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

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SUMMARY

Background: Depression may affect patients’ recovery and even their survival rate after stroke, but it is often overlooked or inadequately managed; data regarding the prophylactic efficacy and safety of fluoxetine are inconsistent in this setting.

Objective: The objective of the study is to systematically assess the prophylactic efficacy and safety of fluoxetine in poststroke depression in patients with stroke.

Methods: We searched electronic databases up to December 2009 for studies evaluating the prophylactic efficacy of fluoxetine in patients with stroke. The pooled odds ratio (OR), weighted mean difference (WMD), incremental efficiency and 95% confidence intervals (95% CI) were calculated.

Results: We collected and evaluated a total of 385 patients identified from six trials. Meta-analysis demonstrated that fluoxetine reduced the incidence of poststroke depression (PSD) (OR = 0.25, 95% CI 0.11 to 0.56), helped recovery in neurological function (WMD = −4.72, 95% CI −8.31 to −1.13) and improved independence in activities of daily living (WMD = −8.04, 95% CI −13.40 to −2.68); fluoxetine is relatively safe in spite of the adverse events (OR = 0.88, 95% CI 0.31 to 2.49, p = 0.82). However, fluoxetine groups and control groups did not differ in change of scores for depression (WMD = −3.97, 95% CI −9.85 to 1.90, p = 0.19).

Conclusions: Fluoxetine was beneficial for the prophylaxis of poststroke depression in patients with stroke but not in reducing symptom severity of PSD.

Introduction

Poststroke depression (PSD) has long been considered as a common neuropsychiatric complication of stroke with a significant negative impact on patients’ rehabilitation, functional recovery, quality of life and even survival rate (1–5). The reported prevalence of PSD is about 20–79% (6–8). At present, studies of antidepressants have provided relatively sufficient evidence for the treatment of PSD. In these studies, PSD was confirmed either by Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria or another validated rating scale for depression. However, cognitive, language and functional impairments in patients with stroke may possibly bring difficulties to the recognition of PSD, resulting in under-diagnosis and under-treatment of the complication. Most PSD happened in 1 or 2 weeks after stroke, whereas antidepressants reach their best effects in 3 or 4 weeks (9), and patients would miss the best recovery time if antidepressants were given after diagnosing of PSD. Therefore, comparing with the treatment of PSD, proper prophylaxis of PSD which means antidepressants are given to patients who have not met the diagnostic criteria of depression scale score, may represent a viable prevention strategy.

Fluoxetine is a selective inhibitor of neuronal serotonin (5-hydroxytryptamine) reuptake, which is commonly used in the treatment of depression nowadays. But there are few randomised clinical trials (RCTs) focusing on fluoxetine prophylaxis of PSD and findings are inconsistent (8,10).

There is no meta-analysis focused on the prevention of PSD with fluoxetine, only some trials of fluoxetine in the three meta-analyses (11–13) on the prevention efficacy of PSD with antidepressants. The meta-analysis by Bhogal et al. (11) drew no firm conclusions; Hackett’s et al. (12) concluded that antidepressant groups reported lower numbers of PSD, but no evidence was found that pharmacotherapy improved mood scores, cognitive function or disability; whereas Chen et al. (13) conclusion based on all antidepressants and did not attempt to address prophylactic efficacy on neurological impairment,
activities of daily living and adverse events. And Hackett’s study included only one trial of fluoxetine whereas Chen’s included only four trials of fluoxetine carried out from 1996 to 2005.

In this study, we conducted a meta-analysis of the clinical trials evaluating the prophylactic efficacy and safety of fluoxetine in patients with stroke.

