Recovery in stroke patients treated with fluoxetine versus placebo: A pooled analysis of 7,165 patients

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Abstract

Purpose

We conducted this study to build clear evidence regarding the outcomes of recovery in stroke patients treated with fluoxetine versus placebo.

Methods

Seventeen randomized clinical trials were identified by searching PubMed, Cochrane, Scopus, and Web of Science until June 2021.

Results

Fluoxetine enhances the National Institutes of Health Stroke Scale (NIHSS) score [MD -0.67, 95% CI (-1.19 to -0.15), $P = 0.01$] and the Fugl-Meyer Motor Scale (FMMS) score [MD 17.36, 95% CI (12.12 to 22.61), $P < 0.00001$] at three months follow up. However, the NIHSS score showed no significant difference between the two groups at two weeks [MD -0.32, 95% CI (-0.72 to 0.07), $p = 0.11$] or at six months [MD -0.17, 95% CI (-0.47 to 0.14), $p = 0.29$]. Fluoxetine and placebo-treated patients had the same overall impact on FMMS scores at one month [MD 7.77, 95% CI (-10.57 to 26.11), $P = 0.41$]. The fluoxetine had a higher risk of broken bone (RR = 2.30, 95% CI [1.59, 3.32], $p < 0.001$) and hyponatremia (RR = 2.12, 95% CI [1.19, 3.76], $p = 0.01$) with lower risk of new depression (RR = 0.72, 95% CI [0.61, 0.84], $p < 0.001$) in comparison to placebo.

Conclusion

The efficacy of fluoxetine on the NIHSS and FMMS is likely to take time to emerge and is expected to be transient. The BI score did not differ between the fluoxetine and placebo groups. The use of fluoxetine increased the incidence of hyponatremia and bone fractures while decreasing the risk of new-onset depression.

Introduction

Stroke is one of the predominant causes of permanent disability, mortality, significant cognitive, physical, and psychosocial morbidity in the world[1], [2]. It has three significant impacts on patients and their families: impairment, disability, and handicap. Furthermore, patients frequently experience depression following injury to either the right or left side of the brain[3]. The most prevalent and well-known disability induced by stroke is motor impairment[4]. At this time, stroke research has put its attention on therapeutic strategies that minimize neurological damage and improve stroke patients' functionality and recovery[5]. Regrettably, medication therapy designed to reduce the neurological damage had little effect[6]. Post-stroke depression and emotional impairment are treated with fluoxetine, an antidepressant, and selective serotonin reuptake inhibitor (SSRI)[7].

It is still unclear exactly how SSRIs impact rehabilitation from motor impairment[8]. SSRIs have been shown to enhance outcomes following a stroke in numerous clinical trials[9]–[11]. In 2011, the results of the FLAME trial showed that fluoxetine may enhance motor recovery and reduce dependence after three months through Modulation of spontaneous brain plasticity[12]. In animal stroke models, there was a significant benefit of therapy with SSRIs on neurobehavioral outcomes, but there was no detectable impact on infarct volume and there was no discernible influence affecting structural or functional outcomes as a result of the type of SSRI usage[13]. After 6 months of fluoxetine treatment, there is no improvement in the patients' modified Rankin Scale (mRS) as reported by the FOCUS trial[7]. Furthermore, the AFFINITY trial[14] reported that taking fluoxetine daily for six months didn't lead to better functional outcomes. They also observed an increased risk of bone fractures and epileptic episodes[7], [14]. In the EFFECTS trial, fluoxetine given orally showed limited benefit in functional outcomes, reduced the signs of depression, raised the chance of bone fractures, and caused hyponatremia[15]. To summarize, their research shows that fluoxetine should not be used in patients who have had an acute stroke[15]. Marquez-Romero et al,[8] suggested that adding fluoxetine to standard treatment early on was safe and helpful to speed up motor recovery 3 months following an intracerebral haemorrhage (ICH)[8].

Currently, the evidence regarding the effectiveness of SSRIs in improving specific cognitive domains, or dependency after stroke, is uncertain[16]. Also, if similar benefits in outcomes may be detected across populations are sustained following treatment cessation[16]. It was shown by Previous meta-analyses that fluoxetine could potentially improve the defective neurologic function if administered to stroke patients early after their accident[17]–[19]. But these studies used a limited number of patients and have low methodological quality in most included studies[17]–[19]. A meta-analysis by Liu et al,[20] detected an improvement in Fugl-Meyer Motor Scale (FMMS) and BI scores with no gain in mRS and National Institutes of Health Stroke Scale (NIHSS) scores which could be caused by the heterogeneity across the trials. Mead et al,[21] found that fluoxetine had no effect on disability or dependency following a stroke. This meta-analysis comprised just four high-quality studies with a significant degree of heterogeneity[21]. There is no subgroup analysis for treatment duration previous meta-analyses[20], [21], despite the fact that fluoxetine was used for three months in some trials and six months in others which could potentially influence the outcome. To elucidate the existing research gap and resolve the conflicting evidence regarding the safety and efficacy of fluoxetine for stroke patients, this comprehensive systematic review and meta-analysis (SR-MA) were conducted.

