CNS Drugs (2018) 32:895–903
https://doi.org/10.1007/s40263-018-0573-x

LEADING ARTICLE

Potential Role of Selective Serotonin Reuptake Inhibitors in Improving Functional Outcome after Stroke

Janne Kaergaard Mortensen[1] · **Grethe Andersen**[1]

Published online: 17 September 2018

Abstract
The great advances in acute stroke treatment during the last decades have changed life after stroke considerably. However, the use of intravenous thrombolysis and endovascular thrombectomy is limited by a relatively narrow time window or contraindications for treatment. Further, patients receiving acute reperfusion therapies may still have cognitive and emotional complications due to underlying brain infarcts even though physical problems may almost disappear. Consequently, stroke is still a frequent cause of adult disability and death worldwide, and an effort to identify additional treatments to enhance recovery, preferably also feasible in the time after the acute phase, is warranted. Albeit several drugs and treatment modalities have been studied for their potential to enhance recovery after stroke, no treatment has unambiguously proven to potentiate the rehabilitation process. A promising candidate for pharmacological treatment is selective serotonin reuptake inhibitors (SSRIs), a group of commonly used antidepressants that may also possess neuro-regenerative properties. The current paper reviews the evidence for SSRIs as potential enhancers of stroke recovery and discusses the potential mechanisms behind the effects reported and the implications for the management of patients post-stoke, including potential adverse events and drug–drug interactions.

Key Points

Promising results indicate a positive effect of selective serotonin reuptake inhibitors (SSRIs) on recovery after stroke.

The results from several ongoing large trials are awaited before routine use after stroke may be considered.

1 Introduction

The main indication for treatment with selective serotonin reuptake inhibitors (SSRIs) is moderate-to-severe depression. Depression after stroke occurs in approximately one in three patients [1], so SSRI treatment is common in stroke [2]. SSRIs inhibit the presynaptic serotonin transporter in neurons, thereby increasing the level of serotonin in the synaptic cleft [3]. Serotonin modulates practically all human behavioral processes as well as other brain functions such as mood, memory, aggression, motor control and sleep [4]. When released from platelets, serotonin facilitates platelet aggregation. The serotonin transporter in platelets is also inhibited by SSRIs, and treatment leads to a reduction of serotonin content in platelets [5], which in theory could lead to an antithrombotic effect as well as an increased risk of bleeding events.

SSRIs have been of interest in the search for potential pharmacological treatments to facilitate neural repair and rehabilitation after stroke. In earlier reports, the main focus was on the antidepressant effect; however, several more recent studies have focused on a potential neurorestorative effect of SSRIs. This effect has an expected therapeutic time window of days to weeks or even longer, corresponding to the recovery stage and the chronic state after stroke [6]. A potential antithrombotic effect caused by the inhibition of platelet aggregation may further play a role in both the acute and the more chronic phase after stroke, an aspect that has also gained attention more recently. This article reviews the evidence behind SSRIs as potential enhancers of stroke recovery.

✉ Janne Kaergaard Mortensen
janne.k.mortensen@clin.au.dk

[1] Department of Neurology, Aarhus University Hospital, Nørrebrogade 44, 8000 Aarhus C, Denmark

A search of all published articles in English until July 2018 was conducted in PubMed using the search terms "serotonin uptake inhibitors," "SSRI" OR "selective serotonin reuptake inhibitors" AND "stroke". Titles, then relevant abstracts, were scrutinized, and the relevant articles were subsequently retrieved. Reference lists from relevant articles were also searched for other potentially relevant references.

2 Selective Serotonin Reuptake Inhibitors (SSRIs) and Functional Outcome after Stroke

Table 1 shows the identified randomized trials of SSRI treatment after stroke that had functional/motor outcome as the primary outcome measure.

Our search identified four randomized placebo-controlled trials [7–10] of SSRI treatment in nondepressed stroke patients with a treatment duration of 1–3 months and a primary outcome measure of motor function (Table 1). The trials were all relatively small but have shown promising results. Dam et al. [7] studied the effect of 3 months of treatment with the SSRI fluoxetine, the tetracyclic antidepressant maprotiline or placebo in 52 stroke patients. They found improvement in motor and functional outcome in all three groups, with the greatest improvement in the fluoxetine group [7]. Acler et al. [8] randomized 20 patients to daily citalopram or placebo treatment for 1 month and found a significant improvement in neurological status and a decrease in motor excitability, measured by transcranial magnetic stimulation, over the unaffected hemisphere in patients receiving citalopram. The FLAME (fluoxetine for motor recovery after acute ischaemic stroke) study [9] randomized 118 ischemic stroke patients with moderate-to-severe motor deficits to fluoxetine or placebo treatment for 3 months within 5–10 days after stroke onset. At day 90, the fluoxetine-treated patients had significantly greater improvement on the Fugl-Meyer motor score (FMMS) compared with the placebo group, and the proportion of independent patients [modified Rankin Score (mRS) of 0–2] was significantly higher in this group [9]. Finally, Savadi Oskouie et al. [10] conducted a randomized, placebo-controlled trial in which 144 ischemic stroke patients were randomized to citalopram or placebo for 3 months within 7 days after stroke onset. Significantly more patients evidenced a reduction in National Institute of Health Stroke Scale (NIHSS) score of at least 50% and a favorable outcome on the mRS (score of 0–2) at 3 months in the citalopram group [10].

