

Section III: Practical Considerations in the Management of Depression in Diabetes

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The possibility of depression causing diabetes was first advanced in 1684 by Thomas Willis, who wrote that diabetes was the result of “sadness, or long sorrow.” Over the years, this view enjoyed little popular support, and depression more often was seen as something that occurred secondary to diabetes—a natural reaction to the arduous nature of the medical illness and its complications. In most cases, this view proved to be oversimplified or plainly mistaken. Studies dating the onsets of depression and diabetes in type 2 diabetes showed a distinct temporal relationship, wherein depression preceded diabetes in 90% of cases by 8–10 years.

Subsequent longitudinal studies (reviewed in the previous articles) confirmed the prognostic significance of depression by showing that it is an independent risk factor both for the development of type 2 diabetes and for the development of complications of

type 1 or type 2 diabetes, particularly coronary heart disease. The mechanisms by which depression imposes these risks have not been clearly established. The list of candidate mediators is long and varied, reflecting multifaceted effects of depression on behavioral and physiological factors that may interact with one another or change over time (Table 1).

Identification of depression mechanisms that are relevant to medical outcome is the focus of much current research. And while the mechanisms involved remain to be clarified, the story outlined in the preceding sections has evolved sufficiently to suggest that potential benefits of depression treatment likely surpass expected improvements in mood and quality of life. Successful treatment of depression also may improve glycemic control, insulin effectiveness, and other measures of diabetes and cardiovascular risk and thereby

Table 1. Mediators of Depression Effects on Diabetes Course

Diabetes Risk Measure	Depression Effect
Obesity	↑ weight
Physical inactivity	↑ fatigue ↓ social involvement ↓ physical functioning
Tobacco use	↑ use
HPA axis hyperactivity	↑ plasma CRF and cortisol levels
Glucose regulation	Hyperglycemia
Autonomic tone abnormalities ↑ sympathetic ↓ parasympathetic	↑ NE metabolites, ↓ HRV
Inflammation	↑ IL-6, TNF-α, and other cytokines
Genetics	? shared genes

CRF, corticotrophin-releasing factor; HPA, hypothalamic-pituitary-adrenal; HRV, heart rate variability; IL-6, interleukin 6; NE, norepinephrine; TNF-α, tumor necrosis factor-α

Table 2. Diagnostic Criteria for Major Depressive Disorder*

1. One of the following:
 - Depressed mood
 - Markedly diminished interest or pleasure in almost all activities
2. Four of the following:
 - Significant weight loss or gain
 - Insomnia or hypersomnia
 - Psychomotor agitation or retardation
 - Fatigue, loss of energy
 - Feelings of worthlessness or guilt
 - Impaired concentration or indecisiveness
 - Recurrent thoughts of death or suicide
3. Symptoms must be present most of the day.
4. Symptoms must be present nearly daily for ≥ 2 weeks.
5. The symptoms must be the source of significant distress or impairment and not be attributable to medications, medical conditions, or bereavement.

*All five criteria are required.

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enhance and prolong life. Realizing these possibilities requires that caregivers possess knowledge of mental and physical health and have the clinical skills and commitment to impart this knowledge to varied patient groups. Toward this end, our discussion now shifts from appreciating advances in the scientific understanding of diabetes-depression interactions to applying this knowledge in the practice setting. We discuss the factors to be considered in managing depression in diabetes and offer our advice as to the strategies that are most effective.

The Many Faces of Depression

What is depression? Is it simply sadness, or is it something more pervasive that includes feelings of fatigue, disinterest, and apathy? Does it encompass moods more mad than sad, irritability that is easily evoked by the inconsequential and predictable stresses of everyday life? Is depression still depression if it arises in the context of a stressful personal problem or a medical illness like diabetes or heart disease?

Of what consequence is depression? Does it adversely affect performance at work, precipitating the need for restorative time off (“mental health days”)? Or does continuing to work prove that one is not depressed?

Before 1974, there was no general or scientific agreement as to the definition of depression, and it was difficult to compare the findings of one study to those of another. That year, Feighner et al. at Washington University in St. Louis, Mo., proposed specific criteria to be used in psychiatric research for the diagnosis of depression and other major psychiatric illnesses. The Feighner criteria for depression were subsequently adopted by the American Psychiatric Association and published in its guidebook of mental illness, the *Diagnostic and Statistical Manual of Mental Disorders* (DSM).

