficacy of another SNRI, venlafaxine, was comparable to TCAs and gabapentin for the treatment of neuropathy,<sup>[130]</sup> although this drug was associated with higher rates of adverse serotonergic effects and dose-dependent hypertension than duloxetine.<sup>[131]</sup>

Other side effects are similar to SSRIs and remain more conducive to use in diabetic patients than TCAs,<sup>[132]</sup> although these drugs should not be abruptly discontinued due to risk of serious withdrawal symptoms. These findings suggest that SNRIs may be a viable treatment option for depressed patients with diabetic neuropathy, although these drugs have yet to be studied in patients with comorbid diabetes and depression.

The NDRI bupropion is the only newer antidepressant to be studied in diabetic patients with depression. Unlike SSRIs, bupropion effectively treated depression without sexual side effects<sup>[96,133]</sup> or concern of altering the metabolism of oral hypoglycemic medications,<sup>[68]</sup> although increased anxiety, nausea, dizziness, and skin irritation were reported. Implications for long-term use of bupropion were promising: patients who stayed on maintenance treatment of the drug had no recurring depression.<sup>[96]</sup> Bupropion has also been shown to be useful for smoking cessation in diabetics and has minimal impact on weight, ranging from no change to modest loss.<sup>[96,133]</sup> Only one study has examined the effects of this NDRI on neuropathy, although the drug was more effective than placebo with nearly 70% of patients reporting improvement.<sup>[134]</sup> Like SNRIs, the NDRI bupropion may be an alternative to SSRIs in diabetic patients with neuropathy, although it should be noted that this is the only antidepressant not effective in relieving symptoms of anxiety.<sup>[135]</sup>

The NASSA mirtazapine has received the least study in the diabetic population. A randomized double-blind trial found mirtazapine relieved depressive symptoms significantly earlier than fluoxetine and was equally tolerable without sexual side effects or other adverse events related to serotonin.<sup>[136]</sup> Commonly reported side effects of somnolence, hyperphagia, and weight gain have led to some concern using mirtazapine in patients with diabetes; although patients taking the drug have experienced significant weight gain, glycemic control actually improved.<sup>[137,138]</sup> While no research to date has examined the use of mirtazapine in diabetic neuropathy, the drug has been shown to increase pain tolerance in healthy individuals<sup>[139]</sup> and provide significant relief to depressed patients with chronic pain.<sup>[140]</sup>

### **Cognitive Behavior Therapy**

Several studies have shown CBT and its variants to be successful in relieving symptoms of depression in diabetics.<sup>[102–106,141]</sup> Unlike antidepressants, there is evidence that the beneficial effects of CBT are maintained for up to a year past the end of treatment.<sup>[103,105]</sup> Therapy has also been shown to improve patients' self-efficacy<sup>[104]</sup> and diabetes management,<sup>[102]</sup> while glycemic control improved in some<sup>[102,105,106,141]</sup> but not all<sup>[103–105,141]</sup> studies. Psychotherapeutic approaches are beneficial in that they lack the side effects of medication, but require active patient participation and may not be well received in all patients. Poor integration with specialty mental health care and the stigma associated with mental illness are also barriers to this form of treatment.<sup>[29,89]</sup> Providers should discuss the option of psychotherapy with depressed diabetic patients as a part of a comprehensive treatment plan, but be aware of potential barriers to this course of treatment.

### **Implications for the PCP**

---

Research supports a clear association between diabetes and depression, even though the mechanisms underlying this relationship are not well understood. PCPs are frequently responsible and well positioned to manage these comorbid disorders and are advised to proactively screen for, diagnose, and treat depression to optimize patient outcomes, yet a number of barriers contribute to depression being inadequately managed in primary care. Suboptimal recognition can be addressed by increasing provider knowledge and following current treatment guidelines for routine depression screening of all diabetic patients, whether or not known risk factors for depression are present. Several screening tools have been validated in diabetic patients that can be completed in less than 10 minutes; use of the PHQ-2 to determine whether further investigation with PHQ-9 is warranted may help optimize the efficiency of the screening process. Providers should also be aware that presenting symptoms of depression can differ and should be sensitive to patients' gender, race, ethnicity, and individual values and beliefs.<sup>[2,108,142]</sup>