Two randomized single-blinded trials were identified where the control group was given standard treatment but not placebo [11, 12] (Table 1). The trials were larger and included a 6-month follow-up after 3 months of treatment with fluoxetine. He et al. [11] included 374 patients and observed improved functional outcome in the treated group at both 3 and 6 months and that neurological function improved at 6 months. Guo et al. [12] included 300 patients within 1 week after stroke and initiated treatment upon, or 1 week after, randomization. They found improved functional outcome and neurological function in the early-treated group compared with the standard-treated group at 3 months; at 6 months, improvement was observed compared with both the standard treated and the later-treated group. It appears that no comparison was made between the group treated upon randomization and those treated within 1 week. The results from these trials may indicate SSRI treatment exerts an effect beyond the treatment period and that treatment initiated in the early phase may be beneficial.

Three small (eight to ten patients) randomized placebo-controlled trials studying the effect of a single dose of SSRI were identified [13–15] (Table 1). Motor function was tested 2–5 h after drug administration, corresponding to presumed maximal plasma concentrations. Pariente et al. [13] and Zittel et al. [14] observed improved motor function. Further, using functional magnetic resonance imaging (fMRI), Pariente et al. [13] found hyperactivation in the ipsilesional primary motor cortex. On the other hand, Gourab et al. [15] found that treatment was associated with increased lower limb spasticity and no increased strength or lower limb function. In a crossover placebo-controlled trial in ten patients, Berends et al. [16] used electromyography to test muscle activation 5 h after a single dose of fluoxetine, and motor function was assessed using grip strength as a secondary outcome. The authors found that fluoxetine increased activation in both agonist and antagonist muscles in the arm, but grip strength was not affected. They argued that the increased rigidity may even decrease motor function. Optimal timing for testing after a single dose of SSRI is unclear, and although Gourab et al. [15] and Berends et al. [16] found no positive effect on motor function but rather increased spasticity and possibly rigidity, these studies indicate that SSRI to some extent influenced motor output and cortical activation. Accordingly, modulation of cerebral motor activity after a single dose of SSRI has also been shown in healthy subjects [17, 18], whereas a more recent study found that a single dose did not enhance corticomotorneuronal excitability, motor performance or practice-dependent plasticity in healthy subjects [19].

Finally, three systematic reviews and meta-analyses on SSRI treatment and functional outcome after stroke were identified [20–22]. A Cochrane review from 2012 included 52 randomized controlled trials comprising 4060 participants in a meta-analysis [20, 23]. Some trials included patients with depression, whereas other trials included only patients without depression. The mean time since stroke to study inclusion was 0–3 months for the majority of trials (31 of 52), but ten trials did not report the time from onset to

Table 1 Chronological list of randomized trials of SSRI treatment after stroke with functional/motor outcome as primary outcome measure

Study	Study design	Study population (*n*)	Drug	Time since stroke	Tx duration/follow-up or time of evaluation	Stroke severity	Outcome	Effect of active treatment
Dam et al. [7]	RCT, PG	Ischemic (middle cerebral artery) stroke (52)	FLU/MAP/PL	1–6 months	3 months/3 months	Patients unable to walk	HSS and BI	Greater improvement in HSS and BI in the FLU group vs. MAP but not PL
Pariente et al. [13]	RCT, CO	Ischemic (pure motor lacunar) stroke (8)	FLU/PL	7–30 days	Single dose/5 h after administration	Pure motor hemiplegia	Finger tapping test, dynamometer, changes in cerebral activation measured by fMRI	Improved motor skills on affected side; hyperactivation in ipsilesional primary motor cortex
Zittel et al. [14]	RCT, CO	Stroke type NR for all patients (8)	CIT/PL	>6 months	Single dose/2 and 3.5 h after administration	Pronounced paresis of distal upper extremity (MRC scale 4)	Nine-hole peg test and grip strength	Improvement in nine-hole peg test for paretic hand but not for unaffected hand. Grip strength unchanged
Acler et al. [8]	RCT, PG	Stroke type NR for all patients (20)	CIT/PL	15–20 days	1 month/1 month	Mean NIHSS 5	NIHSS, BI, Lindmark scale, motor cortex excitability measured by TMS	Improvement on NIHSS; decrease in motor excitability over unaffected hemisphere
Chollet et al. [9]	RCT, PG	Ischemic stroke (118)	FLU/PL	5–10 days	3 months/3 months	Mean NIHSS 13	FMMS and mRS	Improvement on FMMS; more patients achieving independence
Gourab et al. [15]	RCT, CO	Ischemic and hemorrhagic stroke (10)	ESC/PL	>1 year	Single dose/5 h after administration	FMMS lower extremity score < 34	Isometric knee and ankle strength, plantar-flexor stretch reflexes, lower limb locomotion and coordination	Increased lower limb spasticity. No increase in lower limb strength or function
He et al. [11]	PROBE[a]	Ischemic stroke (374)	FLU/standard tx	≤7 days	3 months/6 months	Mean NIHSS 7.2	NIHSS, BI	Improvement in NIHSS score at 6 months; improvement in BI scores at 3 and 6 months