Materials And Methods

When performing this SR-MA, we followed the procedures outlined in the Cochrane Handbook for Systematic Reviews of Interventions[22]. This SR-MA was prepared in accordance with the PRISMA declaration requirements [23].

Literature search:

References were identified for this meta-analysis by searching PubMed, Cochrane Library, Scopus, and Web of Science for articles published from inception to June 2021, using the following MeSH terms “Stroke”, “Fluoxetine”, “MADRS”, “NIHSS” and “Barthel-index”. Only articles written in English were included.

Eligibility criteria:

We worked with Endnote X8 software (Thompson Reuter, CA, USA) to import collected records and to remove duplicate records. To verify the imported randomized controlled trials (RCTs), we screened the titles and abstracts and examined the full text of the relevant papers. We examined the references cited in those papers to find relevant articles. At least two authors worked independently to select studies and extract data. The difference of opinion was settled through discussion.

RCTs that met the following criteria were included: (I) Population: patients who are at least 18 years old and have stroke; (II) Intervention: Fluoxetine 20 mg daily given orally for 3–6 months; (III) Comparator: patients received placebo; (IV) Outcome parameters: efficacy outcomes including the mRS, NIHSS, FMMS, and the Barthel Index (BI); (V) study design: RCTs

The criteria for exclusion were as follows: (1) study type: observational studies, reviews, editorials, abstracts, thesis, letters, books, and chapters; (2) Studies whose data are not extractable or analysable.

Data extraction:

In the data extraction, all study authors participated equally. The following data items were extracted: 1) summary of the included studies: list of authors, site, study design, study arms, sample size, doses, length of follow up, outcomes, and results; 2) baseline characters of the included studies' population: age, sex, hypertension, dyslipidaemia, smoking, coronary artery disease, and diabetes mellitus; 3) efficacy outcomes: poststroke depression, excessive/ inappropriate crying, excessive/ inappropriate laughing, post-stroke anger proneness, Modified Rankin Scale, Montgomery-Asberg Depression Rating Scale (MADRS); 4) safety outcomes: insomnia, nausea, diarrhoea, recurrent stroke, acute coronary events, ischaemic stroke, other major bleeds, upper gastrointestinal bleed, haemorrhagic stroke, epileptic seizures, fall with injury, and death.

Risk of bias assessment:

It was assessed using the Cochrane Risk of Bias tool for each of the included studies[24]. Selection, performance, detection, attrition bias, reporting and other possible biases are assessed by this tool. Third-party reviewers assigned each bias domain a value of "low," "high" or "unclear".

Data synthesis:

For statistical analysis, we use Review Manager 5.4.1. All analyses used a fixed-effects model except if there is substantial heterogeneity in which we used the random-effects model. We calculated mean difference (MD) and 95 percent confidence interval (CI) for continuous data and risk ratios (RRs) and 95% CI for dichotomous data in order to pool the data between the fluoxetine and control arms. A p-value of less than 0.05 was regarded as statistically significant. To determine heterogeneity, the chi-square and I-square tests were applied. When the chi-square P-value was less than 0.1 and the I-value was larger than 50%, heterogeneity was considered.

Results

Results of the literature search:

A total of 1347 unique citations were identified during our search. 127 articles were selected for full-text screening. Subsequently, 17 randomized clinical trials[7], [8], [12], [14], [15], [25]–[36] including 7,165 participants (Fluoxetine arm participants were 3605 while placebo arm participants were 3560) were analysed in the quantitative portion of the study (**Fig. 1**).

Characteristics of included studies:

We were able to include 17 RCTs with 7365 participants in our analysis after we accepted all of the studies that fulfilled our inclusion criteria. We included all placebo-controlled studies assessing fluoxetine's efficacy and safety in poststroke patients. There were 16 studies[7], [8], [12], [14], [15], [25], [26], [28]–[36] which used a fluoxetine dosage of 20 mg per day and only one study[27] began at 20 mg daily and increased to a maximum of 40 mg per day. Placebo is used as the control in all studies. Some studies used a third arm as citalopram[30], combining repetitive transcranial magnetic stimulation with fluoxetine[32], Shu-Gan-Jie-Yu[25], and an herbal drug[28]. Table 1 shows a summary of the design and principal outcomes of included studies, whereas Table 2 contains baseline characteristics of included studies participants.

Risk of Bias Assessment Results:

Based on the Cochrane risk of bias assessment tool, reviewed studies were of moderate to high quality. **Fig. 2** summarises the quality assessment domains for all of the papers that were considered. In Table 5 Online Resource 1, the authors' opinions and explanations are both presented. The mean difference and 95% CI of efficacy outcomes are presented in Online Resource 1: Table 3.

