Depression and treatment nonadherence in type 2 diabetes: Assessment issues and an integrative treatment approach

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Abstract. Research has found that depression is more common among individuals with diabetes and is associated with worse diabetes outcomes including treatment nonadherence, worse glycemic control, higher risk of diabetes complications, greater functional impairment, and increased risk of mortality. These patterns of association have led to an increase in research investigating the relationship between diabetes and depression. There remain important questions about the relationship between depression and diabetes and an unmet need for treatment approaches that are successful in ameliorating depression and improving diabetes outcomes. The current commentary discusses several conceptual issues related to the measurement of depression in diabetes, argues for the importance of health behavior and treatment adherence in approaching the problem of depression in diabetes, and provides an example of a treatment approach that incorporates the treatment of depression with strategies aimed at improving treatment adherence in order to maximize effects on diabetes outcomes.

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INTRODUCTION

The global epidemic of type 2 diabetes is a major public health problem with the world prevalence among adults estimated to be 6.4% for 2010. By 2030, it is expected that the burden of diabetes will affect more than 439 million adults worldwide or 7.7% of the global population. Over the next 20 years, the developed world will see an increase of 20% in the numbers of adults living with diabetes and developing countries will see an increase of 69% (Shaw *et al*., in press). As the prevalence of diabetes rises, so too does the importance of improving the treatment outcomes and the prevention of complications among those affected. Addressing treatment nonadherence and improving health behaviors such as diet and physical activity among patients has the potential to greatly improve the health outcomes and quality of life of patients affected by diabetes and is an important area of behavioral science research as treatment adherence and health behaviors are often suboptimal in patients with diabetes (DiMatteo, 2004; Rubin, 2005). An additional key goal of behavioral science research that has the potential to improve both the quality of life and treatment outcomes of patients with diabetes is addressing the high rates of depression that are found in these patients.

Research has consistently found that depression is more common among individuals with diabetes and meta-analyses of the available literature suggest that depression is prevalent in 15-20% of diabetes patients, a prevalence rate that is approximately double that found in the general population (Anderson *et al*., 2001; Ali *et al*., 2006). Meta-analyses have also shown that depression is associated with worse outcomes in diabetes. For example, depression is associated with treatment nonadherence (Gonzalez *et al*., 2008b), worse glycemic control (Lustman *et al*., 2000), and higher risk of diabetes complications (de Groot *et al*., 2001). Several studies have also shown that depression is associated with greater functional impairment (Ciechanowski *et al*., 2005; Egede, 2004; Von Korff *et al*., 2005), and increased risk of mortality (Black *et al*., 2003; Katon *et al*., 2008; 2005; Zhang *et al*., 2005) in patients with diabetes. These patterns of association have led to an exponential increase in the amount of research investigating the relationship between diabetes and depression and to recommendations for the assessment of depression as part of routine diabetes care (ADA, 2009; Petrak *et al*., 2005). While the last two decades of empirical research have led to more detailed and evidence-based support for observations of an association between depression and diabetes from over 300 years ago (Willis, 1971), the mech-

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anisms for this relationship remain unclear. Furthermore, research on treatments for depression in the context of diabetes has found mixed evidence for effects on diabetes outcomes, even when depression is successfully treated (Markowitz *et al*., "in press"). Thus, there remain important questions about the relationship between depression and diabetes and an unmet need for treatment approaches that are successful in ameliorating depression and improving diabetes outcomes. The current commentary discusses several conceptual issues related to the assessment of depression in diabetes, argues for the importance of health behavior and treatment adherence in approaching the problem of depression in diabetes, and provides an example of a treatment approach that incorporates the treatment of depression with strategies aimed at improving treatment adherence in order to maximize possible effects on diabetes-related outcomes.

CONCEPTUAL AND MEASUREMENT ISSUES

Inconsistency in the conceptualization and measurement of depression is one major complication of much of the research that has been conducted on depression in the context of diabetes and limits many of the conclusions that can be drawn. Much of this research focuses on pathological conceptualizations of depression, particularly major depressive disorder (e.g. Eaton, 2002; Katon, 2003; Lustman *et al*., 1997). Major Depressive Disorder (MDD) is a psychiatric diagnosis that requires depressed mood and/or loss of interest and the presence of at least 4 of the following symptoms: fatigue or low energy; sleep disturbance; change in appetite or weight; feelings of guilt, worthlessness, or low self-esteem; concentration difficulty; psychomotor retardation (slowing) or agitation; thoughts of death or suicidality. To warrant a diagnosis of MDD, these symptoms must be present nearly every day for at least a two-week period and must not be due to the direct effects of a substance, an illness, or bereavement. There must be no prior experience of a manic episode. In addition, the symptoms must interfere with important aspects of functioning and/or cause significant distress (American Psychiatric Association, 2000). MDD is the most common mood disorder recognized by the diagnostic standards of psychiatry and is associated with increased disability, decreased quality of life, and risk for suicide (Katon & Ciechanowski, 2002; Moscicki, 2001).

