# Depression in diabetes: Evidence-based treatment

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Studies have demonstrated that people with diabetes who have comorbid depression often have poor glycaemic control, and are at increased risk of developing diabetes-related complications. In this article, the authors undertook a literature review to investigate depression treatments in this population to assist primary healthcare professionals in making informed decisions regarding effective antidepressant therapy. Current evidence suggests that selective serotonin reuptake inhibitors, particularly sertraline, offer a significant therapeutic advantage for people with diabetes with comorbid depression over tricyclic antidepressants or monoamine oxidase inhibitors.

epression among people with diabetes is an important consideration as it can diminish self-care and cause functional impairment (Musselman et al, 2003). Studies have shown that people with diabetes and depression have poor glycaemic control and are at increased risk of vascular complications (Jacobson and Weinger, 1998; Lustman et al, 2000a; 2007). An estimated 8.3% of people with diabetes in the USA suffer from depression (Li et al, 2008), indicating a substantial portion of this population could benefit from therapy targeting comorbid illness.

In this article, the authors review both pharmacological and non-pharmacological options for the treatment of depression in people with diabetes, and seek to deduce the optimal treatment plan to alleviate depressive symptoms, while maintaining or improving glycaemic control.

### Methods

A literature search was performed using Ovid MEDLINE, PubMed, PsycINFO, Embase and the Allied and Complimentary Health Database for English language articles published during 1960-2008. Key search terms were "diabetes mellitus type 1", "diabetes mellitus "depression", "electroconvulsive therapy", "cognitive behavioural therapy", "collaborative care", "psychosocial" and "psychotherapy". Only publications focusing on people with both diabetes and depression were included.

### Article points

- 1. The current authors conducted a literature review of pharmacological and non-pharmacological options for the treatment of depression in people with diabetes.
- 2. Evidence suggests that selective serotonin reuptake inhibitors, particularly sertraline, offer a significant pharmacological advantage for people with diabetes and depression compared with other antidepressants.
- 3. Non-pharmacological treatments, especially collaborative care models, appear to be effective in the management of depression in people with diabetes.

### Key words

- Cognitive behavioural therapy
- Collaborative care
- Depression
- Electroconvulsive therapy
- Pharmacotherapy

Authors' details can be found at the end of this article.

- All studies reviewed showed a reduction in depression scores and improvements in diabetes markers (blood glucose and HbA<sub>10</sub> levels).
- 2. One randomised controlled trial (RCT) studying the tricyclic antidepressant nortriptyline showed improvement in depression, but diminished glycaemic control.
- 3. The results of an RCT examining concurrent use of cognitive behavioural therapy (CBT) and diabetes education suggested that people with poor diabetes control may have a reduced response to CBT.
- 4. Electroconvulsive therapy (ECT) has shown efficacy in the treatment of depression; however, insulin requirements post-ECT have been highly variable.

### Results

A total of 41 pharmacological and non-pharmacological studies were reviewed. These studies are described in *Tables 1* and 2.

### Pharmacotherapy

The authors identified seven randomised controlled trials (RCTs; n=710) of people with diabetes and depression who received pharmacological treatment (different classes of antidepressants). In addition, there were five open-label trials (n=84), four case studies and two case series (n=28). Results of all these studies are presented in *Table 1*.

Sertraline was the focus of the longest trial reviewed, with a 1-year duration (Lustman et al, 2006; Williams et al, 2007). Although other studies of selective serotonin reuptake inhibitors (SSRIs) were of shorter duration, they did demonstrate improvements in both depression ratings and diabetes markers.

Bupropion, the only noradrenaline and dopamine reuptake inhibitor available for the treatment of depression, has been studied only once in the context of depression and diabetes (Lustman et al, 2007). The results of this trial were also promising: improved short-term blood glucose control, reduced HbA<sub>1c</sub> levels, reduced BMI and improved diabetes self-care.

One RCT studying the tricyclic antidepressant (TCA) nortriptyline showed improvement in depression, but diminished glycaemic control (Lustman et al, 1997a). Moreover, nortriptyline can interact with sulfonylureas, a common antidiabetes drug (OAD), potentially exerting a negative impact on diabetes treatment (Kaplan et al, 1960; True et al, 1987; Sherman and Bornemann, 1988; Lustman et al, 1997a).

