Published in final edited form as:
Psychosomatics. 2011 ; 52(1): 1–18. doi:10.1016/j.psym.2010.11.007.

Treating Depression in Diabetes: Emerging findings

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Abstract

Depression in patients with diabetes is associated with poorer adherence and worse health outcomes, however treating depression may help improve these outcomes. The present systematic review identified published papers evaluating treatments for depression in patients with diabetes. Seventeen studies that met criteria were identified, indicating that psychosocial interventions, particularly cognitive-behavior therapy, anti-depressant medications, and collaborative care are effective in the treatment of depression in patients with diabetes. Evidence for the efficacy of these interventions in improving glycemic control was mixed. No study targeted adherence to treatment or health behaviors in addition to depression, which may be necessary to maximize improvement in diabetes outcomes such as glycemic control.

Introduction

Major depressive disorder is a highly prevalent and serious illness, with lifetime prevalence of 17%, and a point prevalence of 7%.[1,2] It is among the most serious health problems in the country, associated with substantial suffering, lost productivity, and loss of life.[3-5] Individuals with depression experience reduced functioning and decreased quality of life,[6-9] as well as higher health care utilization and costs, and disability.[10-12] Furthermore, depression is more prevalent in patients with chronic illness in general[13] and diabetes in particular, and it is associated with poor adherence to medical regimens in patients with comorbid medical illness.[14,15] The prevalence of type 2 diabetes is approximately 13%, and an additional 30% of individuals have pre-diabetes.[16] Depression may affect diabetes outcomes through either biological or behavioral pathways. Biological pathways through which depression may impact diabetes and its complications include hormonal abnormalities, alterations in glucose transport function, and increased immunoinflammatory activation.[17,18] Evidence suggests that depressive symptoms and heightened distress, even in the absence of a diagnosis of clinical depression, are associated with worse diabetes self-care and poorer diabetes control.[19] Furthermore, the relationship between depressive symptoms and poorer self-care appears to be linear, and is not restricted to comparisons between clinically depressed and non-clinically depressed individuals with type 2 diabetes.[20] For the purposes of this paper, the term “depression” will refer to elevated symptoms of depression, and we will explicitly note how different studies defined depression in their samples.

Patients with type 2 diabetes, previously known as adult-onset diabetes, have a rate of major depression 1.6-2.0 times higher than those in the general population. [21,22] Lifetime rates of

depression in patients with type 2 diabetes are between 24% and 29%,[23-25] and point prevalence is 10%-15%.[21,22] Type 2 is more common than type 1 diabetes (formerly known as childhood-onset diabetes); of the 23.6 million people in the United States diagnosed with diabetes, between 5 and 10% have type 1.[26] Type 1 diabetes is typically diagnosed in younger patients and requires treatment with external insulin, whereas type 2 usually develops later in life and may not necessitate the use of insulin. Research suggests that rates of depression are elevated in both conditions.[21,22,27],

Recognizing and treating depression in patients with diabetes may help avoid downstream adverse health-related outcomes. Patients with diabetes who are depressed have increased rates of mortality,[28-32] cardiac events,[33-35] hospitalizations,[32] diabetes-related complications,[36] functional impairment,[37,38] health-care costs,[39] medical symptom burden,[40] and a decreased quality of life[41] than do patients with diabetes who are not depressed. Meta-analyses have shown that depression is consistently associated with increased hyperglycemia[42] and increased risk of diabetes complications, including diabetic retinopathy, nephropathy, neuropathy, macrovascular complications, and sexual dysfunction.[36]

Self-care in diabetes is extremely important in the prevention of poor health outcomes. Adherence with treatment guidelines decreases rates of mortality and morbidity in diabetes[43] and helps achieve good diabetes control.[44] Self-care activities (e.g., increasing physical activity and maintaining healthy nutrition) can slow disease progression.[45-47] Non-adherence, which is more common in patients with depression, on the other hand, intensifies disease burden.[48-50] A recent meta-analysis of 47 independent studies showed that depressed patients with diabetes are less adherent to diabetes self-care regimens than non-depressed patients.[51] There is evidence that depressive symptoms affect physical symptoms related to glucose regulation through the pathway of poorer self-care.[52] Therefore, effective treatments for depression in patients with diabetes may not only improve depression and quality of life, but also indirectly improve disease outcomes and illness burden.

Meta-analyses also indicate that psychological interventions, which may include cognitive-behavior therapy (CBT), counseling, interpersonal therapy, or brief psychodynamic psychotherapy, are effective in reducing glycosolated hemoglobin A1c (HbA1c) levels by an average of .54%, which is clinically meaningful,[53,54] and improving quality of life[55] in both types of diabetes. One meta-analysis, however, found that psychological interventions were effective in children, but not adults, with type 1 diabetes.[56]

Although meta-analysis has advantages in terms of estimating the overall effects of psychosocial interventions, it is limited in its ability to examine the effects of methodological differences between studies. While these meta-analyses examined the effects of psychological interventions in diabetes, they did not focus on interventions that targeted depression or increased distress. The current paper is a comprehensive review of studies in diabetes that specifically aimed to reduce symptoms of depression, and examines evidence for additional effects on diabetes-related outcomes.

Three types of interventions are examined: psychosocial, pharmacological, and collaborative care. The psychosocial intervention that has received the most attention is CBT, a short-term, skills-based intervention designed to change negative thinking and increase positive behavior, such as problem-solving and relaxation, which has been shown to be effective for the treatment of depression.[57] Among pharmacological interventions, the selective serotonin re-uptake inhibitors (SSRIs) are the most commonly prescribed antidepressants because of their safety profile and their efficacy.[58,59] They have been recommended in depressed patients with diabetes, because they may cause hypoglycemia and weight loss in addition to

their antidepressant properties.[60] Fluoxetine, for example, can improve glycemic control.[61] Bupropion, a norepinephrine/dopamine reuptake inhibitor, is as effective for in the treatment of depression as the SSRIs,[62] and has shown favorable effects on weight in patients with obesity and depressive symptoms[63] and on glycemic control in patients with diabetes.[64] Other effective antidepressant medications, however, have been linked to side effects that are particularly undesirable in patients with diabetes. For example, monoamine oxidase inhibitors (MAOIs) can cause weight gain, and tricyclic antidepressants (TCAs) can cause hyperglycemia, both of which can be problematic in individuals without diabetes, but are especially counterproductive and even dangerous in patients with diabetes.[60] Atypical anti-psychotics, some of which are now approved for and have been shown to be effective in the treatment of depression,[65] can not only cause weight gain[66] but can worsen glycemic control in patients with diabetes and cause glycemic abnormalities (including the development of frank diabetes) in patients without a pre-existing diagnosis.[67] In addition to psychosocial and pharmacological interventions, researchers have also examined the treatment of depression in patients with diabetes in primary care settings, in which primary care practices deliver care in a stepped or algorithm-based approach.