The DSM specifies a set of conditions that must be met in order to make the diagnosis of depression, known formally as major depressive disorder (MDD). The criteria reflect that depression is considered a syndrome, a constellation of symptoms that occur together, are severe, interfere with normal functioning, and persist daily over a period of at least 2 weeks (Table 2). One of the symptoms must be depressed mood or anhedonia (absence of pleasure from

the performance of acts that would otherwise be pleasurable).

Thus, depression is more than sadness—indeed, it is more than any one thing. It is defined as a set of nine symptoms, at least five of which variously combine to make the diagnosis. Other symptoms that commonly accompany depression include anxiety, anger, or irritability, but these are not required for the diagnosis. As a rule, stressful life events (e.g., financial difficulties or job loss) increase the likelihood of depression but do not prevent its diagnosis. Depression almost always presents in the context of conflicted and stressful circumstances. Whether these events cause or are caused by depression is not relevant in making a diagnosis, which instead focuses on the presence or absence of the criterion symptoms. The diagnosis is equally valid in the face of medical illness, as long as criterion symptoms are not directly produced by medical illness or its treatment. A variety of instruments are available to assist clinicians in recognizing and diagnosing depression, have been validated for use in diabetes, and are discussed in the next section of this article.

Depression (or MDD) is a serious medical condition and a source of enormous personal suffering that invades living and pervades functioning. It alters the way one eats and sleeps, lessens the capacity to think rationally, and diminishes interest in all things. MDD imposes a myopic, pessimistic self-focus fraught with misperception and overpersonaliza-

tion of events past, present, and future. In severe cases, depression robs the individual of the will to live. Depression is neither a character defect nor a sign of personal weakness. Continuing to work and maintaining other usual routines does not imply that treatment is unnecessary. People with depression cannot simply “pull themselves together,” and in the absence of treatment, depression can persist for months and even years.

Depression Often Is Overlooked in Patients With Diabetes

The likelihood of depression is doubled in those with diabetes compared to those without. Approximately 20% of diabetic men and 40% of diabetic women suffer an episode of depression at some point during their lifetime. At any single point in time, ~33% have symptoms of depression severe enough to warrant treatment. Yet despite its common occurrence and recognized adverse effects on glycemic control and the course of diabetes, two of every three cases of depression in diabetes do not receive antidepressant treatment. Treatment that is instituted is usually below the standard of care, notwithstanding the availability of national practice guidelines for the treatment of major depression in primary care.⁵² Many patients fail to receive the recommended dosage and duration of antidepressant treatment.

Many factors contribute to underrecognition of depression. Society disdains depression, viewing it as a shameful indication of character weak-

ness. Parents who share this view often pass it on to their children. Not surprisingly, these beliefs permeate the clinic setting, having been adopted in varying degrees by patients and professionals. Underrecognition also reflects a certain complicity between patients and professionals in which both sides appear happy not to discuss depression or to minimize symptoms. Both also may regard depression as a normal consequence of difficult medical illness and, logic notwithstanding, use this as a basis for not requesting or providing treatment. For these reasons, it may be helpful to include a collateral source—a relative, close friend, or caregiver who knows the patient well and can provide additional information concerning moods and symptoms and serve as a useful adjunct in the assessment.

A seismic shift in societal attitudes will be required to remove the stigma associated with depression. Medical education and training should reflect scientific knowledge of depression. Overcoming patient reluctance to discuss depression and consider treatment will require clinicians who are accepting and nonjudgmental, interpersonally skilled, able quickly to establish caring relationships with people of different backgrounds, and capable of motivating patients to adopt and sustain healthful behaviors.

Identifying Depression in Diabetes

The depression assessment process should be sensitive to the values and beliefs of racial and ethnic minorities prone to diabetes and to differences between the sexes and among individuals. For example, men and women may experience or characterize the same mood differently; men may be reluctant to describe dysphoria as depression and more apt to characterize it as anger, irritability, or distress. Women may be more likely to sense the interference of depression with family responsibilities and men more sensitive to interference with work.

The point is less about sex differences per se and more about expecting and recognizing variations in the depression phenotype. Even though the diagnosis of depression is guided by specific criteria, its manifestation is heterogeneous, and clinicians should be sensitive to nuances in presentation. This approach helps establish rapport and fosters open discussion, a climate that in turn enhances the accuracy of assessment and a willing-

ness to accept depression treatment.

Lastly, education as to the benefits of depression treatment may be helpful in overcoming reluctance or opposition to treatment. The positive effects of depression treatment frequently extend well beyond improved mood. Some of these ancillary benefits are listed in Table 3 and occur in conjunction with depression relief.

