Heterocyclics and selective serotonin reuptake inhibitors in the treatment and prevention of poststroke depression

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CRD summary
This review assessed the effectiveness of heterocyclic and serotonin re-uptake inhibitor antidepressant medications for the treatment and prevention of post-stroke depression. The authors concluded that these antidepressants seem to be viable treatments for post-stroke depression, but further research is required. The authors’ cautious conclusions appear appropriate given the limited evidence identified. However, publication bias and language bias may be present.

Authors' objectives
To assess the effectiveness and safety of heterocyclic and serotonin re-uptake inhibitor (SSRI) antidepressant medications for the treatment and prevention of post-stroke depression (PSD).

Searching
MEDLINE, EMBASE, PsycINFO and the Cochrane Library were searched from January 1970 to March 2004; the search terms were reported. The authors also searched the reference lists of review articles and primary studies identified by their electronic searches. The searches were limited to studies published in full in the English language; abstracts were excluded.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies of a heterocyclic or SSRI antidepressant medication compared with either placebo, active control, or both, were eligible for inclusion. The specific heterocyclic medications assessed were nortriptyline, imipramine, desipramine and mianserin. The specific SSRI medications assessed were citalopram, fluoxetine and sertraline. The majority of trials used a placebo control group; others assessed heterocyclic medications versus SSRIs versus placebo, or different heterocyclic medications against each other.

Participants included in the review
Studies of patients at least 45 years of age and with stroke were eligible for inclusion. Studies that included non-stroke patients were excluded. No details of the included participants were reported.

Outcomes assessed in the review
Studies that assessed the outcomes of recovery from or prevention of PSD were eligible for inclusion. Where stated, the definition of response to treatment was a 50% reduction in the baseline Hamilton Depression Rating Scale or Melancholia Scale score. Most studies also reported adverse effects of treatment.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Two reviewers independently assessed the included studies for quality using the following four criteria: randomisation, concealment of allocation, double blinding and intention-to-treat analysis. The authors did not state how any disagreements were resolved.
Data extraction
Two reviewers independently extracted the data from the included studies. The authors did not state how any disagreements were resolved. For the prevention studies, the authors extracted data on the number of patients in each group with and without depression. For the treatment studies, the authors extracted data on the number of patients in each group with symptom remission and calculated the odds ratio (OR) and 95% confidence interval (CI). Also extracted were the mean change in depression scores from baseline and the proportion of patients who dropped out of the studies due to adverse effects.

Methods of synthesis
How were the studies combined?
A fixed-effect model was used to calculate the pooled OR with 95% CI for dichotomous outcomes, and the weighted mean difference (WMD) with 95% CI for continuous outcomes. The average effect size (mean change on depression scales) and standard deviation (SD) were also presented for heterocyclic antidepressants and SSRIs.

How were differences between studies investigated?
Heterogeneity was assessed using the chi-squared and I-squared statistical tests.

Results of the review
Nine RCTs (n=599) were included in the review.

All of the included RCTs fulfilled the quality criteria for randomisation and double-blinding. Only one RCT fulfilled the quality criteria for concealment of allocation. Six RCTs used an intention-to-treat analysis.

Treatment of depression (6 RCTs).
Statistically significantly more patients receiving SSRIs experienced symptom remission than those receiving placebo (OR 0.32, 95% CI: 0.16, 0.62; 4 RCTs); however, there was significant heterogeneity. Statistically significantly more patients receiving a heterocyclic antidepressant experienced symptom remission than those receiving placebo (OR 0.13, 95% CI: 0.02, 0.76; 1 RCT). Statistically significantly more patients receiving a heterocyclic antidepressant experienced symptom remission than those receiving an SSRI (OR 0.05, 95% CI: 0.01, 0.36; 1 RCT). Statistically significantly more patients receiving a heterocyclic antidepressant combination of imipramine and mianserin experienced symptom remission than those receiving the heterocyclic antidepressant combination of desipramine and mianserin (OR 0.05, 95% CI: 0.00, 0.66; 1 RCT).

The mean change in scores from baseline was statistically significantly greater in the treatment group than in the control group for each of the depression scales used: the Hamilton Depression Rating Scale (WMD 3.74, 95% CI: 1.49, 5.98; 3 RCTs), the Melancholia Scale (WMD 2.56, 95% CI: 0.37, 4.76; 2 RCTs) and the Montgomery-Asberg Depression Scale (WMD 8.20, 95% CI: 2.57, 13.83; 1 RCT). However, the average effect size of the mean change in scores from baseline was small; 0.29 (SD=0.19) for heterocyclic antidepressants and 0.37 (SD=0.11) for SSRIs.

Prevention of depression (3 RCTs).
One study found no difference in the number of patients diagnosed with PSD between those receiving mianserin and those receiving placebo. One study found that more patients receiving placebo were diagnosed with PSD than those receiving nortriptyline or fluoxetine. One study found that more patients receiving placebo were diagnosed with PSD than those receiving sertraline.

Proportion of drop-outs due to adverse effects.
Statistically significantly more patients receiving antidepressants dropped out of studies because of adverse effects than patients receiving placebo (OR 3.14, 95% CI: 1.33, 7.43). A greater proportion of drop-outs due to adverse effects was seen for heterocyclic antidepressants than for SSRIs (OR 3.60, 95% CI: 1.33, 9.76 and OR 2.03, 95% CI: 1.33, 7.43, respectively).
**Authors' conclusions**
Heterocyclic antidepressants and SSRIs appeared to be viable treatments for PSD; however, their absolute or relative efficacy has yet to be fully established. The effectiveness of early initiation of antidepressants for the prevention of PSD was unclear and further research is required.

**CRD commentary**
The review question was clear in terms of the study design, participants, interventions and outcomes of interest. Several sources were searched for eligible studies; however, the authors only included studies published in full in English, thus increasing the likelihood of publication bias and language bias. The authors did not state how studies were selected for the review, therefore the potential for reviewer error or bias cannot be assessed. The data extraction and quality assessment procedures were undertaken independently by two reviewers, thereby reducing the potential for errors and bias. The quality of the included studies was assessed using appropriate criteria, and the included studies were of reasonable quality.

Limited information on the included studies was presented. There was no information on participant characteristics or antidepressant regimen, although the authors reported that a description of the included articles was available on request. Appropriate measures of effect were calculated and the authors assessed statistical heterogeneity; the possible reason for the heterogeneous result was discussed. The authors’ cautious conclusions appear appropriate given the limited evidence identified. However, since relevant unpublished or non-English language studies might have been excluded, publication bias and language bias may be present.

**Implications of the review for practice and research**
Practice: The authors did not state any implications for practice.

Research: The authors stated that further trials with larger sample sizes are required to assess the effectiveness of heterocyclic antidepressants and SSRIs in the treatment and prevention of PSD.

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