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ORIGINAL RESEARCH ARTICLE

Use of Selective Serotonin Reuptake Inhibitors and Outcomes in Stroke Rehabilitation: A Prospective Observational Pilot Cohort Study

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Abstract

Purpose The aim of this study was to examine the association between selective serotonin reuptake inhibitor (SSRI) therapy and rehabilitation outcomes, specifically disability and quality of life (QOL), in a real-world setting of multi-ethnic Asian patients with first-ever stroke.

Methods In this prospective observational pilot cohort study, we included patients with first-ever stroke admitted to two inpatient rehabilitation centres in Singapore between January and July 2018. Outcomes were measured using Functional Independence Measure (FIM)-motor scale, modified Barthel Index (MBI) and the Stroke and Aphasia Quality of Life Scale-39 generic (SAQOL-39g) questionnaire. Linear regression was used to assess the association between SSRI therapy and outcomes. Regression coefficients and 95% confidence intervals (CIs) were reported.

Results Among 57 patients included for analyses, 38.6% received SSRIs. Although SSRI therapy was significantly associated with gains in MBI (coefficient 11.35; 95% CI 0.21–22.50) and SAQOL-39g overall score (coefficient 0.45; 95% CI 0.05–0.85) based on simple linear regression, no significant association between SSRI therapy and any of the investigated outcomes was found after adjustment for confounders. However, an increase in the mean number of physiotherapy and occupational therapy (PT/OT) sessions per day significantly improved FIM-motor (coefficient 16.86; 95% CI 2.64–31.07) and MBI (coefficient 22.79; 95% CI 2.35–43.23) scores.

Conclusion SSRI therapy did not improve disability and QOL in multi-ethnic Asian patients with first-ever stroke undergoing rehabilitation.

1 Introduction

Stroke is a leading cause of mortality and morbidity worldwide [1, 2]. About half of survivors will experience long-term residual disability [3], placing an enormous burden on healthcare services and caregivers. Substantial advances have been made in the past few decades in terms of primary and secondary prevention of stroke, mainly via control of cardiovascular risk factors [4–6]. However, little progress has been made to identify novel treatments that may reduce neurological impairments, disability and dependency post-stroke [7].

Previous studies have demonstrated that pharmacological therapies may have the potential to promote stroke recovery [8–13] by modulating the ability of the brain to reorganize itself through plasticity mechanisms [14–18]. Among the investigated agents, selective serotonin reuptake inhibitors (SSRIs) have shown promising effects in reducing inflammation [19, 20], stimulating angiogenesis and neurogenesis [21–24], and secretion of growth factors that augment cortical reorganization [25, 26]. In addition, the Fluoxetine for Motor Recovery after Acute Ischemic Stroke (FLAME) trial conducted in France had reported fluoxetine to be effective for motor recovery in Caucasian ischaemic stroke patients after 3 months of treatment [27]. However, due to the trial's stringent inclusion and exclusion criteria, characteristics of

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Key Points

Use of selective serotonin reuptake inhibitors during rehabilitation did not improve disability and quality of life in multi-ethnic Asian patients with first-ever stroke based on this prospective observational pilot cohort study.

As physiotherapy and occupational therapy were found to enhance post-stroke recovery, increasing the frequency of such therapies (as tolerated) should be considered for all stroke patients.

Although ongoing multi-centre trials, namely AFFINITY and EFFECTS, should provide more conclusive evidence on the efficacy of fluoxetine for stroke recovery in Caucasian populations, further research should also be conducted in Asian populations.

the study participants were unlikely to be reflective of the general stroke population [27], limiting the usefulness of results in real-world clinical practice. To date, there is still no routine pharmacotherapy recommended to aid stroke rehabilitation [28].

Limited research has been performed to investigate the utilization of potentially beneficial drugs such as SSRIs in actual clinical practice, outside of trials [29, 30]. Results from one multi-centre observational study in Switzerland had reported that 55.4% of stroke patients were prescribed with agents that could enhance recovery, including SSRIs, levodopa, serotonin-noradrenaline reuptake inhibitors and cholinesterase inhibitors [30]. Based on a previous systematic review and meta-analysis of randomized controlled trials (RCTs), SSRIs showed the most evidence for enhancing functional outcomes (e.g., disability) after stroke [31]. Observational studies performed in real-world settings can also contribute valuable insights on drug effectiveness that supplement findings from RCTs. In this observational study, we aimed to examine the association between SSRI therapy and rehabilitation outcomes, specifically disability and quality of life (QOL), in a rehabilitation setting of multi-ethnic Asian patients with first-ever stroke.

