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REVIEW ARTICLE

The efficacy and safety of fluoxetine versus placebo for stroke recovery: a meta-analysis of randomized controlled trials

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Abstract

Background Fluoxetine is one of the selective serotonin reuptake inhibitors that can improve motor and function recovery after a stroke. Several randomized controlled trials (RCTs) have investigated the efficacy and safety of fluoxetine compared to placebo in post-stroke recovery. However, the results are still controversial.

Aim This meta-analysis aimed to provide an updated analysis of the efficacy and safety of fluoxetine versus placebo in post-stroke recovery.

Method RCTs were searched from electronic databases of PubMed, Embase, Clinical Trials, and the Cochrane Central Register of Controlled Trials from inception until July 2022. Google Scholar and the reference lists of included studies were screened to identify additional studies. Outcomes were analyzed using risk ratios (RR) and mean differences (MD) with 95% confidence intervals (CI).

Results Fourteen RCTs (6584 patients) were included. The fluoxetine group showed a significantly higher Fugl-Meyer motor scale (FMMS) score than the placebo group (MD 15.93, 95%CI 9.76–22.7, $P<0.01$). No significant differences were observed in the modified Rankin Scale (mRS) (mRS ≤ 2, RR 1.00, 95%CI 0.88–1.15, $P=0.95$), the Barthel index (MD 12.11, 95%CI − 0.71 to 24.92, $P=0.06$), and the National Institutes of Health Stroke Scale scores (MD − 0.19, 95%CI − 0.43 to 0.04, $P=0.1$) between the two groups. The fluoxetine group showed a lower rate of depression or anxiety than the placebo group (RR 0.67, 95% CI 0.49–0.92, $P<0.05$). There were no significant differences between the groups regarding gastrointestinal adverse reactions ($P>0.05$), drowsiness ($P>0.05$) or insomnia ($P>0.05$).

Conclusion Fluoxetine improved FMMS and reduced anxiety and depression. More well-designed and large sample-size RCTs are required to further analyze the efficacy of fluoxetine in post-stroke recovery.

Keywords Efficacy · Fluoxetine · Meta-analysis · Placebo · Recovery · Safety · Stroke

Impact statements

- Fluoxetine could improve motor recovery assessed by the Fugl-Meyer assessment scale (FMMS) in patients who have experienced a stroke.
- Fluoxetine could reduce anxiety or depression in patients after a stroke.

Introduction

Stroke is one of the leading causes of morbidity and mortality worldwide [1]. Recovery of function is the primary goal of these patients. Selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, paroxetine, sertraline, and fluvoxamine, represent an important advance in the pharmacotherapy of mood disorders [2, 3]. Due to their efficacy, tolerability, and safety, SSRIs have been used to treat several mental conditions, including depression, dysthymia, and panic disorders [4, 5]. Studies have shown that SSRIs may improve the recovery of function in stroke patients through stimulation of neurogenesis, anti-inflammatory neuroprotection, and improved cerebral blood flow [6–9]. For example, a previous randomized controlled trial (RCT) reported that patients who suffered an ischemic stroke had

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better motor recovery and reduced dependency after three months of fluoxetine treatment compared to placebo [10]. A meta-analysis of nine placebo-controlled RCTs (n = 6788) in 2020 investigated fluoxetine use in post-stroke neurological recovery. The primary endpoint was disability assessment using the modified Rankin Scale (mRS). Secondary endpoints were motor recovery assessed using the Fugl-Meyer Motor Scale (FMMS) and activities of daily living based on the Barthel index (BI) and the National Institutes of Health Stroke Scale (NIHSS). The pooled analysis showed that fluoxetine did not improve participants' mRS ($P = 0.47$) and NIHSS ($P = 0.08$). However, it improved FMMS ($P < 0.00001$) and BI ($P < 0.0001$) compared to the placebo.

Furthermore, fluoxetine reduced the rate of new-onset depression ($P < 0.0001$) in patients after stroke [11]. Another meta-analysis of six RCTs (n = 3710) conducted in 2018 indicated that fluoxetine did not reduce disability and dependency (the co-primary outcomes) after stroke compared to usual care or placebo. Secondary outcomes included depression and adverse events. Although fluoxetine improved depression scores, there was a higher risk of seizures with fluoxetine use [12]. Thus, motor recovery in stroke patients taking fluoxetine is still unclear, primarily when assessed with mRS and NIHSS. The study on the efficacy and safety of fluoxetine in post-stroke patients is still being investigated [13]. We aimed to summarize the most recent evidence and perform a timely meta-analysis to assess the efficacy and safety of fluoxetine in patients after stroke.

