Effect of interventions for major depressive disorder and significant depressive symptoms in patients with diabetes mellitus: a systematic review and meta-analysis

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CRD summary
The authors concluded that psychotherapeutic interventions, in many cases in combination with a diabetes self-management intervention, had strong effects on depressive symptoms and glycaemic control. Pharmacotherapy (apart from sertraline) had no effect on glycaemic control. The conclusions appear to be reliable, but should be viewed with caution given the limited data available.

Authors' objectives
To assess the effectiveness of anti-depressant therapies (psychotherapy, antidepressant medication, collaborative care) in diabetes patients with comorbid depression.

Searching
PubMed, PsychINFO, EMBASE and The Cochrane Library were searched to December 2009. Search terms were reported. Reference lists of relevant RCTs and reviews were handsearched. No language restriction was applied. Subject experts were consulted to identify additional studies.

Study selection
Randomised controlled trials (RCTs) that evaluated the effects of treatment of crumbled depression by psychotherapy, pharmacology or collaborative care of depression in adult patients with Type 1 or Type 2 diabetes mellitus were eligible for inclusion. Studies that assessed the effects of treatments of depression in patients with diabetes related complications (such as diabetic foot) were selected if they focused on patients with comorbid depression. Studies that utilised crossover designs or waiting list control groups after randomisation were considered for inclusion. Outcome measures were: depression outcomes (such as Hamilton score), blood glucose control (glycosylated haemoglobin, fasting blood glucose and fasting plasma glucose.

Included studies were in developed countries (USA, China, Germany, Finland, Turkey). Most studies included patients with Type 1 and Type 2 diabetes mellitus. Diagnostic methods for depressive disorders were varied (Diagnostic Interview Schedule, Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, use of a validated questionnaire with a cut-off score). Types and durations of included psychotherapy, diabetes self-management, pharmacological therapies (nortriptyline, fluoxetine, paroxetine) and collaborative care interventions were varied (further details reported in the paper).

Two reviewers independently selected studies for inclusion; disagreements were resolved by discussion or by consultation with a third reviewer.

Assessment of study quality
Three reviewers independently assessed study quality according to Cochrane quality criteria. Key criteria assessed included sequence generation, allocation concealment, blinding, reporting of loss to follow-up/intention-to-treat analysis and completeness of outcome reporting.

Data extraction
Two authors independently extracted data (for articles published in English) to calculate effect sizes (Cohen's d) and 95% confidence intervals (CIs). Authors of the included studies were contacted where additional data or clarification was needed.

Methods of synthesis
Depressive symptom severity and blood glucose were combined into one measure of illness burden (weighted effect size). Pooled standardised effect sizes (Cohen's d) and corresponding 95% CIs were calculated using random-effects
meta-analysis. Effect sizes were interpreted as 0.56 to 1.2 (large clinical effect), 0.33 to 0.55 (moderate) and zero to 0.32 (small). Heterogeneity was assessed using $X^2$ and $I^2$ statistics.

Subgroup analyses were done to examine the effects of antidepressive therapies by depressive symptom severity, level of glycaemic control and type of intervention. Sensitivity analysis was done to examine the effects of study quality. Publication bias was assessed using a Begg funnel plot and Duval's trim-and-fill method.

Results of the review
Fifteen RCTs were included (n=1,747, range 13 to 417). Risks of bias for key quality criteria were: sequence generation (adequate for eight studies and unclear for seven studies); allocation concealment (adequate for seven studies, unclear for seven studies and not done for one study), blinding of outcome assessors (done for 10 studies and unclear for five studies); other blinding (done for six studies, unclear for one study and not done for eight studies).

The combined effect of all interventions on clinical impact was moderate (Cohen's $d$ -0.370, 95% CI -0.470 to -0.271), large for psychotherapeutic interventions often combined with diabetes self management (Cohen's $d$ -0.581, 95% CI -0.770 to -0.391; n=310) and moderate for pharmacological treatment (Cohen's $d$ -0.467, 95% CI -0.665 to -0.270; n=281). Delivery of collaborative care was associated with an effect size of -0.292 (95% CI -0.429 to -0.155; n=1,133).

Subgroup analysis of changes of severity of depressive symptoms as the outcome revealed a positive effect (Cohen's $d$ -0.512, 95% CI -0.633 to -0.390, $p=0.215$, $I^2=22\%$).

Subgroup analysis of glycaemic control as the outcome revealed a positive effect (Cohen's $d$ -0.274, 95% CI -0.402 to -0.147, $p=0.236$, $I^2=22\%$). Effect sizes of subgroup analyses on combined outcomes by type of interventions were collaborative care Cohen's $d$ -0.292 (95% CI -0.429 to -0.155), pharmacological treatment Cohen's $d$ -0.467 (95% CI -0.665 to -0.270) and psychotherapy Cohen's $d$ -0.581 (95% CI -0.770 to -0.391) $p=0.044$.

Sensitivity analysis by study quality yielded effect sizes similar to the original analysis for all except for psychotherapy, which revealed a higher effect size with only qualitative good studies.

No evidence of publication bias was found.

Authors' conclusions
The authors concluded that psychotherapeutic interventions, in many cases in combination with a diabetes self-management intervention, had strong effects on depressive symptoms and on glycaemic control. Pharmacotherapy had no effect on glycaemic control; all antidepressants led to a reduction of depressive symptoms.

CRD commentary
The review question was clearly stated. Relevant databases were searched without language restrictions, thus minimising the potential for language bias. The search for unpublished studies was limited and a number of relevant studies may have been missed. Review processes were conducted in duplicate minimising the risk of bias and error. Study quality was assessed using appropriate criteria and results were reported. Statistical methods used to combine data and account for heterogeneity were appropriate and justified. The overall sample size was small.

The authors' conclusions are likely to be reliable, but should be viewed with caution given the limited data available.

Implications of the review for practice and research
Practice: The authors stated that, given the large combined effect of psychotherapy (combined with self management education), the intervention would be the first choice treatment for diabetes mellitus type 2 and type 1.

Research: The authors stated that additional studies in patients with type 1 and type 2 diabetes mellitus were needed and should: investigate the effects of pharmacotherapy interventions and collaborative care combined with specific interventions; compare psychotherapeutic interventions with pharmacological interventions; and develop/adopt
techniques and instruments to improve identifications of depression comorbid with diabetes. Studies should be adequately powered, take into account ethnicity and record impact on glycaemic control and insulin resistance.

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