Comparative efficacy and acceptability of antidepressant treatment in poststroke depression: a multiple-treatments meta-analysis

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ABSTRACT
Objective The aim of this study is to create a rank order of the comparative efficacy and acceptability (risk of all-cause discontinuation) of antidepressant treatment in poststroke depression (PSD) by integrating direct and indirect evidence.

Design Multiple-treatments meta-analysis of randomised controlled trials.

Participants Patients with depression following stroke.

Interventions 10 antidepressants and placebo in the acute treatment of PSD.

Outcome measures The primary outcomes were the overall efficacy, defined as the mean change of the total depression score. The secondary outcome was the acceptability, defined as risk of all-cause discontinuation. These estimates as standardised mean differences or ORs with 95% CIs.

Results We identified 12 suitable trials, with data from 707 participants. All drugs were significantly more effective than placebo apart from sertraline, nefiracetam and fluoxetine. Most of the comparisons for acceptability revealed no significant differences except that paroxetine had significantly lower all-cause discontinuation than doxepin, citalopram and fluoxetine. Standardised mean differences compared with placebo for efficacy varied from −6.54 for the best drug (reboxetine) to 0.51 for the worst drug (nefiracetam). ORs compared with placebo for acceptability ranged from 0.09 for the best drug (paroxetine) to 3.42 for the worst drug (citalopram). For the efficacy rank, reboxetine, paroxetine, doxepin and duloxetine were among the most efficacious treatments, the cumulative probabilities of which were 100%, 85.7%, 83.2%, and 82.4%, respectively. With respect to the acceptability rank, paroxetine, placebo, sertraline and nortriptyline were among the most acceptable treatments, the cumulative probabilities of which were 92.4%, 63.5%, 57.3%, and 56.3%.

Conclusion After weighing the efficacy and acceptability, we conclude that paroxetine might be the best choice when starting acute treatment for PSD, and fluoxetine might be the worst choice.

Trial registration number This systematic review has been registered in the Prospective Register of Systematic Review Protocols (PROSPERO) public database (CRD42017054741; http://www.crd.york.ac.uk/PROSPERO).

INTRODUCTION
Poststroke depression (PSD) is common, affecting approximately one-third of stroke survivors.1 There is abundant evidence indicating that PSD is associated with increased mortality and poor functional outcomes.2–5 Although evidence has emerged from systematic reviews to indicate that there are both validated depression screening tools6 and effective treatment and prevention strategies for depression after stroke,7–9 there has not been any significant reduction in the pooled frequency estimate of patients experiencing PSD (ie, values were 33% in 200510 and 31% in 201411). One reason is the high rates of refusal by stroke clinicians to recommend antidepressant therapy, because they consider the therapeutic efficacy of antidepressants for PSD treatment to be insignificant and also being associated with a significant risk of adverse events.12 Moreover, there are more than 40 different antidepressants in clinical use, which are divided into nine categories. Stroke clinicians seem to have difficulties in making a rational choice about...

which antidepressant to prescribe. Neither the absolute nor the relative efficacy of antidepressants has been fully established. There are even no recommendations in the guideline if any of these different drug classes of antidepressants is superior to the others. Therefore, whether and what antidepressant treatment for PSD should be prescribed remains controversial. Previous conventional pairwise meta-analyses have not been able to generate clear rank orders for the efficacy and acceptability of available treatments, because many antidepressants have not been compared in a head-to-head manner. In addition, the number of included randomised controlled trials (RCTs) is limited, which can introduce some bias into any conclusions. Thus, it would be beneficial to create a rank order taking both efficacy and unwanted effects into consideration.

Multiple-treatments meta-analysis is also known as mixed-treatment comparisons meta-analysis or network meta-analysis. It can provide us with a way to rank different interventions against each other. It also helps
Inferences concerning the relative efficacy and acceptability of antidepressant treatment in PSD.

