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The Comorbidity of Diabetes Mellitus and Depression

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Abstract

Several factors, including sedentary lifestyle, obesity, and an aging population, contribute to epidemic rates of type 2 diabetes mellitus. Depression frequently occurs comorbidly with diabetes although it is unrecognized and untreated in approximately two thirds of patients with both conditions. The course of depression in patients with both diabetes and depression is chronic and severe. Up to 80% of patients with diabetes and depression will experience a relapse of depressive symptoms over a 5-year period. Depression is associated with nonadherence to diabetes self-care—including following dietary restrictions, medication compliance, and blood glucose monitoring—resulting in worse overall clinical outcomes. Due to potential negative health consequences associated with comorbid diabetes and depression, both conditions should be optimally treated to maximize patient outcomes.

Keywords

Antidepressants; Collaborative care; Depression; Diabetes; Diabetes self-care

Despite high rates of comorbid major depression in patients with diabetes mellitus, the affective component of this disease combination is often inadequately treated in the primary care setting. Factors such as sedentary lifestyle, increased prevalence of obesity, and an aging population[1] have combined to produce epidemic rates of type 2 diabetes, a disease that likely results from both inadequate insulin secretion and increased insulin resistance.[2] The course of depression in patients with diabetes is chronic and severe; even with successful treatment, as many as 80% of patients with diabetes will experience depression relapse.[3] Depression remains unrecognized and untreated in approximately two thirds of patients with diabetes[4] despite the important clinical implications associated with the comorbidly occurring conditions. Underdiagnosis of comorbid depression may reflect a perception among clinicians that psychological issues are less important than medical concerns in patients with diabetes[5]; however, important health consequences associated with comorbid depression and diabetes necessitate optimal treatment of both conditions to maximize overall patient outcomes.

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PREVALENCE

The reported prevalence of depression in patients with diabetes varies widely, a fact that may be accounted for by methodologic differences and limitations of existing epidemiologic studies. Factors such as inclusion of patients without distinguishing between type 1 and type 2 diabetes, self-reported depressive symptoms versus clinically diagnosed depression, and lack of documentation regarding relevant factors associated with the disease state (e.g., number of diabetes complications, other medical comorbidity) may confound clinical study results and skew prevalence rates. A meta-analysis that included 39 studies[6] demonstrated that 11% of patients with diabetes met the criteria for comorbid major depressive disorder (MDD) and 31% experienced significant depressive symptoms; in addition, the prevalence of depression in patients with diabetes was significantly higher in women than men (28% and 18%, respectively; $P < 0.0001$). In the controlled studies, the odds of having depression were twice as great in patients with diabetes as in their nondiabetic counterparts (odds ratio [OR], 2.0; 95% confidence interval [CI], 1.8 to 2.2).

A population-based epidemiologic study[7] conducted to determine the behavioral and clinical characteristics of diabetes associated with depression found that 501 of 4,193 study participants (12%) met *Diagnostic and Statistical Manual of Mental Disorders–Fourth Edition* (DSM-IV),[8] criteria for MDD and 357 participants (8.5%) met criteria for minor depression. This study and others[9–11] also identified important sociodemographic risk factors that were associated with depression in patients with diabetes including younger age, low socioeconomic status, less education, being unmarried, poor social support, and female sex. In addition, several studies have found that some racial and ethnic minorities, including African Americans, Hispanic Americans, Asian/Pacific Islanders Americans, and Native Americans, experienced higher rates of both diabetes and associated depression, and that when these conditions were comorbid, they were predictive of suboptimal outcomes in these patient populations.[7,12–15]

A worldwide survey[16] evaluated the effect of depression alone or comorbid with other chronic conditions (i.e., diabetes, asthma, arthritis, and angina) on overall health status among respondents aged >18 years from 60 countries. Of the conditions surveyed, diabetes had the lowest overall prevalence at 2.0%; however, diabetes prevalence was based on self-report, so the potential of reporting bias cannot be disregarded. The worldwide 1-year prevalence of depression alone was 3.2%; depression prevalence was based on International Classification of Diseases (ICD)–10 criteria. Of the respondents with diabetes, 9.3% also had depression. Mean health score was evaluated on a scale (score range, 0 to 100); the best health was reported by individuals without any of the chronic diseases surveyed (score, 90.6). The mean health score was 72.9 for depression alone and 79.3 for diabetes alone. Of note, when diabetes occurred comorbidly with depression the mean health score declined to 58.5. Depression produced the greatest disability in health when compared with the other 5 chronic conditions surveyed; the combination of diabetes and depression was also the most disabling of the comorbidities surveyed.