Table 1 (continued)

Study	Study design	Study population (*n*)	Drug	Time since stroke	Tx duration/follow-up or time of evaluation	Stroke severity	Outcome	Effect of active treatment
Guo et al. [12]	PROBE[a]	Ischemic stroke (300)	FLU initiated upon randomization/ FLU initiated 1 week after randomization/ standard tx	≤7 days	3 months/6 months	Mean NIHSS 7.3	NIHSS, BI	Improvement in NIHSS and BI scores in early tx group vs. standard group at 3 months and vs. later treated group at 6 months
Savadi Oskouieet al. [10]	RCT, PG	Ischemic stroke (144)	CIT/PL	≤7 days	3 months/3 months	Mean NIHSS 10.6	NIHSS, mRS	Improvement in NIHSS and mRS scores

BI Barthel index, *CIT* citalopram, *CO* crossover, *ESC* escitalopram, *FLU* fluoxetine, *FMMS* Fugl-Meyer Motor Score, *fMRI* functional magnetic resonance imaging, *HSS* Hemispheric Stroke Scale, *MAP* maprotiline, *MRC* Medical Research Council, *mRS* modified Rankin Scale, *NIHSS* National Institute of Health Stroke Scale, *NR* not reported, *PG* parallel group, *PL* placebo, *PROBE* prospective randomized open blinded endpoint, *RCT* randomized controlled trial, *SSRI* selective serotonin reuptake inhibitor, *TMS* transcranial magnetic stimulation, *tx* treatment

[a]The authors describe the design as randomized, single blinded with a blinded evaluator

trial inclusion. Duration of treatment varied between trials, ranging from weeks to months, and only eight trials followed patients after the end of the treatment period. As described and also concluded by the authors, there was heterogeneity between the trials, and several trials had substantial methodological limitations. In this comprehensive review and meta-analysis, SSRI treatment appeared to improve dependence, disability, neurological impairment, anxiety and depression after stroke, with an effect also seen in patients without depression. On the other hand, treatment also appeared to be associated with an increased risk of adverse events. The authors concluded evidence was insufficient to recommend routine use of SSRIs in stroke recovery, and questions remained unanswered regarding what class of SSRI to use, when to initiate treatment, length of treatment, and dosage [20]. A more recent meta-analysis of trials studying the effects of different central nervous system drugs on stroke recovery included 17 trials (1575 patients) studying the effects of SSRIs [21]. The studied outcomes were gross motor function, cognition, disability, dependency and quality of life (QOL). They found that SSRI treatment improved gross motor function, disability and QOL. They found insufficient evidence that treatment enhanced global cognition and dependency. Ten of the studies did not consider time since stroke as an inclusion criterion. Five studies included only ischemic stroke patients, and 12 studies included both ischemic and hemorrhagic stroke patients. Most studies included strokes with moderate severity, but four studies did not report severity. Importantly, seven of the trials used no control drug [21]. In another recent meta-analysis, Gu et al. [22] focused on early administration (≤30 days) of SSRI. The primary outcome was decrease in NIHSS, and secondary outcomes were improvement in Barthel Index (BI) score and functional independence, defined as a score of 0–2 on the mRS. They included eight trials comprising 1549 nondepressed patients and found that treatment with SSRIs compared with placebo was associated with a greater decrease in NIHSS, an improved BI score and a significantly higher rate of functional independence. They found that the primary outcome was significantly better among trials with higher NIHSS scores at baseline (≥10), which may partly have been caused by a ceiling effect. They found no significant difference between SSRI and placebo on incidence of depression or the risk of adverse events [22].

The randomized trials in Table 1 were all conducted among nondepressed stroke patients, and primary outcomes were functional and motor outcomes associated with SSRI treatment [7–15, 20–22]. The SSRI escitalopram has also been associated with improvement in cognitive function after stroke [24]. In a recent randomized, double-blind, placebo-controlled study including 478 ischemic or hemorrhagic stroke patients within 21 days after stroke onset with a mean baseline NIHSS of five, patients were treated with

either escitalopram or placebo for 3 months and followed for 6 months [25]. The primary outcome was frequency of depressive symptoms, but secondary outcomes were motor function on the Hemispheric Stroke Scale, NIHSS and BI scores, mRS, and cognitive functioning as measured by the Montreal Cognitive Assessment (MoCA) score at 3 and 6 months. The authors found no difference in outcomes between the two groups [25].

Although the results from most of the reviewed trials are encouraging and indicate a positive effect from SSRI treatment in stroke recovery, the reviewed trials were all relatively small, and the largest trials were not placebo controlled [11, 12]. The results from the meta-analyses also indicate a positive effect of SSRI treatment, but they are based on small heterogeneous trials, and several trials had substantial methodological limitations [20–22]. The single-dose studies by Gourab et al. [15] and Berends et al. [16] and the study by Kim et al. [25] found no positive effect of treatment on functional outcome. The patients in the study by Kim et al. [25] had a relatively low mean NIHSS score, which may have made a potential improvement insignificant. Compared with the FLAME study [9] and that by Savadi Oskouie et al. [10], Kim et al. [25] included patients with more severe depression, and patients were included in a later time window of up to 21 days after stroke onset.