Findings from one open-label trial looking at people with symptoms of depression and schizophrenia suggested that monoamine oxidase inhibitors (MAOIs) may reduce blood glucose levels, with the potential to cause hypoglycaemic events (Wickstrom and Pettersson, 1964). Once again, a possible interaction with sulfonylureas was highlighted.

### Non-pharmacotherapy

In the realm of non-pharmacological treatments, most studies focused on cognitive behavioural therapy (CBT), electroconvulsive therapy (ECT) or combined modalities. Only one descriptive case report was found for non-CBT psychotherapy (Levine, 1976–1977). Results of these studies are presented in *Table 2*.

In the context of diabetes, two studies on the use of CBT have been published. The first was an RCT examining concurrent use of CBT and diabetes education over 10 weeks (Lustman et al, 1998b). The second was an open-label, single-group study of 12 weeks' duration, with 12 weeks of follow-up observation (Georgiades et al, 2007). Both studies demonstrated that CBT contributed to increased rates of depression remission and Lustman et al (1998b) showed improved glycaemic control. The results of the RCT also suggested that people with poor diabetes control may have a reduced response to CBT (Lustman et al, 1998b).

ECT has shown efficacy in the treatment of depression (Fakhri et al, 1980; Yudofsky and Rosenthal, 1980; Thomas et al, 1983; Finestone and Weiner, 1984; Normand and Jenike, 1984; Weiner and Sibert, 1996; Netzel et al, 2002). However, insulin requirements post-ECT have been highly variable: shown to be unchanged (Netzel et al, 2002), reduced (Thomas et al, 1983; Normand and Jenike, 1984) or increased (Thomas et al, 1983). Although data suggest OADs should be stopped the day of ECT, controversy exists over continued modulation of insulin therapy, with one study suggesting it should be withheld until feeding (Rasmussen et al, 2006) and another suggesting reducing the dose by half (Weiner and Sibert, 1996). Blood glucose levels should be carefully monitored post-ECT (Normand and Jenike, 1984).

### Combined therapy

The literature on collaborative care (i.e. care provided by an interdisciplinary team that administer both pharmacological and non-pharmacological treatments) consists of three RCTs (*n*=1330) and one case report. Results of these studies are presented in *Table 2*.

The IMPACT (Improving Mood-Promoting

Antidepressant	Study duration	Findings	References
Selective serotonin	n reuptake inhibitors		
Sertraline	10 weeks to 1 year	Depression: improved with increased time to recurrence.  Glycaemic control: poorly controlled HbA <sub>1c</sub> improved, lower HbA <sub>1c</sub> when depression-free.	Goodnick et al, 1997; Sansone and Sansone, 2003; Lustman et al, 2006; Williams et al, 2007.
Escitalopram	Up to 16 weeks	Depression: reduced ratings. Glycaemic control: improved.	Amsterdam et al, 2006.
Paroxetine	4–12 weeks	Depression and anxiety: improved. Glycaemic control: improved.	Paile-Hyvarinen et al, 2003; Gülseren et al, 2005; Qu and Meng, 2005.
Fluoxetine	2–8 weeks	Depression: improved severity, trend toward remission.  Anxiety: improved ratings.  Glycaemic control: reduced HbA <sub>1c</sub> levels, conflicting data in adolescents, no change in 2-week open-label trial, hypoglycaemic unawareness and hypoglycaemia in people with type 2 diabetes in case report.	Katz et al, 1991; Ghazuiddin et al, 1994; Deeg and Lipkin, 1996; Lustman et al, 2000b Sawka et al 2000; Gülseren et al, 2005.
Noradrenaline ar	nd dopamine reuptake inhib	hitors	
Bupropion	10 weeks acute phase, 24 weeks maintenance	Depression: improved severity. Glycaemic control: improved. BMI: improved. Diabetes self-care: improved.	Lustman et al, 2007.
Tricyclic antidepr	ressants		
Nortriptyline Amitriptyline		Depression: improved. Glycaemic control: negative impact, possible interaction with sulphonylureas, symptomatic hypoglycaemia, hypoglycaemic unawareness.	Kaplan et al, 1960; True et al, 1987; Sherman and Bornemann, 1988; Lustman et al, 1997a.
Monoamine oxid	ase inhibitors		
	6 weeks to 3 years	Glycaemic control: reduced blood glucose levels, interaction with sulphonylureas, potentiated hypoglycaemia.	Wickstrom and Pettersson, 1964; Cooper, 1966.