Aim

This meta-analysis aimed to provide an updated analysis of the efficacy and safety of fluoxetine versus placebo in post-stroke recovery.

Method

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [14].

Search strategy

We systematically searched electronic databases of PubMed, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) from inception to July 8, 2022. The following search strategy was used: (fluoxetine[Title/Abstract]) AND (stroke[Title/Abstract]) for PubMed; "fluoxetine"/exp AND "stroke"/exp for Embase; "fluoxetine" in Title Abstract Keyword AND "stroke" in Title Abstract Keyword for Cochrane Library. A hand search was performed to check for potentially eligible studies by reviewing the reference lists of included studies and searching Google Scholar. Titles, abstracts, and full texts were screened to select studies that met the inclusion criteria. Only articles written in English were included. All records retrieved from electronic databases were imported into Endnote X9 (Thomson Reuters, New York, USA) to remove duplicate documents.

Inclusion criteria and study selection

Studies that met the following criteria were included: (1) an RCT; (2) enrolled patients (≥ 18 years) with an ischemic or hemorrhagic stroke; (3) used fluoxetine (20 mg daily administered orally for at least two months) as an intervention group and placebo as a control group; (4) reported at least one of the following outcomes: efficacy (mRS, FMMS, BI, and NIHSS), depression, anxiety or safety (drowsiness, gastrointestinal reaction, and insomnia). An outcome assessment was included in the analysis only when reported by ≥ 3 RCTs. A stroke is a sudden-onset focal neurological disturbance, assumed to be vascular in origin, and lasts more than one day. Two reviewers independently screened the titles, abstracts, and full texts based on the above inclusion criteria.

Quality assessment and data extraction

Two reviewers independently assessed the risk of bias in trials using the Cochrane Risk of Bias tool. The risk of bias was judged as low risk, high risk, or unclear risk in the following seven domains: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective outcome reporting; and other biases [15]. Any disagreements were resolved by consulting with a third reviewer.

The following data were extracted: first author, year of publication, the country where the study was performed, sample size, and outcomes of interest (mRS, FMMS, BI, NIHSS, depression, anxiety, drowsiness, gastrointestinal reaction, and insomnia). Two authors independently performed the data extraction using a pre-designed data extraction form. Any disagreements were resolved by consulting with a third reviewer.

Statistical analysis

Pooled risk ratios (RR) with 95% confidence intervals (95%CI) were used for dichotomous variables (mRS, depression, anxiety, drowsiness, gastrointestinal reaction, and insomnia). Standardized mean differences (MD) with 95%CIs were used for continuous variables (FMMS, BI, and NIHSS). The I^2 test was used to assess heterogeneity between studies. A fixed-effects model was used to pool the data when $I^2 < 50\%$ (low heterogeneity between studies). Otherwise, a random-effects model was used when $I^2 \geq 50\%$

(high heterogeneity between studies). Sensitive analysis was conducted to explore the reasons for heterogeneity. The publication bias was assessed using a visual inspection of the funnel plot. $P < 0.05$ was considered statistically significant. All statistical analyses were performed with RevMan software (version 5.1; Cochrane Collaboration, Copenhagen, Denmark).

Results

Search results and characteristics of included studies

As shown in the study selection (Fig. 1), 405 studies were identified after removing duplications within the 459 records initially extracted from electronic databases. After screening the titles and abstracts, 388 citations were excluded, and 17 potential studies remained for further evaluation by retrieving their full texts. Three studies were excluded due to the outcome evaluated (Supplemental Table S1). Finally, 14 RCTs (n = 6584) were included [7–10, 13, 16–24]. The characteristics of the included studies are presented in Table 1.

Risk of bias

The risk of bias assessment is shown in Fig. 2. The risks were high for the blinding of participants and allocation concealment (one RCT), the blinding of the outcome assessment (one RCT), the incomplete outcome data (one RCT), and other biases (two RCTs). Seven RCTs were of high methodological quality. Details are shown in Supplemental Table S2.

Efficacy outcomes

The modified Rankin scale—mRS (0–2)

Five studies reported mRS (0–2) [7, 9, 10, 13, 17]. No significant differences in mRS (0–2) were observed between fluoxetine and placebo (RR 1.00, 95%CI 0.88–1.15, $P = 0.95$, Fig. 3A). Significant heterogeneity and publication bias was observed between studies ($I^2 > 50\%$, Supplemental Figure S1). Sensitive analysis showed that the deletion of any study did not change the final result (Supplemental Table S3).