One problem in the research on depression and diabetes involves the selection of appropriate measures to assess for MDD, as it is often measured using methods that are not optimal for identifying psychiatric disorder. Structured clinical interviews that assess the DSM-IV diagnostic criteria and are administered by trained interviewers remain the gold standard for the assessment of MDD. Confounding between physical symptoms known to be associated with diabetes and those that are part of the diagnostic criteria for MDD (e.g., concentration difficulties, appetite disturbance and weight changes, sleep disturbance, fatigue) further complicates the diagnosis of MDD in patients with diabetes and appropriate evaluation of MDD using structured interviews in patients with diabetes requires a high level of interviewer training. Because of the associated cost and complicated nature of administering structured interviews to large samples, this approach is under-utilized. For example, the most recent meta-analysis of studies examining the prevalence of depression in patients with type 2 diabetes located 10 controlled studies including 51,331 individuals; however, only two studies, with a combined sample size of 1,910, used structured clinical interviews to evaluate depression (Ali *et al*., 2006). Despite the wide acknowledgement of the advantages of structured clinical interviews, the most common assessment method for depression in the diabetes literature remains the self-report questionnaire. While a variety of self-report questionnaires have been validated for screening for MDD, with acceptable levels of sensitivity and specificity, they do not adequately assess diagnostic criteria necessary for a diagnosis of MDD and may be particularly problematic in the context of diabetes. For example, one study of type 2 diabetes patients examined elevated symptoms of depression based on a clinical cutoff for self-reported symptoms of depression on the "Center for Epidemiologic Studies Depression Scale" (CES-D) and also evaluated diagnosis of MDD based on a structured clinical interview, the Composite International Diagnostic Interview (CIDI). Although 22% of patients reached the clinical cutoff on the CES-D and 9.9% met criteria for a diagnosis of MDD based on the CIDI, of those who scored above the CES-D cutoff, 70% were not clinically depressed. Furthermore, 34% of those who were clinically depressed did not reach the CESD cut off (Fisher *et al*., 2007b). Thus, there is reason to have reservations about the appropriateness of using self-report measures to identify cases of MDD in patients with diabetes.

A second problem in the conceptualization and measurement of depression in diabetes relates to the potential for confounding of depression and diabetes-related distress in measures that are intended to evaluate depression. Diabetes-related distress has been shown to be common and persistent in diabetes patients, related to worse diabetes control, and is associated with depression scores on self-report measures and with evaluations of MDD based

on structured clinical interviews (Fisher *et al*., 2010; 2008). Thus, it is possible that measures intended to assess symptoms of depression can often be confounded with symptoms of distress related to the burden of managing diabetes. It is also possible that results from depression symptom measures are often confounded with other types of distress such as distress about one's health status or comorbid illnesses, stressful life events, more chronic stress due to environmental factors or lack of resources, or stress resulting from interpersonal difficulties and patterns of poor problem-solving skills. Therefore, there is likely a tremendous degree of heterogeneity in the patients identified as 'depressed' by most investigations that do not employ clinical interviews to diagnosis depression.

One final complication regarding the conceptualization of depression in diabetes relates to whether depression should be treated as a categorical construct that is either present or not (i.e., a syndrome) or as a construct that exists on a continuum (e.g., depression symptom severity). While meta-analyses and reviews of the literature on depression and diabetes often aggregate studies that approach depression as a categorical variable with those that measure depression symptom severity on a continuum, research suggests that this distinction may be important. For example, Fisher and colleagues have reported a series of papers that suggest that the syndrome of MDD may be less related to diabetes control and health behaviors than symptoms of depression measured on a severity continuum or diabetes-specific distress (Fisher *et al*., 2007b; 2010; 2008). Furthermore, continuous depression severity symptom scores have been shown to be better predictors of nonadherence to diet, exercise, and medications than probable diagnosis of MDD in a large sample of type 2 diabetes patients; even among patients who were unlikely to meet criteria for MDD based on screening, more symptoms of depression were incrementally associated with poorer self-care and adherence (Gonzalez *et al*., 2007). A follow-up study also showed that these symptom scores were more closely related to treatment nonadherence than diabetes-specific distress and that relationships between symptoms of depression and diabetes treatment nonadherence persisted even after controlling for diabetes distress. The independence of the depression symptom effect from diabetes distress was also found among patients who were unlikely to meet criteria for MDD (Gonzalez *et al*., 2008a). This work suggests that even low levels of depressive symptoms may have problematic relationships with treatment nonadherence in diabetes. It also suggests that measurement and conceptual issues have important implications for elucidating the relationships between depression and diabetes.