THE RELATION BETWEEN DIABETES AND DEPRESSION

There is growing evidence regarding the bidirectional adverse interaction between diabetes and depression. A longitudinal study found that depressive symptoms at baseline were associated with an increased incidence of type 2 diabetes at follow-up over a 3-year period; an increased risk for developing depressive symptoms over the 3-year period was associated with treated type 2 diabetes, but conversely baseline impaired fasting glucose and untreated type 2 diabetes were associated with reduced risk for depression.[17] Despite study limitations, including imprecise estimation and lack of statistical significance due to small numbers in the

untreated population, this is the first study to demonstrate a bidirectional association between treated type 2 diabetes and depressive symptoms in the same patient cohort.

Additionally, after controlling for demographic and clinical risk factors, other studies have shown that depression is an independent risk factor for the onset of type 2 diabetes,[2,18,19] and a predictive factor for the number and severity of diabetic complications.[20–22] A meta-analysis[23] that examined the relation between depression and diabetes onset found that the risk of developing type 2 diabetes was 37% greater in depressed adults than in adults who do not have depression. In addition, a population-based study of older adults found that a single report of high depressive symptoms, an increase in depressive symptoms over time, and persistently high depressive symptoms were each associated with increased incident diabetes; the association between depression and diabetes was not fully explained by risk factors.[24] Depression early in life may lead to increased risk for type 2 diabetes due to the increased likelihood that patients with depression participate in unhealthy behaviors such as sedentary lifestyle, obesity, and smoking.[7]

The direct negative physiologic effects of depression on glucose metabolism (e.g., increased counterregulatory hormone release and action, changes in glucose transport function, and increased immunoinflammatory activation)[2] may also increase insulin resistance and reduce glucose uptake, increasing the risk for developing type 2 diabetes.[25] Depressive symptoms are associated with decreased glycemic control and increased diabetic complications; conversely, poor metabolic control and functional impairment due to increasing complications may cause or worsen depression and lessen response to antidepressant treatment.[26]

Patients with depression and a medical comorbidity are 3 times as likely as nondepressed medically ill patients to be nonadherent to treatment recommendations.[27] Patients with depression and diabetes are no exception; several behaviorally mediated factors related to lack of self-care, which is the foundation of diabetic symptom management, are implicated in poorer overall clinical outcomes. Self-care in diabetes includes adherence to dietary restrictions, adequate physical activity, smoking cessation, taking medications as prescribed, and blood glucose monitoring. The correlation between depression and poor diabetic self-care is consistent across diverse socioeconomic and cultural groups.[28,29]

Studies have confirmed that patients with both diabetes and depression have worse adherence to multiple components of self-care regimens.[21,27] Even low levels of depressive symptoms have been associated with diabetes self-care nonadherence,[30] suggesting that treating depression across the spectrum of severity may result in better self-care outcomes. Accordingly, behaviors that reflect poor self-care are subsequently related to worse diabetes management.[31–33] Of note, lack of adherence to oral hypoglycemic medication regimens, as demonstrated by percentage of interrupted therapy days, was significantly associated with depressive symptom severity.[33] Poor adherence to antihypertensive and lipid-lowering medication regimens has also been associated with depression in patients with diabetes.[34] Higher body mass index (BMI) and tobacco use among patients with major and minor depression and diabetes are particularly disconcerting aspects of poor self-care, because obesity and smoking are associated with increased insulin resistance and increased morbidity in patients with diabetes.[7,33] Not surprisingly, patients with MDD and diabetes, with or without evidence of cardiovascular disease, were 1.5 to 2 times as likely as nondepressed patients with diabetes to have ≥3 cardiac risk factors.[35]

Comorbid depression in patients with diabetes is also associated with increased numbers and severity of diabetic symptoms and complications.[12,36,37] A meta-analysis demonstrated a clinically significant relation between depression and several diabetic complications: retinopathy (P <0.00006), nephropathy (P <0.0002), neuropathy (P <0.0002), sexual

dysfunction (P <0.00001), and macrovascular complications (P <0.00001).[21] In addition, depression was consistently related to increased severity of diabetic complications, with a similar effect shown for both type 1 and type 2 diabetes. Because type 1 and type 2 diabetes have dissimilar etiologies and disease courses, the consistent effect of depression on diabetic symptoms and complications suggests that common pathways may be responsible for the association between depression and diabetes severity.