Efficacy analysis:

NIHSS score:

Fluoxetine was found to have a greater overall effect than placebo at three months [MD -0.67, 95 % CI (-1.19 to -0.15), $P = 0.01$], the results were homogenous ($p = 0.40$; $I^2 = 0\%$), but there was no difference between the two arms at two weeks [MD -0.32, 95% CI (-0.72 to 0.07), $p = 0.11$], and six months [MD -0.17, 95% CI (-0.47 to 0.14), $p = 0.29$]; pooled analysis were homogeneous at 2 weeks ($p = 0.56$; $I^2 = 0\%$), and at 6 months ($p = 0.06$; $I^2 = 65\%$) respectively (**Fig. 3**).

Barthel index (BI):

The MD of change in BI showed no significance difference between the two arms at three months [MD 3.16, 95 % CI (-1.77 to 8.08); $P = 0.21$] the results were homogenous ($p = 0.86$; $I^2 = 0\%$), and the results were heterogeneous at six months [MD 1.26, 95 % CI (-4.79 to 7.32); $P = 0.68$] under a random effect model ($p = 0.03$; $I^2 = 80\%$) (**Fig. 4**).

FMMS scores:

The overall effect showed no differences between the Fluoxetine group and placebo group at one month [MD 7.77, 95 % CI (-10.57 to 26.11), $P = 0.41$]. Pooled studies were heterogeneous under a random-effect model ($p = 0.02$; $I^2 = 80\%$). However, the overall effect favoured the Fluoxetine group over placebo at three months [MD 17.36, 95 % CI (12.12 to 22.61), $P < 0.00001$] and the results were homogenous ($p = 0.47$; $I^2 = 0\%$), (**Fig. 5**).

Stroke impact scale (SIS):

The MD change of vitality favoured the placebo at six months [MD -2.01, 95 % CI (-3.37 to -0.30), $P = 0.02$], the results were homogeneous ($p = 0.89$; $I^2 = 0\%$), and the other domains showed no significant difference between the two groups (**Fig. 6**).

For all other efficacy outcomes:

Overall, the Fluoxetine group did not outperform the placebo group except in Hamilton Depression Scale (HDS); The MD of change in HDS favoured the Fluoxetine group [MD -2.60, 95 % CI (-5.19 to -0.01); $P = 0.05$] and the results were homogeneous ($p = 0.43$; $I^2 = 0\%$), (Online Resource 1: **Fig. 7**).

Post-stroke depression:

The overall effect shows no differences between the 2 groups at 3- and 6-months ([MD 0.83, 95 % CI (0.46 to 1.52), $P = 0.55$], [MD 0.70, 95 % CI (0.36 to 1.39), $P = 0.31$] respectively) and the results were homogenous ($p = 0.11$; $I^2 = 54\%$), ($p = 0.06$; $I^2 = 73\%$) at 3 and 6 months respectively, (Online Resource 1: **Fig. 8**).

Safety analysis:

There were no significant differences in adverse events between the fluoxetine and placebo groups (Online Resource 1: Table 4) except hyponatremia and fractured bone; their frequency in fluoxetine group was significantly more than placebo group, [(RR = 2.12, 95% CI [1.19, 3.76], $p = 0.01$), (RR = 2.30, 95% CI [1.59, 3.32], $p < 0.001$)], the results were homogeneous ($p = 0.18$; $I^2 = 41\%$) and ($p = 0.62$; $I^2 = 41\%$) (Online Resource 1: **Fig. 9** and **Fig. 10**, respectively)], but the frequency of new depression was significantly higher in the placebo group than fluoxetine group (RR = 0.72, 95% CI [0.61, 0.84], $p < 0.001$), the pooled results were homogeneous ($p = 0.76$; $I^2 = 0\%$) (Online Resource 1: **Fig. 11**).

Discussion

In this meta-analysis of usage of fluoxetine 20 mg for stroke patients, we identified 17 RCTs[7], [8], [12], [14], [15], [25]–[36] Which recruited 7165 (3605 in the treatment group and 3560 in the placebo group). For the efficacy outcome, we have used the changes of the obtained data to describe the degree of recovery. Fluoxetine was favoured on placebo in improving the NIHSS score and the FMMS score in the 3rd month. The stroke impact scale (SIS) assessed the change in strength [MD -1.63, 95 % CI (-4.27, 1.01), $P = 0.23$] and vitality [MD -2.01, 95 % CI (-3.37, -0.30), $P = 0.02$], and the placebo group showed superior improvement in these measurements at six months. Safety data showed that fluoxetine raised the risk of bone fracture and hyponatremia, but it was associated with lower chances of post-stroke depression.

The NIHSS is commonly applied to provide an objective estimation of the severity of a stroke[37]. It calculates an overall score for each ability, ranging from 0 to 4. A normal state is scored 0, while a completely impaired state is scored 4. The NIHSS score is the sum of all of the scale elements, and the maximum score is 42. A higher NIHSS score is associated with a greater level of impairment in stroke patients[37]. Our meta-analysis showed significant improvement in NIHSS score at 3 months but without any significance at 2 weeks or 6 months respectively, suggesting that fluoxetine effect needs time to occur and is considered as temporary from the pooled results of 6 RCTs.