2 Methods

2.1 Study Design, Setting, Study Population and Data Sources

This prospective observational pilot cohort study was conducted in two rehabilitation centres located within a 360-bedded community hospital in Singapore. We included patients with first-ever ischaemic and haemorrhagic stroke aged ≥ 21 years admitted for their first inpatient rehabilitation between January and July 2018. Patients who were not Singapore citizens or permanent residents, with unknown stroke cause, transferred from another rehabilitation centre, unable to comprehend English or Mandarin, or who had incomplete follow-up (e.g. transferred back to acute hospitals) were excluded. Written informed consent was obtained from all enrolled patients. To avoid selection bias due to inclusion of patients with milder stroke, consent was taken from the legally acceptable representative or designated proxy for those who were incapable of consenting due to post-stroke cognitive impairment or severe comprehension deficits (as determined by the physician-in-charge).

A standardized form was used for data collection from hospital case notes and electronic medical records. Information extracted included patient demographics, medical history, premorbid condition prior to stroke, smoking status, drugs prescribed during rehabilitation, therapies received (i.e. physiotherapy, occupational therapy or speech therapy), length of stay (LOS) and rehabilitation outcome measures. We recorded whether the patients were on secondary stroke preventive medications (anti-platelets, oral anti-coagulants or statins) and central nervous system (CNS) drugs including anti-depressants, hypnotics, anti-convulsants, anti-psychotics, anti-Parkinson agents and piracetam, as they may influence stroke recovery [31]. Patients were followed up from admission to discharge from the rehabilitation centres. The study protocol was approved by the National Healthcare Group Domain Specific Review Board (Reference Number: 2016/01206).

2.2 Drug Exposure and Rehabilitation Outcome Measures

We compared outcomes between patients who received SSRIs for any indication during rehabilitation (SSRI group) and those who were not prescribed SSRI therapy (non-SSRI group). All patients, irrespective of SSRI exposure, received standard care based on their individual condition.

2.2.1 Primary Outcome

The primary outcome of interest was the absolute change in Functional Independence Measure (FIM) motor score during rehabilitation. FIM is a widely used clinician-administered measure of disability, with high reliability, validity and responsiveness [32–36]. The FIM-motor domain has 13 items that quantifies the level of function in self-care, sphincter control, transfers and locomotion [37]. Each item is rated on a scale of 1–7, with a higher score indicating less disability.

2.2.2 Secondary Outcomes

Secondary outcomes of our study were (i) absolute change in Shah-modified Barthel Index (MBI) score, (ii) rehabilitation effectiveness, (iii) rehabilitation efficiency, and (iv) absolute change in overall, physical domain, communication domain and psychosocial domain scores of the Stroke and Aphasia Quality of Life Scale-39 generic (SAQOL-39g) questionnaire.

2.2.3 Measures of Disability

The MBI is a validated instrument that measures ten basic aspects of activities in daily living (ADL) [38]. The maximum score is 100 and higher scores correspond to lower disability.

The FIM-motor or MBI scores were routinely assessed at admission and discharge by a multi-disciplinary team involved in the care of the patients. As the two rehabilitation centres used different disability measures (i.e. one centre used the FIM-motor, while the other centre used the MBI), conversion between the scores were performed using crosswalk tables from a published Korean study [39]. The equated test items from the FIM-motor and Korean version of the MBI (K-MBI) had demonstrated good psychometric properties in the three distinct constructs of self-care, involuntary movement and mobility [39]. The K-MBI was previously developed from MBI via translation from English to Korean [40].

Both rehabilitation effectiveness and efficiency were calculated using FIM-motor and MBI scores, respectively. For rehabilitation effectiveness, it was defined as the percentage of functional improvement achieved during rehabilitation and calculated using the following equation [41, 42]:

$$\text{Rehabilitation effectiveness (\%)} = \frac{\text{Discharge score} - \text{Admission score}}{\text{Maximum score} - \text{Admission score}} \times 100\%.$$

Rehabilitation efficiency was defined as the rate of functional recovery during rehabilitation and calculated using the following equation [41, 42]:

$$\text{Rehabilitation efficiency per day} = \frac{\text{Discharge score} - \text{Admission score}}{\text{Rehabilitation LOS}}.$$

As the rehabilitation efficiency value obtained per day was small, it was subsequently multiplied by 30 to obtain a value per 30 days.