Management of depression in diabetes should be approached in a comprehensive manner, which potentially includes both medication and referral for psychotherapy such as CBT. Patients resistant to treatment should be educated to understand that benefits extend beyond improved mood and may include pain relief; decreased anxiety; improved social, occupational, and physical

activity; enhanced general and sexual functioning; decreased preoccupation with somatic symptoms; more normal sleep and eating habits; improved coping skills; and better diabetes care.<sup>[2,94]</sup> Other patient barriers can be circumvented by selecting a treatment(s) that match an individual's symptoms, taking his or her preferences into consideration,<sup>[2]</sup> and including patients' partners or other key family members whenever possible.<sup>[112]</sup> Management barriers imposed at the system level include time constraints limiting close follow-up and monitoring, competing clinical priorities, and poor integration with mental health care. Treatment studies have demonstrated a clear need for PCPs to have additional mental health support,<sup>[12]</sup> which may relieve some of the burden experienced by providers in primary care. Treatment algorithms for pharmacological treatment of depression in primary care patients with diabetes provide further assistance for PCPs clinical decisions.<sup>[31,89]</sup> Concordant with the research summarized here, these guidelines recommend initial treatment with an SSRI or other new antidepressant, taking into account patients' personal or familial responses to specific medications, in addition to side effects.<sup>[31,89]</sup> The timeline and further indications for follow-up assessment based on these recommendations are listed in Figure 1.

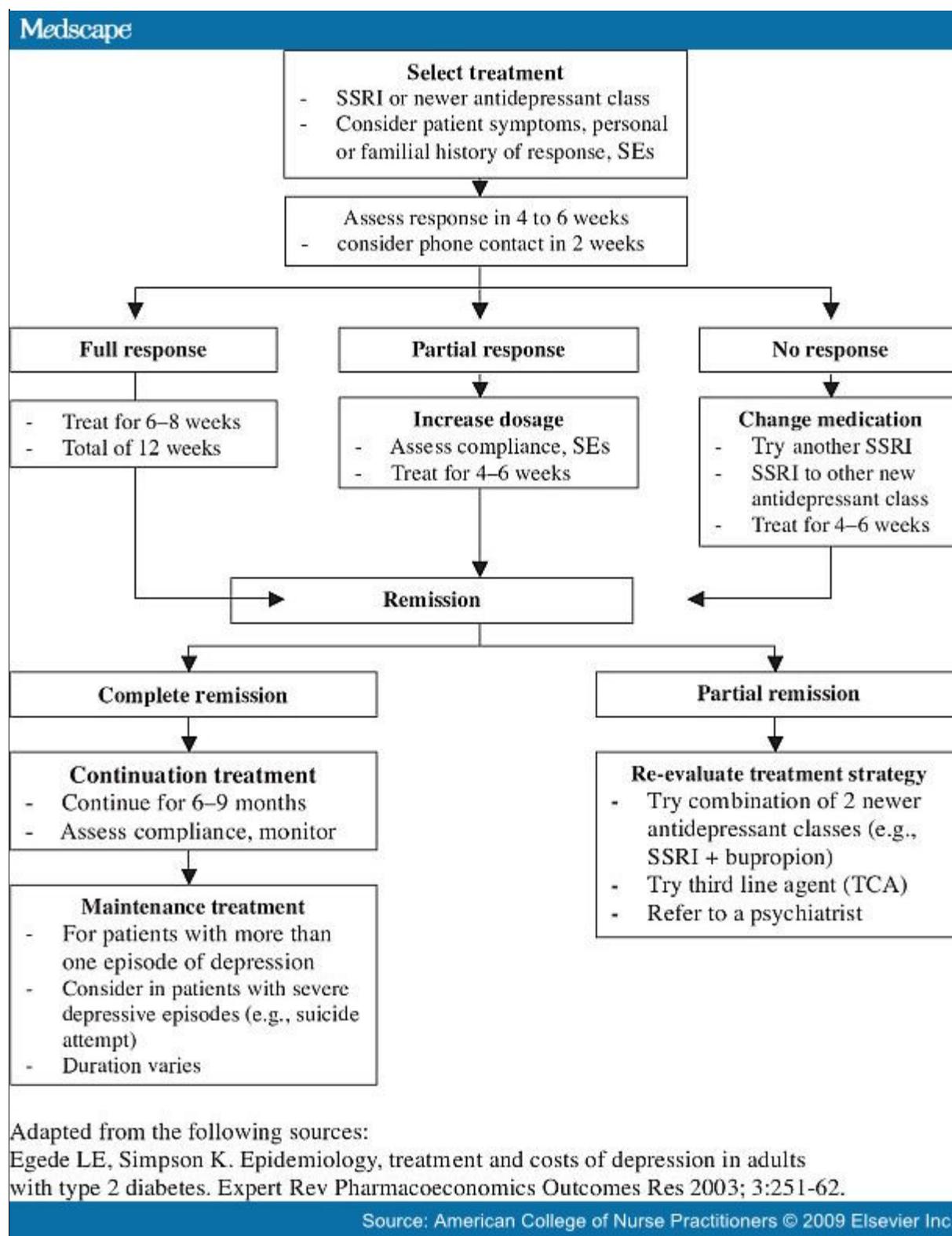


Figure 1. Antidepressant treatment algorithm for primary care patients with diabetes

PCPs are also likely to be aided by future research addressing gaps in the current body of literature. Much of the research on comorbid depression in diabetic patients is limited to MDD; treatment for subclinical or other depressive disorders has received little study, even though these conditions may produce similar effects to MDD. Trials of newer antidepressants are promising, although there is little research on their use in the diabetic population. Antidepressant maintenance therapy has been identified as necessary, yet the long-term outcomes associated with it are unknown. Moreover, there is a need for collaborative care programs to identify effective and efficient ways to integrate treatment for these conditions in primary care.