As for the FMMS score which is an index designed for assessing the motor and joint function, balance, and sensation after stroke-induced hemiplegia[38], [39]. There were no significant differences between the Fluoxetine and placebo groups one month later. At three months, we exhibited a greater improvement, but the outcomes were heterogeneous. Patients and healthcare circumstances vary by trial, which could explain this disparity.

Disability or independence for daily tasks is evaluated by BI, in which higher scores suggest better functioning[40]. Neither the fluoxetine nor the placebo groups showed significant differences at 3 or 6 months.

Fluoxetine showed better improvement in the Hamilton depression scale, which is the most used scale for detecting depression, Fluoxetine specificity resides in its effect in treating depression since it belongs to the SSRI family, and mostly used for its anti-depressive and emotional lability after stroke and also used for the treatment of the obsessive-compulsive disorder, and other mental disorders. The question that needs to be addressed is how fluoxetine affects the neurological scale and induces its post-stroke recovery effect. Some animal experiments have shown how fluoxetine could help with motor recovery[13]. The fact that SSRIs stimulate hippocampal and subventricular zone neurogenesis is quite intriguing[41]. Moreover, through the processes of neurogenesis, this could be a factor in a subsequent recovery following an episode of cerebral ischemia, with the possibility of new neurons migrating to the affected region[42], [43]. Fluoxetine enhances the secretion of the brain-derived neurotrophic factor, a neurotrophin strongly implicated in neuronal growth and survival and brain plasticity within Two suggested mechanisms: 5-HTT blockade and 5-HTT-independent direct activation of tropomyosin receptor kinase B (TrkB), which is the high-affinity receptor of the neurotrophin BDNF[44]. Furthermore, SSRIs can inhibit the inflammatory response the latter is the main cause of brain damage[18], [45], [46].

There is considerable brain damage area reduction and improved neurological function in mice treated with SSRIs 9 hours following the onset of stroke[47]. This reinforces the hypothesis that SSRIs have a beneficial effect on mice's neurological function. Other molecules are upregulated by SSRIs such as heme oxygenase-1 (HO-1) and hypoxia-inducible factor-1alpha which play a particular role in regulating cerebral blood flow[48]. Carbon monoxide is produced as a result of the HO-1 expression, which regulates vascular tone promoting better blood flow to the intended brain regions[49], and also SSRIs have been shown to increase the expression of β -1 adrenergic receptors in the brain of mice. [18]. Expression of these factors may improve functional recovery. Our results go hand in hand with animal studies conclusions and showed better amelioration in the function recovery predicted by the NIHSS score at 3 months, but the effect didn't last for too long and also by the improvement in FMMS score showed in the 3rd month.

In terms of Safety outcomes, our analysis showed a higher risk for bone fracture and hyponatremia among the participants in the fluoxetine group. It is unknown how fluoxetine causes hyponatremia. According to a suggested mechanism, SIADH would be induced when there is an increase in the production of antidiuretic hormone (ADH) (serotonin has an effect on the 5-HT₂ and 5-HT_{1C} receptors) or an increased renal sensitivity to ADH[50], [51]. Another side effect of fluoxetine is the associated bone fracture. The long-term administration of an SSRI as a therapy for depression could lead to osteoporosis. The effects of SSRIs on osteoblasts[52], [53], osteocytes[54], osteoclasts[52], and various bone cell lines[55] have been examined in vitro.

The strengthening of our analysis resides in the included RCTs and their recruited number which is 7165 and it was bigger than the last published one[20] and a double of that of Mead et al[21]. The included RCTs were of high quality. We provide a subgroup analysis according to the duration of the follow-up to provide reliable results. A three-month treatment is not equivalent to a six-month treatment in terms of pharmacology, and the results may vary. This option was not provided in the previously published Meta-analysis. Our primary limitation is that we covered both types of strokes (ischemic and haemorrhagic). Knowing that different compositions of the participant groups may affect the results and induce slight heterogeneity which was observed in our analysis.

Conclusion

Short-term fluoxetine treatment failed to show any substantial improvement in the NIHSS and FMMS scores. There is a positive impact on NIHSS and FMMS scores at three months following therapy, however, at six months there is no significant change in NIHSS score. These findings demonstrate that fluoxetine's effect may take time to manifest and is assumed to be transient. There were no significant variations in BI score between the fluoxetine and placebo groups. Other than vitality, no significant differences were found in the SIS score between the fluoxetine and placebo groups. The only exception to this rule was for vitality, which favoured the placebo. The use of fluoxetine caused an increase in the risk of hyponatremia and bone fracture, but it lowered the possibility of developing a new-onset depression.

Recommendations

Much more research is required to pinpoint other therapies that may bring benefit and quantify such benefit in a clinical setting. Trials will have to be large-sized, of high quality, and their target population must be well defined in order to reduce heterogeneity.

Declarations

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Patient consent for publication: The dissemination of this information does not require consent of patients.