Materials and methods

Search strategy

A computer-aided systematic search of studies published in English was performed in biomedical databases including Medline (1950–December 2009), PubMed (1948–December 2009), Embase (1966–December 2009), the Cochrane Library (1960–December 2009), evidence based medicine reviews (EBMR), centre for reviews and dissemination database (CRDD), Sumssearch, TRIP database, national guideline clearinghouse (NGC), The National Institute for Clinical Excellence (NICE), The national research register (NRR), the ClinicalEvidence website (clinicalevidence.com), the ClinicalTrials website (clinicaltrials.gov) and the Bandolier. Studies published in Chinese were identified in databases including Chinese National Knowledge Infrastructure (CNKI) (1979 – December 2009), Chinese Bio-medicine Database (CBM) (1978 – December 2009) and Chinese Sci-tech Journals Database (VIP) (1989 – December 2009). Combinations of the following search terms were used: fluoxetine, stroke, cerebral apoplexy, acute cerebral accident, cerebral infarction, cerebral haemorrhage, vascular depression, postischaemic brain, prophylaxis, prevention and depression. To complete our literature search, reviews, textbooks and other materials available in our department were examined. Experts in this particular field of study were consulted. Additionally, we reviewed all of the references listed in the trials we had found, and manufacturers were also contacted through telephone calls or emails for unpublished trials.

Inclusion criteria

For this meta-analysis, inclusion criteria were as follows: (i) randomised controlled trials of fluoxetine prophylaxis of PSD and the control interventions were conventional treatment with placebo or without any other medicine; (ii) patients were diagnosed as stroke clinically and/or by computed tomography (CT) scan or nuclear magnetic resonance imaging (MRI); (iii) patients without a diagnosis of depression, as confirmed by Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria or other validated rating scales for depression; (iv) the end-points of the trial included prophylactic efficacy of PSD, neurological impairment, activities of daily living and drop-out rates.

No inclusion restrictions were present on the basis of the patients’ and studies’ characteristics, such as age, gender and duration of the studies. Studies that included mixed patient groups (e.g. depressed patients) were excluded, unless separate results for non-depressed patients were presented. Studies that compared fluoxetine as well as other antidepressants with control were also excluded unless separate results about fluoxetine were included.

Data extraction and quality assessment of studies

Two qualified reviewers assessed each potentially eligible study to see whether it met the inclusion criteria. The characteristics of each study were identified and extracted, such as randomisation, number of patients, characteristics of participants (e.g. age, gender, etc.), detailed experimental, control interventions and main outcomes. The original investigators were contacted for the missing information that was needed; unclear data were not used until they replied.

Poststroke depression was measured by the Hamilton Depression Rating Scale (HDRS/HAMD). Neurological impairment following stroke was measured by the Scandinavian Neurological Stroke Scale (SSS). Measures of functional disability included the Barthel Index (BI) and the Functional Independence Measure (FIM). Measures of adverse events were the rates of drop-out.

At least 25 scales are available to assess the validity and quality of randomised controlled trials. However, the reliability of assigning a quality score to each study and the validity of this score in weighting the results in meta-analyses are debated (14). Therefore, we used the four basic criteria as suggested in the Cochrane Handbook: allocation to conditions by an independent (third) party; adequacy of random allocation concealment to respondents; blinding of assessors to outcomes and completeness of follow-up data (15).

During the process, all the disagreements on data extraction and study evaluation were resolved through discussion.

Statistical analysis

RevMan 5.0.2 (Cochrane Library) was applied to combine the results from two or more separate studies. Statistical heterogeneity was identified and measured with Chi-square test. If heterogeneity was significant (p < 0.05) in a group of trials, random-effects model was applied. Otherwise, combined results based on
fixed-effects model were presented and CIs of pooled effect were calculated. ORs were calculated for dichotomous outcomes, whereas WMDs for continuous outcomes, and the standard normal distribution was expressed as 95% CI. Statistical significance level was set at p < 0.05.

To evaluate the prophylactic efficacy of fluoxetine, incidence of newly developed PSD between fluoxetine groups and control groups was compared. The WMD of scores of HDRS/HAMD, SSS, BI was also compared between the two groups.

To evaluate the safety of fluoxetine, studies reporting the numbers of drop-out in both fluoxetine groups and control groups were selected. The pooled OR of different rates of drop-out was estimated.