The Fugl-Meyer motor scale (FMMS)

Four studies (n = 287) reported FMMS [10, 13, 19, 20]. The fluoxetine group scored significantly higher in FMMS than the placebo group (MD 15.93, 95%CI 9.76–22.70, $P < 0.01$, Fig. 3B]. Significant heterogeneity and publication bias was observed between studies ($I^2 > 50\%$, Supplemental Figure S2). Sensitive analysis showed that the deletion of any study did not change the final result (Supplemental Table S4).

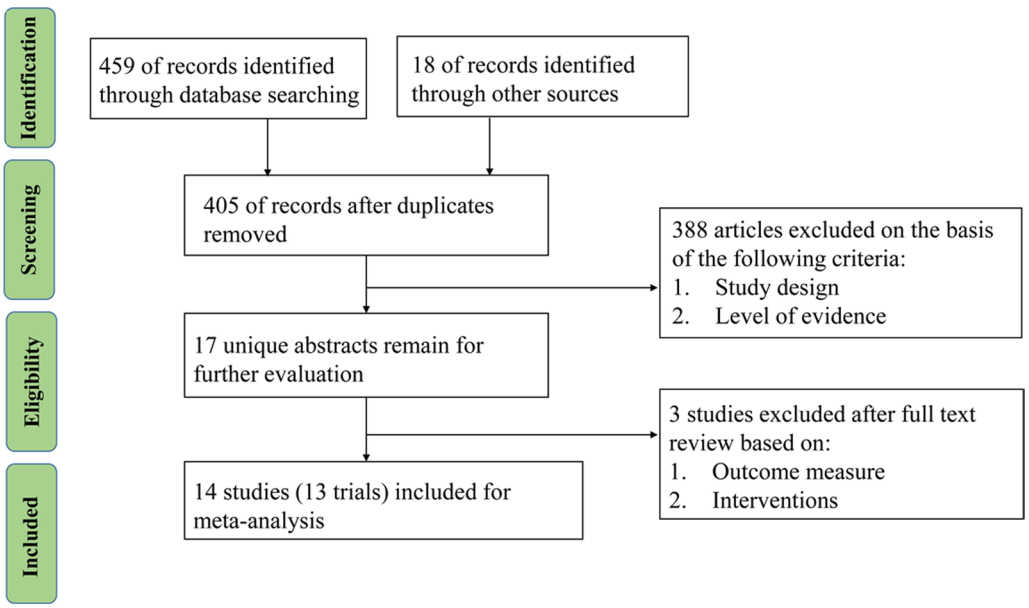

Fig. 1 Flow chart and results of literature screening. *RCT* randomized controlled trial

Table 1 The characteristics of the included studies

Author, year	Country/center	Interventions	No. of patients (F/P)	Age (years)	Male sex: n (F/P)	Outcome of interest	Follow-up (months)
Krishnan et al. [8]	One center in India	Fluoxetine 20 mg/day/P	84/84	18–80	48/54	BI score, anxiety, GI, dizziness, drowsiness and insomnia	3
Lundstrom(b) et al. [7]	35 centers in Sweden	Fluoxetine 20 mg/day/P	750/750	71(11)	575	mRS	12
Marquez-Romero et al. [13]	Three centers in Mexico	Fluoxetine 20 mg/day/P	14/16	54 (10)/60.5 (18)	8/7	FMMS, mRS, NIHSS, drowsiness, GI, insomnia	3
Lundstrom(a) et al. [7]	35 centers in Sweden	Fluoxetine 20 mg/day/P	750/750	71(11)	575	mRS, NIHSS, depression, insomnia	6
Hankey et al. [16]	43 units in Australia, New Zealand, and Vietnam	Fluoxetine 20 mg/day/P	642/638	63.5 (12.5)/64.6 (12.2)	231/245	mRS	6
Focus [9]	103 hospitals in UK	Fluoxetine 20 mg/day/P	1564/1563	71.2 (12.4)/71.5 (12.1)	975/947	mRS	12
Bonin et al. [17]	One center in the USA	Fluoxetine 20 mg/day/P	10/8	50.5 (16.6)/57.4 (10)	3/6	Drowsiness, GI, insomnia	3
Asadollahi et al. [18]	One center in Iran	Fluoxetine 20 mg/day/P	30/30	60.2 (8.5)/ 58.7 (8.5)	15/17	FMMS, insomnia	3
Shah et al. [19]	One center in India	Fluoxetine 20 mg/day/P	42/42	59.9 (8.4)/57.6 (8.1)	29/25	FMMS, anxiety, GI, insomnia	3
He et al. [20]	One center in China	Fluoxetine 20 mg/day/P	177/170	60.4 (10.3)/62.6 (11.6)	120/129	BI, NIHSS	6
Guo et al. [21]	One center in China	Fluoxetine 20 mg/day/P	177/90	61.5 (10.2)/60.5 (11.6)	128/66	BI, NIHSS	6
Collet et al. [10]	Nine centers in France	Fluoxetine 20 mg/day/P	57/56	66.4 (11.7)/ 62.9 (13.4)	37/35	mRS, FMMS, NIHSS	3
Yan et al. [22]	One center in China	Fluoxetine 20 mg/day/P	37/36	64 (7)/62 (7)	22/20	NIHSS	2
Dam et al. [23]	One center in Italy	Fluoxetine 20 mg/day/P	16/16	67.5 (8.9)/68.1 (7.7)	7/6	BI	3