Methods

Studies were identified using the following search criteria on Cochrane Review, PsychINFO, and Pubmed: (diabetes) plus (depression or mood) plus (treatment or intervention or trial). The search covered the years 1995-2008, inclusive. Additional studies were identified manually by reviewing the reference lists of retrieved papers and reviews.

We included studies that investigated individuals with type 1 or type 2 diabetes, including adults, children, and adolescents, analyzed separately from individuals without diabetes if such individuals were also included, and depressive symptoms or a diagnosis of depression; included a psychosocial and/or pharmacological intervention intended to treat depressive symptoms; assessed depression or depressive symptoms as a dependent measure, were published in peer-reviewed English-language journals, and applied pre-post or controlled trial design. Studies were not included if the intervention consisted of only diabetes education or adherence training, or if depression or depression severity was not a main outcome measure. Although studies testing an intervention to improve diabetes adherence have effects on mood, these studies are not designed as an intervention for depression and typically do not have the inclusion criteria of depression or depressive symptoms.

Intervention type was defined as psychosocial, pharmacological, or collaborative care. Psychosocial interventions were those in which the participants received some type of talk therapy designed to improve depressive symptoms, which includes but is not limited to cognitive, behavioral, and supportive interventions, and no medication. Pharmacological interventions were those in which the participants received an anti-depressant medication and no psychosocial intervention. Collaborative care interventions were those in which individuals received anti-depressant medication and/or psychosocial intervention, usually in a stepped care or algorithm-based approach.

We evaluated studies based on the methodological characteristics of study design (including comparison group and follow-up interval), analyses, inclusion criteria (including participants' age, diabetes type, and depression entry criteria), and use of HbA1c as an outcome measure. Routine blood tests measuring HbA1c are conducted every three months as part of the recommended standard of care of diabetes patients to monitor glycemic control over time and represent average glycemic control over an 8-12 week period, which should be maintained below 7%.

Results

Our search returned 17 studies that met our inclusion criteria. Six studies employed psychosocial interventions, eight studies employed pharmacological interventions, and three studies employed collaborative care interventions. Below, we review each intervention in detail.

Psychosocial interventions for depression in patients with diabetes

We found one published and completed randomized controlled trial (RCT) of CBT for depression in diabetes,[68] two RCTs of CBT interventions with methods but not results published,[69,70] one RCT of supportive psychotherapy,[71] and two uncontrolled pilot studies of group CBT.[72,73]

The published and completed RCT was conducted by Lustman and colleagues.[68] This team enrolled 51 patients age 21-70 with type 2 diabetes and MDD, as determined by the Diagnostic Interview Schedule (DIS), and a Beck Depression Inventory (BDI) score of >= 14 (see Table 1 for assessment descriptions and Table 2 for study information). All participants received individual one-hour diabetes education sessions with a trained diabetes educator every other week. Participants who were randomly assigned to the experimental condition also received ten weeks of individual CBT for depression. Pre-treatment mean HbA1c levels were 10.2% +/- 3.6% for patients in the intervention group and 10.4% +/- 3.1% for patients in the control condition. An intent-to-treat analysis revealed that 87% of the patients in the CBT group achieved remission (defined as a BDI score <9); this was significantly greater than that of patients in the control condition who achieved remission (27.3%, $p<.001$). The authors also found that 66.6% of patients in the CBT group achieved clinically significant improvement (defined as >= 50% reduction in the BDI score), compared with 29.6% of patients in the control group. At 6-month follow-up, 58.3% of the patients who received CBT remained in remission, which was significantly greater than for the education-only group (25.9%, $p=.03$); 58.3% of the CBT group had clinically significant improvement, while only 29.6% of the education-only group manifested clinically significant improvement ($p=.01$). Assessment after treatment revealed no difference in HbA1c levels between the two groups, but at 6-month follow-up, those in the CBT group had significantly lower (9.5% v. 10.9%, $p=.03$) levels than did those in the education-only group. There were no statistically significant differences in self-monitoring of blood glucose levels between the two groups. An analysis of time-by-group interaction revealed that adherence to blood glucose monitoring declined among participants in the CBT group compared to the control group.

This is a well-designed study, with several methodological strengths, including use of RCT design with education-only comparison group and 6-month follow-up, intent-to-treat analyses, and use of HbA1c levels as a primary outcome measure. Adding to the internal validity and the clinical significance, only patients with a diagnosis of MDD and type 2 diabetes were included. Poorly controlled diabetes was not an inclusion criterion, though it was common among patients in the study. This allowed for the possibility that improving depressive symptoms could have an effect on glucose control. At six-month follow-up, patients in the CBT condition did indeed have significantly better glucose control than those in the education-only condition.

Two RCTs have examined CBT for patients with depression and diabetes whose methods, but not results, have been published. The Depression in Elderly with Long-Term Afflictions study is a randomized controlled trial that examined the effectiveness and cost-effectiveness of Minimal Psychological Intervention, which consists of up to ten sessions over three months of individual CBT delivered by a nurse during home visits.[69] Researchers enrolled

180 elderly adults with type 2 diabetes and minor or mild to moderate MDD, as assessed by the Mini International Neuropsych Interview (MINI) and Hamilton Depression Rating Scale (HDRS) score >= 18. Patients were assigned to either treatment as usual or the intervention, with the BDI as the main outcome measure. Results of the trial are forthcoming, but will be important due to inclusion of patients with type 2 diabetes over the age of 60, a population at high risk for depression and for medical complications.

A Dutch group has designed an RCT to compare an eight-week web-based CBT self-help intervention to a waitlist control condition for adults (18 and over) with type 1 or type 2 diabetes and depression, assessed by score >=16 on the Center for Epidemiological Studies Depression scale (CES-D) and confirmed by the Composite International Diagnostic Interview (CIDI).[70] In this study, the primary outcome measures are the CES-D and patient HbA1c levels, with 286 patients expected to enroll. One of the significant aspects of the study is the planned HbA1c outcome analysis. Though generalizable if efficacious, interpretability may require differentiating effects for type 1 and type 2 patients, the wide age range of patients, and the range of depressive symptoms at entry.

The single published RCT of supportive therapy for depression in diabetes is a pilot study and provides initial support for its efficacy. Researchers randomized 30 inpatients with type 1 or type 2 diabetes and diabetic foot syndrome (ulcer, infection and deep tissue damage, caused in part by diabetic neuropathy of the extremities, and can result in amputation) and any depressive symptoms, as assessed by the Hospital Anxiety and Depression Scale (HADS).[71] Patients had a pre-treatment mean HbA1c of 8.1% +/- 1.9%. Patients were assigned to either treatment as usual or weekly individual supportive psychotherapy (average five sessions) during their hospital stay. There was an average change of -1.6 in the therapy group and 0.3 in the treatment as usual group on the depression scale of the HADS (p=.02). As a pilot study, this study has the methodological strength of RCT design with usual care comparison group, though it lacked a follow-up interval. Additionally, likely due to power, it is limited by the use of pre-post analyses instead of comparing the treatment conditions to each other, and the inability to test for HbA1c as an outcome measure. Accordingly, this is a promising intervention approach, with potential real-world significance, in need of further testing.