Conversely, the psychosocial demands of diabetes management and the incidence of complications and resulting functional impairment may influence depression severity in patients who experience this common comorbidity. Psychological response to diabetic complications may result in prolonged or recurrent episodes of depression.[38] The burden of caring for diabetes, which includes managing complications, adhering to dietary restrictions, and monitoring glucose levels, can significantly diminish quality of life and contribute to affective disturbance.

Research has shown a greater correlation between subjective symptom burden and depressed mood than between subjective symptom burden and objective measures of glucose control in patients with depression and diabetes.[32] In a large population-based study of patients with diabetes, the overall number of diabetes symptoms was linearly related to the number of major depression symptoms after controlling for objective measures of diabetes severity (i.e., glycosylated hemoglobin [HbA_{1c}] and number of diabetes complications). Compared with nondepressed patients, patients with MDD were 2 to 5 times more likely to report the presence of 10 diabetic symptoms after controlling for the number of diabetes complications.[22] These findings corroborate results from earlier studies[32,39] and support evidence that the presence of depression in patients with chronic illness causes nonspecific amplification of physical symptoms associated with the medical condition.[40] Patients with comorbid depression were significantly more likely to report common diabetes symptoms, such as thirst, polyuria, and blurred vision, even after controlling for diabetes severity.[32]

DEPRESSION ASSESSMENT

Assessing symptoms of depression is not as difficult in patients with diabetes as it is in patients with certain other medical comorbidities. In spite of some overlap between depression and physiologic diabetes symptoms, depression screening tools (e.g., Beck Depression Inventory [BDI][41]), the Center for Epidemiologic Studies Depression Scale (CES-D),[42] and case-finding instruments (e.g., Patient Health Questionnaire [PHQ]–9[43]) appear to retain sensitivity and validity in this comorbid population.[5] In screening for MDD, the sensitivity and specificity of the BDI has been confirmed by receiver-operating characteristics analysis for both type 1 and type 2 diabetes.[2] In a primary care setting, the BDI, a brief, self-report measure, and DSM-IV criteria are useful and effective screening tools that accurately identify patients in need of attention and treatment for depression in addition to diabetes care. The depression module of the PHQ-9 demonstrates high validity correlation with structured psychiatric interviews[44] and may also be a valuable instrument in busy primary care settings.

Clinical Trials

Several controlled and open-label studies have evaluated the effects of antidepressant treatment in patients with diabetes. A retrospective study reported that only 31% of patients with comorbid diabetes and depression received adequate antidepressant treatment and only 6.7% received ≥4 psychotherapy visits during a 12-month period.[45] This nominal treatment level suggests that more effective management of depression in patients with diabetes is imperative.

An 8-week, randomized, double-blind, placebo-controlled study evaluated the effects of nortriptyline, a secondary amine tricyclic antidepressant (TCA), in 68 patients with diabetes

who had poor glycemic control; 28 patients also had active DSM-III diagnosed MDD.[46] Nortriptyline was dosed to therapeutic plasma levels (50 to 150 ng/mL); depression response was determined by improvement on the BDI and glucose control was measured by HbA_{1c} levels. Reduction in depression symptoms was significantly greater in depressed patients treated with nortriptyline than placebo (−10.2 and −5.8, respectively; $P = 0.03$); however, nortriptyline was not statistically better than placebo in reducing HbA_{1c} in depressed patients ($P = 0.5$). In this study, nortriptyline was associated with a trend toward worsened glucose control ($P < 0.07$). TCAs are also associated with significant weight gain in approximately 25% of patients, which limits their usefulness in patients with diabetes. TCA treatment is further limited because of its association with risk for arrhythmia and hypotension in patients with coronary artery disease, a frequent complication in patients with diabetes.

Another 8-week, randomized, double-blind, placebo-controlled study evaluated the effects of fluoxetine on MDD in 60 patients with diabetes (type 1, n = 26; type 2, n = 34).[47] Fluoxetine, a selective serotonin reuptake inhibitor (SSRI) was initiated at 20 mg/day and could be increased to 40 mg/day depending on adverse events and clinical response. Improvement in depression was measured by change in BDI and Hamilton Depression Rating Scale (HAM-D) [48] scores; HbA_{1c} levels were used to evaluate glycemic control. Reduction in depression was significantly greater for patients treated with fluoxetine than placebo (BDI, −14.0 and −8.8, respectively, $P = 0.03$; HAM-D, −10.7 and −5.2, respectively, $P = 0.01$). Significant improvement in depressive symptoms as measured by the BDI was demonstrated in 18 of 27 patients treated with fluoxetine (66.7%) compared with 10 of 27 patients given placebo (37%) ($P = 0.03$), but improvement in glycemic control was not statistically significant between treatment groups ($P = 0.13$).