F/P fluoxetine/placebo, *mRS* modified Rankin scale, *FMMS* Fugl-Meyer motor scale, *BI* Barthel index, *NIHSS* National Institutes of Health Scale, *GI* gastrointestinal

Age (years): mean age (SD)

The Barthel index (BI)

Four studies reported the outcome of BI [8, 21, 22, 24]. No significant differences were observed in BI between the fluoxetine and placebo groups (MD 12.11, 95%CI − 0.71 to 24.92, $P = 0.06$, Fig. 3C). Significant heterogeneity and publication bias was observed between studies ($I^2 > 50\%$, Supplemental Figure S3). Sensitive analysis showed that significant differences were observed between the two groups after the deletion of the following two studies: "He et al. [21]" or "Krishnan et al. [8]" (Supplemental Table S5).

The National Institutes of Health Stroke Scale (NIHSS)

When combining data from six RCTs [6, 10, 13, 21–23], the fluoxetine group did not show significant differences

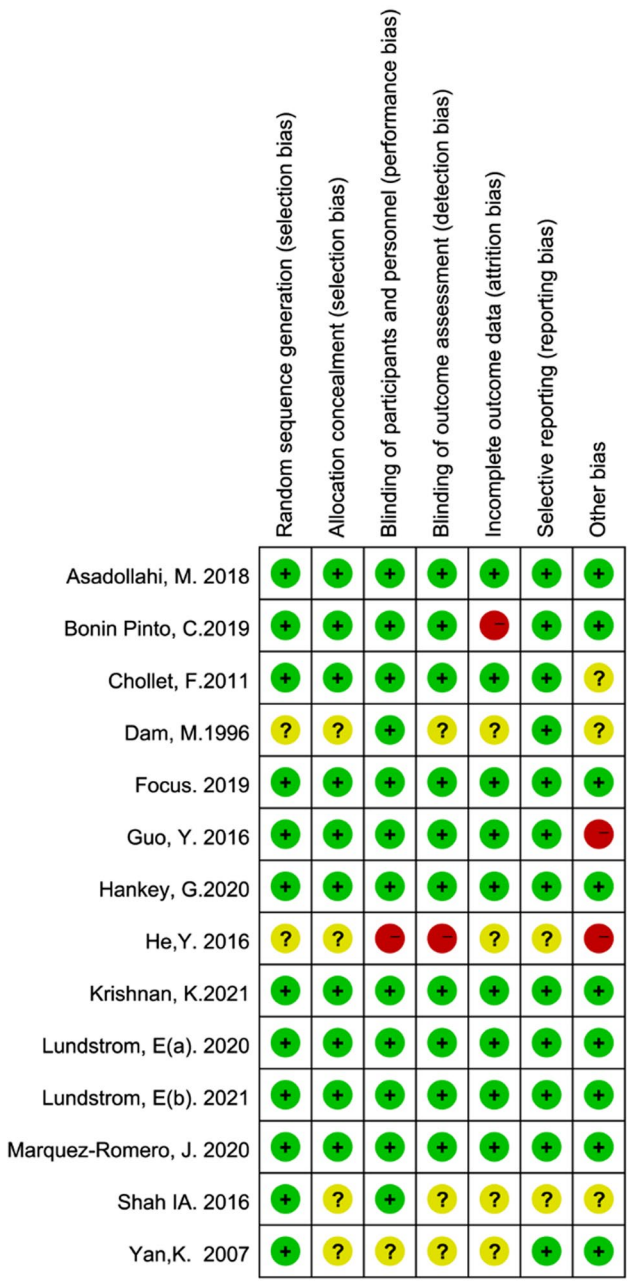

Fig. 2 The risk of bias evaluation of randomized controlled trials

compared to the placebo group (MD − 0.19, 95%CI − 0.43 to 0.04 $P = 0.1$, Fig. 3D). No significant heterogeneity was observed between the studies ($I^2 < 50\%$), and no publication bias was present (Supplemental Figure S4).