2.2.4 Measure of Quality of Life (QOL)

Health-related QOL is a multi-dimensional concept that encompasses an individual's subjective evaluation of their physical, mental and social functioning [43]. The SAQOL-39g is a stroke-specific QOL scale, consisting of 39 items, each scored from 1 to 5 [44]. The SAQOL-39g overall and individual domain (physical, communication and psychosocial) scores are mean values calculated by adding up scores for the relevant items and dividing by the number of items. Higher scores indicate better QOL. Both the English and Chinese versions of SAQOL-39g used in this study had been previously validated, demonstrating good internal consistency, reliability and validity in Singapore stroke patients with and without aphasia [45]. Enrolled study participants or their proxies were interviewed at admission and discharge using a standardized printed questionnaire and scoring sheet by the same study investigator. Although self-reported QOL is generally more accurate than proxy report, using SAQOL-39g responses from proxies have been suggested to be a viable alternative to self-report [46].

2.3 Sample Size Calculation

Sample size estimation was based on the number to detect the minimal clinically important difference (MCID) of 17 on the FIM-motor scale between groups [47]. Assuming an alpha value of 0.05, power of 0.9 and expected standard deviation (SD) of 16.1 [48], the estimated minimum target sample size required to evaluate the primary outcome of disability on the FIM-motor scale was 40 patients (20 in the SSRI and non-SSRI groups, respectively).

2.4 Statistical Analysis

Categorical variables were presented as *n* (%) and continuous variables as mean ± SD. Patient characteristics, baseline rehabilitation measures, drug utilization and therapies received during rehabilitation were compared between the SSRI and non-SSRI groups using the Chi-square test or Fisher's exact test for categorical variables, and Student's *t* test for continuous variables. Categorization of continuous variables was avoided, except for number of comorbidities in which we considered the median as the cut-off for dichotomization. For the SSRI group, we also tabulated the documented indication, total duration and proportion of days during rehabilitation on SSRIs.

The within-group changes in scores from baseline for FIM-motor, MBI and SAQOL-39g were compared using paired t-test. Changes in scores from baseline for FIM-motor, MBI and SAQOL-39g, as well as rehabilitation effectiveness and rehabilitation efficiency, were compared between the SSRI and non-SSRI groups using Student's *t* test. Simple and multiple linear regression analyses were conducted to assess the association between use of SSRIs

and rehabilitation outcomes. Confounders (e.g. age, premorbid condition, comorbidities, physiotherapy and occupational therapy) to be adjusted for in the multiple linear regression models were identified from the univariable analyses based on a cut-off p value of 0.05. The respective baseline score was also included for adjustment to improve the precision of estimates in the multiple linear regression models [49]. Listwise deletion was used to handle missing data in regression analyses.

As an earlier systematic review and meta-analysis (which included the FLAME trial) had showed fluoxetine to be promising in enhancing post-stroke recovery [31], subgroup analyses were conducted by restricting to patients on fluoxetine in the SSRI group. Other reasons for choosing fluoxetine were that it is a commonly prescribed SSRI, with a good safety profile and is generally well tolerated in patients [3]. Sensitivity analyses were also conducted to evaluate the association between SSRI use and SAQOL-39g scores by performing separate analyses for patients who completed the questionnaire by self-report and by proxy, respectively.

Regression coefficients and corresponding 95% confidence intervals (CIs) were reported. A p value of <0.05 was considered statistically significant. All statistical analyses were conducted using Stata 13.0 (StataCorp LP, College Station, TX, USA).