Depression may go undetected, in addition to the reasons given above, because primary care physicians lack sufficient training and face financial disincentives to perform psychodiagnostic assessments. It is estimated that the average patient-physician contact in managed care settings is 8–12 minutes long in the United States and shorter still in Britain and Japan. Despite these evident realities, some things can be done to improve depression recognition. Acceptable strategies for detecting depression are summarized in Figure 1 and include the techniques discussed below.

Look for tip-offs to depression. A careful medical history should be given with an ear toward elements that are suspicious for depression (Table 4). Other tip-offs to depression may emerge during the course of clinical management. When these tip-offs are present along with prominent sadness, loss of interest, or anhedonia, more systematic evaluation is indicated as outlined below.

Offer a self-administered screening instrument. A number of self-administered “paper-and-pencil” tests are available that can be completed in a few minutes and accurately identify patients likely to have depression. Some of the more commonly used measures include the Beck Depression Inventory (BDI), the Hamilton Rating

Scale for Depression, the Centers for Epidemiologic Studies Depression Questionnaire, and the 9-item Patient Health Questionnaire.

The BDI is the tool most widely used in clinical studies and has been validated in patients with diabetes.⁵³ It measures the presence and severity of 21 symptoms on a scale from 0 (not present/mild) to 3 (present/severe); higher scores indicate greater depression. In the practice setting, a total score ≥ 16 is likely to capture $> 70\%$ of the patients with MDD while providing $> 70\%$ certainty that a person screening positive actually has MDD. Some clinicians may prefer to refer at the point of a positive screen, but additional questioning can improve the accuracy of the referral or better suggest a need to begin treatment directly.

Perform a focused psychiatric interview. Another method employs current psychiatric interview techniques to establish a DSM-based diagnosis of MDD (Table 2). Criterion symptoms can be extracted during the medical history—taking as long as clinicians ask the appropriate questions. In clinical research, the diagnosis of depression is most often established using available diagnostic interviews such as the National Institute of Mental Health Diagnostic Interview Schedule or the Structured Clinical Interview for DSM. Interviews establish the chronicity as well as the presence of the psychiatric diagnosis, a feature that helps determine the ultimate course of therapy.

Optimizing the Outcomes of Depression Management

Selecting candidates for depression treatment and setting reasonable goals.

Because depression broadly impairs functioning, initiation of treatment should be considered for all diagnosable forms of the illness, whether the presentation is conspicuous or subtle. These include:

- major depression meeting the criteria for MDD outlined in Table 2
- minor depression (fewer symptoms than MDD with less impairment)
- dysthymia (minor but chronic depression, with symptoms persisting for ≥ 2 years) and
- nondysphoric depression (MDD without evident sadness that commonly presents with marked irritability or, conversely, with marked inhibition of emotional expression, a condition sometimes referred to as alexithymia)

Table 3. Potential Benefits of Depression Management

- Depression relief, anxiolysis
- Restoration of normal sleep and eating habits
- Behavioral activation*
- Pain relief, improved pain tolerance
- Improved illness coping and general functioning
- Decreased somatic preoccupation
- Enhanced sexual functioning
- Improved treatment compliance and glycemic control

*For example, increased social, occupational, and physical activity.
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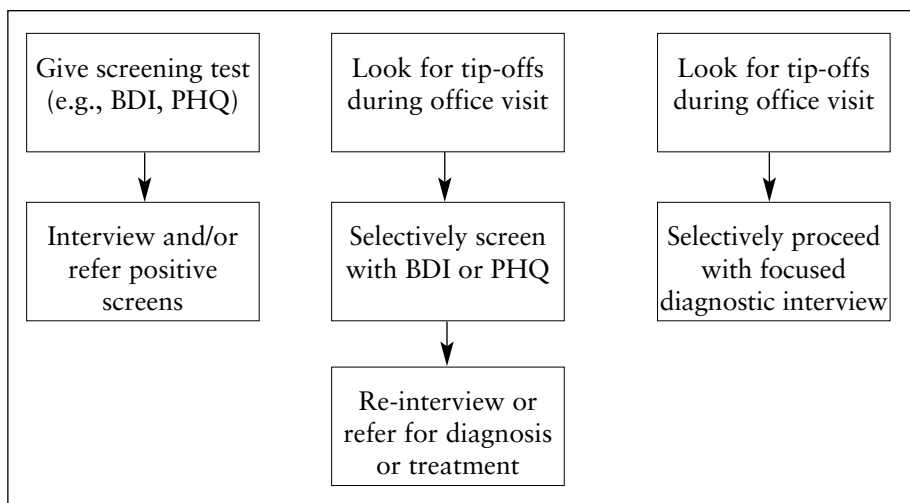


Figure 1. Strategies for detecting depression in diabetes patients by medical physicians. The first strategy relies heavily on non-physician resources, whereas the third is more dependent upon direct physician involvement. PHQ, Patient Health Questionnaire. Reprinted with permission from Ref. 59.