Sertraline, an SSRI, was evaluated in a 2-part trial of patients with diabetes and MDD.[49] A 16-week open-label period served as an induction phase and included 351 patients who received an initial sertraline dosage of 50 mg/day, with uptitration to a maximum 200 mg/day depending on adverse events and clinical response. According to DSM-IV criteria, 152 patients recovered from depression during open-label treatment; recovery was defined as a period of ≥2 months without significant symptoms of depression. Recovered patients were randomized to double-blind sertraline treatment (n = 79) or identically-appearing placebo (n = 73). Maintenance treatment lasted for up to 52 weeks or until depression recurrence. Compared with placebo, sertraline treatment significantly prolonged the depression-free period (hazard ratio, 0.5; 95% CI, 0.31 to 0.85; $P = 0.02$). HbA_{1c} levels, which had decreased in the overall group during open-label treatment (mean ± SD HbA_{1c} reduction, −0.4% ± 1.5%; $P = 0.002$), remained significantly lower than baseline levels during depression-free maintenance ($P = 0.002$) but did not differ significantly between treatment groups ($P = 0.90$). A post hoc analysis of data using age stratification[50] revealed that sertraline significantly decreased time to depression recurrence in younger patients (aged <55 years) but no treatment response was detected in patients aged ≥55 years owing to a high placebo response rate.

In a 2-phase open-label trial, 93 patients with type 2 diabetes and MDD were treated with the atypical antidepressant buproprion.[51] Those who completed the first phase (75 patients) and attained depression remission (63 patients) continued buproprion during a 24-week maintenance phase. Measurements of PHQ-9, BMI, total fat mass, and HbA_{1c} significantly decreased, and composite diabetes self-care improved ($P < 0.01$ for each) during the acute phase, and positive BMI, HbA_{1c}, and self-care effects persisted through the maintenance phase ($P \leq 0.01$ for each). Buproprion is a particularly useful medication for patients with diabetes because of the lack of drug-associated weight gain, or the occurrence weight loss, and the lack of adverse effects related to sexual functioning[51]: compared with SSRIs, buproprion appears to be far less likely to cause sexual problems, especially orgasmic dysfunction.[52] Along with

venlafaxine and duloxetine, buproprion has also been shown to be more effective than placebo for the treatment of neuropathic pain.[53]

Further information concerning the effects of SSRIs on glucose control may be acquired through studies conducted with nondiabetic patients. For example, a study was conducted comparing the effects of fluoxetine and imipramine on fasting blood glucose in 60 nondiabetic patients with MDD.[54] At the 8-week end point of this randomized double-blind trial, significantly decreased fasting glucose levels were observed in patients receiving fluoxetine (P <0.001) and significantly increased levels were observed in patients receiving imipramine (P <0.001). Although the changes in fasting glucose levels were within normal range and may not be considered clinically significant, in populations at high risk for developing diabetes (e.g., family history of diabetes, obesity) these findings should limit prescribing of TCAs.

A controlled trial of 51 patients with type 2 diabetes and MDD evaluated the efficacy of cognitive behavior therapy (CBT) in patients with diabetes.[55] Patients were randomized to receive 10 weeks of individualized CBT or no antidepressant treatment; all patients participated in a diabetes education program. Outcomes for depression and glycemic control were assessed by the BDI and HbA_{1c} levels, respectively, immediately after treatment and 6 months later. The percentage of patients who attained remission (BDI score ≤9) was greater in the CBT group than in the control group at both assessment time points (**Table 1**). Immediate posttreatment HbA_{1c} levels were not different between treatment groups; however, at 6-month follow-up, HbA_{1c} levels were significantly better for CBT-treated patients than control patients (Table 1). At follow-up, HbA_{1c} levels had decreased by 0.7% in the CBT group and increased by 0.9% in the control group (P = 0.04). Paradoxically, the addition of CBT to diabetes education had a statistically significant adverse effect on self-monitoring of blood glucose levels during treatment.