3 Results

3.1 Characteristics of Study Population and Use of SSRI Therapy

Between January and July 2018, 214 patients with first-ever stroke were assessed for study eligibility and 76 were enrolled (Fig. 1). Nineteen patients were subsequently excluded due to inability to complete the SAQOL-39g at admission ($n=2$), transfer back to acute hospitals ($n=16$) and unwillingness to continue study participation ($n=1$). Among the 57 patients who successfully completed the SAQOL-39g at both admission and discharge, 22 (38.6%) were prescribed SSRIs. The non-SSRI and SSRI groups were largely balanced in terms of demographic characteristics, baseline rehabilitation measures and drug utilization during rehabilitation (Table 1). However, the mean age was lower in the SSRI group (59.3 ± 12.9 vs 67.9 ± 13.7 years; $p=0.022$). On average, the SSRI group received more physiotherapy, occupational therapy and speech therapy sessions compared with the non-SSRI group ($p<0.05$). Patients in the SSRI group were also more likely to be ADL-independent prior to stroke (100% vs 82.9% of patients; $p=0.072$), without atrial fibrillation (0.0% vs 17.1% of patients; $p=0.072$), and with lower mean baseline FIM-motor (37.5 ± 18.7 vs 47.4 ± 21.0; $p=0.077$) and MBI (36.1 ± 29.0 vs 49.9 ± 31.4; $p=0.101$) scores. In the SSRI group, the SSRIs were prescribed to aid motor recovery and/or to improve mood (Table 2). SSRI therapy was prescribed for a mean of 31.4 ± 17.4 days and 80.6 ± 27.2% of the rehabilitation LOS (Table 2). Of the patients, 77.3% were prescribed fluoxetine, and the rest received either fluvoxamine (18.2%) or escitalopram (4.5%) (Fig. 2).

After restricting to patients on fluoxetine in the SSRI group, 52 patients were available for analysis (Supplementary Table A, see electronic supplementary material [ESM]). The non-SSRI and fluoxetine groups were largely similar in terms of demographic characteristics, baseline rehabilitation measures and drug utilization during rehabilitation. However, patients in the fluoxetine group may have received more physiotherapy, occupational therapy and speech therapy sessions. In the fluoxetine group, the therapy was prescribed on average for 30.7 ± 17.5 days (Supplementary Table B, see ESM). The mean proportion of days on fluoxetine therapy during rehabilitation was 82.1 ± 25.0%.

Patients who completed the SAQOL-39g via proxy were older, with poorer premorbid condition (i.e. requiring ADL assistance), had longer rehabilitation LOS, with lower baseline rehabilitation measures (including FIM-motor, MBI, SAQOL-39g overall and individual domain scores) and received more speech therapy sessions compared with those who completed the SAQOL-39g by self-report ($p<0.05$) (Supplementary Tables C and D, see ESM).

3.2 Rehabilitation Outcomes and Their Associations with SSRI Therapy

In the overall study population ($n=57$), both the non-SSRI and SSRI groups made significant improvements in FIM-motor, MBI and SAQOL-39g overall scores after rehabilitation (Table 3). In the simple linear regression models, use of SSRI therapy was significantly associated with gains in MBI (coefficient 11.35; 95% CI 0.21–22.50), SAQOL-39g overall (coefficient 0.45; 95% CI 0.05–0.85), SAQOL-39g communication domain (coefficient 0.63; 95% CI 0.16–1.09) and SAQOL-39g psychosocial domain (coefficient 0.46; 95% CI 0.02–0.89) scores. However, after adjustment for confounders, use of SSRI therapy was no longer significantly associated with any of the investigated rehabilitation outcomes. However, among the independent variables included for adjustment in multiple linear regression analyses, an increase in the number of physiotherapy and occupational therapy sessions per day was found to be significantly associated with improvements in FIM-motor (coefficient 16.86; 95% CI 2.64–31.07) and MBI (coefficient 22.79; 95% CI 2.35–43.23) scores, as well as their respective rehabilitation effectiveness (Supplementary Table E, see ESM).