Authors' Contribution

Conception and design of the work by Ahmed Elsnhory and Mohamed Fahmy Doheim.

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Critical revision of the article by Abdulrahman Ibrahim Hagrass, Khaled Mohamed Ragab, and Mohamed Fahmy Doheim.

Final approval of the version to be published by Khaled Mohamed Ragab, and Mohamed Fahmy Doheim.

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Tables

Table 1: A summary of the design and main results of included studies

Study ID	Site	Study design	Study arms, samples, and doses	length of follow up (weeks)	protocol registration	Primary outcomes	secondary outcomes	Conclusion	result
Asadollahi 2018	university-affiliated teaching hospital in Tehran, Iran	RCTs 3 arms	3 arms (fluoxetine 20mg N=30 & placebo N=30 & citalopram 20mg N=30)	13.036	IRCT20141116019971N3	Functional status at 90 days by the Fugl-Meyer Motor Scale score.		Citalopram and fluoxetine were similarly effective in motor recovery for ischemic stroke patients. In contrast to a placebo, both medications were found to be effective in improving motor function after a stroke.	In comparison to the baseline FMMS score, the FMMS score revealed significant increase in the fluoxetine and citalopram group (P=0.00
Bembenek 2020	Institute of Psychiatry and Neurology in Warsaw	RCTs double armed	2 arms (fluoxetine 20mg N=30 & placebo N=31)	2 measures period (6 month=26.7 weeks & 12 month=52.14)	Pol 2020; 54 (6): 544-551)	Disability on mRS at six months.	BI & NIH after 6 and 12 months	At six and twelve months, fluoxetine did not affect motor recovery or overall stroke prognosis. Fluoxetine treated patients required fewer antidepressant drugs.	Fluoxetine treatment of patients was less likely to be prescribed a new antidepressant than the placebo who received the placebo throughout the months [6.67%] vs [12.90%
boninpinto2019	Spaulding Neuromodulation Center, Boston, Massachusetts	RCTs 3 arms	3 arms (Combined (Fluoxetine + rTMS) (n = 9)) & (Fluoxetine 20mg (n = 10) Placebo (n = 8))	12.86	NCT02208466	motor function scales: JTHF and FMA upper extremity changes from day 0 to day 90	MAS, BDI, MMSE, diary of drugs, adverse reactions of antidepressants, and assessments on rTMS adverse reactions.	Fluoxetine administration along with rTMS has been shown to improve stroke-related motor functions better than fluoxetine administration alone and placebo. Fluoxetine's effects on intracortical facilitation show a possible diffuse mechanism that could inhibit motor recovery gains.	Comparison of fluoxetine placebo showed that fluoxetine have a negative impact on scale (respectively JTHF: -5 vs -117 seconds, 0.038; a FMA: 6.7 vs 15.55 points, p = 0.038) suggest that fluoxetine may have negative consequences on the health. In combined fluoxetine groups, unaffected hemispheres exhibited significant decreases in intracortical inhibition while the fluoxetine group showed enhanced intracortical facilitation
choi-kwon2005	Asan Medical Center	RCTs double armed	2 arms (fluoxetine 20mg N=67 &	26.07	Stroke. 2006;37:156-161	The scores of emotional disturbances at	% improvements in BDI scores, % improvements in VAS scores and	Fluoxetine is successful in curing PSEI and PSAP. It is	Despite the fact that individual the fluoxetine

			placebo N=76)			each follow-up assessment	PSAP scores; In contrast to the patient's original replies before enrolment, the patients' subjective responses are reported as "aggravated," "no change," and "improved".	currently unknown whether or not PSD is significantly impacted by it.	group withdrew more frequently to side eff fluoxeti medicat was relat safe. PSE PSAP w greatl enhance fluoxeti however apprecia improver of PSD v detecte PSAP w enhanced after 3 mo after tl medicat was cea
choi-kwon2006	clinics at the Asan Medical Center	RCTs double armed	2 arms (fluoxetine 20mg N=40 & placebo N=43)	26.07		Mean VAS score for PoSF and the mean FSS score	The % changes in VAS and FSS scores, compared to their original scores.	While some associated mental disturbances improved dramatically, fluoxetine does not improve PoSF. Our findings indicate that PoSF might be related to a variety of etiologies, but does not appear to be closely tied to serotonin- related dysfunction.	The init mean fat VAS score the me: overall F score wer & 2.0 and & 1.2 respectiv Howev PoSF pati who rece fluoxetine more improver in emotio incontin (p=0.05) depress (p=0.05) those in placebo i
chollet2011	enrolled from nine stroke units in France	RCTs double armed	2 arms; 20 mg fluoxetine qd (n = 59) & placebo (n = 59)	13.036	NCT00657163.	The mean change in FMMS score.	The NIHSS, mRS, and MADRS are used, along with all scores at baseline, day- 30, and day-90.	The use of fluoxetine and rehabilitation services in patient populations with ischemic stroke and motor impairments improves motor recovery after three months. the promising treatment avenue for patients with ischemic stroke and motor impairments is modulation of spontaneous brain plasticity.	Hyponatra tempor digesti disorde includi nausea diarrhea, abdomi discomf hepati enzym proble psychia disorde sleepless and par seizure v the prim side eve seen in fluoxetine placeh group:
dam 1998		RCTs double armed	2 arms; 20 mg fluoxetine qd (n = 16) & placebo (n = 16)	12		Degree of neurological impairment, Depressive symptoms, Autonomy in activities of		One possible interpretation is that fluoxetine might help or, alternatively, maprotiline may delay	Improver ranging f 9% to 1 were rep at the en the rese independ treatmer