3 Safety of SSRI Treatment after Stroke

The results from the FLAME study [9] boosted discussion around the use of SSRIs as part of routine treatment after stroke [26–31]. Although the results gave rise to optimism, several concerns were also raised. One concern included potential drug–drug interactions, specifically a potential interaction with clopidogrel, which is often used in secondary prophylaxis after stroke. Fluoxetine inhibits cytochrome P450 2C19, which is involved in the activation of clopidogrel into its active metabolite, and thus may inhibit the activation and thereby the efficacy of the drug [27]. Other concerns include potential side effects and a lack of knowledge about potential mechanisms, about the optimal timing and duration of treatment, and about the effect on milder strokes and on deficits other than motor impairment [30]. Besides the more well-known SSRI-related side effects such as gastrointestinal symptoms, hyponatremia, and sexual dysfunction, SSRIs have also been associated with an increased risk of hemorrhagic stroke, ranging from one expected additional intracerebral hemorrhage per 33,333 individuals in a meta-analysis by Shin et al. [33] to one in 10,000 treated individuals in a meta-analysis by Hackam and Mrkobrada [32]. The increased bleeding risk could be explained by the inhibition of serotonin uptake in platelets by SSRIs and corresponds with the well-described risk of gastrointestinal bleedings [34–36]. Importantly, the studies included in the meta-analyses by Shin et al. [33] and Hackam and Mrkobrada [32] were all conducted in nonstroke populations. The risk of stroke recurrence associated with SSRI treatment was studied in a follow-up study by Mortensen et al. [37] including 5833 ischemic stroke patients treated with SSRIs and 5833 propensity score-matched controls not treated with SSRIs. SSRI treatment was associated with a significantly increased risk of bleeding complications, but the absolute risk of intracranial bleedings was low and not statistically significant [37]. SSRI treatment was associated with a reduced risk of recurrent ischemic stroke, which is possibly due to an antithrombotic effect [37]. On the other hand, vasospastic effects and serotonin syndrome have been proposed as possible mechanisms behind the increased risk of ischemic stroke [38, 39] found in a cohort study by Juang et al. [40], conducted among 16,770 stroke patients. SSRI treatment was not associated with an increased risk of hemorrhagic stroke in this study [40]. Wang et al. [41] conducted a case–control study that included 3536 cases and 6679 controls and found no association between the use of SSRIs and recurrent stroke risk. Importantly, in the study by Juang et al. [40], a distinction between ischemic and hemorrhagic stroke was not made for incident strokes, and in the case–control study by Wang et al. [41], neither incident nor recurrent events were distinguished between ischemic and hemorrhagic events. Further, in observational studies, the risk of potential residual confounding, despite controlling for potential confounding variables in the statistical analysis, needs to be considered. In particular, confounding by indication should be considered, as depression is associated with an increased risk of cardiovascular disease [42]. He et al. [43] studied the risk of stroke recurrence in a randomized controlled trial. A reduced risk of 3-year recurrence of ischemic stroke was found in a randomized controlled trial of 404 ischemic stroke patients treated with fluoxetine or placebo for 90 days. The risk of hemorrhagic stroke was not studied.

In line with the possible increased risk of bleeding complications associated with SSRI treatment, the risk of bleeding complications in acute ischemic stroke patients treated with thrombolysis and pre-stroke SSRI treatment has been studied [44–46]. The cohorts in these studies included relatively small groups of pre-stroke SSRI-treated patients (135, 266 and 22, respectively). Overall, however, treatment with thrombolysis did not appear to increase the risk of bleeding complications.

4 Mechanisms

The exact mechanism(s) behind a potential beneficial effect of SSRIs in stroke recovery is not clear. A beneficial effect on remission of depression and reduction of depressive symptoms with antidepressant treatment could contribute

to an increased functional recovery, as post-stroke depression itself increases the risk of suboptimal recovery, recurrent vascular events, poorer QOL and mortality [47, 48]. Treating depression could increase patients' motivation and participation in rehabilitation efforts and thus the functional outcome. On the other hand, a positive effect on functional recovery was found in studies including clinically nondepressed patients, such as the FLAME study [9], and an effect of pharmacological therapy on the prevention of depression after stroke has not been established [49]. It is worth mentioning that 7% of the patients in the FLAME study developed depression during follow-up, and these patients were not excluded from the final analyses. In this particular study, a positive effect on outcome, at least partly due to an antidepressant effect, cannot be ruled out. Several previously mentioned studies found an effect of a single dose of SSRI on both cortical excitability and functional performance, and the antidepressant effect is not likely to be the sole mechanism [13, 14, 17, 18]. Further, in their randomized controlled trial, Dam et al. [7] found fluoxetine to be superior to the tetracyclic antidepressant maprotiline in enhancing recovery, whereas both drugs improved depressive symptoms significantly. The modulation of cerebral motor activity has been proposed as one of the more specific mechanisms behind an enhancement of motor function. Stroke leads to a disruption of the excitation–inhibition balance, and it has been proposed that SSRIs may reestablish this balance, possibly through an acute effect on enhancement of excitatory activity followed by an increase in inhibitory activity [50]. Several other possible mechanisms have been identified in animal models, including a neurotrophic effect promoting brain plasticity, which can be defined as the capacity of cerebral neurons and neural circuits to structurally and functionally change [51]. SSRIs have thus been found to promote both neurogenesis [52] and angiogenesis [53], possibly mediated through the regulation of brain-derived neurotrophic factor and vascular endothelial growth factor [54, 55]. Whereas neurotrophic agents exert their effect days to weeks or even longer after stroke, agents with a neuroprotective effect, i.e., agents with the ability to preserve neurons, exert their effect within the initial hours, or at most days, after stroke [6]. It has been proposed that at least part of the positive effect of SSRIs on rehabilitation after stroke is caused by neuroprotection possibly mediated through an anti-inflammatory effect [56] or through the enhancement of specific protein expression [57].