Despite these issues in the conceptualization and measurement of depression in diabetes, the empirical literature is consistent in demonstrating that depression; however it is measured, is often associated with worse treatment outcomes in patients with diabetes. Therefore, depression should be considered a risk factor for worse diabetes control (Lustman *et al*., 2000) and for increased risk of diabetes complications (de Groot *et al*., 2001). While the mechanisms for these relationships are not clearly understood, they may have important implications for designing the most effective treatments for depression in the context of diabetes.

DEPRESSION, TREATMENT NONADHERENCE, AND DIABETES

A comprehensive review of the evidence for the mechanisms linking depression and worse diabetes outcomes is beyond the scope of the current paper but biological (Golden, 2007; Musselman *et al*., 2003) and behavioral explanations are plausible. The available literature does not yet provide clear answers about whether biological processes associated with depression such as HPA-axis dysregulation and associated inflammation processes may mediate the relationship between depression and diabetes outcomes or whether negative health behaviors associated with depression such as inactivity, poor diet, smoking, and nonadherence to treatment recommendations and self-care may be important explanatory factors. However, it is clear that health behavior is extremely important for the successful management of diabetes and that negative health behaviors such as smoking, heavy drinking, physical inactivity, obesity (Strine *et al*., 2008) and treatment nonadherence across chronic health conditions (DiMatteo *et al*., 2000) are consistently associated with depression. Furthermore, effective behavioral interventions have been shown to have important positive impacts on diabetes outcomes and diabetes self-management (e.g., Diabetes Control and Complications Trial Research Group, 1993; Norris *et al*., 2004). A recent meta-analysis of 47 studies confirmed that depression is consistently related to diabetes treatment nonadherence, including nonadherence to prescribed medications, glucose monitoring, diet and physical activity recommendations. Those who are more depressed are also significantly less likely to attend scheduled medical visits with diabetes care providers (Gonzalez *et al*., 2008b). Thus, treatment nonadherence and health behaviors have important relationships to both depression and to health outcomes and could represent a behavioral pathway through which depression is associated with worse outcomes in diabetes.

While there is reason to suspect that health behaviors could form part of the link between depression and worse diabetes outcomes, the available evidence is not conclusive in supporting this hypothesis. Although two previous studies of adults with type 1 diabetes did not find evidence of mediation of the depression – hyperglycemia link by health behaviors (Lustman *et al*., 2005; Van Tilburg *et al*., 2001), one study does suggest that self-care, defined by glucose monitoring, may mediate a substantial portion (37.5%) of the relationship between depression and hyperglycemia in type 1 adolescents (McGrady *et al*., 2009). However, the ability of these studies to evaluate causal mechanisms is limited by their cross-sectional design. One recent longitudinal study did find evidence for significant partial mediation of a relationship between depressive symptoms at baseline and HbA1c measured 5 years later by a set of indicators of health behavior including exercise frequency, BMI, and smoking status, measured at baseline and at 2 years post baseline using structural equation modeling (Chiu *et al*., in press). While the mediation effect was significant, the year 2 health behaviors accounted for only 13% of the depression symptom – hyperglycemia link. Still, given that the interval between the measure of depression symptoms and A1c was quite long and the health behavior indicator variables measured were rather limited, this study provides the most promising evidence to date for the possibility that health behaviors and treatment adherence may account for some of the relationship between depression and diabetes outcomes. While this longitudinal study is an improvement over existing cross-sectional data, experimental data would provide the strongest test for a causal link between depression, poor health behaviors, and hypeglycemia. The limited experimental data that have examined this sequence of relationships have failed to demonstrate evidence for a mediating effect. Data from an experimental manipulation of depression in an open label design suggest that treatment of depression with buprioprion was associated with improvements in depression, body weight, self-care, and HbA1c. However, self-care was not associated with changes in HbA1c and therefore did not meet criteria to be evaluated as a potential mediator of the relationship between changes in depression and changes in HbA1c in this study. Only changes in depression and changes in body weight were associated with changes in HbA1c (Lustman *et al*., 2007). Randomized controlled trials of depression treatments have failed to show any resulting improvement in self-care or treatment adherence (Lustman *et al*., 1998; Lin *et al*., 2009). Thus, although depression and diabetes treatment nonadherence are consistently related, the strength of their association is somewhat modest and there is reason for caution in assuming that the treatment of depression would result in improved treatment adherence or health behavior in patients with diabetes.

