CRD summary
This review concluded that fluoxetine could lead to reductions in weight loss, fasting plasma glucose, HbA1C and triglyceride in type 2 diabetes patients. Concerns about heterogeneity, as well as the quality, size and age of the studies mean that the authors’ conclusions may not be reliable.

Authors’ objectives
To assess the efficacy of fluoxetine for the treatment of patients with type 2 diabetes mellitus.

Searching
PubMed, EMBASE and The Cochrane library were searched up to March 2011. Search terms were reported. References of included studies were searched manually and related articles provided by PubMed were screened. No language or date restrictions were applied.

Study selection
Published randomised controlled trials (RCTs) that compared the effect of fluoxetine with placebo in type 2 diabetic patients were eligible for inclusion. Studies had to report data that allowed the calculation of a weighted mean difference (WMD) and 95% confidence interval (CI).

Four studies had follow-up time that ranged from six to 12 months. One trial lasted two months. Participants’ mean age varied between studies and ranged from 44 to 67 years across study groups. Participants from included studies had poor levels of glycaemic control overall. One study enrolled patients who used insulin. The other four excluded patients who received insulin therapy.

Fluoxetine dosage was consistent (60mg daily) across all studies. Two studies reported a dietary intervention in both fluoxetine and control groups. In two trials, including one in which patients were diet controlled for type 2 diabetes, previous treatments that could alter weight were not maintained during the study. Previous oral hypoglycaemic agent therapy was maintained in one study. Patients treated with concurrent anti-obesity drugs were excluded from all five trials. One trial only selected patients with good levels of treatment compliance.

Two reviewers independently selected studies for inclusion.

Assessment of study quality
Quality of included studies was assessed based on the 5-point Jadad scale which covered randomisation, blinding and treatment of withdrawals and drop-outs.

The authors did not state how many reviewers assessed the validity of the studies.

Data extraction
Patients’ baseline characteristics and the following outcomes data were recorded: body weight loss, total cholesterol reduction, levels of fasting plasma glucose, glycosylated hemoglobin (HbA1c) and triglyceride.

Two reviewers independently extracted data. Discrepancies were resolved by discussion. In case of duplication of data between multiple studies, the trial with the largest sample was included and the others were excluded. Authors were contacted for data clarification where necessary.

Methods of synthesis
Outcomes data were pooled to calculate weighted mean difference (WMD) and 95% confidence interval (CI). Heterogeneity was assessed with $I^2$ and $X^2$. A random-effects model was used in case of significant heterogeneity ($p<0.10$). Otherwise, a fixed-effect model was used. $U$-tests were performed to assess statistical significance of the
weighted mean differences.

A meta-regression was performed to evaluate potential interactions of weight loss, HbA1c and fasting plasma glucose with patient characteristics (mean age, gender distribution in fluoxetine and placebo groups, baseline BMI) and with treatment duration.

**Results of the review**

Five RCTs that compared fluticasone with placebo in parallel were included and pooled. All studies scored 2 points on the Jadad scale, which suggested some significant gaps in the reporting of the trials. No studies discussed allocation concealment or randomisation methods.

Pooled analyses suggested that fluoxetine therapy resulted in significant weight loss (-4.27kg) compared with placebo (95% CI -5.97 to -2.58; five studies; 167 participants; $I^2=84.7\%$), in significant fasting plasma glucose reductions compared with placebo (-1.41mmol/L, 95%CI -2.64 to -0.19; five studies; 167 participants; $I^2=92.1\%$) and in significant triglyceride level reductions (0.54mmol/L decrease, 95% CI 0.35 to 0.73; three studies; 113 participants; $I^2=31.1\%$). Pooled analyses found a non significant effect of fluoxetine on HbA1c compared with placebo (0.78% decrease, 95%CI -0.23 to 1.78; five studies; 167 participants; $I^2=98.0\%$) and no effect on total cholesterol levels.

None of the results of the meta-regression were significant.

**Authors' conclusions**

Fluoxetine therapy can lead to reductions in weight, fasting plasma glucose, HbA1C and triglyceride in patients with type 2 diabetes mellitus.

**CRD commentary**

The review question and inclusion criteria were clear. Literature searches were thorough, but there was no indication that unpublished material was sought. Study selection and data extraction were carried out with appropriate attempts to minimise bias. It was unclear whether quality assessment of the studies was carried out with similar attempts to minimise bias. This may have limited the reliability of the quality assessment findings. The tools used to assess study validity were limited and the quality of the studies was not taken fully into account when interpreting the results, which may limit the reliability of the review findings.

Study and participants details were adequately reported. Pooling of data appeared appropriate and suitable methods were used to assess heterogeneity. Significant heterogeneity was identified for three of the five outcomes. The source of heterogeneity was unclear. This may limit the reliability of the findings. All trials were placebo-controlled but with significant gaps in reporting of methodology. Therefore the quality of the evidence base was unclear. The pooled analysis included few studies with relatively small numbers of participants. This may limit the reliability of the conclusions.

Trials were published between 1992 and 1996. This suggests that the evidence may not reflect current practice, which may limit the external validity of the review findings. Four of the five studies excluded patients who received insulin therapy which should be considered when interpreting the generalisability of the findings.

Concerns about heterogeneity, as well as quality, size and age of the studies mean that the authors’ conclusions may not be reliable.

**Implications of the review for practice and research**

**Practice:** The authors stated that weight loss pharmacotherapy should be used in conjunction with behavioural interventions for patients with type 2 diabetes mellitus where lifestyle modification was insufficient.

**Research:** The authors suggested that studies which evaluated the effect of fluoxetine on weight loss in the long term and that included larger study populations were needed. They mentioned that further research was needed to investigate the combination of lifestyle modification and pharmacotherapy to identify optimal dosage and sequence of the two types of interventions. They emphasised the need for more research on the effect of fluoxetine on obese patients with type 2 diabetes.
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