Does citalopram effectively treat post-stroke depression?
A protocol for systematic review and meta analysis

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Abstract

Background: This study aims to assess the efficacy and safety of citalopram for the treatment of patients with post-stroke depression (PSD).

Methods: We will comprehensively search Cochrane Library, PUBMED, EMBASE, WorldSciNet, Web of Science, VIP Database, CBM database, and China National Knowledge Infrastructure. The search period is limited from the construction of each database to the February 1, 2020. No language and publication status are limited. Two investigators will independently carry out study choosing, data extraction, study methodological quality assessment, and quality of evidence. A third investigator will help to resolve any disagreements between 2 investigators. RevMan 5.3 software will be employed for statistical analysis.

Results: This study will summarize the up-to-date evidence and synthesize the data to explore the efficacy and safety of citalopram for patients with PSD.

Conclusions: The results of this study may present helpful evidence to determine whether citalopram is an effective management for patients with PSD.

PROSPERO registration number: PROSPERO CRD42020171015.

Abbreviations: PSD = post-stroke depression, RCTs = randomized controlled trials.

Keywords: citalopram, efficacy, post-stroke depression, safety

1. Introduction

Post-stroke depression (PSD) is considered as the most frequent and important neuropsychiatric complication experienced following stroke.\textsuperscript{[1–5]} It often affects functional recovery, quality of life, and rehabilitation, and is associated with a variety of disability, morbidity and mortality.\textsuperscript{[6–11]} It is estimated that its incidence ranges from 23.0% to 76.1% in China.\textsuperscript{[12]} Other studies reported that about 20% to 50% patients with stroke suffer from PSD.\textsuperscript{[13–14]} Thus, it is very essential to treat PSD timely and effectively.

Despite a variety of clinical trials have reported that citalopram is effective and safety management for patients with PSD,\textsuperscript{[15–34]} there are inconsistent conclusions at literature levels. In addition, the present level of evidence-based medical evidence is still insufficient because of the limited number of high quality trials and sample sizes. Thus, we hope this study will provide high quality evidence to appraise the efficacy and safety of citalopram for the treatment of PSD.

2. Methods

2.1. Study registration

This study has been funded and registered through PROSPERO (CRD42020171015). It has been reported base on the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols statement.\textsuperscript{[35]}

2.2. Criteria for including studies

2.2.1. Types of studies. All randomized controlled trials (RCTs) that focusing on the citalopram for the treatment of patients with PSD will be included without language and publication time restrictions.

2.2.2. Types of interventions. We will adopt citalopram treatment alone on patients with PSD as experimental interventions. As for control intervention, it can be any therapies, such as placebo, acupuncture, and any other management. However, we will not consider any treatments including any forms of citalopram.
2.2.3. Types of participants. We will include any participants who had a confirmed clinical diagnosis of PSD. We will not place any restrictions upon the ethnicity, sex, age, and economic status.

2.2.4. Types of outcome measurements. The primary outcome indicator is depression. It can be assessed by any validated scales, such as Hamilton Depression Scale. The secondary outcomes are anxiety (as measured by any validated tools, such as Hamilton Depression Scale), health-related quality of life (as identified any related indexes, such as 36-Item Short Form Survey), and any expected or unexpected adverse events.

2.3. Search strategy
2.3.1. Electronic databases searches. The following electronic databases will be searched comprehensively from the construction of each database to the February 1, 2020: Cochrane Library, PUBMED, EMBASE, WorldSciNet, Web of Science, VIP Database, CBM database, and China National Knowledge Infrastructure. There are no restrictions on the language and publication time. The complete Cochrane Library search strategy is created and summarized (Table 1). Similar search strategies of other electronic databases will be modified and built.

2.3.2. Other literature resources. We will also identify any potential trials from other relevant literature resources, such as conference proceedings, and reference lists of included trials or connected reviews.

2.4. Study identification
All sought resources will be imported into EndNote 7.0 to remove any duplicates. Titles/abstracts of remaining papers will be filtered by 2 independent investigators, and those clearly do not conform to the study eligibility criteria will be removed. After that, we will obtain full manuscripts of the potential trials and carefully read whole documents. Any unqualified trials will be filtered out according to the full inclusion criteria. As for the literatures those cannot be ensured, we will invite a third investigator by discussion and a final decision will be made after discussion. We will present the process of study identification in a flow diagram with details.

2.5. Data extraction and management
Two independent investigators will complete the data extraction from the qualified trials based on the data form uniformly developed by the experienced expert. Any uncertainty will be disentangled by the help of a third investigator through discussion or consultation. The extracted information is as follows:

General information: Title, first author, year of publication, contact information.

Participants: Age, ethnicity, sex, diagnostic criteria, inclusion and exclusion criteria, severity and duration of the disease.