QUALITY OF CARE FOR PATIENTS WITH COMORBID DIABETES MELLITUS AND DEPRESSION

Even though depressive symptoms severe enough to warrant treatment are found in 1 of 4 patients with diabetes,[6] adequate treatment of the affective component of this comorbidity is lacking. Because the majority of patients with diabetes and MDD are treated in the primary care setting,[31] suitable intervention in this treatment environment is essential. The Pathways Study,[56] a population-based epidemiologic investigation, included an evaluation of the comparative effectiveness of collaborative care versus usual primary care for patients with comorbid depression or dysthymia and diabetes being treated in primary care. Collaborative care included a multimodal intervention, which provided enhanced exposure to guideline level antidepressant treatment and/or brief psychotherapy. The investigators hypothesized that an intervention that significantly improved depressive symptoms would also improve diabetes control, measures of self-care, and medical costs.

Registered nurses proficient in problem-solving therapy (PST) and medication management implemented collaborative care treatment in the randomized controlled arm of the study. The primary outcome variables were change in depression, global improvement, and patient satisfaction with care; functional changes were considered important secondary outcomes. Patients were offered an initial choice of starting treatment with PST or antidepressant medication. Stepped-care algorithms and clinical supervision of nurses by psychiatrists ensured that patients not responding to initial treatment would receive augmentation with medication or psychotherapy. Results demonstrated that patients who were randomized to collaborative depression intervention had significant improvements in quality of treatment for depression, were more satisfied with depression care, and had significantly greater improvement in depressive symptoms during a 12-month period than patients receiving usual care.[31] A 24-

month follow-up analysis demonstrated that significantly lower depression scores were maintained in the group that received collaborative depression intervention as compared with the usual-care group ($P = 0.048$) even though all intervention activities ended at 12 months.[57]

There was no significant difference between patients given collaborative care and patients receiving usual care with regard to HbA_{1c} level at 6, 12, or 24 months.[31,57] Collaborative care was especially effective compared with usual primary care in the most complex patients with diabetes. Compared with usual care, collaborative care intervention resulted in significant reduction of depression symptoms in patients with ≥2 diabetic complications[38]; good clinical outcome for depression symptom reduction was demonstrated for both collaborative care and usual care in patients with ≤1 diabetes complication. The collaborative care depression intervention was not associated with better diabetes medication adherence than usual care, but it was associated with greater weight loss.[58] Results of the Pathways Study suggest that care managers may need skills to address treatment of both comorbid depression and diabetes to successfully manage depression and improve some aspects of diabetes care.

HEALTHCARE COSTS RELATED TO COMORBID DIABETES AND DEPRESSION

Regardless of the temporal and causative influences that depression and diabetes exert on each other, there remains no doubt that patients with these comorbid disorders incur higher healthcare costs than nondepressed patients with diabetes. A study comparing healthcare costs in patients with diabetes who were divided into high, medium, or low tertiles based on depression severity found that healthcare costs increased as depression severity increased.[33] Patients with highly severe depression, when compared with patients with low depression severity, were significantly more likely to have higher costs in multiple healthcare areas, including primary care, emergency care, laboratory and x-ray, inpatient care, and mental health; there were no significant differences between the medium- and low-severity groups. The comparative unadjusted mean 6-month cost of healthcare was US$3,654, $2,653, and $2,094 for patients in high, medium, and low depression severity tertiles, respectively. Additional research has substantiated these findings by demonstrating 4.5-times greater total annual healthcare costs for Medicare patients with comorbid diabetes and depression than for nondepressed patients with diabetes in the United States ($247,000,000 and $55,000,000, respectively; $P < 0.0001$ [cost adjusted to reflect August 2001 dollars]).[59] These data suggest annual increased total US healthcare expenditures of approximately $192,000,000 associated with comorbid diabetes and depression.

Studies have demonstrated that the increased cost of enhanced mental health treatment associated with the collaborative care treatment model in patients with depression and diabetes is associated with a greater savings in medical costs (i.e., cost-offset effect).[57,60] Subanalysis from the Improving Mood–Promoting Access to Collaborative Treatment (IMPACT) trial,[61] a study that evaluated collaborative care for improving primary care treatment of late-life depression, and results from the Pathways Study[31] both found that over a 2-year period the increased costs associated with enhanced mental health treatment were offset by savings in total medical expenditures.[57,60]

Recent research has also found that better adherence to antidepressant medication regimens in patients with depression and diabetes is correlated with better adherence to comorbid disease medication and to decreased healthcare costs.[62] As depression severity increases, medication adherence decreases and healthcare costs increase,[33] suggesting the need for improved depression treatment in patients with diabetes to accomplish both optimal treatment outcome and lower medical expenditures.