Depression or anxiety

Three studies reported the outcomes of depression or anxiety [7, 8, 19]. Fluoxetine significantly decreased the number of patients with depression or anxiety compared to placebo (RR 0.67, 95%CI 0.49–0.92, $P < 0.05$, Fig. 4A). No significant heterogeneity or publication bias was observed between studies ($I^2 < 50\%$) (Supplemental Figure S5).

Safety outcomes

There were no significant differences between the fluoxetine and placebo groups in drowsiness (RR 0.47, 95%CI 0.02–14.46, $P > 0.05$, Fig. 4B), gastrointestinal reaction (RR 0.51, 95%CI 0.10–2.73, $P > 0.05$, Fig. 4C) or insomnia (RR 93, 95%CI 0.51–1.70, $P > 0.05$, Fig. 4D). Significant heterogeneity or publication bias was observed for drowsiness or gastrointestinal reaction ($I2 > 50\%$, Supplemental Figures S6 and S7). In contrast, no significant heterogeneity or publication bias was observed for insomnia ($I2 < 50\%$, Supplemental Figure S8). Sensitive analysis showed that deletion of any study did change the final results of drowsiness and gastrointestinal reaction (Supplemental Tables S6 and S7).

Discussion

This updated meta-analysis identified that patients treated with fluoxetine had significantly higher FMMS scores than those who received a placebo. No significant differences in mRS (0–2), BI, and NIHSS scores were observed between the fluoxetine and placebo groups. The two groups also had similar rates of adverse events of drowsiness, gastrointestinal reaction or insomnia. mRS ≤ 2 was one of the main efficacy outcomes in this meta-analysis, and the results did not show significant differences between the fluoxetine and placebo groups.

Typically, mRS is used to assess disability in patients who suffer from a stroke. A relatively high score means poor recovery, and a lower score indicates better recovery [25]. Most of the studies included in this meta-analysis adopted mRS ≤ 2 as the primary outcome. Patients with low scores of mRS ≤ 2 were considered independent. This analysis showed that fluoxetine-treated patients did not have a better functional recovery than placebo in post-stroke recovery. Significant heterogeneity and publication bias was observed between studies. However, the sensitivity analysis indicated that the deletion of any study could not change the result.