Study methods: Study design, sample size, details of randomization, blind, and concealment.

Interventions and controls: types of modality, modality methods, dosage, period, and frequency.

Outcome indicators: primary and secondary outcomes, and number of adverse events.

Others: Funding sources, and conflict of interest.

2.6. Risk of bias assessment
As for study quality assessment, we will utilize Cochrane risk of bias tool, which is the recommended tool to appraise the risk of bias in RCTs in Cochrane Reviews. It covers different aspects of study design, conduct, and reporting through 7 domains. Each 1 is graded as low, unclear or high risk of bias. Two investigators will appraise them independently for each eligible trial, and any differences will be fixed with the help of a third investigator.

2.7. Statistical analysis
2.7.1. Data synthesis. RevMan 5.3 software will be employed for statistical analysis. According to the different types of statistical data, binary categorical values will be expressed as risk ratio and 95% confidence intervals, and continuous values will be calculated as mean difference or standardized mean difference and 95% confidence intervals. I² statistic test will be used to explore the heterogeneity of the research results. If possible, we will conduct a meta-analysis if sufficient data are collected from the eligible trials with similar study characteristics, intervention and control modalities, and outcome

| Number | Search terms |
|--------|--------------|
| 1      | MeSH descriptor: (stroke) explode all trees |
| 2      | MeSH descriptor: (cerebral hemorrhage) explode all trees |
| 3      | MeSH descriptor: (depressive disorder) explode all trees |
| 4      | MeSH descriptor: (depression) explode all trees |
| 5      | (cerebrovascular) or (accidental) or (cerebral infarction) or (stroke) or (apoplexy) or (hemiplegia) or (cerebral hemorrhage) |
| 6      | Or 1–5 |
| 7      | MeSH descriptor: (citalopram) explode all trees |
| 8      | (citalopram) or (Citalopram) or (Selective Serotonin Reuptake Inhibitor) |
| 9      | Or 7–8 |
| 10     | MeSH descriptor: (randomized controlled trials) explode all trees |
| 11     | MeSH descriptor: (clinical trials as topic) explode all trees |
| 12     | (randomly) or (blind) or (allocation) or (placebo) or (control) or (comparator) or (trial) or (study) |
| 13     | Or 10–12 |
| 14     | 6 and 9 and 13 |

MeSH = medical subject headings.
indicators. Otherwise, \(I^2 > 50\%\) suggests high level of heterogeneity, and a random-effects model will be exerted. Additionally, we will perform subgroup analysis to explore any possible causes for the high level of heterogeneity. If a meta-analysis can not be conducted, we will report findings using a descriptive summary.

2.7.2. **Subgroup analysis.** Subgroup analysis will be performed based on the different types of general study information, patient characteristics, interventions, comparators, and outcome indicators.

2.7.3. **Sensitivity analysis.** Sensitivity analysis will be carried out to check whether the findings are robust according to the sample size, study quality and statistical model.

2.7.4. **Reporting bias.** If at least 10 included trials entered in a meta-analysis, we will investigate the potential reporting bias using funnel plot and Egger regression test.[16,37]

2.8. **Quality of evidence**

Quality of evidence for each outcome indicator will be appraised by Grading of Recommendations Assessment, Development, and Evaluation,[38] and each level of evidence will be judged as very low, low, moderate, or high level.

2.9. **Ethics and dissemination**

This study will not need ethical approval, because we will only use published data. We will publish this study on a peer-reviewed journal.

3. **Discussion**

In recent years, the clinical RCTs of citalopram for the treatment of PSD have been increasing, but their conclusions are still contradictory at literature level.[16–34] Thus, this systematic review will summarize the available direct high quality evidence to assess the efficacy and safety of citalopram for the treatment of PSD. Its results will provide literature evidence to judge whether citalopram is effective for the treatment of PSD, which may benefit clinical practice and health-related policy makers.

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**References**

[1] Gawronski DW, Reding MJ. Post-stroke depression: an update. Curr Atheroscler Rep 2001;3:307–12.

[2] Gall A. Post stroke depression. Hosp Med 2001;62:268–73.

[3] Gupta A, Pansari K, Shetty H. Post-stroke depression. Int J Clin Pract 2002;56:351–7.

[4] Garte JM, Bogunskovsky J. Post-stroke depression. Expert Rev Neurother 2008;8:75–92.

[5] Levada OA, Slivko EL. Post-stroke depression. Zh Nevrol Psikhiatr Im S S Korsakova 2006;Suppl 16:73–9.

[6] Lenz GL, Altermi M, Maestri M. Post-stroke depression. Rev Neurol (Paris) 2008;164:837–40.

[7] Zavoreo I, Basica-Kes V, Bosnar-Puretic M, et al. Post-stroke depression. Acta Clin Croat 2009;48:329–33.