TOWARDS AN INTEGRATIVE APPROACH TO TREATMENT

A review of the available intervention research on depression in diabetes shows that while a number of pharmacological and psychological interventions have been tested, usually with positive effects on depression outcomes, when taken together, they have generally failed to provide compelling evidence to suggest that treating depression on its own would result in improvements in diabetes treatment adherence or glycemic control (Markowitz *et al*., in press). However, these interventions have almost exclusively focused on reducing depression severity, either through pharmacological treatment, psychological counseling, or a combination of the two. In the few instances when education or support for diabetes management was provided as part of the intervention, it was also provided to the control group (e.g., Lustman *et al*., 1998). Thus, the question of whether the integration of intervention strategies aimed at improving diabetes treatment adherence with those aimed at reducing depression severity remains unanswered. However, there is emerging evidence to suggest that this approach may have promise for maximizing intervention effects on both depression and health outcomes.

Safren *et al*. (2008a, b) have developed a psychological treatment model for the integration of cognitive behavioral therapy (CBT) with adherence counseling for patients with chronic illness, CBT for adherence and depression (CBT-AD). The integration of adherence training with cognitive behavioral techniques in CBT-AD is based on the belief that the strategies employed in CBT for depression (e.g., activity scheduling and mood monitoring, cognitive restructuring) have important applications in facilitating successful treatment adherence in patients with chronic illness (e.g., increasing physical activity, monitoring behavior change, correcting maladaptive beliefs about the illness and treatment). It is also based on the belief that there is often a bidirectional relationship between depression and the management of medical illness and interventions that improve patients' ability to successfully manage their illness will result in an improved sense of self-efficacy and mastery, which will in turn improve patient cognitions underlying negative mood states. Each session of the treatment focuses on

the difficulties that the patient is having with disease management, the symptoms of depression that the patient is experiencing, and how these two problems influence each other. The strategies employed are presented to the patient as equally applicable to the difficulties of illness management as to the symptoms of depression.

CBT-AD is an individually delivered program consisting of seven modules addressing motivational enhancement and orientation to the program, adherence counseling, behavioral activation, cognitive restructuring, problem solving, relaxation training, and relapse prevention and maintenance. The sequencing of modules and the number of sessions spent on each module is flexible though it is intended to take approximately 10-12 sessions in total. This approach has been shown to be successful in a recent two-arm randomized crossover trial comparing CBT-AD to enhanced usual care in 45 depressed individuals with HIV/AIDS. Results showed that those who received CBT-AD achieved significantly greater improvements in medication adherence and depression relative to the control group, with control participants who crossed-over to CBT-AD after the acute outcome assessment achieving similar improvements in both depression and adherence outcomes. Treatment gains for those in the intervention group were generally maintained at 6- and 12-month follow-up assessments (Safren et al., 2009).

CBT-AD is currently being evaluated in an ongoing randomized controlled trial in depressed patients with type 2 diabetes (NIH 1R01 MH078571). While outcome data are not yet available, data from an open phase pilot of 5 depressed type 2 diabetes patients has been reported (Gonzalez *et al*., in press). This study provides preliminary evidence for a successful adaptation of CBT-AD, originally developed for patients with HIV, for patients with type 2 diabetes. CBT-AD appears to have been acceptable to all patients and successful in improving diabetes self-care and depression. All participants experienced an improvement in depressive symptoms and four of five patients demonstrated improvements in both depression and glycemic control. All participants reported improvement in self-reported glucose testing and all participants reported either a maintenance or improvement in self-reported medication adherence.

CONCLUSION

Depression and treatment nonadherence are two related problems that may significantly impact the health outcomes of patients with diabetes. While questions remain as to the aspects of depression that are most problematic for diabetes and regarding the mechanisms underlying the relationship between depression and worse diabetes outcomes, it is clear that depression is common among patients and that successful treatment would have important benefits for quality of life and functioning. It is also clear that treatment adherence among patients with diabetes is often suboptimal and that interventions that improve treatment adherence and health behaviors would have important benefits for the health of diabetes patients. The integration of strategies to improve treatment adherence and health behaviors with the treatment of depression provides an opportunity to maximize the likelihood of effects on diabetes treatment outcomes for these patients who appear to be at high risk for poor diabetes control, increased risk of diabetes complications, and early mortality. CBT-AD represents a promising approach toward this end. Ongoing studies will provide a more conclusive empirical evaluation of the efficacy of CBT-AD in the treatment of depressed patients with type 2 diabetes. Further studies are needed to address the need for interventions that would be appropriate for individuals with diabetes that may not be clinically depressed but may be struggling with problems with diabetes management and distress. As the CBT-AD approach has applicability across a wide range of chronic illnesses, patient populations, and treatment modalities, it is hoped that future studies will continue to build on this work to improve mental and physical health outcomes for patients struggling with chronic illness and distress.

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