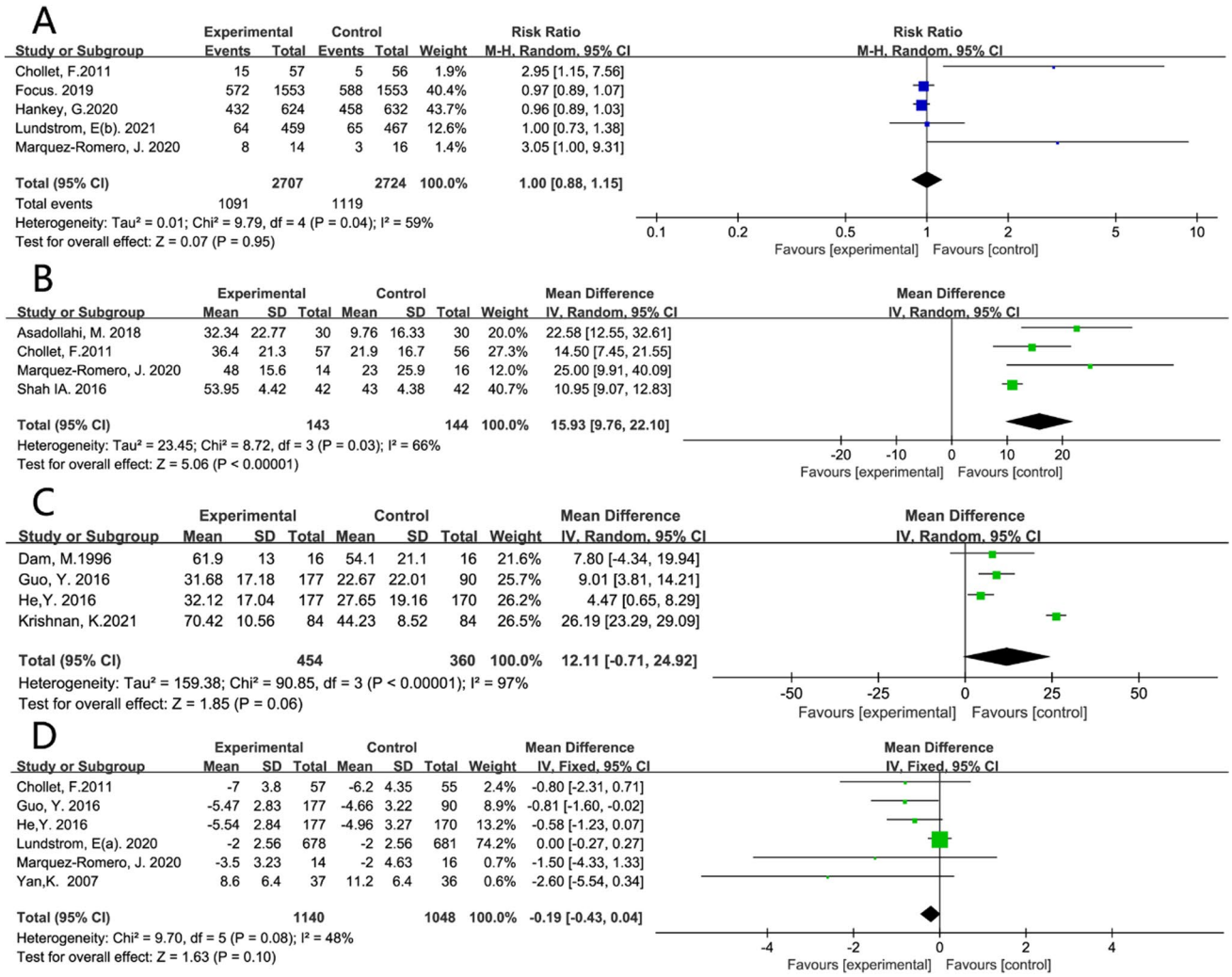

Fig. 3 Comparison of mRS(0–2) (**A**), FMMS (**B**), BI (**C**), and NIHSS (**D**) between fluoxetine (experimental) and placebo (control) groups. *mRS* modified Rankin scale, *FMMS* Fugl-Meyer motor scale, *BI* Barthel index, *NIHSS* National Institutes of Health Stroke Scale

Higher scores were observed in the fluoxetine group regarding FMMS, an index designed to assess motor function, balance, sensation, and joint function in patients with post-stroke hemiplegia [26, 27]. Although significant heterogeneity and publication bias were observed between studies, the final result did not change based on the sensitivity analysis. BI is used to assess daily activities of daily living, which is another assessment of disability or independence, with higher scores indicating better functional status [28]. Fluoxetine did not show higher BI scores than those in the placebo group based on the included studies with significant heterogeneity. Sensitive analysis indicated that patients treated with fluoxetine had higher scores than those in the placebo group after removing two studies [8, 21]. Although a previous meta-analysis demonstrated a higher BI score in the fluoxetine group, the results were based on a limited number of studies [11]. NIHSS is commonly used to assess the severity of stroke [29]. Fluoxetine did not show a significant difference in NIHSS compared to the placebo group based on existing data.

This meta-analysis showed that fluoxetine significantly decreased the number of patients developing depression or anxiety compared to placebo. One possible reason is that fluoxetine has been the treatment of choice for many mental health indications including depression, dysthymia, and panic disorder. Regarding adverse events, the fluoxetine and placebo groups had similar safety profiles. Sensitive analysis showed that deletion of any study did not change the final result, although significant heterogeneity and publication bias were observed for some adverse events. Based on the above results, RCTs that pay more attention to safety outcomes are necessary.

This meta-analysis has some limitations: (1) a subgroup analysis was not performed due to limited studies assessing