METHODS
Criteria for considering studies
This systematic review has been registered in the Prospective Register of Systematic Review Protocols (PROSPERO) public database (CRD42017054741; http://www.crd.york.ac.uk/PROSPERO).

We included only RCTs that compared antidepressants as monotherapy in the acute-phase treatment of patients with PSD.

The patients with stroke had to be diagnosed clinically and/or by CT scan or MRI. They had also received a diagnosis of depression following stroke, as confirmed by either Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria or some other validated rating scale for depression. There were no inclusion restrictions on the basis of patient and study characteristics, such as age, sex and classes of antidepressants.

We also included placebo in the comparison group, because there is no consensus about either the efficacy or acceptability of antidepressant therapy.

Search methods and study selection
We searched Medline, Embase, PsycINFO, Cochrane Central Register of Controlled Trials, Web of Science (science and social science citation index) prior to December 2016. Further relevant trials were obtained by manual search of reference lists of all available records identified in the initial search. The authors were contacted for further information regarding unpublished trials and reports found in published databases. Keywords used in the searches were ‘depress* AND stroke’ (see online supplementary file 1). Various combinations of the search terms were used to retrieve the maximum number of relevant studies.

Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias

Low risk of bias
Unclear risk of bias
High risk of bias

Figure 2  Network plot of the included studies for the multiple-treatments meta-analysis for efficacy. The width of the lines is proportional to the number of studies comparing each pair of treatments, and the size of each node is proportional to the number of randomised participants (sample size). The network plot of included studies for acceptability analysis is similar.

Figure 3  Risk of bias graph: review authors’ judgements about each risk of bias item presented as percentages across all included studies.
Outcome measures and data extraction

The primary outcomes were the overall efficacy. We defined overall efficacy as the mean change of the total score of the Hamilton Depression Rating Scale (HDRS) or Montgomery-Asberg Depression Rating Scale or Beck Depression Inventory or Bech-Rafaelsen Melancholia Scale or Zung Self-Rating Depression Scale (ZDS) from baseline to end point. When trials reported results from all of the above rating scales, we used them in the order described above. Intention-to-treat datasets were used whenever available.

The secondary outcome was the acceptability of the antidepressant treatment. We defined acceptability of treatment (treatment discontinuation) as the proportion of patients who left the study early for any reason out of the total number of patients randomly assigned to each antidepressant.

Because a multiple-treatments meta-analysis requires reasonable homogeneity, we focused on acute treatment, which we defined as 6 weeks' duration taking the main guidelines into account.9 16 17 If 6-week data were not available, we used data from between 4 and 12 weeks (the data point closest to 6 weeks was given preference).

In the included studies, data were extracted by two reviewers (YS, HQ) independently. Once completed, any disagreements on data extraction and study evaluation were resolved through discussion. Information including study name, study characteristics, patient characteristics, depression diagnosis criteria, depression rating scale, comparators, dose range, treatment duration, sample size, effect sizes for two outcomes were extracted from each included study. Corresponding authors would be contacted for any missing information. If the article could not provide the mean change of the total score, we calculated the score based on a difference between the end point and the initial value or by measuring graphs presented in article.

We used network plots to explore the geometry of the treatment network of the included studies. The width of the lines is proportional to the number of studies comparing each pair of treatments, and the size of each node is proportional to the number of randomised participants (sample size).

The Cochrane risk of bias tool was used to assess the risk bias in the included studies.18 The tool contains seven domains, which are random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. The judgement for each domain includes a low risk of bias, a high risk of bias or unclear risk of bias. Two authors independently evaluated the risk of studies.