## Conclusion

Family and adult NPs and other PCPs can optimize health outcomes by increasing their understanding of the relationship between depression and diabetes and by systematically screening for, diagnosing, and managing depression in diabetic patients. While research in the area is limited, appropriate screening strategies have been identified and benefits and risks of certain pharmacological and psychotherapeutic treatments have been shown. Findings presented in this paper should serve as a guide in clinical decision making for the diagnosis and treatment of primary care patients with comorbid depression and diabetes.

## References

1. Anderson RJ, Freedland KE, Clouse RE, Lustman PJ. The prevalence of comorbid depression in adults with diabetes: a meta-analysis. *Diabetes Care*. 2001;24:1069–1078.
2. Lustman PJ, Clouse RE. Section III: practical considerations in the management of depression in diabetes. *Diabetes Spectr*. 2004;17:160–166.
3. Lustman PJ, Griffith LS, Freedland KE, Clouse RE. The course of major depression in diabetes. *Gen Hosp Psychiatry*. 1997;19:138–143.
4. DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. *Arch Intern Med*. 2000;160:2101–2107.
5. Katon W, Sullivan MD. Depression and chronic medical illness. *J Clin Psychiatry*. 1990;51:3–11.
6. Ford DE. Optimizing outcomes for patients with depression and chronic medical illnesses. *Am J Med*. 2008;121:S38–S44.
7. Ciechanowski PS, Katon WJ, Russo JE. Depression and diabetes: impact of depressive symptoms on adherence, function, and costs. *Arch Intern Med*. 2000;160:3278–3285.
8. Ciechanowski PS, Katon WJ, Russo JE, Hirsch IB. The relationship of depressive symptoms to symptom reporting, self-care and glucose control in diabetes. *Gen Hosp Psychiatry*. 2003;25:246–252.
9. McKellar JD, Humphreys K, Piette JD. Depression increases diabetes symptoms by complicating patients' self-care adherence. *Diabetes Educ*. 2004;30:485–492.
10. Park H, Hong Y, Lee H, Ha E, Sung Y. Individuals with type 2 diabetes and depressive symptoms exhibited lower adherence with self-care. *J Clin Epidemiol*. 2004;57:978–984.
11. Lin EHB, Katon W, Von Korff M, et al. Relationship of depression and diabetes self-care, medication adherence, and preventive care. *Diabetes Care*. 2004;27:2154–2160.
12. Anderson D, Horton C, O'Toole ML, et al. Integrating depression care with diabetes care in real-world settings: lessons from the Robert Wood Johnson Foundation Diabetes Initiative. *Diabetes Spectr*. 2007;20(1):10–16.
13. Gonzalez JS, Safren SA, Cagliero E, et al. Depression, self-care, and medication adherence in type 2 diabetes: relationships across the full range of symptom severity. *Diabetes Care*. 2007;30:2222–2227.
14. Lin EH, Simon GE, Katzelnick DJ, Pearson SD. Does physician education on depression management improve treatment in primary care?. *J Gen Intern Med*. 2001;16:614–619.
15. Kilbourne AM, Reynolds CF, Good CB, et al. How does depression influence diabetes medication adherence in older patients?. *Am J Geriatr Psychiatry*. 2005;13:202–210.
16. Ludman EJ, Katon W, Russo J, et al. Depression and diabetes symptom burden. *Gen Hosp Psychiatry*. 2004;26(6):430–436.
17. Lustman PJ, Anderson RJ, Freedland KE, et al. Depression and poor glycemic control: a meta-analytic review of the literature. *Diabetes Care*. 2000;23:934–942.
18. De Groot M, Anderson R, Freedland KE, Clouse RE, Lustman PJ. Association of depression and diabetes complications: a meta-analysis. *Psychosom Med*. 2001;63:619–630.
19. Rush WA, Whitebird RR, Rush MR, Solberg LI, O'Connor PJ. Depression in patients with diabetes: does it impact clinical goals?. *J Am Board Fam Med*. 2008;21(5):392–397.
20. Clouse RE, Lustman PJ, Freedland KE, et al. Depression and coronary heart disease in women with diabetes. *Psychosom Med*. 2003;65:376–383.
21. Katon W, Von Korff M, Ciechanowski P, et al. Behavioral and clinical factors associated with depression among individuals with diabetes. *Diabetes Care*. 2004;27:914–920.
22. Zhang X, Norris SL, Gregg EW, et al. Depressive symptoms and mortality among persons with and without diabetes. *Am J Epidemiol*. 2005;161:652–660.
23. Katon WJ, Rutter C, Simon G, et al. The association of comorbid depression with mortality in patients with type 2 diabetes. *Diabetes Care*. 2005;28:2668–2672.
24. Egede LE, Nietert PJ, Zheng D. Depression and all-cause and coronary heart disease mortality among adults with and