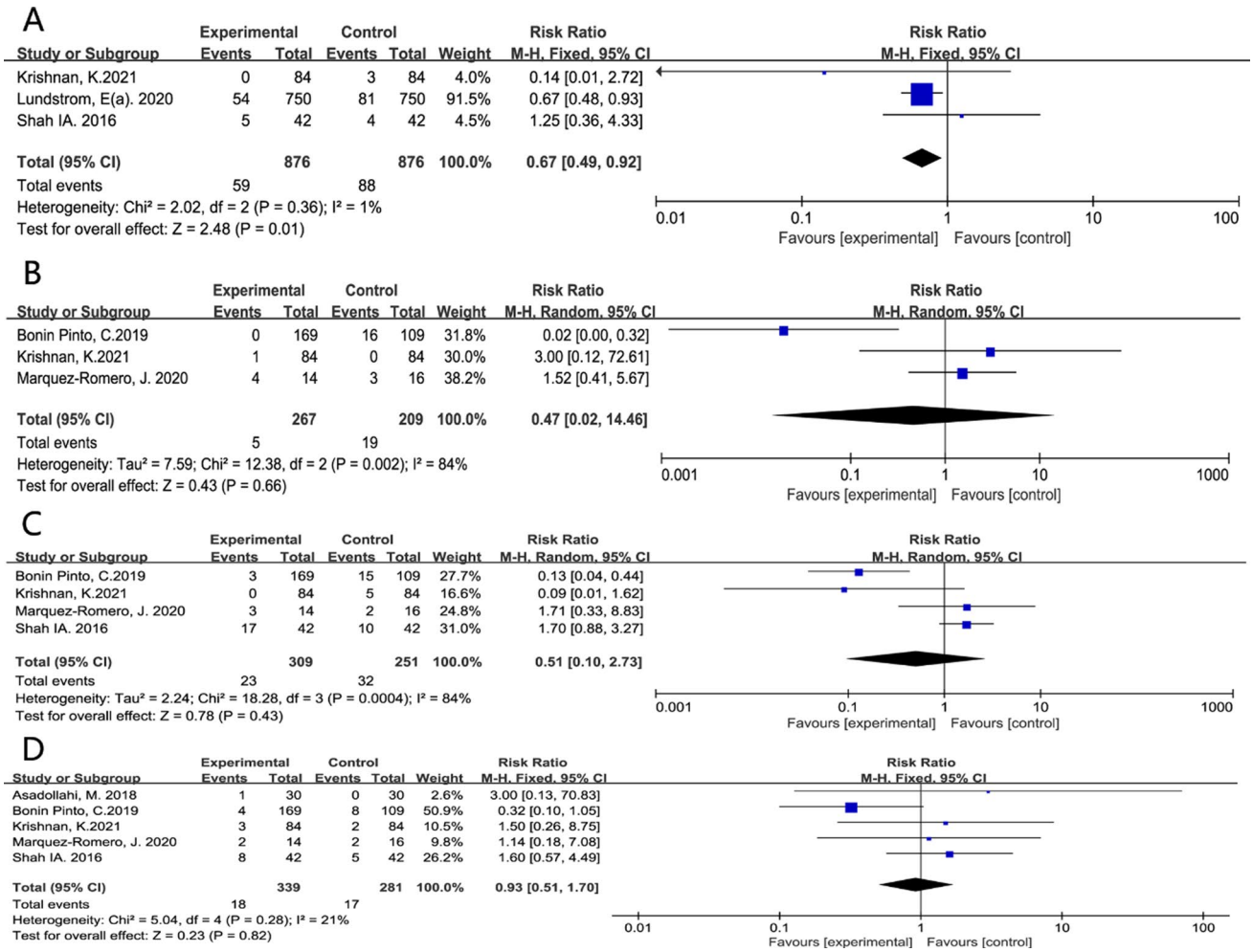

Fig. 4 Comparison of depression or anxiety (**A**), drowsiness (**B**), gastrointestinal reaction (**C**), and insomnia D) between fluoxetine (experimental) and placebo (control) groups

specific outcomes, (2) there were inconsistencies in the trials that tested participants' motor and functional recovery, and (3) other outcomes, such as complications with fluoxetine use, were not analyzed due to insufficient relevant studies.

Conclusion

Fluoxetine improved neurological scores of FMMS and reduced depression or anxiety in patients after a stroke. More well-designed and large sample-size RCTs are required to further evaluate the role of fluoxetine in post-stroke recovery.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11096-023-01573-1.

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Conflicts of interest The authors declare that they have no conflicts of interest.

References

1. GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2015;388:1545–602.
2. Lochmann D, Richardson T. Selective serotonin reuptake inhibitors. Handb Exp Pharmacol. 2019;250:135–44.
3. Masand PS, Gupta S. Selective serotonin-reuptake inhibitors: an update. Harv Rev Psychiatry. 1999;7:69–84.
4. DeFilippis M, Wagner KD. Management of treatment-resistant depression in children and adolescents. Paediatr Drugs. 2014;16:353–61.
5. Murphy SE, Capitao LP, Giles SLC, et al. The knowns and unknowns of SSRI treatment in young people with depression and anxiety: efficacy, predictors, and mechanisms of action. Lancet Psychiatry. 2021;8:824–35.