Access to Collaborative Treatment) trial studied a general diabetes population, including a subgroup of 417 people with depression (Williams et al, 2004; Katon et al, 2006). Participants were followed by depression clinical specialists (trained nurses and psychologists) for 12 months, and an evidence-based algorithm was used to suggest either a course of antidepressant or a course of problem-solving treatment in primary care

(PST-PC) consisting of six to eight sessions of structured psychotherapy. A stepwise approach to treatment was implemented. Participants who recovered from depression were enrolled in a relapse prevention plan. For those who did not respond to initial treatment, a "step 2" treatment plan involving augmentation of antidepressant, switch to a new antidepressant or PST-PC was used. For those who did not respond after 10 weeks

Table 2. Outcomes for studies on non-pharmacological therapies for depression.				
Intervention	Study duration	Findings	References	
Electroconvulsive therapy		Insulin requirements: conflicting data. Diabetes remission: complete in eight of 14 participants. Data lacking for type 1 diabetes.	Fakhri et al, 1980; Yudofsky and Rosenthal, 1980; Thomas et al, 1983; Finestone and Weiner, 1984; Normand and Jenike, 1984; Weiner and Sibert, 1996; Netzel et al, 2002; Rasmussen et al, 2006.	
Cognitive behavioural therapy	10-24 weeks	Depression: reduced severity, increased remission rates. Glycaemic control: improved.	Lustman et al, 1998a; 1998b; Georgiades et al, 2007.	
Collaborative care	12 months to 5 years	Depression: reduced severity, increased depression-free days.  Mortality: reduced rates.  Glycaemic control: unchanged.  Self-management: no improvement.	Katon et al, 2004; Williams et al, 2004; Glasgow and Price, 2005; Ciechanowski et al, 2006; Gask et al, 2006; Katon et al, 2006; Kinder et al, 2006; Lin et al, 2006; Zrebiec, 2006; Bogner et al, 2007; Simon et al, 2007.	

- 1. The Pathways study
  (Pathways Collaborative
  Care Intervention) used
  a stepped-care approach
  for a 329-participant
  sample; the results of this
  study showed reduced
  severity of depression, but
  no change in glycaemic
  control.
- 2. Bogner et al conducted the PROSPECT (Prevention of Suicide in Primary Care Elderly: Collaborative Trial), aimed at preventing suicide among older people by reducing suicidal ideation and depression.

of step 2 treatment, additional treatments such as new medications, psychotherapy, hospitalisation, and ECT were considered. Overall, participants in this study showed a reduction in depression severity, but there were no significant changes in glycaemic control.

The Pathways study (Pathways Collaborative Care Intervention) also used a stepped-care approach (Katon et al, 2004; Glasgow and Price, 2005; Ciechanowski et al, 2006; Lin et al, 2006). In this RCT, 329 participants were assigned to either the Pathways steppedcare case-management intervention or usual care, in which subjects consulted with their primary care physian regarding depression treatment. Initial therapy in the Pathways stepped-care arm was either antidepressant Participants medication or PST. depressive symptoms persisted (<50% reduction in severity based on Patient Health Questionnaire-9) after 10-12 weeks proceeded to step 2. Step 2 consisted of a psychiatric consultation, augmentation of initial therapy, additional antidepressant added to the regimen or switching to the alternative treatment. Step 3 (referral to specialty care) was used if participants received more than one step 2 intervention, depressive symptoms persisted, or there was a lack of participant and/or clinician

satisfaction with outcomes after 8–12 weeks of step 2 treatment. In comparison with usual care, the Pathways stepped-care group showed reduced severity of depression, higher participant-rated global improvement and higher participant satisfaction with care, but no change in glycaemic control or diabetes care. Greater improvements in depressive symptoms and participant satisfaction were observed for those with a more independent relationship style (Ciechanowski et al, 2006).