Data synthesis and analysis

We conducted two types of meta-analysis using a frequentist model. First, we conducted a pairwise meta-analysis for all direct comparisons with a random-effects model,19 assessing heterogeneity in these analyses with

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Figure 4  Risk of bias summary: review of the authors' judgements about each type of risk of bias for each included study.
Figure 5  Efficacy and acceptability of the 11 antidepressants for PSD. Drugs are reported according to efficacy ranking. Comparisons between treatments should be read from left to right and the estimate is in the cell in common between the column-defining treatment and the row-defining treatment. For efficacy, SMDs lower than 0 favour the column-defining treatment. For acceptability, ORs higher than 1 favour the column-defining treatment. To obtain SMDs for comparisons in the opposite direction, negative values should be converted into positive values and vice versa. To obtain ORs for comparisons in the opposite direction, reciprocals should be taken. Significant results are in bold and underlined. CIT, citalopram; DOX, doxepin; DUL, duloxetine; FLU, fluoxetine; NEF, nefiracetam; NOR, nortriptyline; PAR, paroxetine; PBA, placebo; PSD, poststroke depression; REB, reboxetine; SER, sertraline; SMD, standard mean differences; TRA, trazodone.
meta-analysis model would be fitted when statistical inconsistency was present.

To rank the treatments for an outcome, we used surface under the cumulative ranking (SUCRA) probabilities, which are expressed as a percentage the total efficacy or acceptability of every intervention relative to an imaginary intervention that is always the best without uncertainty.23 Thus, large SUCRA scores should indicate a more effective or acceptable intervention.

The funnel plot was used to identify the possible publication bias if the number of studies was larger than 10. We conducted several sensitivity analyses on the primary outcome to explore potential reasons for heterogeneity or inconsistency, such as whether it was early treatment. It has to be recalled that in the early stage (during the first 3 to 4 months after a stroke), PSD poses serious problems, such as worsened functional27 28 and vital prognoses27 29 as well as worsened quality of life of the patient and his/her caregiver,30 and therefore we defined the start of antidepressant treatment within 3 months after a stroke as early treatment. Meta-analyses were performed with Stata V.13.1 (StataCorp), using a suite of ‘network’23 and mvmeta command.22

RESULTS
Study identification and characteristics
The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of studies selection was depicted in figure 1. A total of 9651 references in the primary search were identified. After removal of the duplicates, 4026 records were screened. Of these, 3989 were excluded based on screening of titles and abstracts.
Figure 10 Comparison-adjusted funnel plot for acceptability. (01) citalopram; (02) doxepin; (03) duloxetine; (04) fluoxetine; (05) nefiracetam; (06) nortriptyline; (07) paroxetine; (08) placebo; (09) reboxetine; (10) sertraline; (11) trazodone.

and thus 37 were included in the narrative review, and data from 12 of these studies were included in the meta-analysis. In the study conducted by Robinson et al., we selected the comparison between nefiracetam (600 mg) and placebo instead of the comparison between nefiracetam (900 mg) and placebo, because there was no statistically significant difference between the two doses. Whereas, the group of patients receiving nefiracetam (600 mg) seemed to enjoy greater efficacy when the treatment duration was 9 weeks.

The characteristics of 12 studies published from 1984 to 2012 are shown in online supplementary file 2. A total of 707 participants were included in the review and the study sample size ranged from 22 to 123. The mean age of all patients was above 50. About half of the participants (51%) were female and 42% had a right-sided stroke location. With respect to the nine studies in which a specific time of assessment after stroke was available, three studies were early treatment. Treatment duration ranged from 4 weeks to 12 weeks.

The network plot of the included studies for the multiple-treatments meta-analysis for efficacy is shown in figure 2. A total of 11 antidepressants were eligible, including placebo. Eighteen possible comparisons could be made, 12 of which were examined directly in 1 study, and two of which (nortriptyline vs placebo, fluoxetine vs placebo) were examined directly in three studies. The network plot of the included studies for acceptability analysis was similar.

Risk of bias in included studies

Figure 3 and 4 reveal the risk bias in all 12 studies. Five studies described random sequence generation and adequate allocation concealment. Eight studies described blinding of participants and personnel while one study had a high risk of bias since it was an open label. The study, an open-label trial, was also considered as a high risk of bias about blinding of outcome assessment, while eight studies exhibited a low risk. All of studies had a low risk of incomplete outcome data except for one. Seven studies had a low risk of selectively reporting results.