To evaluate the robustness of the pooled estimates, the meta-analysis was repeated on the basis of the quality of studies, which was determined by sample size and adequate information about randomisation, blinding and concealing.

Considering the tendency that studies with positive findings are more likely to be published compared with those with negative findings, the fail-safe number (Nfs) was calculated to evaluate publication bias.

**Results**

**Trial flow and study characteristics**

In the English literature search, we first identified 487 studies, of which the abstracts were reviewed. Of these, 23 studies were considered potentially relevant and were further reviewed in detail. Three studies met all the inclusion criteria and included in the final analysis (6,8,16). Of the remaining 20 studies, one was excluded because it focused on the prevalence of depression and usage of antidepressants, one because the result of fluoxetine was not separated from other antidepressants, one because of repeat data, seventeen because fluoxetine was used to treat rather than prevent PSD.

In the Chinese literature search, we first identified 85 studies, and all were reviewed in detail. Three studies (17–19) met all inclusion criteria and were included in the final analysis. Of the remaining, 78 studies were excluded because fluoxetine was used to treat rather than prevent PSD, two were because the results of prevention was not separated, one because of lack of blindness and one because of lack of randomisation.

In total, six RCTs, containing 385 cases using fluoxetine to prevent PSD, were included (Figure 1). Conventional treatment with fluoxetine was compared with conventional treatment with placebo in three of the six studies (6,8,16), and conventional treatment without any other medicine in three of the six studies (17–19). The duration of studies ranged from 4 weeks (18) to 12 weeks (6,16,19).

Most studies (3/6) (6,8,16) appeared to have an appropriate blinding design. However, only two studies (8,18) described an adequate detailed randomisation sequence and concealing. Reported drop-out rates because of adverse events ranged from 0% (17–

![Figure 1](image-url)
19) to 11.1% (6) in fluoxetine groups and from 0% (17–19) to 14.3% (8) in control groups (Table 1).

**Prophylactic efficacy of depression**

Three studies (16,18,19) with 176 patients reported incidence of newly developed depression, compared with control groups. Baseline depression scores were comparable in both groups. At endpoint, the pooled OR was 0.25 (95% CI 0.11 to 0.56, p = 0.0009), indicating that fluoxetine was effective in lowering the incidence of newly developed depression (Figure 2).

Among the included studies, two studies reported intervals between stroke onset and administration of fluoxetine. Table 2 shows the prophylactic effects of fluoxetine associated with intervals between stroke onset and administration of fluoxetine. Reductions in the occurrence rate of PSD were related with interval between stroke onset and administration of fluoxetine, and patients had a better effect when given fluoxetine in 1 week after stroke. As patients with different type, severity and involved lesions of stroke were mixed and the average age of patients were all above 60 in the three studies, it was hard to tell apart which kind of patient would benefit from fluoxetine prophylaxis.

Four studies (6,8,16,17) with 217 patients reported scores of depression rating scales of fluoxetine groups compared with control groups, using Hamilton Depression Rating Scale. Baseline depression scores were comparable in both groups. As a result of significant heterogeneity in the four RCTs, random-effects model was applied. At endpoint, patients in both groups showed no statistically significant difference in depression rating scale scores (pooled WMD = 3.97, 95% CI 9.85 to 1.90, p = 0.19), indicating that prophylactic fluoxetine could not reduce symptom severity of PSD (Figure 3).

**Prophylactic efficacy on neurological impairment**

Two studies (8,17) of 157 patients reported prophylactic efficacy on the recovery of neurological impairment using the Scandinavian Stroke Scale. Statistically significant difference was observed in both groups (pooled WMD = −3.97, 95% CI −9.85 to 1.90, p = 0.19), indicating that prophylactic fluoxetine could not reduce symptom severity of PSD (Figure 4).