6. Siepmann T, Penzlin AI, Kepplinger J, et al. Selective serotonin reuptake inhibitors to improve outcome in acute ischemic stroke: possible mechanisms and clinical evidence. Brain Behav. 2015;5:e00373.
7. Lundstrom E, Isaksson E, Greilert NN, et al. Effects of fluoxetine on outcomes at 12 months after acute stroke: results from effects, a randomized controlled trial. Stroke. 2021;52:3082–7.
8. Krishnan K, Teja YD, Reddy VS, et al. Role of fluoxetine in pharmacological enhancement of motor functions in stroke patients: A randomized, placebo-controlled, single-blind trial. Contemp Clin Trials Commun. 2021;23:100800.
9. Collaboration FT. Effects of fluoxetine on functional outcomes after acute stroke (FOCUS): a pragmatic, double-blind, randomised, controlled trial. Lancet. 2019;393:265–74.
10. Chollet F, Tardy J, Albucher JF, et al. Fluoxetine for motor recovery after acute ischaemic stroke (FLAME): a randomised placebo-controlled trial. Lancet Neurol. 2011;10:123–30.
11. Liu G, Yang X, Xue T, et al. Is fluoxetine good for subacute stroke? A meta-analysis evidenced from randomized controlled trials. Front Neurol. 2021;12:633781.
12. Mead GE, Legg L, Tilney R, et al. Fluoxetine for stroke recovery: Meta-analysis of randomized controlled trials. Int J Stroke. 2020;15:365–76.
13. Marquez-Romero JM, Reyes-Martinez M, Huerta-Franco MR, et al. Fluoxetine for motor recovery after acute intracerebral hemorrhage, the FMRICH trial. Clin Neurol Neurosurg. 2020;190:105656.
14. Moher D, Liberati A, Tetzlaff J et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009;339:b2535.
15. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928.
16. Lundström E, Isaksson E, Näsman P, et al. Safety and efficacy of fluoxetine on functional recovery after acute stroke (EFFECTS): a randomised, double-blind, placebo-controlled trial. Lancet Neurol. 2020;19:661–9.
17. Hankey GJ, Hackett ML, Almeida OP et al. Safety and efficacy of fluoxetine on functional outcome after acute stroke (AFFINITY): a randomised, double-blind, placebo-controlled trial. Lancet Neurol. 2020;19:651–60.
18. Bonin PC, Morales-Quezada L, de Toledo PPV, et al. Combining fluoxetine and rTMS in poststroke motor recovery: a placebo-controlled double-blind randomized phase 2 clinical trial. Neurorehabil Neural Repair. 2019;33:643–55.
19. Asadollahi M, Ramezani M, Khanmoradi Z, et al. The efficacy comparison of citalopram, fluoxetine, and placebo on motor recovery after ischemic stroke: a double-blind placebo-controlled randomized controlled trial. Clin Rehabil. 2018;32:1069–75.
20. Shah IA, Asimi RP, Kawoos Y. Effect of fluoxetine on motor recovery after acute haemorrhagic stroke: a randomized trial. J Neurol Neurophysiol Clin. 2016;7:364.
21. He YT, Tang BS, Cai ZL, et al. Effects of fluoxetine on neural functional prognosis after ischemic stroke: a randomized controlled study in China. J Stroke Cerebrovasc Dis. 2016;25:761–70.
22. Guo Y, He Y, Tang B, et al. Effect of using fluoxetine at different time windows on neurological functional prognosis after ischemic stroke. Restor Neurol Neurosci. 2016;34:177–87.
23. Kong Y, Dong W, Liu C. Fluoxetine for poststroke depression a randomized placebo controlled clinical trial. Neural Regener Res. 2007;2:162–5.
24. Dam M, Tonin P, De Boni A, et al. Effects of fluoxetine and maprotiline on functional recovery in poststroke hemiplegic patients undergoing rehabilitation therapy. Stroke. 1996;27:1211–4.
25. van Swieten JC, Koudstaal PJ, Visser MC, et al. Interobserver agreement for the assessment of handicap in stroke patients. Stroke. 1988;19:604–7.
26. Fugl-Meyer AR, Jaasko L, Leyman I, et al. The post-stroke hemiplegic patient. 1 a. method for evaluation of physical performance. Scand J Rehabil Med. 1975;7:13–31.
27. Gladstone DJ, Danells CJ, Black SE. The fugl-meyer assessment of motor recovery after stroke: a critical review of its measurement properties. Neurorehabil Neural Repair. 2002;16:232–40.
28. Uyttenboogaart M, Stewart RE, Vroomen PC, et al. Optimizing cutoff scores for the Barthel index and the modified Rankin scale for defining outcome in acute stroke trials. Stroke. 2005;36(9):1984–7.
29. Brott T, Adams HP Jr, Olinger CP, et al. Measurements of acute cerebral infarction: a clinical examination scale. Stroke. 1989;20:864–70.