- without diabetes. *Diabetes Care*. 2005;28:1339–1345.
25. Egede LE. Diabetes, major depression, and functional disability among U.S. adults. *Diabetes Care*. 2004;27:421–428.
  26. Egede LE, Zheng D, Simpson K. Comorbid depression is associated with increased health care use and expenditures in individuals with diabetes. *Diabetes Care*. 2002;25:464–470.
  27. Goldney RD, Phillips PJ, Fisher LJ, Wilson DH. Diabetes, depression, and quality of life. *Diabetes Care*. 2004;27:1066–1070.
  28. Finkelstein EA, Bray JW, Chen H, et al. Prevalence and costs of major depression among elderly claimants with diabetes. *Diabetes Care*. 2003;26:415–420.
  29. Williams JW, Katon W, Lin EHB, et al. The effectiveness of depression care management on diabetes-related outcomes in older patients. *Ann Intern Med*. 2004;140:1015–1024.
  30. Lustman PJ, Clouse RE. Identifying depression in adults with diabetes. *Clin Diabetes*. 1997;15:78–81.
  31. Egede LE, Simpson K. Epidemiology, treatment and costs of depression in adults with type 2 diabetes. *Expert Rev Pharmacoeconomics Outcome Res*. 2003;3:251–262.
  32. Katon WJ, Simon G, Russo J, et al. Quality of depression care in a population-based sample of patients with diabetes and depression. *Med Care*. 2004;42:1222–1229. MEDLINE | CrossRef
  33. Eaton WW. Epidemiologic evidence on the comorbidity of depression and diabetes. *J Psychosom Res*. 2002;53:903–906.
  34. Talbot F, Nouwen A. A review of the relationship between depression and diabetes in adults: is there a link?. *Diabetes Care*. 2000;23:1556–1562.
  35. Connell CM, Davis WK, Gallant MP, Sharpe PA. Impact of social support, social cognitive variables, and perceived threat on depression among adults with diabetes. *Health Psychol*. 1994;13:263–273.
  36. Talbot F, Nouwen A, Gingras J, Belanger A, Audet J. Relations of diabetes intrusiveness and personal control to symptoms of depression among adults with diabetes. *Health Psychol*. 1999;18:537–542.
  37. Bailey BJ. Mediators of depression in adults with diabetes. *Clin Nurs Res*. 1996;5:28–42.
  38. De Groot M, Auslander W, Williams JH, Sherranden M, Haire-Joshu D. Depression and poverty among African American women at risk for type 2 diabetes. *Ann Behav Med*. 2003;25:172–181.
  39. Macrodimitris SD, Endler NS. Coping, control, and adjustment in type 2 diabetes. *Health Psychol*. 2001;20:208–216.
  40. Egede LE, Zheng D. Independent factors associated with major depressive disorder in a national sample. *Diabetes Care*. 2003;26:104–111.
  41. Li C, Ford ES, Strine TW, Mokdad AH. Prevalence of depression among U.S. adults with diabetes: findings from the 2006 Behavioral Risk Factor Surveillance System. *Diabetes Care*. 2008;31:105–107.
  42. Peyrot M, Rubin RR. Levels and risks of depression and anxiety symptomatology among diabetic adults. *Diabetes Care*. 1997;20:585–590.
  43. Bell RA, Smith SL, Arcury TA, et al. Prevalence and correlates of depressive symptoms among rural older African Americans, Native Americans, and whites with diabetes. *Diabetes Care*. 2005;28:823–829.
  44. Golden SH, Lazo M, Carnethon M, et al. Examining a bidirectional association between depressive symptoms and diabetes. *JAMA*. 2008;299(23):2751–2759.
  45. Everson SA, Maty SC, Lynch JW, Kaplan GA. Epidemiologic evidence for the relation between socioeconomic status and depression, obesity, and diabetes. *J Psychosom Res*. 2002;53:891–895.
  46. Kessler RC, Berglund P, Demler O, et al. National Comorbidity Survey Replication: the epidemiology of major depressive disorder: results from the National Comorbidity Replication (NCS-R). *JAMA*. 2003;289:3095–3105.
  47. Fisher L, Chesla CA, Mullan JT, Skaff MM, Kanter RA. Contributors to depression in Latino and European-American patients with type 2 diabetes. *Diabetes Care*. 2001;24:1751–1757.
  48. Jacobson AM, Samson JA, Weinger K, Ryan CM. Diabetes, the brain, and behavior: is there a biological mechanism underlying the association between diabetes and depression?. *Int Rev Neurobiol*. 2002;51:455–479.
  49. Rubin RR, Peyrot MF. Quality of life and diabetes. *Diabetes Metab Res Rev*. 1999;15:205–218.
  50. Rajala U, Keinänen-Kiukaanniemi S, Kivelä S-L. Non-insulin-dependent diabetes mellitus and depression in a middle-aged Finnish population. *Soc Psychiatry Psychiatr Epidemiol*. 1997;32:363–367.
  51. De Groot M, Jacobson AM, Samson JA, Welch G. Glycemic control and major depression in patients with type 1 and type 2 diabetes mellitus. *J Psychosom Res*. 1999;46:425–435.
  52. van Tilburg MAL, McCaskill CC, Lane JD, et al. Depressed mood is a factor in glycemic control in type 1 diabetes. *Psychosom Med*. 2001;63:551–555.
  53. Lustman PJ, Freedland KE, Griffith LS, Clouse RE. Predicting response to cognitive behavior therapy of depression in type 2 diabetes. *Gen Hosp Psychiatry*. 1998;20:302–306.
  54. Lustman PJ, Griffith LS, Clouse RE, Cryer PE. Psychiatric illness in diabetes mellitus: relation to symptoms and glucose