There are two uncontrolled studies of group CBT for depression in diabetes. Georgiades and colleagues enrolled 90 adults (age 18 and over) with type 1 or type 2 diabetes and depressive symptoms, as assessed by a BDI score of 10 or greater, in a 14-week study of group CBT (16 90-minute sessions) with 12 month follow-up period.[72] The intervention included cognitive restructuring, problem solving, communication, and goal-setting skills, applied especially to diabetes-related thoughts and activities. Participants had a significant reduction on the BDI from baseline over the 12-month period (p<.001), and a significant reduction in the HDRS from baseline to 3-month follow-up (p<.001). There were no significant changes in HbA1c level (from baseline of 7.6% +/- 1.6%). Follow-up analyses that split the sample into high (>8%) and low (<6.5%) HbA1c level subgroups also did not find a significant reduction in HbA1c level in either group. This study was designed to test differences in response to treatment between patients with type 1 and type 2 diabetes, so it is limited by its open-label design without a comparison group and use of a pre-post completer analyses. However, it used HbA1c levels as a primary outcome measure.

The other uncontrolled study of group CBT was a pilot study for type 1 diabetes, with 11 Puerto Rican adolescents with any depressive symptoms, as assessed by the Children's Depression Inventory (CDI); participants who enrolled in 12 week CBT group had a significant reduction (p<.05) on the CDI pre- and post-intervention.[73] They did not, however, exhibit significant changes in HbA1c level (pre-intervention mean of 9.3% +/-

1.9% and post-intervention mean of 9.8% +/- 2.5%). The intervention consisted of 12 2-hour sessions including psycho-education about depression and diabetes, cognitive restructuring, activity scheduling, and communication skills training. This is a pilot study, so it is therefore in need of replication with an RCT design, larger sample size, and follow-up interval, and intent-to-treat analyses. It has the strength of HbA1c as an outcome measure.

Conclusions regarding psychosocial intervention studies

Treating depression in patients with diabetes is an emerging area of research, and the existing literature is appropriately limited to this stage. The existing completed studies of CBT for depression in diabetes include one RCT of type 2 patients[68] and two open-label studies of group CBT, one with type 1 adolescent patients,[73] and the other with type 1 and 2 adult patients.[72] Including both type 1 and type 2 increased external validity; however, stronger effects might have emerged for one or the other condition should the inclusion criteria have been restricted to just one type. These studies have used various measures to define and measure depression and this may have resulted in some heterogeneity within and between samples. Further, no study selected patients based on poor diabetes control; this may have limited the ability of the interventions to find an effect on HbA1c. Finally, little attention has been paid to mediating pathways (e.g., improvements in self care or potential biological pathways) that may explain potential effects on HbA1c. For example, only Lustman and colleagues reported data on changes in self-care but, surprisingly, found that the intervention condition exhibited a decrease in glucose monitoring relative to the control condition. It is surprising that the CBT condition experienced decreased adherence to self-monitoring of blood glucose. The authors explain this result by suggesting that individuals in the CBT condition may have directed their attention toward depression management and away from glucose monitoring.[68] The fact that the intervention achieved a beneficial effect on HbA1c without increased glucose monitoring is consistent with growing evidence suggesting that consistent self-monitoring of blood glucose may not necessarily result in improved control for type 2 diabetes patients who are not on insulin, and therefore adherence to glucose monitoring may not be an appropriate self-care outcome variable.[74]

These studies suggest that psychosocial interventions, particularly CBT, are effective in improving depression in patients with diabetes, a population with increased levels of depression. Whether these interventions are also effective in improving self-care and physical health outcomes like glucose control requires further investigation.[75] Additionally, the studies that did treat depression with CBT did not include or integrate skills for adherence to self-care. Treating depression with CBT and not adherence may decrease the ability to see effects on self-care because it is more distal to the intervention target. However, one well-designed and controlled psychosocial intervention detailed above found that CBT was more effective at improving HbA1c levels at six-month follow-up than education alone,[68] suggesting that this is an area worthy of future investigation.

Psychopharmacological interventions for depression in patients with diabetes

SSRIs—To date, there are four published randomized placebo-controlled trials of SSRIs in depressed patients with diabetes (see Table 3); one compared fluoxetine to a placebo,[76] one compared sertraline to a placebo,[77] and two compared paroxetine to a placebo.[78,79] There is one open-label trial of s-citalopram[80] and one RCT comparing fluoxetine to paroxetine.[81]

Lustman and colleagues[76] enrolled 60 patients age 21-64 with either type 1 or type 2 diabetes and MDD, as determined by the DIS and a score>= 14 on the BDI or the HDRS and randomized them to receive either fluoxetine or a placebo for eight weeks. They found a significantly (p=.03) greater reduction in depression severity in the fluoxetine group (with an average BDI reduction of 14 and an average HDRS reduction of 10.7) than in the placebo

group (with an average BDI reduction of 8.8 and an average HDRS reduction of 5.2). Additionally, they found significantly (*p*=.03) greater clinical improvement (defined as greater >=50% reduction in the depression severity score) in the fluoxetine group when measured by the BDI, but not when measured by the HDRS. During the trial, patients in the fluoxetine group and the placebo group did not show statistically significant differences in HbA1c. The inclusion of type 1 and type 2 diabetes patients, however, could possibly have reduced the ability to find HbA1c outcomes.

In another double-blind RCT, researchers enrolled 351 patients age 18-80 with type 1 or type 2 diabetes and MDD, as assessed by the DIS and a BDI score of 14 or an HDRS >= 16, and treated them with open-label sertraline.[77] At baseline, patients had an average HbA1c level of 8.2% +/- 1.7%. One hundred fifty-two (42%) achieved remission, defined as BDI score of 9 for four consecutive bi-weekly visits; patients were then randomized to maintenance therapy on sertaline or a placebo for 52 weeks or until depression recurrence. Sertraline maintenance conferred greater protection from recurrence of depression (hazard ratio = .51) than did the placebo. HbA1c levels improved during open treatment phase, and remained significantly lower than pre-treatment levels during the maintenance phase, and did not differ significantly between groups. Secondary analysis of these data indicated that among patients less than age 55, sertraline conveyed significantly greater prophylaxis against depression (hazard ratio = .37) than did placebo, but in patients over the age of 55, this was not the case (hazard ratio = .94); there was no difference between age groups for time to recurrence on sertraline, but older patients took longer until recurrence on placebo than did younger patients.[82]

Paile-Hyvarinen and colleagues recruited 15 mildly depressed (as defined by a score of 2.5-12 on the Mongtomery-Asberg's Depression Rating Scale [MADRS]) post-menopausal women with type 2 diabetes that was not optimally-controlled (defined by an HbA1c level >=6.5% or a fasting blood glucose level >=7 mmol/l).[78] They were randomized to receive up to 10 weeks of either paroxetine or a placebo. No significant differences between groups were detected with regard to depression scores on the MADRS or the BDI. There was, however, a statistical trend (*p*=.08) for more improved HbA1c in the paroxetine-treated group (-.44% from baseline of 7.5% +/- .8%) than in the placebo group (-.07% from baseline of 6.9% +/- .4%). The inclusion of only patients with non-optimally-controlled diabetes provided the opportunity to demonstrate improvement in glucose control. However, the levels of depressive symptom severity in this sample were quite low and this could have limited the ability to find an effect on depression. A difference between the groups in this domain might have been evident with a larger sample. The focus on type 2 post-menopausal women with mild depressive symptoms may limit its generalizability, though internal validity is increased.