Efficacy analysis and acceptability analysis

The results of the direct comparisons for efficacy and acceptability analysis are shown in the online supplementary file 3.

Figure 5 summarises the results of the multiple-treatments meta-analysis. With respect to overall efficacy, all drugs were significantly superior to placebo (range of mean effect sizes –0.59 to –6.54) apart from sertraline, nefiracetam and fluoxetine. Reboxetine was significantly more effective than all of the other drugs. With respect to acceptability (all-cause discontinuation), most of the comparisons revealed no significant differences except that paroxetine had significantly lower all-cause discontinuation than doxepin, citalopram and fluoxetine.

Figure 6 and 7 show the distribution of probabilities of 11 treatments being ranked for efficacy and acceptability, respectively. For the efficacy rank (figure 6), reboxetine, paroxetine, doxepin, duloxetine were among the most efficacious treatments, the cumulative probabilities of which were 100%, 85.7%, 83.2%, 62.4%, respectively. The following drugs were less effective; trazodone (59.8%), nortriptyline (54.5%), citalopram (35.7%), sertraline (36.1%), placebo (16.3%), nefiracetam (14.1%), fluoxetine (2.3%). With respect to the acceptability rank (figure 7), paroxetine, placebo, sertraline and nortriptyline were among the most acceptable treatments, the cumulative probabilities of which were 92.4%, 63.5%, 57.3% and 56.3%. The following drugs were less acceptable; trazodone (55.1%), reboxetine (54.6%), nefiracetam (47.4%), duloxetine (41.8%), doxepin (31.6%), fluoxetine (27.5%) and citalopram (22.5%). Figure 8 shows the clustered ranking based on the probabilities of efficacy and acceptability. The exploration of inconsistency is described in detail in the online supplementary file 4.

Reporting biases and sensitivity analyses

Comparison-adjusted funnel plots for efficacy (figure 9) and acceptability (figure 10) reveal the reporting bias in all 12 studies. Both of the plots were basically symmetrical. Sensitivity analyses where the three studies with the early treatment with antidepressants for PSD were excluded did not substantially change the results for efficacy and acceptability, excepting that citalopram and sertraline exchanged the ranking order in SUCRA rank for efficacy, and sertraline and nortriptyline exchanged the ranking order in SUCRA rank for acceptability. In other words, sertraline became more effective but less acceptable after removal of the three studies with the early treatments.
DISCUSSION

Although PSD is one of the most common complications after stroke and has been recognised by psychiatrists for more than 100 years, controlled systematic studies did not begin until the 1970s. However, there is still no consensus on the efficacy of antidepressants to treat PSD, and the relevant RCTs are few. At present, the Guidelines for Adult Stroke Rehabilitation and Recovery: A Guideline for Healthcare Professionals from the American Heart Association/American Stroke Association only indicated that treatment with heterocyclic antidepressant medications (tricyclic and tetracyclic antidepressants (TCAs)) and selective serotonin reuptake inhibitors (SSRIs) were stated as viable options for PSD. However, we found that not every TCA or SSRI is viable. In our study, reboxetine, a novel selective norepinephrine reuptake inhibitor (NARI) was ranked first for efficacy followed by paroxetine (SSRI), doxepin (TCA), duloxetine (serotonin and norepinephrine reuptake inhibitors (SNRIs)), trazodone (serotonin receptor antagonists and serotonin reuptake inhibitors), nortriptyline (TCA), citalopram (SSRI), sertraline (SSRI), placebo, nefiracetam (nicotinic acetylcholine receptors (nAChRs)), fluoxetine (SSRI). In terms of acceptability, paroxetine (SSRI), placebo, sertraline (SSRI), nortriptyline (TCA) and reboxetine (NARI) were better tolerated than trazodone (serotonin receptor antagonists and serotonin reuptake inhibitors), nefiracetam (nAChR), duloxetine (SNRI), doxepin (TCA), fluoxetine (SSRI) and citalopram (SSRI). When weighing the efficacy and acceptability, it seems that paroxetine might be the best choice when starting acute treatment for PSD, and fluoxetine might be the worst choice. Hence, acute treatment referred to the treatment duration of 6–12 weeks. There are several studies suggesting that the results of comparison between different drugs would change as the treatment duration became longer,

which indicated that the results of the ranking may also change. Clinicians need to know whether (and to what extent) antidepressant drug treatments work within a clinically reasonable period.