SUMMARY

Approximately 200 million people worldwide and 21 million Americans have diabetes,[23] with an estimated worldwide increase to 333 million by 2025 if steps are not taken to slow the epidemic advance of the disease.[63] The risk for developing MDD increases from 2.8% for people without existing medical conditions to 4.0% in patients with ≥1 or more long-term medical condition.[64] Conversely, depressed adults have a 37% increased risk of developing type 2 diabetes.[23] Depression imparts a serious deleterious effect on chronic medical conditions, with potentially adverse influences on self-care (e.g., adherence to diet, exercise, cessation of smoking, use of medication), disease control, symptom burden, development of medical complications, quality of life, and the cost of healthcare. Similarly, chronic medical conditions, especially one as psychologically demanding as diabetes, are affectively stressful for patients and may influence pathophysiologic mechanisms as well as mood. Understanding the bidirectional relation between depression and diabetes is an essential component of optimal patient care.

Most patients with comorbid diabetes and depression are treated in a primary care setting.[31] Patients with diabetes in primary care are more likely to have type 2 diabetes, less likely to be treated with insulin, and likely to have fewer diabetic complications and medical comorbidities.[18,32,33] Although both pharmacologic and psychotherapeutic interventions have demonstrated efficacy in patients with depression and diabetes, for most patients antidepressants are often the first-line treatment in primary care because providing them is less labor intensive than other treatments, the medication has a lower initial cost, and it is more similar to the usual treatments offered.[18]

The favorable profiles of SSRIs, serotonin norepinephrine reuptake inhibitors, and atypical antidepressants (e.g., buproprion) make them the preferred pharmacologic interventions for patients with depression and diabetes.[2] Monoamine oxidase inhibitors and TCAs, while effective in treating depressive symptoms, are usually avoided because they are associated with adverse events that may be particularly detrimental to patients with diabetes (e.g., weight gain, effects on cardiac conduction, postural hypotension).[2,18,46] Newer antidepressants have fewer antiadrenergic, anticholinergic, and antihistaminic effects, lack quinidine-like action, and have less potential for lethal overdose.[2]

Alternatively, some pharmacologic interventions for depression appear to offer identifiable advantages for diabetic symptom management. For example, fluoxetine and buproprion have been associated with decreases in fasting glucose blood levels, better glycemic control, and short-term weight loss.[47,51,54,65–67] Continuation therapy after an acute response with both sertraline and buproprion is associated with less relapse of depression, as well as with improved dietary adherence and improvements in HbA_{1c} levels for a duration ≥1 year.[49] For maximum efficacy, treatment options should be individually evaluated based on the patient's symptom profile.

Comorbid diabetes and depression is associated with increased healthcare costs that are highly related to the greater use of general medical services as opposed to the cost of depression treatment.[68] It has been demonstrated that improvement in depression is associated with decreased use of general medical care and improved work productivity.[69,70] Lower utilization of general healthcare services suggests that the cost of improved depression treatment may be offset by decreases in the cost of other medical care.[69,70] In general, improved depression treatment for patients with diabetes is associated with decreased economic burden and improved clinical outcomes.[57,60]

In diabetes, the preponderance of symptom management is the responsibility of the patient, making it among the most psychologically and behaviorally demanding chronic medical

conditions. Because of the prevalent nature of comorbid depression and diabetes, the American Diabetes Association (ADA) now recommends routine depression screening for patients with diabetes (especially those with poor adherence),[71] and patients who present with depression should be monitored over time for the development of diabetic symptoms and risk factors[26] including glucose dysregulation, diet, exercise, smoking, and medication adherence. Antidepressant regimens for patients with diabetes should be individualized for tolerance, preference, and simplicity to encourage adherence in patients who already shoulder substantial responsibility for disease management.[26] Managing both the affective and medical components of comorbid depression and diabetes requires addressing the full spectrum of symptoms, may optimize patient outcomes, and may reduce healthcare costs in this large patient population. Given the health-related and socioeconomic importance of these commonly co-occurring conditions, additional controlled studies are warranted.

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