						daily living (ADL)		poststroke patients' recovery in a rehabilitation setting. Since combining fluoxetine with physical therapy may lead to better functional outcomes after a stroke, further evaluation of this treatment should be done.	all arms. 5 participa who rece fluoxeti experien an improver of 36% in HSS G mean scc 16% improver in the maprotil arm, and improver in the pla arm. the mean val Shaw & improver of 61%, 5 and 55' respectiv
dennis2018	at 103 hospitals in the UK	RCTs double armed	2 arms (fluoxetine 20mg N=1564 & placebo N=1563)	26.07	ISRCTN83290762	functional status, measured with the mRS, at the 6-month follow- up.	Survival at six and twelve months, functional status at twelve months, health status, arm, hand, leg, and foot power.	It does not appear that the administration of fluoxetine for six months following a stroke will improve functional outcomes.	Fluoxetine placeb treate patients h similar de of disper across n categories month (common ratio adju for minimiza variabl 0.951 [95 0.839–1.0 p=0.43 patients were giv fluoxeti were le likely to l new case depress emerge & six mon (210 [13.0 patients 269 [17.2 differer 3.78% [95 1.26–6.0 p=0.003 But mo broken b were pre (45 [2.88 23 [1.47 differer 1.41% [95 0.38–2.4 p=0.007 There we significa changes i results of other eve both 6-m and 12-m timefram
fruehwald2003	St.- Pölten General Hospital or Maria- Theresien- Schlössel	RCTs double- armed	2 arms (fluoxetine 20mg N=26 & placebo N=24)	2 time parts first at 13.036 weeks & then at 78.2 weeks by open-label methods		The change in HDS after 4 weeks of treatment	HDS average fluctuations at three months and long-term follow-up, the SSS, BDI, and	Therapeutic interventions may have contributed to spontaneous recovery from	In the fluoxeti group, F values f over time elevated &

						CGI estimates over visits, and also the number of respondents.	depression, but antidepressant medication might have been impeded because of these attempts. Fluoxetine therapy was generally well tolerated.	in the placebo group Fluoxetine produced negative effects in people receiving therapy	
gong2020	Shuguang Hospital and Pudong Hospital	RCTs 4 arms	4 arms: Group A (Shu-Gan-Jie-Yu only, 720 mg/once PO, three times per day), Group B (fluoxetine 20mg PO daily), Group C (Shu-Gan-Jie-Yu and fluoxetine), and Group D (placebo)	12.86	SHZYY-SGY211605-18	FMMS score, cerebral-infarction site, NIHSS score, FMMS score, and modified Rankin Scale (mRS) score	Shu-Gan-Jie-Yu (a traditional Chinese medicine) gave equal gains in motor recovery after ischemic stroke to Western medicine (fluoxetine).	enhanced motor ability (P < 0.05) the three groups) V the number of cases with mRS score 0-1 increased so did the percentage all 3 groups < 0.01) contrast placebo	
hankey 2020	A total of 43 units located in Australia (n=29), New Zealand (n=4), and Vietnam (n=10).	RCTs double armed	2 arms (fluoxetine 20mg N=642 & placebo N=638)	26.07	ACTRN12611000774921	mRS at 6 months after randomization	Depression, cognitive ability, communication, motor control, HRQoL, overall health status, adherence to the intervention, and a new diagnosis of depression to be treated with antidepressants, were studied.	Following a stroke, an additional 6 months of oral fluoxetine treatment did not result in any functional benefits and was associated with a higher risk of fractures, falls, and seizures. The findings don't encourage using fluoxetine to help stroke patients.	In the fluoxetine group patients experienced significantly more falls [3%] vs placebo [1%]; p=0.014; broken bones (19 [3%] vs placebo [1%]; p=0.014), convulsions (ten [2%] vs placebo two [<1%] p=0.038) month
he 2016	China	RCTs double armed	2 arms (fluoxetine 20mg N=642 & placebo N=638)	25.7	ChiCTR-TRC-12002078.	The NIHSS scores on days 15, 90, and 180 after enrollment	The BI scores at days 90 and 180 after enrollment	In treating patients following an ischemic stroke with fluoxetine for 90 days, patients can have long-term improvements in their brain functional results.	The mean post-treatment NIHSS scores in the treatment group were lower than control group (P = .00). There was no significant difference between the mean scores on 90 and 180 days between treatment (P = .026), the control arm (P = .011). In the treatment group, benefits