In the other RCT of paroxetine, 49 mildly depressed (as defined by meeting criteria for, but having fewer than 6 DSM-IV symptoms of, MDD, as determined by clinical interview) patients with non-optimally controlled type 2 diabetes (HbA1c>=6.5% or a fasting blood glucose level >=7 mmol/l) patients aged 50-70 years were randomized to six months of paroxetine or a placebo.[79] There were no significant differences in HADS scores between the groups. After three months, HbA1c levels were significantly (*p*=.018) lower in patients in the paroxetine group (7.9% +/- 0.6% down from baseline 8.5% +/- 0.9%) than in the placebo group (8.5% +/- 0.6% down from baseline 8.7% +/- 1.3%), but this difference was not maintained at six months. Again, the inclusion of only patients with non-optimally-controlled diabetes provided the opportunity to demonstrate improvement in glucose control, and a difference between groups was observed.

One published open-label study has been completed of SSRI treatment in depressed patients with diabetes.[80] Researchers gave 14 patients age 19 and over with comorbid MDD (assessed by the SCID and HDRS score >=16) and type 1 or type 2 diabetes, open-label s-citalopram for up to 16 weeks. They found a significant reduction in mean HDRS scores and a limited non-significant decrease in HbA1c levels (–0.36%). As a pilot study, without comparison group or follow-up interval, the results require replication and extension.

Finally, there has been one published randomized double-blind study that has compared the efficacy of two different SSRIs. Gulseren and colleagues enrolled 23 patients with type 2 diabetes and MDD (as determined by the SCID and an HDRS score >= 16) from a hospital in Turkey and randomized them to either fluoxetine or to paroxetine for 12 weeks.[81] Baseline HbA1c was 6.9% +/- 1.2% in the paroxetine group and 6.9% +/- 1.7% in the flouxetine group. Both groups had statistically significant improvement in their HDRS score, while the fluoxetine group had a non-significant decrease in HbA1c levels. Though the strength of double-blind RCT design gives it high internal validity, the lack of a placebo or no-treatment control makes it hard to determine if the effects may have been regression to the mean. Taken together, the studies of SSRIs suggest that SSRIs are effective in reducing depressive symptoms and preventing relapse in patients with depression and diabetes. There is also the suggestion from these data that SSRIS may also help reduce HbA1c levels, though this needs to be confirmed in larger trials. Presently, no SSRI has been shown more effective than another at reducing symptoms of depression or HbA1c levels in this patient population.

TCAs—While the SSRIs have shown efficacy in the treatment of depression, and reduction of HbA1c levels in patients with MDD and diabetes, the TCAs have not been examined as closely in this population, perhaps because of their unfavorable side effect profile. One published double-blind RCT of a TCA in depressed diabetic patients has been published.[83] Lustman and colleagues randomized 68 patients with type 1 or type 2 diabetes and poor glycemic control (defined as HbA1c >= 9%) 28 of whom had current MDD (as determined by the DIS) to receive either notriptyline or placebo for eight weeks. Baseline HbA1c levels were 11.8% +/- 2.9% in the nortiptyline group and 11.6% +/- 3.1% in the placebo group. They found a significantly greater reduction in depression among depressed patients on nortriptyline (57% remitted, defined as a final BDI score of < 10) than on placebo (35.7% remitted). Nortriptyline was not, however, superior to placebo in reducing HbA1c levels; in fact, path analysis indicated a direct hyperglycemic effect of nortriptyline, but improvement in depression helped glycemic control, such that there was a hyperglycemic effect in non-depressed nortriptyline-treated participants, which was significantly different from placebo-treated patients. In depressed patients, glycemic control improved in both conditions without a significant difference.

Other—There has been one published study of another antidepressant in patients with diabetes and depression. Lustman and colleagues enrolled 93 patients with type 2 diabetes and MDD (as assessed by the DIS) who received open-label bupropion for 10 weeks; the 63 patients (84%) whose depression remitted were followed for an additional 24 weeks.[64] They found that Body Mass Index (-0.5 +/- 1.1 kg/m^2 from baseline 36.0 +/- 7.5), body fat (-0.7 +/- 1.8 kg), and HbA1c levels (-0.5% +/- 1.0% from baseline 8.3% +/- 2.0%) decreased significantly (all $p<.01$) in the acute phase, and that these changes were maintained in the maintenance phase. Reductions in BMI and depression severity independently predicted lower HbA1c levels after the acute phase, whereas only decrease in depression severity predicted lower HbA1c levels over the maintenance trial. Patients reported significant improvement in adherence to diet and exercise on the Summary of Diabetes Self-Care Activities scale during the acute phase and remained significantly improved compared to baseline during the maintenance phase; adherence to glucose testing, however, did not

change.[64] A strength of this study is that it is the only published intervention found in our review that comprehensively measured diabetes self-care pre- and post-treatment. This is also the first study to suggest that an intervention aimed at reducing depression severity was also associated with improvements in diabetes self-care. It is limited, however, by its open-label design without comparison group, and pre-post design.

Conclusions regarding psychopharmacotherapy studies

In studies of comorbid diabetes and depression, nortriptyline (a TCA) has led to worsening of indices of glucose control, whereas fluoxetine and sertraline (both SSRIs) produced results consistent with reductions in glucose levels.[61] Buproprion has shown promise as an effective antidepressant with favorable effects on glucose control. Most psychopharmacotherapy studies have been well designed; many are double-blind placebo-controlled RCTs. Four included only type 2 patients, and four included both type 1 and 2 patients. One study used intent-to-treat analyses,[78] whereas the other seven relied on completer analyses. The field could, however, benefit from studies with longer follow-up periods. It would be useful to know if gains are maintained effectively over time, or if patients decline or continue to improve, in both depression and glucose control. There is also promising evidence that improvements in depression could be associated with improvements in self-care, but the only study designed to examine this possibility was an open-label trial, and therefore further investigation is warranted.