**Prophylactic efficacy on activities of daily living**

Prophylactic efficacy of fluoxetine on ADL was reported in three studies (6,8,16) of 105 patients, among which two used the BI scale (6,8), one used the FIM scale (16). Statistically significant difference was

| Trials | No. of randomised patients | Gender (%female) | Mean age, years | Fluctine/Control | Measure | Treatment, week | Method of randomisation | Concealing | Blinding | ITT | Fluoxetine/Control | Fluoxetine/Control | Fluoxetine/Control |
|--------|-----------------------------|------------------|----------------|------------------|---------|----------------|------------------------|------------|---------|----|------------------|------------------|------------------|
| Kong 2007 | 48/42 | 40/43 | 64/63 | 90 | HAMD,ADL,SSS | 8 | Computer-generated | DB | No | Yes | No | No | 12 |
| Robinson 2000 | 17/16 | 33/25 | 66/68 | 35 | HDRS,FIM,HFI | 12 | Computer-generated | DB | No | Yes | No | No | 12 |
| Dam 2006 | 18/17 | 35/25 | 66/68 | 30 | HDRS,BI | 12 | Computer-generated | DB | Yes | No | No | No | 12 |
| Zhou 2008 | 36/34 | 40/36 | 57/58 | 61 | HAMD,FIM | 8 | Computer-generated | DB | No | No | No | No | 9 |
| Wen 2006 | 42/42 | 84/84 | 57/58 | 62 | HDRS,FIM | 12 | Computer-generated | DB | No | Yes | No | No | 12 |
| Li 2004 | 33/35 | 67/27 | 60/60 | 61 | HAMD,CSS | 20 | Computer-generated | DB | No | Yes | No | No | 12 |
observed in patients in the two groups in terms of BI (pooled WMD = -8.04, 95% CI -13.40 to -2.68, p = 0.003) and FIM scores (Mean ± SD = 59.2 ± 11.6 in the fluoxetine group and 56.2 ± 7.8 in the control group, p < 0.05), indicating that prophylactic fluoxetine can help improving activities of daily living of patients with stroke (Figure 5).

**Adverse events and safety**

Three studies (6, 8, 16) of 158 patients reported rates of drop-out in both fluoxetine groups and control groups. At endpoint, patients in both groups showed no statistically significant difference (pooled OR = 0.88, 95% CI 0.31 to 2.49, p = 0.82), indicating that fluoxetine was safe for the prophylaxis of PSD although it had adverse events (Figure 6). Table 3 shows reported adverse events of fluoxetine in all the six studies, patients in both groups showed no statistically significant difference, but nausea, insomnia and epileptic seizure were of higher proportion in reported adverse events.

**Sensitivity analysis**

To exclude low-quality trials and small sample research data, no incidence of reversal meta-analysis results of incidence of newly developed PSD, recovery of neurological function impairment, improvement of activities of daily living and safety of

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**Table 2** Rate of newly developed PSD cases and interval between onset of stroke and treatment

| Interval | Study ID     | Occurrence rate of PSD (%) | Fluoxetine | Control | OR (95% CI) |
|----------|--------------|-----------------------------|------------|---------|-------------|
| ≤1 week  | Zhou 2008    | 11.1 (4/36)                 | 45.0 (18/40)| 0.15 (0.05, 0.51) |
| ≥4 weeks | Robinson 2000| 17.6 (3/17)                 | 18.6 (3/16) | 0.93 (0.16, 5.45) |

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Figure 2 Meta-analysis of newly developed depression rates of fluoxetine groups vs. control groups

Figure 3 Meta-analysis of depression rating scale scores of fluoxetine groups vs. control groups

Figure 4 Meta-analysis of neurological impairment rating scale scores of fluoxetine groups vs. control groups

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fluoxetine were observed, indicating that the conclusions of this study had certain reliability (Table 4).

**Publication bias**

Publication bias was assessed with fail-safe number (Nfs) according to the formula \( \text{Nfs} = \frac{P}{Z / 1.645}^2 - k \) \((k = \text{number of studies}, Z = \text{the independent study of the Z value})\) (20). The Nfs value of this study was 9.3, higher than the number of trials included, indicating that the conclusions of this study had certain reliability.