Bogner et al (2007) conducted the PROSPECT (Prevention of Suicide in Primary Care Elderly: Collaborative Trial), aimed at preventing suicide among older people by reducing suicidal ideation and depression. This study involved a subgroup analysis to assess the effect of a collaborative-care intervention on mortality rates in people with diabetes. The intervention involved primary care physician recognition of geriatric depression and suicidal ideation and application of a treatment algorithm by health specialists (i.e. nurses, social workers, psychologists) for 24 months. Participants in the collaborative-care group showed lower mortality rates compared with those receiving usual care. Thus, the results suggested a possible survival benefit.

One qualitative study analysed multiple

- 1. The authors found that selective serotonin reuptake inhibitors demonstrate fairly consistent improvement in depressive symptoms and in glycaemic control.
- Tricyclic antidepressants and monoamine oxidase inhibitors may interact with sulphonylureas, leading to periods of hypoglycaemia.
- 3. The few studies examining cognitive behavioural therapy have consistently shown promising results: improvement of depression severity and glycaemic control in the short-term.

psychosocial modalities across nine primary care clinics (Gask et al, 2006). Qualitative analysis of nursing consultations demonstrated that multiple modalities, including motivational interviewing and active therapeutic models (PST-PC), could all be effective in the management of diabetes and depression.

### Discussion

Numerous medications are available to practitioners for the treatment of depression, several of which have been studied in the context of people with diabetes. Compared with other antidepressant classes, SSRIs have been most extensively studied for use in this population, although the studies are limited in duration and size. SSRIs have demonstrated fairly consistent improvement in depressive symptoms and in glycaemic control (Katz et al, 1991; Lustman et al, 2000a; Gülseren et al, 2005).

The SSRIs paroxetine and fluoxetine have been the focus of a greater number of studies, but these have been of a relatively short duration, from 10 weeks to 1 year, in people with diabetes and depression. Given that both depression and diabetes are managed over the span of months to years, and given that adequate antidepressant trials may require a minimum of 12 weeks of treatment, it has been demonstrated that longerterm effectiveness is particularly important in selecting an antidepressant for people with diabetes, both in terms of depression and diabetes outcomes. Therefore, among SSRIs, the evidence may, in fact, show most support for the use of sertraline as an effective treatment of depression in people with diabetes.

Less data exist for escitalopram and sertraline, but both of these drugs have shown promising results. Among SSRIs, the evidence shows most support for the use of sertraline as an effective treatment of depression in people with diabetes (Lustman et al, 2006). At the time of this review, the remainder of the SSRIs had not yet been studied in the context of diabetes.

Although few studies have explored the use of other antidepressant classes, there is some evidence from small-size, open-label trial data that bupropion may also improve depression, glycaemic control and self-care in people with diabetes (Lustman et al, 2007), whereas TCAs may have a negative impact on glycaemic control (True et al, 1987; Lustman et al, 1997a). TCAs and MAOIs also may interact with sulphonylureas, leading to periods of hypoglycaemia (Wickstrom and Pettersson, 1964; Cooper, 1966; True et al, 1987; Sherman and Bornemann, 1988).

Although previous literature reviews and studies have primarily focused on pharmacotherapy (Goodnick et al, 1995; Skaer et al, 1999; Jones et al, 2006), the current authors have included other treatment modalities for depression in the context of diabetes. Data on ECT in people with diabetes are limited and conflicting regarding its effect on blood glucose levels (Fakhri et al, 1980; Yudofsky and Rosenthal, 1980; Thomas et al, 1983; Finestone and Weiner, 1984; Normand and Jenike, 1984; Weiner and Sibert, 1996; Netzel et al, 2002; Rasmussen et al, 2006). These studies only referred to type 2 diabetes; data for type 1 diabetes and depression are lacking in current literature. The few studies examining CBT have consistently shown promising results: improvement of depression severity and glycaemic control in the short-term (Lustman et al, 1998a; 1998b; Simon et al, 2007).