- control. *J Nerv Mental Dis.* 1986;174:736–746.
55. Katon WJ. The comorbidity of diabetes mellitus and depression. *Am J Med.* 2008;121:S8–S15.
  56. Yoshida S, Hirai M, Suzuki S, Awata S, Oka Y. Neuropathy is associated with depression independently of health-related quality of life in Japanese patients with diabetes. *Psychiatry Clin Neurosci.* 2009;63:65–72.
  57. Engum A. The role of depression and anxiety in onset of diabetes in a large population-based study. *J Psychosom Res.* 2007;62:31–38.
  58. Lustman PJ, Griffith LS, Clouse RE. Depression in adults with diabetes: results of 5-yr follow-up study. *Diabetes Care.* 1988;11:605–612.
  59. Cameron OG, Kronfol Z, Greden JF, Carroll BJ. Hypothalamic-pituitary-adrenocortical activity in patients with diabetes mellitus. *Arch Gen Psychiatry.* 1984;41:1090–1095.
  60. Björntorp P, Holm G, Rosmond R. Hypothalamic arousal, insulin resistance and type 2 diabetes mellitus. *Diabet Med.* 1999;16:373–383.
  61. Rosmond R, Björntorp P. The hypothalamic-pituitary-adrenal axis activity as a predictor of cardiovascular disease, type 2 diabetes and stroke. *J Intern Med.* 2001;247:188–197.
  62. Brown ES, Varghese FP, McEwen BS. Association of depression with medical illness: does cortisol play a role?. *Biol Psychiatry.* 2004;55:1–9.
  63. Schmidt MI, Duncan BB, Sharrett AR, et al. Markers of inflammation and prediction of diabetes mellitus in adults (Artherosclerosis Risk in Communities Study): a cohort study. *Lancet.* 1999;353:1649–1652.
  64. Dandona P, Aljada A, Bandyopadhyay A. Inflammation: the link between insulin resistance, obesity and diabetes. *Trends Immunol.* 2004;25:4–7.
  65. Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. *JAMA.* 2001;286:327–334.
  66. Han TS, Sattar N, Williams K, Gonzalez-Villalpando C, et al. Prospective study of C-reactive protein in relation to the development of diabetes and metabolic syndrome in the Mexico City Diabetes Study. *Diabetes Care.* 2002;25:2016–2021.
  67. Knol MJ, Twisk JWR, Beekman ATF, et al. Depression as a risk factor for the onset of type 2 diabetes mellitus: a meta-analysis. *Diabetologia.* 2006;49:837–845.
  68. Musselman DL, Betan E, Larson H, Phillips LS. Relationship of depression to diabetes types 1 and 2: epidemiology, biology, and treatment. *Biol Psychiatry.* 2003;54:317–329.
  69. Williams MM, Clouse RE, Lustman PJ. Treating depression to prevent diabetes and its complications: understanding depression as a medical risk factor. *Clin Diabetes.* 2006;24:79–86.
  70. Eaton WE, Armenian H, Gallo J, Pratt L, Ford DE. Depression and risk of onset of type II diabetes: a prospective population-based study. *Diabetes Care.* 1996;19:1097–1102.
  71. Kawakami N, Takatsuka N, Shimizu H, Ishibashi H. Depressive symptoms and the occurrence of type 2 diabetes among Japanese men. *Diabetes Care.* 1999;22:1071–1076.
  72. Arroyo C, Hu FB, Ryan LM, et al. Depressive symptoms and risk of type 2 diabetes in women. *Diabetes Care.* 2004;27:129–133.
  73. Carnethon MR, Biggs ML, Barzilay JI, et al. Longitudinal association between depressive symptoms and incident type 2 diabetes mellitus in older adults. *Arch Intern Med.* 2007;167:802–807.
  74. van den Akker M, Schuurman A, Metsemakers J, Buntinx F. Is depression related to subsequent diabetes mellitus?. *Acta Psychiatr Scand.* 2004;110:178–183.
  75. Palinkas LA, Lee PP, Barrett-Connor E. A prospective study of type 2 diabetes and depressive symptoms in the elderly: the Rnacho Bernardo Study. *Diabet Med.* 2004;21:1185–1191.
  76. Brown LC, Majumdar SR, Newman SC, Johnson JA. Type 2 diabetes does not increase risk of depression. *Can Med Assoc J.* 2006;175:42–46.
  77. Brown LC, Majumdar SR, Johnson JA. Type of antidepressant therapy and risk of type 2 diabetes in people with depression. *Diabetes Res Clin Pract.* 2008;79:61–67.
  78. Chida Y, Hamer M. An association of adverse psychological factors with diabetes mellitus: a meta-analytic review of longitudinal cohort studies. *Diabetologia.* 2008;51:2168–2178.
  79. Knol MJ, Heerdink ER, Egberts ACG, et al. Depressive symptoms in subjects with diagnosed and undiagnosed type 2 diabetes. *Psychosom Med.* 2007;69:300–305.
  80. Lustman PJ, Freedland KE, Carney RM, Hong BA, Clouse RE. Similarity of depression in diabetic and psychiatric patients. *Psychosom Med.* 1992;54:602–611.
  81. Simon GE, Von Korff M. Medical co-morbidity and validity of DSM-IV depression criteria. *Psychol Med.* 2005;35:1–10.
  82. Yates WR, Mitchell J, Rush AJ, et al. Clinical features of depressed outpatients with and without co-occurring general