**Discussion**

We conducted a meta-analysis of fluoxetine for the prophylaxis of PSD in patients with stroke and provided some clinical basis for clinical use of fluoxetine to prevent PSD.

Bhogal et al. (11) included three randomised controlled trials of antidepressants; no relevant results were acquired because meta-analysis could not be used in the included trials. Hackett et al. (12) included five randomised controlled trials with one...
using fluoxetine; Chen et al. (13) included 10 randomised controlled trials of antidepressants, with three using fluoxetine; both the results showed that the number of patients developed PSD decreased, but no evidence was found that prophylactic antidepressants could reduce the degree of PSD and improve cognitive function.

Our study included six trials of fluoxetine. The results indicated that the fluoxetine groups were better than the control groups in reducing the incidence of PSD, had better recovery in neurological function impairment, better improvement in activities of daily living and fluoxetine was relatively safe in spite of adverse events. However, fluoxetine had no efficacy in reducing symptom severity of PSD. As nausea may lead to aspiration pneumonia, insomnia and epileptic seizure are both stroke complications; they all may lead to deterioration of stroke. Patients with stroke should be watched out for these side effects while using fluoxetine for the prophylaxis of PSD, and patients who had a history of insomnia and epileptic seizure better not use fluoxetine.

**Strengths and weaknesses of the study**

Two of the results of our study are that prophylactic fluoxetine could reduce the incidence of PSD, but the efficacy of reducing symptom severity of PSD was not observed. They are somewhat consistent with the results of Hackett’s and Chen’s studies that prophylactic antidepressants could reduce the incidence of PSD, but there was no evidence to prove that the degree of depression could be improved. At the same time, this study included more recent studies and showed that prophylactic fluoxetine could help the recovery of neurological function impairment, improvement of activities of daily living and was relatively safe. Our study carried out a deeper and wider analysis than the former ones.

Our study included a total of six trials (385 patients). Among the included trials, only two trials (8,18) gave a detailed description of randomisation and allocation concealment methods, and the remaining was simply described as randomised trials. Although all the trials reported the number of drop-out patients, only one trial (16) carried out ITT analysis; so that the control effect of attrition bias could not be made clearer. In addition, as there are several different outcome scales for depression used in stroke patients and there is no common ‘language’, data of some scales in the included studies were limited, making it hard to carry a better meta analysis with these scales. And, most of the studies available were about the treatment of PSD, in which fluoxetine was taken by patients diagnosed as PSD; studies on the prevention of PSD were few and there were difficulties in separating studies on treatment vs. prevention of depression, making included studies limited. Moreover, as to the limited data available, no conclusion of which kind of patient would benefit from fluoxetine prophylaxis was made. The conclusion that patients had a better effect when given fluoxetine in 1 week after stroke needs further analysis with more data.

**Clinical implications and conclusion**

Prophylactic fluoxetine reduced the incidence of PSD, had better recovery in neurological function impairment, better improvement in activities of daily living and was relatively safe in spite of adverse events, but could not reduce symptom severity of PSD. Reductions in the occurrence rate of PSD were related with interval between stroke onset and administration of fluoxetine, and patients had a better effect when given fluoxetine in 1 week after stroke. But which kind of patient would benefit from fluoxetine prophylaxis was not clear yet. Patients with stroke should be watched out for nausea, insomnia and epileptic seizure while using fluoxetine for the prophylaxis of PSD, and patients who had a history of insomnia, and epileptic seizure better not use fluoxetine.

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| Criteria of quality   | Trials          | After treatment, pooled OR, (95% CI) |
|-----------------------|-----------------|---------------------------------------|
| Sample size ≥50       | Li 2004         | 0.17 (0.06, 0.45), p = 0.0004          |
|                       | Zhou 2008       |                                       |
| Randomisation         |                 |                                       |
| Inadequate information| Robinson 2000   | 0.26 (0.10, 0.68), p = 0.006          |
|                       | Zhou 2008       |                                       |
affiliations with or involvement in any organisations or entity with financial interests in the subject matter of the study. The contents are sole responsibilities of the authors.

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