Selective serotonin reuptake inhibitors (SSRIs) for stroke recovery

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Stroke is a major cause of adult disability. Selective serotonin reuptake inhibitors (SSRIs) have been used for many years to manage depression and other mood disorders after stroke. Small studies suggested that SSRIs might also promote motor recovery by direct effects on the brain. In this Cochrane review, we aimed to determine the effects of SSRIs in improving outcomes in people less than 12 months after stroke, and to determine whether treatment with SSRIs is associated with adverse effects.

Methods

We searched the Cochrane Stroke Group Trials Register, Cochrane Controlled Trials Register, MEDLINE, Embase, CINAHL, PsycINFO, and AMED by 7 Jan 2021. PsycBITE had previously been searched (16 July 2018). We included randomised controlled trials (RCTs) recruiting stroke survivors within the first year, which compared effects of SSRIs (any type, any dose and for any period) with placebo or usual care. The co-primary outcomes were independence at the end of treatment and disability score at the end of the treatment, and secondary outcomes included impairments (assessed by neurological deficits scores such as National Institute of Health Stroke Scale), depression, anxiety, quality of life, fatigue, cognition, healthcare cost, death, adverse events, and leaving the study early. Two reviewers independently screened abstracts, extracted data and appraised risk of selection bias, performance and detection bias, attrition bias, reporting bias, and other potential threats to validity. Risk ratio (RR) and standardised mean difference (SMD) were calculated as effect sizes and outcome data were pooled in meta-analysis using a fixed-effect model and methodological quality was assessed using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach.

Results

We included 76 clinical trials involving 13029 participants. Of these, only six studies with 6090 participants were at low risk of bias across all domains, which all used fluoxetine and did not require participants to have depression to enter. These high-quality studies suggested that fluoxetine did not improve disability (SMD -0.00;

95% CI -0.05 to 0.05; 5 studies, 5436 participants) nor independence (RR 0.98; 95% CI 0.93 to 1.03; 5 studies, 5926 participants) (Figure). In addition, in participants who did not have depression at baseline, fluoxetine reduced the risk of depression (RR 0.75, 95% CI 0.65 to 0.86; 3 studies, 5907 participants) and the severity of depression (SMD -0.14, 95% CI -0.19 to -0.08; 4 studies; 5356 participants). For adverse events, the use of fluoxetine was associated with an increasing risk of bone fractures (RR 2.35, 95% CI 1.62 to 3.41; 6 studies, 6080 participants) and seizures (RR 1.40, 95% CI 1.00 to 1.98; 6 studies, 6080 participants).

Conclusions

High-quality studies indicated that fluoxetine did not reduce disability or dependency after stroke. This was consistent with the previous version of this Cochrane Review in 2019. We found new evidence that fluoxetine reduced the risk of future depression and the severity of depression. However, due to insufficient evidence revealed in this review, we do not know whether SSRIs might reduce disability in people who do have depression after stroke and we do not know what effect of SSRIs other than fluoxetine might have on recovery after stroke, which need further investigation.

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Footnotes

1. Legg LA, Rudberg A-S, Hua X, Wu S, Hackett ML, Tilney R, Lindgren L, Kutlubaev MA, Hsieh C-F, Barugh AJ, Hankey GJ, Lundström E, Dennis M, Mead GE. Selective serotonin reuptake inhibitors (SSRIs) for stroke recovery. Cochrane Database of Systematic Reviews 2021, Issue 11. Art. No.: CD009286. DOI: 10.1002/14651858.CD009286.pub4

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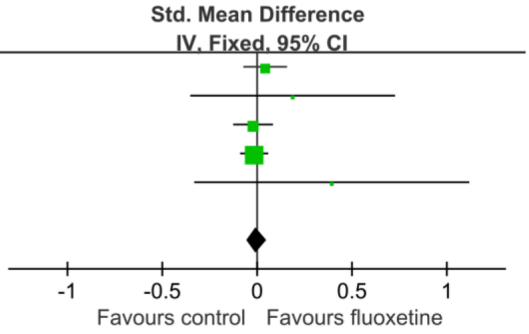
Figure. Forrest plot for (**A**) primary outcome: disability and (**B**) primary outcome: independence (modified Rankin score 0-2). Fluoxetine versus control at end of treatment. Studies at low risk of bias only.

A

Study or Subgroup	Fluoxetine Mean	Fluoxetine SD	Fluoxetine Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
AFFINITY 2020	81.3	23.4	569	80.3	23.5	591	21.3%	0.04 [-0.07, 0.16]
Bembenek 2020	78.75	23.42	26	74.07	25.71	27	1.0%	0.19 [-0.35, 0.73]
EFFECTS 2020	79.3	23.8	697	79.8	23.1	697	25.7%	-0.02 [-0.13, 0.08]
FOCUS 2019	59.66	31.16	1402	60.15	31.5	1397	51.5%	-0.02 [-0.09, 0.06]
Marquez Romero 2013	65	11.85	14	45	66.67	16	0.5%	0.39 [-0.33, 1.12]
Total (95% CI)			**2708**			**2728**	**100.0%**	**-0.00 [-0.05, 0.05]**

Heterogeneity: Chi² = 2.45, df = 4 (P = 0.65); I² = 0%
Test for overall effect: Z = 0.02 (P = 0.99)



B

Study or Subgroup	Fluoxetine Events	Fluoxetine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
AFFINITY 2020	432	624	458	632	29.6%	0.96 [0.89, 1.03]
Bembenek 2020	20	27	17	28	1.1%	1.22 [0.84, 1.77]
EFFECTS 2020	466	737	475	742	30.8%	0.99 [0.91, 1.07]
FOCUS 2019	572	1553	588	1553	38.3%	0.97 [0.89, 1.07]
Marquez Romero 2013	8	14	3	16	0.2%	3.05 [1.00, 9.31]
Total (95% CI)		**2955**		**2971**	**100.0%**	**0.98 [0.93, 1.03]**
Total events	1498		1541			

Heterogeneity: Chi² = 5.84, df = 4 (P = 0.21); I² = 32%
Test for overall effect: Z = 0.89 (P = 0.37)