Collaborative care interventions for depression in diabetes

In two of three published collaborative care intervention studies, researchers enrolled a large group of depressed patients, and then performed additional analyses of the data on a subset of patients with diabetes (see Table 4).[84,85] The Pathways study (described below), on the other hand, recruited only patients with diabetes and depression.[86]

In the Pathways study, 329 patients with diabetes and depression (as assessed by a Hopkins Symptom Checklist 20 Depression Scale (HSCL-20) score > 1.1 and a Patient Health Questionnaire-9 (PHQ-9) score >=10) were recruited from nine primary care clinics that were randomized to the Pathways intervention or treatment as usual.[86] Baseline HbA1c was 8.0% +/- 1.5% in the usual care group and 8.0% +/- 1.6% in the intervention group. The Pathways intervention consisted of an initial one-hour interview, followed by twice-monthly half-hour visits (in-person or telephone) for 12 weeks. Patients had an initial choice of pharmacotherapy or problem-solving treatment, an empirically supported nurse-administered depression intervention consisting of problem solving how to increase activity and change negative thinking. Patients in primary care practices randomized to the Pathways intervention had less severe depression over 12 months (z=2.84, p=.04) than those in the treatment as usual practices, but there was no difference between groups in HbA1c levels. The Pathways intervention was significantly more successful at reducing depression in patients with two or more complications than treatment as usual (z=-2.26, p=.02), whereas patients with fewer than two complications did not have significantly different outcomes between pathways and treatment as usual.[87] The Pathways intervention was not associated with improved adherence to diabetes self-care regimens (e.g., healthy nutrition, exercise, and smoking cessation), and was associated with *worse* adherence to oral hypoglycemic medications over the 12-month follow-up period; it is not known why this was the case, but perhaps the addition of enhanced depression treatment for the intervention group to the standard management of diabetes all patients were already engaged in, without the integration of adherence training, was overwhelming to patients.[88] The intervention did not focus on improving skills to better manage diabetes but instead focused on the treatment of depression. On the other hand, patients in practices in intervention groups had outpatient health costs of $314 less than those in treatment as usual practices, and had 61 additional

depression-free days; when depression-free days are valued at $10/day, the Pathways intervention results in a net economic benefit of $952 per patient.[89]

The Improving Mood Promoting Access to Collaborative Treatment (IMPACT) study is one of the two depression trials that were large enough to examine a subset of individuals with both diabetes and depression. Four –hundred seventeen patients age 60 years or older with diabetes and MDD or dysthymia (as assessed by the SCID) were randomized in primary care practices to either the intervention or to treatment as usual.[85] Baseline HbA1c levels were 7.3% +/- 1.5% in the usual care group and 7.3% +/- 1.3% in the intervention group. Patients in practices assigned to the intervention received psychoeducation about depression through a 20-minute videotape and were encouraged to meet with a depression care manager, who worked collaboratively with the patients primary care physician. Similar to the Pathways intervention, patients had an initial choice of six to eight sessions of problem-solving treatment delivered by the depression care manager or antidepressant medication (usually an SSRI) prescribed by the primary care physician. For patients already receiving antidepressant medication but still experiencing depression, the recommendation for partial responders was to increase the dose or add problem solving therapy, and the recommendation for non-responders was to switch medications or try the problem solving therapy. Patients in practices in the intervention condition had less severe depression (as measured by the HSCL-20) at 12-month follow-up than patients in the treatment as usual group (difference of 0.43 on 0-4 scale on HSCL-20). There was no difference in HbA1c levels in the two groups, but this may be due to the fact that the average HbA1c levels at baseline were well controlled. Patients in practices in the intervention condition had 115 more depression-free days over 24 months than did patients in the treatment as usual practices, with no greater cost than was found in the treatment as usual group.[90]

A large sample of 584 individuals with MDD (as assessed by the SCID) or minor depression (with at least four neurovegetative symptoms and an HDRS score >=10) in the Prevention of Suicide in Primary Care Elderly: Collaborative Trial (PROSPECT) were randomized by primary care practice to receive depression care management or to usual care for 12 weeks and followed for five years.[85] Similar to Pathways and IMPACT, practices in the depression care group had a depression care manager who collaborated with the physician by helping to recognize depression, by offering guideline-based treatment recommendations, by monitoring clinical status, and by providing follow-up.[91] The guidelines included use of citalopram as a first-line treatment. If this was declined, the physician could recommend Interpersonal Psychotherapy, which is an empirically supported psychosocial intervention for depression,[92] provided by the depression care manager. Among the 123 patients with diabetes in the study (70 assigned to the intervention condition and 50 assigned to the usual care condition), at the end of five years, those in the treatment condition had significantly lower (HR = .49) rates of mortality (68.2/1,000 person-years) than did those in the usual care condition (103.4/1,000 person-years). Methodological strengths of PROSPECT include RCT design with usual care comparison group and 5-year follow-up period.

The stepped care approach is cost-effective and improves depression in patients with diabetes in primary care. It does not, however, appear to confer the benefits on HbA1c levels that were present in CBT and SSRI interventions examined separately. These studies have the advantages of large sample sizes and long follow-up periods. They include patients who may not meet diagnostic criteria for MDD, which can increase generalizability, but may potentially somewhat limit internal validity. Two of the studies are also limited by performing additional analyses on a subset of patients with diabetes from the original sample, from which conclusions about causality cannot be drawn.

Conclusion

CBT and antidepressants (including SSRIs, nortryptyline, and buproprion) examined separately or in collaborative care approaches are effective in treating depression in patients with diabetes, but evidence for benefit in glycemic control is mixed. Our review identified a mix of smaller studies, and studies that were large well-controlled RCTs using appropriate statistical methods. Some examined HbA1c as an outcome measure, whereas others only considered changes in depressive symptoms. Several methodological issues could have had an impact on the ability to find an effect on glycemic control in the reviewed studies.

Most of these studies did not attempt to recruit patients with poorly controlled HbA1c levels in particular, so they did not necessarily examine the interventions' effects on glycemic control in the patients most in need of improvement. Among the psychosocial intervention studies, only two studies examined HbA1c outcomes, and the one with patients with poorly controlled diabetes at baseline (mean baseline level greater than 10%)[68] found a significant treatment outcome difference in HbA1c, whereas the one with patients with better controlled baseline levels (mean baseline level of 7.6%) did not.[72] Among the psychopharmacological and collaborative care intervention studies, there was no evidence that studies with higher baseline HbA1c levels were more able to show a treatment effect on glucose control. Future intervention studies may maximize the potential effects on diabetes control by focusing on patients who are in poor control.

Only two studies measured changes in self-care or treatment adherence as a possible mechanism of the effect of depression treatment on glycemic control. The Pathways study was the only one reviewed here that comprehensively examined adherence to self-care regimens as a potential pathway to improved glycemic control, and patients in the intervention group (collaborative care) had the same or worse adherence as patients in the usual care group.[88] Similarly, Lustman and colleagues reported that participants assigned to the CBT intervention had worse adherence to self-monitoring of blood glucose, as compared to controls.[68] Neither of these studies tested interventions that were designed to directly improve diabetes self-care or adherence; it may be that this represents a missed opportunity to maximize the effect of depression treatment on diabetes outcomes. Treating depression may be a necessary but not sufficient step in improving glycemic control in patients with diabetes. While it appears plausible that depression may interfere with patients' ability to successfully manage the diabetes self-care regimen,[51] there is not evidence that alleviating depressive symptoms will automatically result in improvements in self-care and adherence.[68, 88] Meta-analyses of depression's relationship to hyperglycemia,[42] diabetes-complications,[36] and diabetes treatment nonadherence,[93] suggest that while the relationship between depression and these important diabetes outcomes is robust, it is also in the small to medium range. Novel intervention approaches that integrate adherence training with strategies aimed at decreasing depressive symptom severity may capitalize on the consistent relationship between depression and nonadherence and may result in greater improvements in diabetes control than interventions that focus on depression alone. Thus, future trials and clinical intervention with depressed diabetes patients may be strengthened by an integrative, multidisciplinary, approach that simultaneously treats depression and diabetes treatment nonadherence from a behavioral perspective.