However, the results of the ranking are only for reference and are subject to the following limitations. First, although the examined related RCTs were heterogeneous, typically they had small sample sizes. Due to the variety of antidepressants, the research objectives were somewhat fragmented, and the number of studies on the same kind of antidepressant was too small, which meant that most of the comparisons in this review included only one study. Second, the results of inconsistency test for efficacy when examined by the loop-specific approach indicated that the loop of fluoxetine versus nortriptyline versus placebo was heterogeneous, and the inconsistency factor (IF) was obvious (IF=1.23) even though the loop was consistent. So we should cautiously explain the result of the loop. In addition, we did not take the subtype of PSD into account, because the inconsistency test revealed no significant difference even after excluding those studies which identified the subtypes of the participants. It should be noted that the response of the patients with PSD might be related to the subtype of depression, similarly to what was observed for primary depression. Therefore, it is important to emphasise that in this review, reboxetine was administered to patients with ‘retarded’ PSD. With respect to sertraline, the indirect comparison was consistent with the direct comparison, although the direct comparison of sertraline versus placebo had been undertaken in patients with stroke and minor depression and less severe major depression. For this reason, we speculated that the result of sertraline may not be related to the severity of depression. However, sertraline became more effective but less acceptable after removal of the three studies with the early treatments. We cannot judge whether the outcomes of early treatment is related to the severity of depression. Furthermore, some studies have shown that PSD was related with other factors such as sex, stroke location, which may influence the results. But it was not possible to carry out the relevant analyses due to the lack of individual data. Finally, we did not investigate important outcomes of acceptability, such as side effects, toxic effects and discontinuation symptoms, as only a few studies reported this kind of data. Therefore, the treatment discontinuation may not have been attributable only to the antidepressant itself.

Conventional pairwise meta-analyses of the treatment of antidepressants in PSD were less, few of which conducted meta-analysis based on different antidepressants. Tan et al. showed that citalopram was superior to the other SSRIs and TCAs in improving the total HDRS scores of PSD with acute treatment. The only other SSRIs included in that study were fluoxetine and sertraline. Nonetheless, the results were consistent with our rank order. The TCAs included also amitriptyline and imipramine, which were not included in our analysis since we excluded Chinese articles. Xu et al demonstrated a significant advantage associated with antidepressants in comparison with placebo treatment in PSD (SMD=−0.96; 95% CI −1.41 to −0.51; p<0.0001). In that previous meta-analysis, the subgroup analyses demonstrated that when compared with placebo, other antidepressants (SMD=−2.01; 95% CI −3.13 to −0.89; p=0.10) were better than TCAs (SMD=−1.41; 95% CI −2.51 to −0.31; p=0.02) and SSRIs (SMD=−0.53; 95% CI −0.97 to −0.09; p<0.0001), which are not at odds with the results found here.

All in all, in the treatment of PSD, there are many unresolved factors that could influence the choice of the optimal antidepressant compound that is, subtype of depression, sex, stroke location. One topic for future exploration would be to determine whether the duration of treatment affects the response. There is an urgent
need for more high-quality research on antidepressant treatment in PSD.

Contributors YS designed the study, extracted the data, wrote and approved the manuscript. YL ran the network meta-analysis, revised and approved the manuscript. YJ and JL identified the relevant outcomes, discussed the validity of the trials, revised and approved the manuscript. CZ conducted the systematic review, evaluated the quality of the studies, participated in the elaboration of the manuscript and approved the manuscript.

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