- medical conditions in STAR\*D. *Gen Hosp Psychiatry*. 2004;26(6):421–429.
83. Peterson T, Iosifescu DV, Papakostas GI, Shear DL, Fava M. Clinical characteristics of depressed patients with comorbid diabetes mellitus. *Int Clin Psychopharmacol*. 2006;21:43–47.
  84. Hermanns N, Kulzer B, Krichbaum M, Kubiak T, Haak T. How to screen for depression and emotional problems in patients with diabetes: comparison of screening characteristics of depression questionnaires, measurement of diabetes-specific emotional problems and standard clinical assessment. *Diabetologia*. 2006;49:469–477.
  85. Lustman PJ, Griffith LS, Clouse RE. Depression in adults with diabetes. *Semin Clin Neuropsychiatry*. 1997;2:15–23.
  86. American Diabetes Association. Standards of medical care in diabetes — 2008. *Diabetes Care*. 2008;31:S12–S54.
  87. U.S. Preventive Services Task Force (USPSTF). Screening for depression: recommendations and rationale. *Ann Intern Med*. 2002;136:760–764.
  88. Kroenke K, Taylor-Vaisey A, Dietrich AJ, Oxman TE. Interventions to improve provider diagnosis and treatment of mental disorders in primary care. A critical review of the literature. *Psychosomatics*. 2000;41:39–52.
  89. Rubin RR, Ciechanowski P, Eggede LE, Lin EHB, Lustman P. Recognizing and treating depression in patients with diabetes. *Curr Diabetes Rep*. 2004;4:119–125.
  90. Katon W, Von Korff M, Lin E, Bush T, Ormel J. Adequacy and duration of antidepressant treatment in primary care. *Med Care*. 1992;30:67–76.
  91. Nau DP, Chao J, Aikens JE. The relationship of guideline-concordant depression treatment and patient adherence to oral diabetes medications. *Res Social Adm Pharm*. 2005;1:378–388.
  92. 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.
  93. 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.
  94. Lustman PJ, Clouse RE. Treatment of depression in diabetes: impact on mood and medical outcome. *J Psychosom Res*. 2002;53:917–924.
  95. 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.
  96. 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.
  97. Goodnick PJ, Henry JH, Buki VM. Treatment of depression in patients with diabetes mellitus. *J Clin Psychiatry*. 1995;56:128–136.
  98. Goodnick PJ, Kumar A, Henry JH, Buki VMV, Goldberg RB. Sertraline in coexisting major depression and diabetes mellitus. *Psychopharmacol Bull*. 1997;33:261–264.
  99. Goodnick PJ. Use of antidepressants in treatment of comorbid diabetes mellitus and depression as well as in diabetic neuropathy. *Ann Clin Psychiatry*. 2001;13:31–41.
  100. GÅ¼lseren L, GÅ¼lseren S, Hekimsoy Z, Mete L. Comparison of fluoxetine and paroxetine in type II diabetes mellitus patients. *Arch Med Res*. 2005;36:159–165.
  101. Paile-Hyvärinen M, Wahlbeck K, Eriksson JG. Quality of life and metabolic status in mildly depressed women with type 2 diabetes treated with paroxetine: a double-blind randomised placebo controlled 6-month trial. *BMC Fam Pract*. 2007;8:34.
  102. 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.
  103. Georgiades A, Zucker N, Friedman KE, et al. Changes in depressive symptoms and glycemic control in diabetes mellitus. *Psychosom Med*. 2007;69:235–241.
  104. van der Ven NC, Hogenelst MH, Tromp-Wever AM, et al. Short-term effects of cognitive behavioural group training (CBGT) in adult type 1 diabetes patients in prolonged poor glycaemic control. A randomized controlled trial. *Diabetic Med*. 2005;22:1619–1623.
  105. Snoek FJ, van der Ven NCW, Twisk JWR, et al. Cognitive behavioural therapy (CBT) compared with blood glucose awareness training (BGAT) in poorly controlled type 1 diabetic patients: long-term effects on HbA1c moderated by depression. A randomized controlled trial. *Diabetic Med*. 2008;25:1337–1342.
  106. Ismail K, Winkley K, Rabe-Hesketh S. Systematic review and meta-analysis of randomised controlled trials of psychological interventions to improve glycaemic control in patients with type 2 diabetes. *Lancet*. 2004;363:1589–1597.
  107. Katon WJ, Von Korff M, Lin EHB, et al. The Pathways Study: a randomized trial of collaborative care in patients with diabetes and depression. *Arch Gen Psychiatry*. 2004;61:1042–1049.
  108. De Groot M, Pinkerman B, Wagner J, Hockman E. Depression treatment and satisfaction in a multicultural sample of type 1 and type 2 diabetic patients. *Diabetes Care*. 2006;29:549–553.