Diabetes is a complex disease that requires intensive self-care involving adherence to prescribed medications, monitoring of blood glucose, adherence to dietary and physical activity recommendations, preventive foot care, attendance at medical appointments and regular screening for complications. It has been estimated that approximately two hours per day are required to meet the American Diabetes Association recommended guidelines for self-care for patients taking oral hypoglycemics.[94] Patients who have been depressed may

need an intervention that targets adherence to this demanding regimen in addition to treatment for their depression alone. Comprehensive treatment with emphasis on both the diabetes and the depression may be required for optimal outcome.[95]

Behavioral management strategies for depression and diabetes are similar in important ways, suggesting that there is the potential for the treatments to be synergistic. There is, however, little empirical evidence to suggest how these treatments may be optimally integrated. It is imperative that researchers examine how to effectively integrate care to improve treatment outcome as the behavioral treatment of both conditions may be an area of synergistic overlap. For example, behavioral activation, which has demonstrated efficacy in the treatment of depression[96] can also be helpful in the management of diabetes, as it encourages individuals to engage in activities (e.g., exercise, healthy eating strategies, and diabetes self-care) that give them a sense of mastery. Considerable evidence supports the benefits of exercise for improved diabetes.[97,98] There is also an expanding body of literature that exercise has a beneficial effect on mood and stress reactivity.[99]

Diabetes self-care behaviors themselves may have an impact on mood. If a patient has low self-efficacy regarding his or her diabetes self-care (e.g., believes that he or she is unable to perform adequate self-care), or negative thoughts about the future regarding his or her disease, struggles with diabetes self-care may worsen mood, because these negative thoughts are triggered. If, on the other hand, a patient can learn to reframe his or her thoughts to see diabetes self-care as a positive step toward taking care of his or her health, he or she may experience a sense of mastery, and thus mood improvement, from engaging in diabetes self-care activities. Integrated treatments, particularly CBT for depression and adherence,[100] may help change thought patterns so that these necessary and important activities can synergistically enhance both mood and diabetes management. An intervention that incorporates cognitive behavioral therapy with training in medication adherence skills has been effective in HIV/AIDS, with large effect sizes for both adherence and depression compared to an enhanced treatment as usual condition, and may serve as a model for future work in diabetes.[51,100] Non-pharmacological interventions should target negative diabetes-related cognitions and diabetes self-care and adherence in addition to depressive cognitions and behavior. A recently published intervention to improve diabetes self-care that integrated diabetes education with mindfulness and acceptance skills applied to diabetes-related thoughts and feelings was successful at significantly improving glucose control, compared to education alone.[101] While this intervention did not meet our inclusion criteria because it did not recruit patients with depressive symptoms per se, it is suggestive that integrative treatments can be effective.

Currently available treatments for depression are effective in reducing depression, but do not consistently reduce HbA1c levels in depressed patients with diabetes. Meta-analyses of depression's relationship to hyperglycemia,[42] diabetes-complications,[36] and diabetes treatment nonadherence,[93] however, suggest that while the relationship between depression and these important diabetes outcomes is robust, it is also in the small to medium range. Novel intervention approaches that integrate adherence training with strategies aimed at decreasing depressive symptom severity may capitalize on the consistent relationship between depression and nonadherence and may result in greater improvements in diabetes control than interventions that focus on depression alone.

The available evidence reviewed here also suggests that the SSRIs may have a synergistic effect on both mood and HbA1c levels in depressed diabetes patients. Nortryptyline, on the other hand, appears to have a potentially antagonistic effect; while it helps with depressive symptoms, it can adversely affect glucose control.[83] While antidepressants may have an important role to play in the treatment of depression in diabetes, there is also some cause for

concern. Use of anti-depressant medications was shown to be associated with increased risk of developing diabetes in a large sample of patients participating in the Diabetes Prevention Program who are already at elevated risk for diabetes (through overweight, elevated fasting glucose, and impaired glucose tolerance). This relationship was maintained even after controlling for depressive symptoms and other factors known to increase risk of diabetes.[102] Antidepressant use was also found to be associated with a range of cardiovascular disease risk factors (e.g., elevated blood pressure and serum lipids) in a large sample of overweight type 2 diabetes patients participating in the Look AHEAD trial, again independent of depression symptoms.[103]

Recommendations for Future Research

Further research is needed in order to examine the mechanisms and potential causal nature of the relationship between diabetes and depression. Randomized controlled trials could provide a useful methodology to examine mediators and moderators of the effect of depression treatment on diabetes outcomes and there are several areas that remain understudied. First, no psychological intervention targeting depression in type 1 diabetes patients with clinically significant depression has been tested in an RCT. This may represent an important opportunity to conduct a depression treatment study in patients with type 1 diabetes that is designed to test whether improvements in depression result in improved self-care, as the self-care regimen is more focused on insulin adherence rather than the wide variety of self-care behaviors that are important in type 2 diabetes. The internal validity would be improved by reducing the heterogeneity of self-care regimens among participants. A recent study reported evidence to support self-care as a mediator between depression and hyperglycemia in a sample of type 1 adolescents; blood glucose monitoring accounted for 37.5% of the depression symptoms – glycemic control link in a cross-sectional design.[104]

Second, future studies could be strengthened by expanding the focus on outcomes beyond HbA1c to include additional health outcomes as well as proposed mechanisms for the relationship between depression and hyperglycemia (e.g., treatment adherence, weight, cortisol, inflammatory cytokines). While depression in diabetes is associated with increased cardiac events,[33-35] hospitalizations,[32] diabetes-related complications,[36] functional impairment,[37,38] medical symptom burden,[40] and a decreased quality of life,[41] none of the studies reviewed here examined potential effects on these other important health and quality of life outcomes. This may be due to the fact that to examine distal outcomes would require much larger sample sizes and statistical power. However, it may be valuable for studies to identify markers of risk for these more distal outcomes and evaluate the effect of treating depression on these risk-markers (e.g., cardiovascular disease risk factors, proposed biological mediators of the link between depression and hyperglycemia). One study that suggested that there might be a benefit for mortality risk, but design limitations (i.e. a subset of participants in a larger trial who had diabetes were analyzed) of that study require caution in interpreting the results.[84] Future intervention studies would be strengthened by an examination of whether treatment of depression has an effect on any of these important health and quality of life outcomes. They would also contribute to progress in this field by examining changes in potential mediators for the depression – hyperglycemia link. To date, while there is much evidence for the consistency of this link, there is little evidence to support its causal nature or to explain the underlying mechanisms. RCTs that are well designed to measure changes in potential mechanisms over time would be valuable.