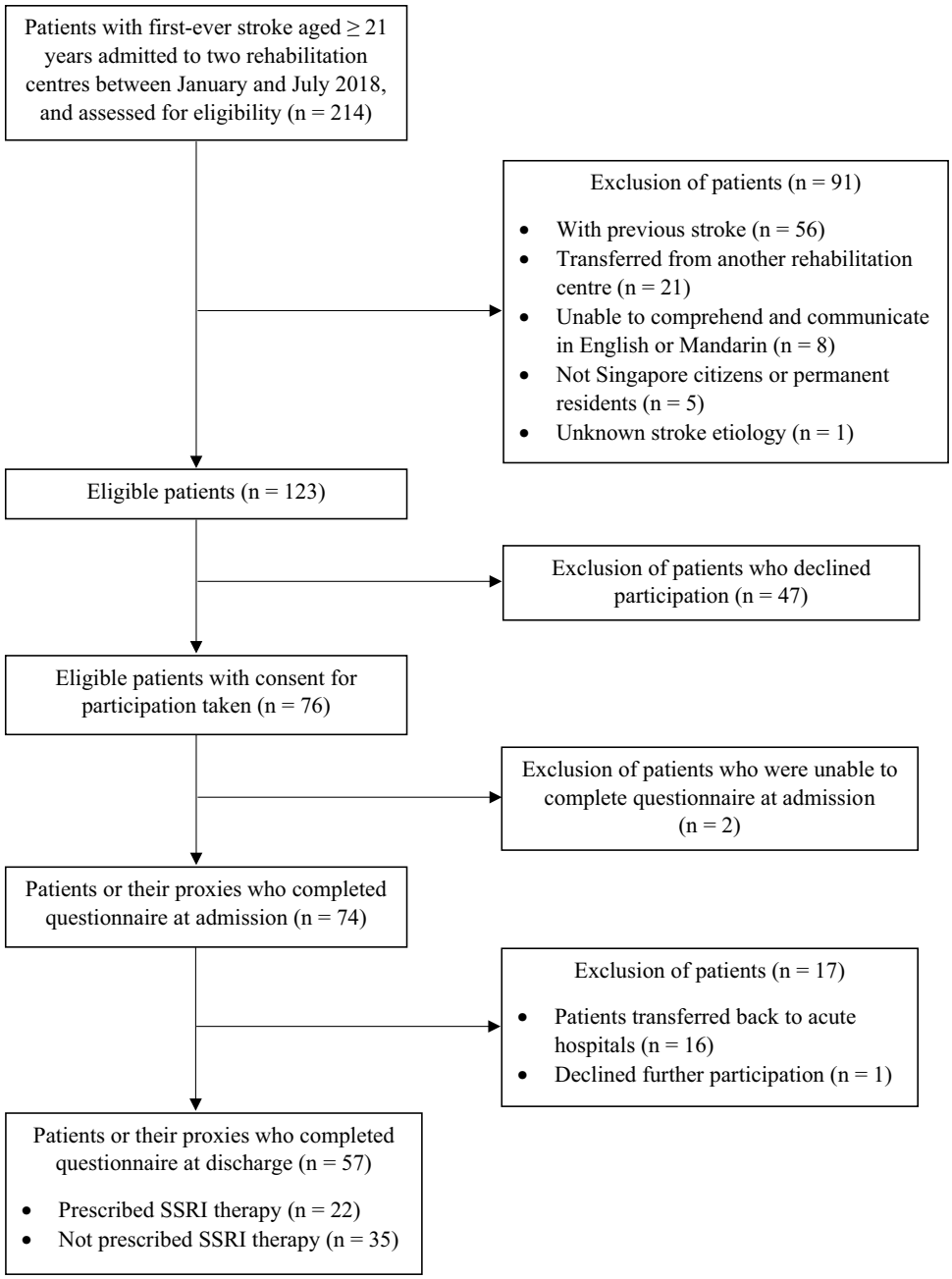

Fig. 1 Flow diagram of patient inclusion and exclusion. *SSRI* selective serotonin reuptake inhibitor

Similar results were observed in the analyses restricted to patients on fluoxetine in the SSRI group ($n = 52$). After adjustment, the regression models did not show that fluoxetine therapy was significantly associated with the rehabilitation outcomes (Supplementary Table F, see ESM). An increase in the number of physiotherapy and occupational therapy sessions per day was observed to be significantly associated with gains in FIM-motor and MBI scores, as well as their respective rehabilitation effectiveness and efficiency (Supplementary Table G, see ESM).

Among patients who completed the SAQOL-39g by self-report ($n = 39$), use of SSRIs was associated with significant improvements in SAQOL-39g overall, communication domain and psychosocial domain scores in the simple linear regression models (Supplementary Table H, see ESM). However, after adjustment, SSRI therapy did not significantly influence any aspect of the QOL (Supplementary Tables H and I, see ESM). Results from the multiple linear regression models were generally consistent with those for patients who completed the SAQOL-39g by proxy ($n = 18$) (Supplementary Tables J and K, see ESM), suggesting that findings after adjustment for confounders were robust with self-report and proxy report.