Patients with elevated symptoms of depression that fall short of the criteria for one of the diagnoses listed above should be monitored and reevaluated for development of psychiatric illness. The small proportion of patients with bipolar disorders (a condition with wide swings in mood, also called manic depression), active suicidal ideas, a history of suicide, or a history of hospitalization for depression are probably best referred to a mental health specialist.

In most cases, depression in diabetic patients is not permanently curable; goals are oriented toward remitting individual episodes and reducing the likelihood of recurrence. Individual episodes tend not to remit spontaneously, and untreated episodes appear to last longer than the 6- to 9-month duration reported for depressed nondiabetic patients. More than half of depressed diabetic patients successfully treated for depression suffer a recurrence of the psychiatric disorder

in the ensuing 12 months. Thus, clinicians caring for depressed diabetic patients can anticipate treating many episodes over the course of their patients' lifetime. Each episode should be treated aggressively, aiming for a depression-free state, because partial remission increases the risk of recurrence.

Choosing appropriate depression therapy. Perhaps because depression is viewed as resulting from diabetes, usual care for depression in the practice setting often remains directed at the medical illness. Nonspecific support is provided along with intensified diabetes management. Research has shown that this approach is not an acceptable alternative to direct depression management, and the rate of depression improvement (~ 30%) approximates that of placebo treatment.

The treatment choice depends in part on patients' readiness, preference, resources (including time and money), and tolerance. Some who are unwill-

ing to accept formal treatment may welcome suggestions or materials that would help them help themselves. Some common-sense advice for mood improvement includes:

- Get out and do something—consider those things that you normally enjoy.
- Be with people; don't isolate yourself.
- Exercise regularly. Whether mild (like walking) or more vigorous, this almost always helps.
- Do what you can, as you can. Break large tasks into small ones.
- Expect gradual improvement. Feeling better is a day-by-day process.
- Postpone important decisions until depression resolves.
- Keep your family and friends involved in your life. Allow them to help you.

Self-help techniques may relieve depression in some cases. Specific interventions have been designed, however, that optimize the likelihood for rapid and effective relief. Major depression is best treated with antidepressant medication and/or psychotherapy. Several randomized controlled studies have been conducted that demonstrate the efficacy of these treatments in diabetic populations (Figure 2). Successful depression treatment was associated with significant improvement in glycemic control in two of the three studies; the study of nortriptyline revealed a direct hyperglycemic effect of this agent.

Cognitive behavior therapy (CBT) is a form of psychotherapy that has been widely studied and proven effective for depression in general psychiatric (i.e., nondiabetic) samples. CBT is a comprehensive approach that treats depression by using 1) activation strategies to re-involve patients in pleasurable social and physical activities; 2) problem-solving methods to resolve stressful circumstances; and 3) cognitive techniques to identify distorted or maladaptive patterns and replace them with more accurate, adaptive, and useful ways of thinking. CBT appears to this point to be the most potent of the conventional short-term treatments (counseling or medication) for depression occurring in the presence of diabetes. In one study, fully 85% of depressed diabetic patients treated with weekly 1-hour sessions of CBT were free of depression after 10 weeks.

Table 4. Tip-Offs to Major Depression in Primary Care Patients With Diabetes

In the Medical History

- History of depression, anxiety, or substance abuse (alcohol or drugs)
- History of mental health treatment
- Family history of depression or mental health treatment

In the Clinical Presentation

- Symptoms (e.g., of hypoglycemia) that lack a solid medical explanation or are out of proportion to the objective findings
- Persistent focus on somatic complaints
- Failure of reassurance therapy for innocuous medical complaints
- Sexual dysfunction with or without an organic basis
- Chronic pain as a dominant complaint