Different mechanisms may be behind the different effects on outcome. Hippocampal neurogenesis may improve post-stroke cognitive function, whereas the effect on cortical excitability may affect motor function. There may be a more immediate effect, including the inhibition of serotonin reuptake and longer-term effects such as the regulation of neurotrophic factors. As previously stated, the exact mechanisms behind a beneficial effect of SSRIs after stroke are not clear, but a multimodal effect is likely, as SSRIs affect different brain structures and the balance between different neurotransmitters. Some of the effects, particularly excitation and inhibition, may even be opposing, and, as indicated by the single-dose studies by Gourab et al. [15] and Berends et al. [16], SSRIs may increase motor tone, possibly through an effect on the spinal canal, and thereby affect motor function negatively.

5 Future Trials and Implications for the Management of Recovering Stroke Patients

The possible increased risk of hemorrhagic stroke, and the less unequivocal association with ischemic stroke in SSRI treatment may be acceptable when treating patients with post-stroke depression or emotional lability, as these are potentially devastating consequences of stroke. When using SSRIs to potentiate rehabilitation, it is equally important that the potential gain outweighs the potential adverse effects. An antithrombotic effect that could potentially reduce the rate of recurrent ischemic events after stroke has been studied in the TALOS trial. In this trial, 600 ischemic stroke patients were randomized to citalopram or placebo treatment for 6 months with two co-primary outcomes: mRS score at 6 months and a composite vascular endpoint of transient ischemic attack/stroke, myocardial infarction or vascular mortality during the first 6 months [58]. The results from the TALOS trial are awaiting publication. The randomized controlled trials, FOCUS (UK), AFFINITY (Australia, New Zealand and Vietnam) and EFFECTS (Sweden) are studying the effects of 6 months of fluoxetine treatment in acute (2–15 days after onset) ischemic and hemorrhagic stroke patients with persisting neurological deficits. The primary outcome is mRS at 6 months. A core protocol for the three trials has been published, and a total of 6000 patients will be included [59]. Plans are for inclusion and follow-up for FOCUS to be completed by the end of 2018 and for AFFINITY and EFFECTS by 2020. As FOCUS, AFFINITY and EFFECTS include both ischemic and hemorrhagic stroke patients, the results from these trials may help resolve the question of safety also in hemorrhagic stroke. The results will hopefully also help answer the question of whether SSRI treatment after stroke facilitates rehabilitation and whether these drugs should be considered as part of the routine treatment after stroke. Regardless, a decision must always be based on considerations of indication and potential gain versus drug–drug interactions and potential side effects in individual patients. A potential aspect to consider in future trials when studying personalized medicine, is genetics. As an example, serotonin transporter (*SERT*) gene polymorphisms have been

associated with the risk of stroke [60], the risk of post-stroke depression [61] and, finally, post-stroke neurological recovery after SSRI use [62]. This is also an important aspect to consider when comparing trials with different ethnic profiles, as the distribution of *SERT* gene polymorphisms may differ according to ethnicity [63].

6 Conclusions

SSRIs may have neurorestorative effects with the potential to facilitate rehabilitation in the sub-acute and chronic phase after stroke and improve outcome in a greater proportion of stroke patients. A neuroprotective effect may also be present if treatment is given in the acute phase. Several possible mechanisms may be behind these potential effects, although they remain speculative. The effect is most likely multimodal, and excitatory and inhibitory effects may affect motor outcome in opposing directions. Results from several large ongoing trials are awaited before a potential beneficial effect may be clarified and before routine treatment may be considered. Further, studies exploring the underlying mechanisms, optimal timing, treatment duration, interactions and effects on bleeding complications and other potential adverse effects as well as genetic implications are warranted. A potential beneficial effect of treatment must always be weighed against potential adverse effects in each individual patient.

Compliance with Ethical Standards

Conflict of Interest Janne Kaergaard Mortensen and Grethe Andersen have no conflicts of interest.

Funding No funding was received to assist with the preparation of this review.