Table 1 Patient characteristics, baseline rehabilitation measures, drug utilization and therapies received during rehabilitation, stratified by use of selective serotonin reuptake inhibitors

	Total ($n=57$)	Non-SSRI group ($n=35$)	SSRI group ($n=22$)	p Value
Patient characteristics				
Male gender, *n* (%)	35 (61.4)	19 (54.3)	16 (72.7)	0.164
Age, mean ± SD	64.5 ± 13.9	67.9 ± 13.7	59.3 ± 12.9	0.022*
Ethnic group, *n* (%)				1.000
Chinese	48 (84.2)	29 (82.9)	19 (86.4)	
Non-Chinese	9 (15.8)	6 (17.1)	3 (13.6)	
Highest attained education, *n* (%)[a]				0.506
No formal qualification	10 (17.5)	8 (22.9)	2 (9.1)	
Primary	15 (26.3)	8 (22.9)	7 (31.8)	
Secondary	21 (36.8)	13 (37.1)	8 (36.4)	
Post-secondary	10 (17.5)	5 (14.3)	5 (22.7)	
Rehabilitation ward class, *n* (%)[b]				0.361
Private (Class A and B1)	12 (21.1)	6 (17.1)	6 (27.3)	
Subsidized (Class B2 and C)	45 (78.9)	29 (82.9)	16 (72.7)	
Stroke type, *n* (%)				0.682
Ischaemic	37 (64.9)	22 (62.9)	15 (68.2)	
Haemorrhagic[c]	20 (35.1)	13 (37.1)	7 (31.8)	
Premorbid condition, *n* (%)				0.072
ADL-independent	51 (89.5)	29 (82.9)	22 (100.0)	
ADL-assisted	6 (10.5)	6 (17.1)	0 (0.0)	
Comorbidities, *n* (%)				
Transient ischaemic attack	1 (1.8)	1 (2.9)	0 (0.0)	1.000
Hypertension	41 (71.9)	25 (71.4)	16 (72.7)	0.915
Hyperlipidaemia	30 (52.6)	20 (57.1)	10 (45.5)	0.390
Diabetes mellitus	21 (36.8)	11 (31.4)	10 (45.5)	0.285
Atrial fibrillation	6 (10.5)	6 (17.1)	0 (0.0)	0.072
Ischaemic heart disease	10 (17.5)	7 (20.0)	3 (13.6)	0.725
Valvular heart disease	1 (1.8)	1 (2.9)	0 (0.0)	1.000
Peripheral vascular disease	9 (15.8)	7 (20.0)	2 (9.1)	0.458
History of depression	2 (3.5)	1 (2.9)	1 (4.5)	1.000
Post-stroke depression	4 (7.0)	2 (5.7)	2 (9.1)	0.635
Dementia	2 (3.5)	2 (5.7)	0 (0.0)	0.518
Number of comorbidities, *n* (%)				0.533
≤ 2	36 (63.2)	21 (60.0)	15 (68.2)	
> 2	21 (36.8)	14 (40.0)	7 (31.8)	
Smoking status, *n* (%)[d]				0.313
Current or ex-smoker	12 (21.1)	6 (17.1)	6 (27.3)	
Non-smoker	44 (77.2)	29 (82.9)	15 (68.2)	
Alcohol dependence, *n* (%)	3 (5.3)	3 (8.6)	0 (0.0)	0.276
Acute hospital LOS, mean ± SD[e]	14.1 ± 10.5	14.2 ± 11.8	13.7 ± 8.4	0.875
Rehabilitation LOS, mean ± SD	32.1 ± 18.3	28.7 ± 17.7	37.6 ± 18.4	0.073
Baseline rehabilitation measures				
FIM-motor score, mean ± SD[f]	43.6 ± 20.5	47.4 ± 21.0	37.5 ± 18.7	0.077
MBI score, mean ± SD[g]	44.6 ± 31.0	49.9 ± 31.4	36.1 ± 29.0	0.101
SAQOL-39g overall score, mean ± SD[h]	3.0 ± 1.0	3.2 ± 1.0	2.8 ± 1.0	0.136
Physical domain[h]	2.8 ± 1.3	2.9 ± 1.4	2.5 ± 1.3	0.225
Communication domain[h]	3.6 ± 1.4	3.8 ± 1.3	3.4 ± 1.5	0.275
Psychosocial domain[h]	3.0 ± 0.9	3.1 ± 0.8	2.8 ± 0.9	0.092