109. 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. *New Engl J Med.* 2000;342:1462–1470.
110. Lustman PJ, Anderson R. Depression in adults with diabetes. *Psychiatric Times.* 2002;19(1):  
<http://www.psychiatrictimes.com/display/article/10168/47911>.
111. Roose SP, Spatz E. Treating depression in patients with ischaemic heart disease: which agents are best to use and to avoid?. *Drug Safety.* 1999;20:459–465.
112. Clark M. Identification and treatment of depression in people with diabetes. *Diabetes Primary Care.* 2003;5:124–127.
113. Mason J, Freemantle N, Eccles M. Fatal toxicity associated with antidepressant use in primary care. *Br J Gen Pract.* 2000;50:366–370.
114. Zimmermann U, Kraus T, Himmerlich H, Schuld A, Pollmächer T. Epidemiology, implications, and mechanisms underlying drug-induced weight gain in psychiatric patients. *J Psychiatr Res.* 2003;37:193–220.
115. Max MB, Lynch SA, Muir J, et al. Effects of desipramine, amitriptyline, and fluoxetine in diabetic neuropathy. *New Engl J Med.* 1992;326:1250–1256.
116. Ghaeli P, Shahsavand E, Mesbahi M, et al. Comparing the effects of 8-week treatment with fluoxetine and imipramine on fasting blood glucose of patients with major depressive disorder. *J Clin Psychopharmacol.* 2004;24:386–388.
117. Rabelomanana S, Depont F, Forest D, et al. Antidepressants: general practitioners' opinions and clinical practice. *Acta Psychiatr Scand.* 2006;113:460–467.
118. Stafford RS, Ausiello JC, Misra B, Saglam D. National patterns of depression treatment in primary care. *Prim Care Companion J Clin Psychiatry.* 2000;2:211–216.
119. Williams MM, Clouse RE, Nix BD, et al. Efficacy of sertraline in prevention of depression recurrence in older versus younger adults with diabetes. *Diabetes Care.* 2007;30:801–806.
120. Paile-Hyvärinen M, Wahlbeck K, Eriksson JG. Quality of life and metabolic status in mildly depressed women with type 2 diabetes treated with paroxetine: a single-blind randomised placebo controlled trial. *BMC Fam Pract.* 2003;4:7–12.
121. Norris SL, Zhang X, Avenell A, et al. Efficacy of pharmacotherapy for weight loss in adults with type 2 diabetes mellitus: a meta-analysis. *Arch Intern Med.* 2004;164:1395–1404.
122. Sindrup SH, Gram LF, Brøsen K, Eshøj O, Mogensen EF. The selective serotonin reuptake inhibitor paroxetine is effective in the treatment of diabetic neuropathy symptoms. *Pain.* 1990;42:135–144.
123. Sindrup SH, Bjerre U, Dejgaard A, et al. The selective serotonin reuptake inhibitor citalopram relieves the symptoms of diabetic neuropathy. *Clin Pharmacol Ther.* 1992;52:547–552.
124. Sindrup SH, Jensen TS. Efficacy of pharmacological treatments of neuropathic pain: an update and effect related to mechanism of drug action. *Pain.* 1999;83:389–400.
125. Goodnick PJ, Jimenez I, Kumar A. Sertraline in diabetic neuropathy: preliminary results. *Ann Clin Psychiatry.* 1997;9:255–257.
126. DUBY JJ, Campbell RK, Setter SM, White JR, Rasmussen KA. Diabetic neuropathy: an intensive review. *Am J Health Syst Pharm.* 2004;61:160–173.
127. Raskin J, Pritchett YL, Wang F, et al. A double-blind, randomized multicenter trial comparing duloxetine with placebo in the management of diabetic peripheral neuropathic pain. *Pain Med.* 2005;6:346–356.
128. Raskin J, Smith TR, Wong K, et al. Duloxetine versus routine care in the long-term management of diabetic peripheral neuropathic pain. *J Palliat Med.* 2006;9:29–40.
129. Hardy T, Sachson R, Shen S, Armbruster M, Boulton AJM. Does treatment with duloxetine for neuropathic pain impact glycemic control?. *Diabetes Care.* 2007;30:21–26.
130. Rowbotham MC, Goli V, Kunz NR, Lei D. Venlafaxine extended release in the treatment of painful diabetic neuropathy: a double-blind, placebo-controlled study. *Pain.* 2004;110:697–706.
131. Stahl SM, Grady MM, Moret C, Briley M. SNRIs: their pharmacology, clinical efficacy, and tolerability in comparison with other classes of antidepressants. *CNS Spectr.* 2005;10:732–747.
132. McKeage K. Treatment options for the management of diabetic painful neuropathy: best current evidence. *Curr Opin Neurol.* 2007;20:553–557.
133. Rowland DL, Myers L, Culver A, Davidson JM. Bupropion and sexual function: a placebo-controlled prospective study on diabetic men with erectile dysfunction. *J Clin Psychopharmacol.* 1997;17:350–357.
134. Semenchuk MR, Sherman S, Davis B. Double-blind, randomized trial of bupropion SR for the treatment of neuropathic pain. *Neurology.* 2001;57:1583–1588.
135. Hilty DM, McCarron RM, Ton H. Management of mental illness in patients with diabetes. *Prim Care Clin Office Pract.* 2007;34:713–730.
136. Fawcett J, Barkin RL. Review of the results from clinical studies on the efficacy, safety and tolerability of mirtazapine for the treatment of patients with major depression. *J Affect Disord.* 1998;51:267–285.

