Fluoxetine for the prophylaxis of poststroke depression in patients with stroke: a meta-analysis

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CRD summary
This review found that fluoxetine reduced incidence of newly diagnosed depression in patients with stroke, but did not reduce the symptom severity of post-stroke depression. The authors’ conclusion on the benefits of fluoxetine is likely to be reliable, but the conclusion on symptom severity was influenced by extensive variation in the included trials.

Authors’ objectives
To assess the prophylactic efficacy and safety of fluoxetine for post-stroke depression in patients with stroke.

Searching
Sixteen databases, including PubMed, EMBASE, the Cochrane Library and Chinese databases were searched up to December 2009 for relevant studies published in English or Chinese; search terms were reported. Ongoing trial registers were also searched. Reference lists of retrieved studies and textbooks and materials from the authors’ department were scanned. Experts in the field and manufacturers contacted for additional published or unpublished studies.

Study selection
Eligible for inclusion were randomised controlled trials (RCTs) that compared fluoxetine prophylaxis for post-stroke depression with control interventions (placebo or no treatment) in patients with a clinical diagnosis of stroke and without a diagnosis of depression. Eligible outcomes were the incidence of newly developed post-stroke depression, neurological impairment, activities of daily living and adverse events (categorised as drop-out rates).

In the included trials, the mean age of participants ranged from 57 to 68 years; the percentage of female patients ranged from 12 to 62%. Most of the included trials used a fluoxetine dose of 20mg daily, but one trial used doses ranging from 10mg to 40mg daily; treatment duration ranged from four to 12 weeks. Post-stroke depression was measured by the Hamilton Depression Rating Scale. Neurological impairment was measured by the Scandinavian Neurological Stroke Scale and the Chinese Stroke Scale. Activities of daily living were measured by the Activity of Daily Living Scale, the Barthel Index, Functional Independence Measure or the John Hopkins Functioning Inventory.

Two reviewers performed study selection, with disagreements resolved through discussion.

Assessment of study quality
Quality of the included trials was assessed according to Cochrane criteria: adequacy of randomisation, allocation concealment, blinding of outcome assessors, and completeness of follow-up data.

Two reviewers undertook quality assessment of studies, with disagreements resolved by discussion.

Data extraction
Odds ratios (ORs) of the incidence of post-stroke depression and drop-out rates, and mean differences (MDs) of depression rating scale scores, neurological impairment scores and activity of daily living scores, with their 95% confidence intervals (CIs), were extracted. Authors of included trials were contacted for missing information.

Two reviewers undertook data extraction, with disagreements resolved by discussion.

Methods of synthesis
Trials were pooled in meta-analyses and summary odds ratios and weighted mean differences (WMDs) calculated, using a fixed-effect model. Statistical heterogeneity was identified and measured with the $X^2$ test; if heterogeneity was
significant (p<0.05), a random-effects model was used to pool the studies. $I^2$ was also calculated to measure the variation between trials.

Sensitivity analyses were undertaken to determine the effects of low quality and small sample size trials on the estimates.

Publication bias was assessed using the fail-safe number.

**Results of the review**

Six RCTs were included in the review (n=385 patients, range 33 to 90). Two trials had adequate randomisation sequences and allocation concealment. One trial had intention-to-treat analysis. All the trials were double blind.

The incidence of post-stroke depression was significantly reduced with fluoxetine compared to control (OR 0.25, 95% CI 0.11 to 0.56; three RCTs). Reductions in the rate of post-stroke depression were significantly different when fluoxetine was given within one week after the occurrence of stroke (OR 0.15, 95% CI 0.05 to 0.51; one RCT), but there was no evidence of a difference when fluoxetine was given four weeks or more after stroke (one RCT). There was no evidence of a significant difference in depression scores on the Hamilton Depression Rating Scale between groups (WMD -3.97, 95% CI -9.85 to 1.9; four RCTs); this finding had substantial heterogeneity ($p<0.00001; I^2=97\%$).

A statistically significant difference was found in the recovery of neurological impairment between groups (WMD -4.72, 95% CI -8.31 to -1.13; two studies); there was substantial heterogeneity ($p=0.02; I^2=82\%$). There was a significant reduction in the Barthel Index scores for activities of daily living with fluoxetine compared with control (WMD -8.04, 95% CI -13.4 to -2.68; two studies) and in the Functional Independence Measure scores (difference not reported; $p<0.05$; one RCT).

There was no evidence of a difference between groups in drop-out rates (OR 0.88, 95% CI 0.31 to 2.49; three RCTs). There was also no evidence of a difference between groups in the rates of individual adverse events. However, incidence of nausea, insomnia and epileptic seizure were greater than 10% in the fluoxetine group compared with 0% in the control group.

Sensitivity analysis with the recalculations of summary effects in trials with sample sizes greater than 50 patients and trials with unclear randomisation method indicated that results were similar.

There was no evidence of publication bias from the fail-safe number.

**Authors’ conclusions**

Fluoxetine was beneficial for the prevention of post-stroke depression in patients with stroke, but not in reducing symptom severity of post-stroke depression.

**CRD commentary**

The review addressed a clear research question and inclusion criteria were clearly specified and appropriate. It appeared that blinding may have been an inclusion criterion, as a study was excluded because of lack of blinding; but this criterion was not specifically reported. A large number of databases and registers were searched for relevant studies, using appropriate search terms. Comprehensive attempts were also made to find studies by searching reference lists, other materials and consultation with experts and manufacturers. Studies were restricted to English or Chinese languages, so language bias could not be excluded. Appropriate methods (designed to reduce reviewer bias and error) were used to select studies, assess studies for quality and extract data.

An appropriate tool was used for trial quality assessment. The quality of the included trials was mixed; double blinding was used in all trials, but only two had evidence of adequate randomisation and allocation concealment and one used intention-to-treat analysis. All trials had fewer than 100 participants. Assessment of heterogeneity was appropriate. Sensitivity analysis was used to determine the reliability of the findings with the exclusion of small trials and trials with adequate randomisation, but given the small number of trials, no major changes were seen. Assessment of publication bias confirmed that this was unlikely.
The authors' conclusion on the efficacy of fluoxetine for preventing newly diagnosed depression reflected the evidence presented and is likely to be reliable. However, the conclusion that fluoxetine did not reduce symptom severity was influenced by extensive heterogeneity.

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

**Practice:** The authors stated that patients with stroke with a history of insomnia or epileptic seizure should not use fluoxetine and those patients taking fluoxetine to prevent depression should be monitored for incidence of nausea, insomnia and epileptic seizure.

**Research:** The authors stated that the finding that fluoxetine was more beneficial when given within one week of stroke needs further investigation. They also stated that they were unable to confirm which kind of patient would benefit from fluoxetine prophylaxis.

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