Table 1 (continued)

	Total ($n=57$)	Non-SSRI group ($n=35$)	SSRI group ($n=22$)	p Value
Drug utilization during rehabilitation, *n* (%)				
Anti-thrombotics	37 (64.9)	22 (62.9)	15 (68.2)	0.682
Anti-platelets	34 (59.6)	19 (54.3)	15 (68.2)	0.298
Oral anti-coagulants	3 (5.3)	3 (8.6)	0 (0.0)	0.276
Statins	45 (78.9)	29 (82.9)	16 (72.7)	0.361
Hypnotics[i]	5 (8.8)	2 (5.7)	3 (13.6)	0.364
Anti-convulsants	5 (8.8)	3 (8.6)	2 (9.1)	1.000
Anti-psychotics	3 (5.3)	2 (5.7)	1 (4.5)	1.000
Anti-Parkinson agents	2 (3.5)	1 (2.9)	1 (4.5)	1.000
Piracetam	4 (7.0)	1 (2.9)	3 (13.6)	0.288
Other non-SSRI anti-depressants	4 (7.0)	2 (5.7)	2 (9.1)	0.635
Therapies received during rehabilitation				
PT and OT, *n* (%)	57 (100.0)	35 (100.0)	22 (100.0)	–
Total number of PT and OT sessions, mean ± SD	36.4 ± 21.9	30.2 ± 20.3	46.3 ± 21.3	0.006*
Number of PT and OT sessions per day, mean ± SD[j]	1.1 ± 0.3	1.0 ± 0.3	1.2 ± 0.1	< 0.001*
Speech therapy, *n* (%)	35 (61.4)	19 (54.3)	16 (72.7)	0.164
Total number of speech therapy sessions, mean ± SD	7.1 ± 8.4	4.5 ± 5.8	11.4 ± 10.1	0.007*
Number of speech therapy sessions per day, mean ± SD[k]	0.2 ± 0.2	0.1 ± 0.2	0.3 ± 0.2	0.014*

ADL activities of daily living, *AMK-THKH* Ang Mo Kio – Thye Hua Kwan Hospital, *FIM* Functional Independence Measure, *LOS* length of stay, *MBI* Modified Barthel Index, *OT* occupational therapy, *PT* physiotherapy, *SAQOL-39g* Stroke and Aphasia Quality of Life-39 generic questionnaire, *SD* standard deviation, *SSRI* selective serotonin reuptake inhibitor, *TTSH* Tan Tock Seng Hospital

*$p < 0.05$

[a]Missing data for one patient in non-SSRI group

[b]Patients admitted into Class A and Class B1 wards were considered as private patients, while those in Class B2 and Class C wards were considered as subsidized patients

[c]Comprised intracerebral and subarachnoid haemorrhage patients

[d]Missing data for one patient in SSRI group

[e]Prior to admission for rehabilitation

[f]MBI scores for 22 AMK-THKH patients were transformed to FIM-motor scores using crosswalk tables from a previous study [39]

[g]FIM-motor scores for 35 TTSH patients were transformed to MBI scores using crosswalk tables from a previous study [39]

[h]The SAQOL-39g overall score is a mean score and is calculated by adding up scores for all the items and dividing by the number of items. Domain scores are calculated in the same way. Overall, domain and item mean scores can vary from 1 to 5

[i]Includes benzodiazepines and non-benzodiazepines

[j]Calculated using total number of PT and OT sessions divided by the rehabilitation LOS

[k]Calculated using total number of speech therapy sessions divided by the rehabilitation LOS

4 Discussion

This prospective, observational, pilot cohort study had evaluated the association between SSRI therapy and outcomes related to disability and QOL in a real-world setting of patients with first-ever stroke undergoing rehabilitation in Singapore. Among the 57 study participants, 38.6% were on SSRIs. SSRI therapy was used predominantly to aid in motor recovery. On average, SSRIs were prescribed for 31.4 ± 17.4 days and 80.6 ± 27.2% of the rehabilitation LOS. Patients prescribed with SSRIs were younger and received more rehabilitation therapies compared with those not on SSRIs. Although SSRI therapy appeared to be beneficial in improving rehabilitation outcomes, differences between the SSRI and non-SSRI groups were no longer significant after adjustment for confounders. Multiple linear regression results were consistent in subgroup analyses conducted among patients on fluoxetine in the SSRI group.