Finally, although the issue of whether treating depression could improve diabetes control directly is an important research question, we should not underestimate the importance of treating depression as an end in itself in patients with diabetes. Depression in patients with diabetes is prevalent, associated with increased functional disability, and reduced quality of life.[31,105] Further research is needed to maximize the efficacy of our interventions on

depression in diabetes as an outcome in its own right. Although our review suggests that treatments can significantly improve depressive symptoms in patients with diabetes, many patients were not treated to remission. In the Pathways study, only 37% of patients in the treatment condition achieved response of at least 50% reduction in scores of depressive symptoms from baseline at 6-month follow-up.[88] While this was significantly higher than usual care, it still indicates that further investigation is warranted to develop more powerful treatments to more successfully treat depression. Furthermore, the fact that many patients are not achieving remission could be part of the reason why we do not see improvement HbA1c values. In the study of CBT for depression by Lustman and colleagues, 85% of patients in the treatment condition were remitted at the end of treatment; this is also one of only two studies to show a significant difference in HbA1c between treatment and control patients. [68] Thus, more work is needed to develop and refine depression treatments that are more powerful than those previously studied.

The current literature supports the utility for both psychosocial and pharmacological interventions for depression in patients with diabetes. Still required, however, is the study of integrated treatment that combines treatment for depression and adherence to diabetes self-care regimens in a synergistic fashion. The field has advanced in the identification of treatments that are effective in improving depression in this population, but still has not reached the stage where optimal treatment results in long-term psychological and physical benefits. The development and testing of integrated treatment to simultaneously manage both depression and diabetes should be a high priority for further investigation.

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Table 1

Measures

Measure	Format	Outcome	# of Items	Score Range
Diagnostic Interview Schedule (DIS)	Clinician-administered semi-structured interview	DSM-IV diagnosis of MDD, dysthymia, other psychiatric disorders	Response dependent	Presence or absence of diagnosis
Beck Depression Inventory (BDI)	Self-report	Depression severity	21	0-63
Mini International Neuropsych Interview (MINI)	Clinician-administered semi-structured interview	DSM-IV diagnosis of MDD, dysthymia, other psychiatric disorders	Response dependent	Presence or absence of diagnosis
Hamilton Depression Rating Scale (HDRS)	Clinician-administered rating scale	Depression severity	21	0-66
Center for Epidemiological Studies Depression Scale (CES-D)	Self-report	Depression severity	20	0-60
Composite International Diagnostic Interview (CIDI)	Clinician-administered semi-structured interview	ICD-9 diagnosis of MDD, dysthymia, other psychiatric disorders	Response dependent	Presence or absence of diagnosis
Hospital Anxiety and Depression Scale (HADS)	Self-report	Depression and anxiety severity	14	0-42 Total 0-21 Depression subscale 0-21 Anxiety subscale
Children's Depression Inventory (CDI)	Self-report	Depression severity	27	0-54
Montgomery-Asberg's Depression Rating Scale (MADRS)	Clinician-administered rating scale	Depression severity	10	0-60
Structured Clinical Interview for DSM-IV (SCID)	Clinician-administered semi-structured interview	DSM-IV diagnosis of MDD, dysthymia, other psychiatric disorders	Response dependent	Presence or absence of diagnosis
Hopkins Symptom Checklist-20 Depression Scale (HSCL-20)	Self-report	Depression severity	20	0-4
Patient Health Questionnaire-9 (PHQ-9)	Self-report	DSM-IV diagnosis of depression and depression severity	9	0-27

Table 2

Psychosocial interventions

Reference	Study Design	Depression Entry Criteria	M(SD) Baseline HbA1c levels	Enrolled/Completed	Treatment modality/Duration/Type	Depression Measures	Significant Depression Outcomes	Significant Health/Glucose Outcomes	Methodological Characteristics
Lustman et al., 1998	RCT of CBT w/ education, education only	DIS diagnosis of MDD, BDI>13	10.2 (3.6)% for patients in the intervention group, 10.4 (3.1)% in the control group	51/42	CBT, 10 weeks, individual	BDI	ITT: 70.8% CBT achieved remission (BDI<9) v. 22.2% education (p<.001) and 66.6% CBT achieved clinical improvement v. 29.6% education (p=.01). At 6-mo f/u, 58.3% CBT in remission v. 25.9% education (p=.03) and 58.3% CBT achieved clinical improvement v. 29.6% education (p=.01).	No difference in HbA1c levels at post-treatment. At 6-mo f/u, CBT = 9.5% and education-only = 10.9% (p=.03)	RCT w/education-only comparison & 6-month follow-up interval, ITT analyses, age 21-70, type 2 only, MDD criterion, HbA1c as primary outcome measure
Lamers et al., 2006	RCT of MPI, TAU	MINI diagnosis of Major or Minor Depression, HDRS > 18	TBA	Goal of 180	CBT, up to 10 visits over 3 mos., individual at-home nurse-delivered	BDI	TBA	N/A	RCT w/ TAU comparison and 9 month follow-up interval, planned ITT analyses, age 60 and over, type 2, Major and Minor Depressive Disorder, HbA1c not an outcome
Van Bastelaar et al., 2008	RCT of web-based CBT, wait-list control	CES-D > 16	TBA	Goal of 286	CBT, 8 weeks, web-based	CES-D	TBA	TBA	RCT design w/waitlist control and 6 month follow-up, planned ITT analyses, age 18 or over, type 1 or 2, elevated depressive symptoms, HbA1c a secondary outcome measure
Simson et al., 2008	RCT of supportive psychotherapy, TAU	HADS > 7	8.1 (1.9)%	30/30 Hospitalized for diabetic foot syndrome	Supportive psychotherapy, weekly (avg. 5) sessions, individual	HADS	HADS depression change SP: -1.6 TAU: 0.3, p=.02 HADS anxiety change SP: -0.5 TAU: 1.6, p=.02 PAID change SP: -5.5 TAU: 2.1, p=.008	N/A	RCT design w/TAU comparison and limited follow-up, pre-post completer analyses, age <= 75 years, type 1 or 2, elevated depressive symptoms, HbA1c not an outcome measure
Georgiades et al., 2007	Open-label of group CBT	BDI>=10	7.6 (1.6)%	90/65	CBT, 16 sessions over 14 weeks for 90 minutes, group	BDI, HDRS	BDI decreased significantly from baseline to 12-month follow-up (p<.001). HDRS decreased significantly from baseline to 3-month follow-up (p<.001)	No significant change on HbA1c. Within subjects changes on BDI had no significant effect on HbA1c	Single-group open-label quasi-experimental design with 12-month follow-up, pre-post completer analyses, 18 and over, type 1 and 2, depressive symptoms, HbA1c outcome measure
Rossello & Himenez-Chafey, 2006	Open-label pilot study of group CBT	Depressive symptoms on CDI	9.3% (1.9)%	16/11	CBT, 12 weeks for 2 hours, group	CDI	Pre CDI=19.4 and post CDI=9.9, p<.05. No difference in glycemic control or diabetes self-care	N/A	Open-label pilot without randomization, control group or follow-up, pre-post completer analyses, age 13-17, type 1, elevated depressive symptoms, HbA1c outcome measure