References

1. Hackett ML, Pickles K. Part I: frequency of depression after stroke: an updated systematic review and meta-analysis of observational studies. Int J Stroke. 2014;9(8):1017–25. https://doi.org/10.1111/ijs.12357.
2. Mortensen JK, Johnsen SP, Andersen G. Prescription and predictors of post-stroke antidepressant treatment: a population-based study. Acta Neurol Scand. 2018. https://doi.org/10.1111/ane.12947.
3. Fuller RW, Wong DT. Serotonin reuptake blockers in vitro and in vivo. J Clin Psychopharmacol. 1987;7(6 Suppl):36S–43S.
4. Berger M, Gray JA, Roth BL. The expanded biology of serotonin. Annu Rev Med. 2009;60:355–66. https://doi.org/10.1146/annurev.med.60.042307.110802.
5. Wgner A, Montero D, Martensson B, Siwers B, Asberg M. Effects of fluoxetine treatment of platelet 3H-imipramine binding, 5-HT uptake and 5-HT content in major depressive disorder. J Affect Disord. 1990;20(2):101–13. https://doi.org/10.1016/0165-0327(90)90123-P.
6. Cramer SC. Drugs to enhance motor recovery after stroke. Stroke. 2015;46(10):2998–3005. https://doi.org/10.1161/STROKEAHA.115.007433.
7. 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(7):1211–4.
8. Acler M, Robol E, Fiaschi A, Manganotti P. A double blind placebo RCT to investigate the effects of serotonergic modulation on brain excitability and motor recovery in stroke patients. J Neurol. 2009;256(7):1152–8. https://doi.org/10.1007/s00415-009-5093-7.
9. 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(2):123–30. https://doi.org/10.1016/S1474-4422(10)70314-8.
10. Savadi Oskouie D, Sharifipour E, Sadeghi Bazargani H, et al. Efficacy of citalopram on acute ischemic stroke outcome: a randomized clinical trial. Neurorehabil Neural Repair. 2017;31(7):638–47. https://doi.org/10.1177/1545968317704902.
11. He YT, Tang BS, Cai ZL, Zeng SL, Jiang X, Guo Y. Effects of fluoxetine on neural functional prognosis after ischemic stroke: a randomized controlled study in china. J Stroke Cerebrovasc Dis. 2016;25(4):761–70. https://doi.org/10.1016/j.jstrokecerebrovasdis.2015.11.035.
12. 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(2):177–87. https://doi.org/10.3233/RNN-150535.
13. Pariente J, Loubinoux I, Carel C, et al. Fluoxetine modulates motor performance and cerebral activation of patients recovering from stroke. Ann Neurol. 2001;50(6):718–29.
14. Zittel S, Weiller C, Liepert J. Citalopram improves dexterity in chronic stroke patients. Neurorehabil Neural Repair. 2008;22(3):311–4. https://doi.org/10.1177/1545968307312173.
15. Gourab K, Schmit BD, Hornby TG. Increased lower limb spasticity but not strength or function following a single-dose serotonin reuptake inhibitor in chronic stroke. Arch Phys Med Rehabil. 2015;96(12):2112–9. https://doi.org/10.1016/j.apmr.2015.08.431.
16. Berends HI, Nijlant J, van Putten M, Movig KL, IJzerman MJ. Single dose of fluoxetine increases muscle activation in chronic stroke patients. Clin Neuropharmacol. 2009;32(1):1–5.
17. Loubinoux I, Boulanouar K, Ranjeva JP, et al. Cerebral functional magnetic resonance imaging activation modulated by a single dose of the monoamine neurotransmission enhancers fluoxetine and fenozolone during hand sensorimotor tasks. J Cereb Blood Flow Metab. 1999;19(12):1365–75. https://doi.org/10.1097/00004647-199912000-00010.
18. Loubinoux I, Pariente J, Boulanouar K, et al. A single dose of the serotonin neurotransmission agonist paroxetine enhances motor output: double-blind, placebo-controlled, fMRI study in healthy subjects. Neuroimage. 2002;15(1):26–36. https://doi.org/10.1006/nimg.2001.0957.
19. McDonnell MN, Zipser C, Darmani G, Ziemann U, Muller-Dahlhaus F. The effects of a single dose of fluoxetine on practice-dependent plasticity. Clin Neurophysiol. 2018;129(7):1349–56.
20. Mead GE, Hsieh CF, Lee R, et al. Selective serotonin reuptake inhibitors (SSRIs) for stroke recovery. Cochrane Database Syst Rev. 2012;11:CD009286. https://doi.org/10.1002/14651858.cd009286.pub2.
21. Yeo SH, Lim ZI, Mao J, Yau WP. Effects of central nervous system drugs on recovery after stroke: a systematic review and meta-analysis of randomized controlled trials. Clin Drug Investig. 2017;37(10):901–28. https://doi.org/10.1007/s40261-017-0558-4.