[8] Arseniou S, Arvaniti A, Samakouri M. Post-stroke depression: recognition and treatment interventions. Psychiatrki 2011;22:240–8.

[9] Espiárrago Llorca G, Castilla-Guerra L, Fernández Moreno MC, et al. Post-stroke depression: an update. Neurologia 2015;30:23–31.

[10] Schulte-Aldehornburg M, Bereczki D. Post-stroke depression. Orv Hetil 2014;155:1335–43.

[11] Robinson RG, Jorge RE. Post-stroke depression: a review. Am J Psychiatry 2016;173:221–31.

[12] Huang BY, Liao ZA, Fang MH. The clinical research overview of post stroke depression. Chin J Phys Med Rehabil 2005;27:315–7.

[13] Dam M, Tonin P, De Boni A, et al. Effects of fluoxetine and mirtazapine on functional recovery in post-stroke hemiplegias patients undergoing rehabilitation therapy. Stroke 1996;27:1211–4.

[14] Kong Y, Dong W, Liu CF. Fluoxetine for post-stroke depression: a randomized controlled trial. Neu Regen Res 2007;2:162–5.

[15] Tan S, Huang X, Dong L, et al. Efficacy and safety of citalopram in treating post-stroke depression: a meta-analysis. Eur Neurol 2015;74:188–201.

[16] Sondergaard MP, Jarden JO, Martiny K, et al. Dose response to adjunctive light therapy in citalopram-treated patients with post-stroke depression. A randomised, double-blind pilot study. Psychother Psychosom 2006;75:244–8.

[17] Wang SH, Zhang ZJ, Guo YJ, et al. Establishment of rat model of post-stroke depression and the effects of citalopram on behavior thereof. Zhonghua Yi Xue Za Zhi 2007;87:1355–7.

[18] Zhao K, Yang Y, Gu DD. The effect of citalopram on the recovery of neurological function in patients with depression after acute stroke. Modern Doctor of China 2014;32:30–2.

[19] Li XF. A controlled study of escitalopram in the treatment of post-stroke depression and anxiety comorbidities. Modern Chinese Medicine Application 2014;8:151–2.

[20] Ye F, Li C. A comparative study of escitalopram in the treatment of post-stroke depression. China Minkang Medicine 2014;26:31–2.

[21] Liu W. The efficacy of escitalopram in the treatment of post-stroke depression. Modern Diagnosis and Treatment 2014;25:2162–5.

[22] Chen ML, Chen J. Clinical analysis of citalopram in the treatment of post-stroke depression. China Medical Science 2014;4:91–3.

[23] Yang YC, Yang YW. Clinical analysis of citalopram in the treatment of 100 patients with post-stroke depression. Chinese Journal of Pharmacoeconomics 2013;6:195–7.

[24] Li XH, Kong QX. Clinical efficacy and safety of citalopram in the treatment of post-stroke depression. China Modern Drug Application 2008;23:570–1.

[25] Zheng XH. Observation of the effect of escitalopram on depression after stroke. PLA Journal of Medicine 2012;24:10–1.

[26] Shao J, Qin XG. The effect of escitalopram on the mental state and quality of life of post-stroke depression patients. Chinese Journal of Hospital Pharmacy 2012;32:1047–50.

[27] Fang YM. A controlled study of citalopram in the treatment of post-stroke depression. China Minkang Medicine 2010;22:108.

[28] An WF. Observation of the effect of citalopram on post-stroke depression. Clin Med 2009;29:94.

[29] Chen DX, Fan XH. Clinical observation of citalopram in the treatment of post-stroke depression. Sichuan Mental Health 2009;22:45–6.

[30] Wang SS, Wang YG, Chen HY, et al. Expression of genes encoding cytokines and corticotropin releasing factor are altered by citalopram in

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the hypothalamus of post-stroke depression rats. Neuro Endocrinol Lett 2013;34:773–9.

[31] Qi CL. Clinical analysis of citalopram in clinical treatment of post-stroke depression. The World’s Latest Medical Information Digest 2016;16:264–7.

[32] Ju HL. The effect of citalopram on mental symptoms and rehabilitation compliance of post-stroke depression patients. China Minkang Medicine 2016;28:74–5.

[33] Ji W. Observation of the therapeutic effect of escitalopram on post-stroke depression. Electronic Journal of Clinical Medical Literature 2015;2:3905–6.

[34] Ma YB, Gao YL. Analysis of the effect of citalopram on post-stroke depression. Journal of Aerospace Medicine 2014;25:1136–7.

[35] Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ 2015;350:g7647.

[36] Sutton AJ, Duval SJ, Tweedie RL, et al. Empirical assessment of effect of publication bias on meta-analyses. BMJ 2000;320:1574–7.

[37] Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.

[38] Guyatt GH, Oxman AD, Vist G, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924–6.