							observed days 90 180 relative to baseline significantly larger than those observed in the control group (P = .033, P = .013, .019, respectively). On day 14, after therapy, the effect of fluoxetine was found to be independent of affective scores.
kong2007	First Hospital Affiliated to Soochow University	RCTs double armed	2 arms (fluoxetine 20mg N=642 & placebo N=638)	8	HAMD, ADL, and neurological impairment, and plasma and platelet 5-HT concentrations after two, four, and eight weeks.	Early fluoxetine therapy plainly hinders PSD development. As the level of platelet 5-HT rises, recovery of neurologic function becomes possible.	In the the group, HAMD-21, a neurologic function differed significantly from placebo after eight weeks (15.3 vs. 13.7; 8.6 vs. 11.2; 6.4 vs. 12.5, P = 0.01). In therapy group, platelet 5-HT concentrations were considered lower after eight weeks treatment [(325.3 ± 10.5 mg/L vs (653.6 ± 13.5 mg/L, P = 0.05], which not only variated were four plasma 5-HT levels (P = 0.05).
li2008	in Qilu Hospital of Shandong University	RCTs 3 arms	3 arms: FEWP group, 18g twice daily (N=60) & fluoxetine, 18g twice daily group (N= 60) & placebo (Vit C), 18 g, twice daily group (N=30).	8	Variations of HDS and BI	FEWP had efficacy and safety in patients with PSD. Based on these findings, we can infer that FEWP appears to be well tolerated and may be a potential therapeutic alternative for patients with PSD.	At the end of this study, there was no statistically significant difference in response between FEWP group and the fluoxetine group (6.2 versus 6.2, p = 0.05). FEWP produced significant better improvement in depression as opposed

									fluoxetine two weeks (15% versus 3.3%, 2.4 0.05) Additional: FEWP was shown to provide less ADL improvement than fluoxetine at the end of this trial 43.8 ± 5 versus 43.7, p = 0
lundstorm 2020	stroke and rehabilitation units in Sweden	RCTs double- armed	2 arms (fluoxetine 20mg N=750 & placebo N=750)	26.07	NCT02683213	Functional status at 6 months, the time elapsed from the commencement of the stroke to randomization, motor impairment or aphasia, pathological type of stroke, and age	Score in the assessed domains of the SIS version NIHSS score; MoCA score	After an ischemic stroke, there was no better functional outcome with the administration of fluoxetine. The rate of depression was lowered, but the danger of bone fractures and hyponatremia was enhanced by the drug. Our findings do not support fluoxetine use in stroke patients.	Fluoxetine was associated with more bone fracture cases [4%] versus [2%]; differences 2.27% [0- 3.87]. p=0.0058 hyponatremia (11 [1% one (<1% differences 1.33% [0- 2.23]. p=0.0034 additional less cases new depression [7%] patients versus 81 [1% patient differences 3.60% [- to -0.7%] p=0.015) month
marquez- romero2020	Mexico City	RCTs double- armed	2 arms (fluoxetine 20mg N=14 & placebo N=16)	12.86	NCT01737541	FMMS score between enrollment (day 0) and 90 ± 7 days.	The change in NIHSS, BI, and mRS	Along with traditional treatment, early fluoxetine prescription proved safe and helped to increase recovery in 90 days after ICH. This finding adds to the growing evidence demonstrating its effectiveness in helping with the symptoms of stroke- related impairment.	More than two-thirds patients had basal ganglia hematomas while in the fifth of patients, hematomas was found in the lobes region. The FMMS score improved significantly more in the treatment group than the placebo group (median score 48), p = 0 There were major adverse events
Wiat2001		RCTs double- armed	2 arms (fluoxetine 20mg/d N=16 & placebo N=15)	6	Stroke. 2000;31:1829- 1832.	the measure was the mean change in Montgomery- Asberg Depression	Mean changes in (MI), (MMS), and (FIM) at the endpoint.	FLX is an effective and well-tolerated therapy for PSD symptoms in the early stages. further	A FLX was shown to have significant better results when compared

Rating Scale (MADRS)	investigation is required to fully understand the long-term effects and safety of this medication.	placebo a: the endp with a differenc MADRS sc of (11.8 ± [mean ± versus 18 10.0, respectiv P50.05 Addition the FLX displaye high response (62.5% ve 33.3% respectiv and a big mean dro the MAI (16.6 ve 8.4, respectiv P50.02). FLX treatme There are no chang motor cognitive function improven with th exception patient v consider and temp transamin elevatio
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Table 2: Baseline characteristics of the enrolled patients in included studies