137. Himmerich H, Fulda S, Schaaf L, et al. Changes in weight and glucose tolerance during treatment with mirtazapine. *Diabetes Care*. 2006;29:170–171.
138. Weber-Hamann B, Gilles M, Schilling C, et al. Improved insulin sensitivity in 51 nondiabetic depressed inpatients remitting during antidepressive treatment with mirtazapine and venlafaxine. *J Clin Psychopharmacol*. 2008;28:581–584.
139. Arnold P, Vuadens P, Kuntzer T, Gobelet C, Deriaz O. Mirtazapine decreases the pain feeling in healthy participants. *Clin J Pain*. 2008;24:116–119.
140. Freynhagen R, Muth-Selbach U, Lipfert P, et al. The effect of mirtazapine in patients with chronic pain and concomitant depression. *Curr Med Res Opin*. 2006;22:257–264.
141. Winkley K, Landau S, Eisler I, Ismail K. Psychological interventions to improve glycaemic control in patients with type 1 diabetes: systematic review and meta-analysis of randomised controlled trials. *BMJ*. 2006;333:65–68.
142. Wagner J, Tsimikas J, Abbott G, De Groot M, Heapy A. Racial and ethnic differences in diabetic patient-reported depression symptoms, diagnosis, and treatment. *Diabetes Res Clin Pract*. 2007;75:119–122.