22. Gu SC, Wang CD. Early selective serotonin reuptake inhibitors for recovery after stroke: a meta-analysis and trial sequential analysis. J Stroke Cerebrovasc Dis. 2018;27(5):1178–89.
23. Mead GE, Hsieh CF, Lee R, et al. Selective serotonin reuptake inhibitors for stroke recovery: a systematic review and meta-analysis. Stroke. 2013;44(3):844–50. https://doi.org/10.1161/STROKEAHA.112.673947.
24. Jorge RE, Acion L, Moser D, Adams HP Jr, Robinson RG. Escitalopram and enhancement of cognitive recovery following stroke. Arch Gen Psychiatry. 2010;67(2):187–96. https://doi.org/10.1001/archgenpsychiatry.2009.185.
25. Kim JS, Lee EJ, Chang DI, et al. Efficacy of early administration of escitalopram on depressive and emotional symptoms and neurological dysfunction after stroke: a multicentre, double-blind, randomised, placebo-controlled study. Lancet Psychiatry. 2017;4(1):33–41.
26. Robinson RG, Adams HP. Selective serotonin-reuptake inhibitors and recovery after stroke. Lancet Neurol. 2011;10(2):110–1. https://doi.org/10.1016/S1474-4422(10)70326-4.
27. Gonzenbach RR, Taegtmeyer AB, Luft A, Russmann S. Fluoxetine and motor recovery after ischaemic stroke. Lancet Neurol. 2011;10(6):499–500. https://doi.org/10.1016/s1474-4422(11)70112-0 **(author reply 500-1)**.
28. Cramer SC. Listening to fluoxetine: a hot message from the FLAME trial of poststroke motor recovery. Int J Stroke. 2011;6(4):315–6. https://doi.org/10.1111/j.1747-4949.2011.00618.x.
29. Adams HP Jr, Robinson RG. Improving recovery after stroke: a role for antidepressant medications? Stroke. 2012;43(10):2829–32. https://doi.org/10.1161/STROKEAHA.111.640524.
30. Marshall RS. Should every patient with stroke be on selective serotonin reuptake inhibitors? no. Stroke. 2012;43(11):3152–3. https://doi.org/10.1161/STROKEAHA.112.657627.
31. Selim MH, Molina CA. Poststroke treatment with selective serotonin reuptake inhibitors: a journey from sadness to motor recovery. Stroke. 2012;43(11):3154–5. https://doi.org/10.1161/STROKEAHA.112.657635.
32. Hackam DG, Mrkobrada M. Selective serotonin reuptake inhibitors and brain hemorrhage: a meta-analysis. Neurology. 2012;79(18):1862–5. https://doi.org/10.1212/WNL.0b013e318271f848.
33. Shin D, Oh YH, Eom CS, Park SM. Use of selective serotonin reuptake inhibitors and risk of stroke: a systematic review and meta-analysis. J Neurol. 2014;261(4):686–95. https://doi.org/10.1007/s00415-014-7251-9.
34. de Abajo FJ, Rodriguez LA, Montero D. Association between selective serotonin reuptake inhibitors and upper gastrointestinal bleeding: population based case-control study. BMJ. 1999;319(7217):1106–9.
35. Dalton SO, Johansen C, Mellemkjaer L, Norgard B, Sorensen HT, Olsen JH. Use of selective serotonin reuptake inhibitors and risk of upper gastrointestinal tract bleeding: a population-based cohort study. Arch Intern Med. 2003;163(1):59–64. https://doi.org/10.1001/archinte.163.1.59.
36. Dalton SO, Sorensen HT, Johansen C. SSRIs and upper gastrointestinal bleeding: what is known and how should it influence prescribing? CNS Drugs. 2006;20(2):143–51. https://doi.org/10.2165/00023210-200620020-00005.
37. Mortensen JK, Larsson H, Johnsen SP, Andersen G. Post stroke use of selective serotonin reuptake inhibitors and clinical outcome among patients with ischemic stroke: a nationwide propensity score-matched follow-up study. Stroke. 2013;44(2):420–6. https://doi.org/10.1161/STROKEAHA.112.674242.
38. John S, Donnelly M, Uchino K. Catastrophic reversible cerebral vasoconstriction syndrome associated with serotonin syndrome. Headache. 2013;53(9):1482–7. https://doi.org/10.1111/head.12202.
39. Singhal AB, Caviness VS, Begleiter AF, Mark EJ, Rordorf G, Koroshetz WJ. Cerebral vasoconstriction and stroke after use of serotonergic drugs. Neurology. 2002;58(1):130–3.
40. Juang HT, Chen PC, Chien KL. Using antidepressants and the risk of stroke recurrence: report from a national representative cohort study. BMC Neurol. 2015;15:86. https://doi.org/10.1186/s12883-015-0345-x.
41. Wang MT, Chu CL, Yeh CB, Chang LC, Malone DC, Liou JT. Antidepressant use and risk of recurrent stroke: a population-based nested case-control study. J Clin Psychiatry. 2015;76(7):e877–85. https://doi.org/10.4088/JCP.14m09134.
42. Lippi G, Montagnana M, Favaloro EJ, Franchini M. Mental depression and cardiovascular disease: a multifaceted, bidirectional association. Semin Thromb Hemost. 2009;35(3):325–36. https://doi.org/10.1055/s-0029-1222611.
43. He Y, Cai Z, Zeng S, et al. Effect of fluoxetine on three-year recurrence in acute ischemic stroke: a randomized controlled clinical study. Clin Neurol Neurosurg. 2018;168:1–6.
44. Schellen C, Ferrari J, Lang W, Sykora M. VISTA Collaborators. Effects of SSRI exposure on hemorrhagic complications and outcome following thrombolysis in ischemic stroke. Int J Stroke. 2017. https://doi.org/10.1177/1747493017743055.
45. Scheitz JF, Turc G, Kujala L, et al. Intracerebral hemorrhage and outcome after thrombolysis in stroke patients using selective serotonin-reuptake inhibitors. Stroke. 2017;48(12):3239–44. https://doi.org/10.1161/STROKEAHA.117.018377.
46. Miedema I, Horvath KM, Uyttenboogaart M, et al. Effect of selective serotonin re-uptake inhibitors (SSRIs) on functional outcome in patients with acute ischemic stroke treated with tPA. J Neurol Sci. 2010;293(1–2):65–7. https://doi.org/10.1016/j.jns.2010.03.004.
47. Towfighi A, Ovbiagele B, El Husseini N, et al. Poststroke depression: a scientific statement for healthcare professionals from the american heart association/american stroke association. Stroke. 2017;48(2):e30–43. https://doi.org/10.1161/STR.0000000000000113.
48. Hackett ML, Anderson CS, House A, Xia J. Interventions for treating depression after stroke. Cochrane Database Syst Rev. 2008. https://doi.org/10.1002/14651858.cd003437.pub3.
49. Hackett ML, Anderson CS, House A, Halteh C. Interventions for preventing depression after stroke. Cochrane Database Syst Rev. 2008. https://doi.org/10.1002/14651858.cd003689.pub3.
50. Pinto CB, Saleh Velez FG, Lopes F, et al. SSRI and motor recovery in stroke: reestablishment of inhibitory neural network tonus. Front Neurosci. 2017;11:637. https://doi.org/10.3389/fnins.2017.00637.
51. Sale A, Hannan AJ, Maffei L, Guzzetta A. Noninvasive strategies to optimise brain plasticity: from basic research to clinical perspectives. Neural Plast. 2013;2013:863970. https://doi.org/10.1155/2013/863970.
52. Li WL, Cai HH, Wang B, et al. Chronic fluoxetine treatment improves ischemia-induced spatial cognitive deficits through increasing hippocampal neurogenesis after stroke. J Neurosci Res. 2009;87(1):112–22. https://doi.org/10.1002/jnr.21829.
53. Ma L, Lu ZN, Hu P, Yao CJ. Neuroprotective effect of escitalopram oxalate in rats with chronic hypoperfusion. J Huazhong Univ Sci Technolog Med Sci. 2015;35(4):514–8. https://doi.org/10.1007/s11596-015-1462-x.
54. Shimizu E, Hashimoto K, Okamura N, et al. Alterations of serum levels of brain-derived neurotrophic factor (BDNF) in depressed patients with or without antidepressants. Biol Psychiatry. 2003;54(1):70–5.
55. Fournier NM, Duman RS. Role of vascular endothelial growth factor in adult hippocampal neurogenesis: implications for the