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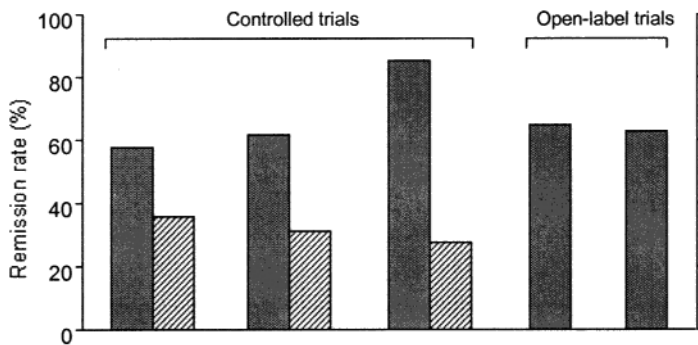


Figure 2. The efficacy of pharmacological and psychotherapeutic interventions for depression in diabetes has been proven in several double-blind, placebo-controlled clinical trials. The percentage of subjects achieving remission with therapeutic interventions exceeds that seen for placebo or control (hatched bars) for nortriptyline, fluoxetine, and cognitive behavior therapy. Comparable levels of remission were seen for open-label sertraline in two trials. Reprinted with permission from Ref. 1.

Use of antidepressant medications in patients with diabetes is limited by the presence of common comorbid conditions, potential drug-drug interactions, and adverse effects. These effectively limit the use of monoamine oxidase inhibitors, atypical antipsychotics (as mood stabilizers), and tricyclic antidepressants in diabetic patients, particularly elderly ones. Because of more favorable side effect profiles, the serotonin selective reuptake inhibitors, as well as bupropion, mirtazapine, and venlafaxine, may be more appropriate for bringing depression under control.

Electroconvulsive therapy (ECT) may be particularly useful in elderly patients with diabetes. Recent research indicates that ECT is safe, efficacious, and provides a rapid rate of symptom improvement without adverse effects on glycemic control. ECT is most appropriate in the face of an intolerance to antidepressant medication, medication-refractory depression, or severe and life-threatening depression. This must be weighed against concerns for potential cognitive impairment, as ECT may compound effects of diabetes and aging.

Preventing depression recurrence: strategies for the long haul. Depression in diabetes typically is a recurrent problem requiring long-term or lifelong antidepressant therapy. As few as 15% of depressed patients

remain well following successful treatment, and the same percentage suffer chronic depression unresponsive to available treatments.⁵⁴ Each new episode brings renewed risks of chronicity, psychosocial impairment, and suicide,⁵⁵ perhaps because of cumulative effects.

Maintenance treatment refers to the practice of keeping patients on antidepressant medication beyond the point of depression relief to prevent or delay recurrences. To this point in time, there has only been one empirical test of this approach in diabetic patients. We found that maintenance treatment with sertraline effectively prevented depression recurrence in a placebo-controlled trial but was associated with a deterioration in glycemic control in the subset who remained free of depression over the 1-year follow-up interval (Lustman et al., unpublished observations). Whether behavioral approaches are better suited to long-term management of depression in this population has not been tested, and such studies are badly needed.

A successful strategy must consider the potential interference of hyperglycemia with depression management. Data from investigations using a hyperglycemic clamp demonstrated that hyperglycemia provokes dysphoric symptoms in diabetic patients.⁵⁶ A prospective study by Gonder-Frederick et al. found suggestive evidence that

blood glucose fluctuations in diabetic patients may have affective consequences.⁵⁷ In two randomized, controlled clinical trials assessing the efficacy of diabetes interventions, metabolic control and depression were correlated: as metabolic control improved, so did depression, despite the lack of specific antidepressant therapy.^{24,25} Higher hemoglobin A_{1c} also predicted diminished responsiveness to antidepressant interventions and a worse course of depression over 5 years of observation.⁵⁸ Therefore, just as hyperglycemia is responsible for the development of microvascular and macrovascular complications in diabetic patients, it also may be a factor in the development, management, and course of depression in this population. Enhanced efforts toward good glycemic control may contribute to improvements in mood and perceptions of well-being.

Conclusion

Approximately one of every four patients with diabetes (type 1 or type 2) has depression severe enough to warrant consideration of treatment. The affective illness diminishes all aspects of functioning, aggravates symptoms of the medical illness, interferes with diabetes self-management, and imposes additional risk for diabetes complications. The co-occurrence of depression and diabetes complicates management of both conditions, because depression leads to poor metabolic control and hyperglycemia exacerbates depression. A contemporary treatment strategy demands a multifaceted approach oriented toward both disease processes to optimize long-term outcome. Within this strategy, diabetes education, physical activity, and good glycemic control become integral components of depression treatment, just as successful management of depression becomes important for improving the course and outcome of diabetes.

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