Study ID	Arms	total number	Age M±SD	sex		Risk factors N				
				male n(%)	female n(%)	HTN	Dyslipidemia	Smoking	CAD	diabetes
Asadollahi 2018	Fluoxetine	30	60.2 (8.52)	15(50)	15(50)	22	14	7	8	
	placebo	30	61.7 (9.6)	18 (60)	12(40)	23	10	9	5	
Bembenek 2020	Fluoxetine	30	66.60 (12.60)	22(73.3)	8(26.7)	19	6	20	5	6
	placebo	31	66.35 (12.46)	18(58.06)	13(41.9)	17	5	22	6	9
boninpinto2019	Fluoxetine	10	50.5 (16.57)	5(50)	5(50)					
	placebo	8	57.38 (9.96)	6(75)	2(25)					
choi-kwon2005	Fluoxetine	76	58.41 (8.92)	57(75)	19(25)	67 (88.2)	21 (27.6)	15 (19.7)	4 (5.3)	22 (28.9)
	placebo	76	58.18 (8.85)	60(78.9)	16(21.05)	54 (71.1)	16 (21.1)	11 (14.5)	3 (3.9)	22 (28.9)
choi-kwon2006	Fluoxetine	40	57.2(8.3)	32 (80.0)	8(20)	26 (65.0)	11 (27.5)	7 (17.5)	1 (2.5)	12 (30.0)
	placebo	43	56.4(8.4)	35 (81.4)	8(18.6)	32 (74.4)	10 (23.3)	6 (14.0)	2 (4.7)	11 (25.6)
chollet2011	Fluoxetine	59	66.(11.7)	37(63)	22(37.29)	39(66)	36 (61)	30 (51)	34 (58)	14 (24)
	placebo	59	62.9(13.4)	35(59)	24(40.68)	40(68)	33 (56)	26 (44)	28 (47)	11 (19)
dam 1998	Fluoxetine	16	67.5(8.9)	7(43.75)	9(56.25)					
	placebo	16	68.4(5.5)	7(43.75)	9(56.25)					
dennis2018	Fluoxetine	1564	71.2(12.4)	975 (62)	589 (38)				281	337
	placebo	1563	71.5(12.1)	947 (61)	616 (39)				300	303
fruehwald2003	Fluoxetine	26	64.8(13.8)	12(46.15)	14(53.85)					
	placebo	24	64.0(14.3)	17(70.8)	7(29.167)					
gong2020	Fluoxetine	56	56.68(17.59)	36(64.29)	20(35.71)	32	27	17		17
	placebo	54	57.79(17.54)	33(61.11)	21(38.89)	30	26	15		18
hankey 2020	Fluoxetine	642	63.5(12.5)	411 (64)	231 (36)				58	143
	placebo	638	64.6(12.2)	393 (62)	245 (38)				57	147
he 2016	Fluoxetine	179	60.46(10.35)	129 (72.1)	50(27.9)	133		60		55
	placebo	171	62.66(11.69)	120 (70.2)	51(29.8)	130		50		64
kong2007	Fluoxetine	37	64(7)	22(60)	15(40)					
	placebo	36	62(7)	20(55.556)	16(44.4)					
li2008	Fluoxetine	60	69.2(3.50)	25(41.667)	35(58.33)					
	placebo	30	67.8(3.9)	17(56.667)	13(43.33)					
lundstorm 2020	Fluoxetine	750	70.6(11.3)	463 (62)	287 (38)				123	140
	placebo	750	71.0(10.50)	462 (62)	288 (38)				111	159
marquez-romero2020	Fluoxetine	14	54(7.41)	8(57.14)	6(42.86)	13	2	4		2
	placebo	16	60.5(13.33)	7(43.75)	9(56.25)	15	1	4		3
Wiat2001	Fluoxetine	16	66.3(7.1)	9(56.25)	7(43.75)					
	placebo	15	68.9(11.6)	6(40)	9(60)					

Figures

Figure 1

The study search, selection, and inclusion process

	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
Asadollahi 2018	+	+	+	+	+	+	?
Bembenek 2020	+	+	+	+	+	+	+
boninpinto2019	+	+	+	+	+	+	?
choi-kwon2005	+	+	+	?	+	+	+
choi-kwon2006	+	+	+	?	+	+	+
chollet2011	+	+	+	+	+	+	+
dam 1998	?	?	?	?	+	?	+
dennis2018	+	+	+	+	+	+	+
fruehwald2003	+	+	+	+	+	+	?
gong2020	+	+	+	+	+	+	+
hankey 2020	+	+	+	+	+	+	+
he 2016	+	?	+	+	+	+	+
kong2007	+	+	+	+	+	+	?
li2008	+	+	+	?	+	+	?
lundstorm 2020	+	+	+	+	+	+	+
marquez-romero2020	+	+	+	?	+	+	?
Wiat2001	?	?	+	?	+	+	?

Figure 2

Risk of bias: a summary table for each risk of bias item for each study

Figure 3

The pooled mean difference of the National Institutes of Health Stroke Scale (NIHSS)

Figure 4

The pooled mean difference of the Barthel Index (BI)

Figure 5

The pooled mean difference of the Fugl-Meyer Motor Scale (FMMS)

Figure 6

The pooled mean difference of the Stroke Impact Scale (SIS)

Supplementary Files

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