pathophysiology and treatment of depression. Behav Brain Res. 2012;227(2):440–9. https://doi.org/10.1016/j.bbr.2011.04.022.
56. Lim CM, Kim SW, Park JY, Kim C, Yoon SH, Lee JK. Fluoxetine affords robust neuroprotection in the postischemic brain via its anti-inflammatory effect. J Neurosci Res. 2009;87(4):1037–45. https://doi.org/10.1002/jnr.21899.
57. Shan H, Bian Y, Shu Z, et al. Fluoxetine protects against IL-1beta-induced neuronal apoptosis via downregulation of p53. Neuropharmacology. 2016;107:68–78.
58. Kraglund KL, Mortensen JK, Grove EL, Johnsen SP, Andersen G. TALOS: a multicenter, randomized, double-blind, placebo-controlled trial to test the effects of citalopram in patients with acute stroke. Int J Stroke. 2015;10(6):985–7. https://doi.org/10.1111/ijs.12485.
59. Mead G, Hackett ML, Lundstrom E, Murray V, Hankey GJ, Dennis M. The FOCUS, AFFINITY and EFFECTS trials studying the effect(s) of fluoxetine in patients with a recent stroke: A study protocol for three multicentre randomised controlled trials. Trials. 2015. https://doi.org/10.1186/s13063-015-0864-1.
60. Mortensen JK, Kraglund KL, Johnsen SP, Mors O, Andersen G, Buttenschon HN. The serotonin transporter gene polymorphisms and risk of ischemic stroke. Cerebrovasc Dis. 2018;45(3–4):187–92. https://doi.org/10.1159/000488364.
61. Kohen R, Cain KC, Mitchell PH, et al. Association of serotonin transporter gene polymorphisms with poststroke depression. Arch Gen Psychiatry. 2008;65(11):1296–302.
62. Lee EJ, Oh MS, Kim JS, et al. Serotonin transporter gene polymorphisms may be associated with poststroke neurological recovery after escitalopram use. J Neurol Neurosurg Psychiatry. 2018;89(3):271–6. https://doi.org/10.1136/jnnp-2017-316882.
63. Gelernter J, Cubells JF, Kidd JR, Pakstis AJ, Kidd KK. Population studies of polymorphisms of the serotonin transporter protein gene. Am J Med Genet. 1999;88(1):61–6. https://doi.org/10.1002/(SICI)1096-8628(19990205)88:13.0.CO;2-K.