Table 3

Psychopharmacological interventions

Reference	Study Design	Depression Entry Criteria	M(SD) Baseline HbA1c levels	Enrolled/Completed	Antidepressant/Dosage/Duration	Depression Measures	Significant Depression Outcomes	Significant Health/Glucose Outcomes	Methodological Characteristics
SSRIs									
Lustman et al., 2000	Double-blind RCT of fluoxetine or placebo	DIS MDD HDRS or BDI >= 14	8.4 (1.7)% fluoxetine group, 8.6 (1.6)% placebo group	60/54	Fluoxetine 20-40mg 8 weeks	BDI HDRS	Greater reduction in BDI (-14 v. –8.8, *p*=.03) and HDRS (-10.7 v. –5.2, *p*=.01) score in fluoxetine than placebo	HbA1c improved non-significantly (p=.13) more in fluoxetine (-.4%) than placebo (-.07%)	Double-blind placebo-controlled RCT with no follow-up interval, completer analyses, age 21-64, MDD inclusion criterion, type 1 or 2, HbA1c outcome measure
Lustman et al., 2006	Double-blind RCT of sertraline or placebo	HDRS>=16 or BDI >=14 initially; BDI<=9 for 2 mos.	8.2 (1.7)%	152/130	Sertraline 50-200mg 12 mos	BDI	Patients in sertraline group less likely to relapse (HR=.51, *p*=.01)	HbA1c level did not differ between groups	Double-blind placebo-controlled RCT with 1 year follow-up interval, completer analyses, age 18-80, type 1 or 2, MDD inclusion criterion, HbA1c outcome measure
Paile-Hyvarinen et al., 2003	Single-blind RCT of paroxetine or placebo	MADRS 2.5-12	7.5 (.8)% in paroxetine group, 6.9 (.4)% placebo group	15/13	Paroxetine 20mg 10 weeks	MADRS BDI	No difference in BDI or MADRS between groups	HbA1c improved non-significantly (*p*=.08) more in paroxetine (-.44%) than placebo (-.07%)	Single-blind placebo-controlled RCT design with no follow-up interval, ITT analyses, post-menopausal women over 50, type 2, mild depressive symptoms, HbA1c outcome measure,
Paile-Hyvarinen et al., 2006	Double-blind RCT of paroxetine or placebo	<= 6 sxs of MDD on interview	8.5 (0.9)% paroxetine group, 8.7 (1.3)% placebo group	49/37	Paroxetine 20mg 6 months	HADS	No significant difference in HADS depression	At 3 mos, but not 6 mos, HbA1c was significantly (*p*=.018) lower in paroxetine group (7.9) than placebo (8.5)	Double-blind placebo-controlled RCT design with 6-month follow-up interval, completer analyses, age 50-70, type 2, mild depressive symptoms, HbA1c outcome measure
Amsterdam et al., 2006	Open-label	SCID MDD, HDRS>=16	Not reported	17/14	S-citalopram 10-20mg up to 16 weeks	HDRS	Significant reduction in HDRS score	Non-significant reduction in HbA1c	Open-label uncontrolled trial with no follow-up, pre-post completer analyses, age 18 or over, MDD diagnosis, type 1 or 2, HbA1c outcome measure
Gulseren et al., 2005	Double-blind RCT of paroxetine or fluoxetine	SCID MDD, HDRS>=16	6.9 (1.2)% paroxetine group, 6.9 (1.7)% flouxetine group	23/20	Paroxetine, fluoxetine 20-40mg 12 weeks	HDRS	Both groups had significant reduction in HDRS score	Flouxetine group had non-significant reduction in HbA1c	Double-blind RCT design with no follow-up or control condition, pre-post completer analyses, MDD inclusion criterion, type 2, HbA1c outcome measure
Tri-cyclics									
Lustman et al., 1997	Double-blind RCT of nortriptyline or placebo	DIS MDD	11.8 (2.9)% nortiptyline group, 11.6 (3.1)% placebo group	35/28	Nortriptyline 50-150mg 8 weeks	BDI	Significantly greater (*p*=.03) reduction in nortriptyline group (-10.2) than placebo group (-5.8)	No difference in HbA1c	Double-blind placebo-controlled RCT with no follow-up interval, completer analyses, age 21-65, type 1 or 2, MDD criterion, HbA1c outcome measure
Other									
Lustman et al., 2007	Open-label buproprion	DIS MDD	8.3 (2.0)%	93/75	Buproprion 150-450mg 10 weeks	BDI	84% depression remitted Reduction in depression severity predicted HbA1c	-.5% reduction in HbA1c levels	Open-label trial with no comparison group and 4-month follow-up interval, pre-post completer analyses, age 18-80, type 2, MDD criterion, HbA1c and other physiological outcome measures

Table 4

Collaborative care interventions

Reference	Study Design	Depression Entry Criteria	M(SD) Baseline HbA1c levels	Enrolled/Completed	Treatment modality/Duration/Type	Depression Measures	Significant Depression Outcomes	Significant Health/Glucose Outcomes	Methodological Characteristics
Katon et al., 2004	RCT of collaborative case management, TAU	PHQ>=10 and HSCL-20 depression score>1.1	8.0 (1.6)% intervention group ,8.0 (1.5)% usual care group	329/288	Depression care management, pharmacotherapy or education/problem solving	HSCL-20	Patients in depression care management had less depression severity over time than those in TAU (z=2.84, p=.04)	No difference in HBA1c	RCT design with TAU comparison and 12-month follow-up, completer analyses, type 1 or 2, depressive symptoms, HbA1c outcome measure
Williams et al., 2004	RCT of depression care management, TAU	SCID MDD or Dysthymia	7.3 (1.3)% intervention group, 7.3 (1.5)% usual care group	417/350	Depression care management, pharmacotherapy or education/problem solving	HSCL-20	Depression care management patients had lower rate of depression (0.43 on 0-4 scale) than TAU	No difference in HBA1c	RCT design with TAU comparison and 12-month follow-up, ITT analyses, age 60 and over, type 1 and 2, MDD or dysthymia criterion, HbA1c outcome measure
Bogner et al., 2007	RCT of depression care management, TAU	SCID MDD CES-D>20	Not reported	123	Depression care management, pharmacotherapy or IPT	HDRS	Depression care management patients had lower rate of mortality than TAU patients (adjusted hazard ration 0.49%)	N/A	RCT design with TAU comparison and 5-year follow-up period, separate survival analyses on patients with diabetes from larger sample, age 60 and over, type 1 or 2, MDD or dysthymia criterion, no HbA1c measure or depression outcome