With regard to studies assessing collaborative care in the management of depression and diabetes, three large-scale RCTs - IMPACT (Williams et al, 2004; Katon et al, 2006), Pathways (Katon et al, 2004; Glasgow and Price, 2006; Kinder et al, 2006; Lin et al, 2006; Simon et al, 2007) and PROSPECT (Bogner et al, 2007) - have shown cost-effective reductions in depression severity with collaborativecare models, but have not demonstrated significant impact on glycaemic control. As such, these approaches may be effective as a part of a multimodal intervention that includes pharmacotherapy for glycaemic control. The collaborative-care models were found to be more cost-effective compared with "usual care" in the treatment of depression, leading to reduced depression severity and increased depression-free days (Simon et al, 2007). Other studies have also reported increased satisfaction of depression care with use of collaborative-care

- With regard to the pharmacotherapy studies, there are little to no data for some antidepressant classes such as serotonin noradrenaline reuptake inhibitors.
- 2. It is evident that the literature supports the notion that people with diabetes and depression require unique considerations, particularly in terms of the impact of treatment on glycaemic control.
- 3. Multiple treatment modalities may offer beneficial outcomes pertaining to both the treatment of depression and improvement of glycaemic control in people with diabetes.

models (Ciechanowski et al, 2006).

## Limitations of the data and future directions

The primary difficulty in this area is the overall scarcity of high-quality data available to inform treatment decisions for people with diabetes with comorbid depression. More specifically, there are relatively few high-quality studies on the use of non-pharmacological treatments other than collaborative care. This may be an avenue of further research.

With regard to the pharmacotherapy studies, there are little to no data for some antidepressant classes such as serotonin noradrenaline reuptake inhibitors. are few direct, head-to-head comparisons of agents to clearly demonstrate preference of one antidepressant over another. Furthermore, there is some variability in the analysis of the data, with some authors using intention-totreat and others analysing the data as per protocol. The majority of studies are of short duration, limiting the conclusions that can be made regarding long-term outcomes. This is especially relevant for measuring outcomes of diabetes occurring over many years.

Many studies used "usual care" to compare against the treatment group; however, usual care was poorly defined, given that there is currently no standard for treating depression in people with diabetes. Many of the studies allowed for some variability of treatment within the usualcare group. This variation in management regimens may have introduced significant confounders, particularly into outcomes of glycaemic control. More specifically, with regard to the studies of psychosocial therapies, the therapies used were often inadequately described, and the descriptions showed much variability in techniques. There were also a lack of "sham" therapies used as a control; however, this is because ethical considerations mandate the treatment of depression. Moreover, owing to the nature of the treatment, it is difficult to conceal allocation and blind the practitioners.

Finally, most of the studies featured a primarily white, older adult population. Large, diverse samples would better account

for comorbidities and eliminate confounding variables, as well as enhance external validity of the studies. The authors acknowledge that this information is not completely generalisable.

### Conclusion

The findings of this review provide healthcare professionals with some preliminary directions in making informed decisions regarding effective antidepressant therapy in people with diabetes and depression. In addition to supporting the close association between depression and glycaemic control, it is evident that the literature supports the notion that people with diabetes and depression require unique considerations, particularly in terms of the impact of treatment on glycaemic control. Multiple treatment modalities may offer beneficial outcomes pertaining to both the treatment of depression and improvement of glycaemic control in people with diabetes. Consideration of the significant comorbidity in people with both depression and diabetes has valuable implications for the selection of effective antidepressant therapy available.

In comparing the different classes of antidepressant agents, the current available evidence suggests that SSRIs, particularly sertraline, offer a significant therapeutic advantage for people with diabetes and comorbid depression over TCAs or MAOIs. In addition, non-pharmacological treatments, especially collaborative-care models, appear to be effective in the management of this population.

While this review has served to highlight some of the most effective therapies in the treatment of depression in people with diabetes, it is evident that further prospective research is necessary to facilitate direct comparisons both within and across treatment modalities. Large sample, long-term, doubleblinded, randomised, placebo-controlled trials will likely provide the high-quality results necessary to provide definitive comparisons of the interventions of interest. Perhaps even more interesting would be direct comparisons pharmacological and psychosocial interventions in this population.

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