Since the publication of results from the FLAME trial [27], use of SSRIs in stroke rehabilitation has generated considerable interest. In the FLAME trial, 118 ischaemic stroke patients with motor deficit (Fugl-Meyer motor score, FMMS ≤ 55) were randomized to receive fluoxetine or placebo [27]. At the end of 90 days, the improvement in motor function from baseline was significantly higher in the fluoxetine group. Although results from the trial are promising,

Table 2 Documented indication, duration and proportion of days on selective serotonin reuptake inhibitors for patients prescribed them during rehabilitation

	Total ($n=22$)
Documented indication of SSRIs, *n* (%)	
Motor recovery	15 (68.2)[a]
Low mood or depression	7 (31.8)[a]
Unspecified	2 (9.1)[a]
Duration of SSRI therapy in days	
Mean ± SD	31.4 ± 17.4
Median (IQR)	34.0 (20.0–43.0)
Proportion of days on SSRI therapy during rehabilitation (%)[b]	
Mean ± SD	80.6 ± 27.2
Median (IQR)	90.8 (77.3–100.0)

FIM Functional Independence Measure, *IQR* interquartile range, *SD* standard deviation, *SSRI* selective serotonin reuptake inhibitor

[a]As SSRIs were used for both motor recovery and low mood/depression in two patients, the percentages do not add up to 100%

[b]Not all patients were on SSRI therapy for the entire duration of rehabilitation

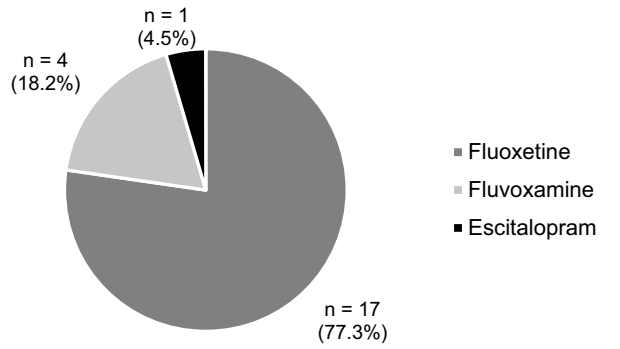

Fig. 2 Type of selective serotonin reuptake inhibitor used for patients prescribed them during rehabilitation ($n=22$)

the current evidence for SSRI therapy to augment post-stroke recovery are still not compelling enough for stroke guidelines to recommend its routine use in clinical practice [28]. In our study, SSRI therapy was prescribed for about a third of study participants undergoing stroke rehabilitation. Among the majority of patients who received SSRIs (68.2%), the documented drug indication was for improvement of motor function. A drug utilization study conducted in Switzerland had reported a similar proportion of stroke patients (26.9%) being prescribed SSRIs [30]. However, unlike our study, the use of SSRIs was mostly for treatment of depressive symptoms instead. The uncertainty over the benefits of SSRI therapy in promoting stroke recovery could explain the observed difference in intended use of pharmacotherapy.

Our study has provided insights into the characteristics of stroke rehabilitation patients whom physicians may perceive as more likely to benefit from SSRI therapy. In addition to being younger, patients in the SSRI group may have a better premorbid condition (i.e. ADL-independent prior to stroke), with no atrial fibrillation, and with greater disability (lower baseline FIM-motor or MBI score) at admission for rehabilitation. Previous studies have reported that although younger age and better premorbid function are predictive of more favourable post-stroke outcomes, severe disability at admission is associated with worse functional outcome at discharge from rehabilitation [50–53]. Based on results from the FLAME trial, which showed that fluoxetine is beneficial in patients with more severe motor impairment (FMMS ≤ 55) [27], physicians may have prescribed SSRIs with the intention of maximizing the likelihood of functional recovery during rehabilitation in patients with greater baseline disability. For patients with atrial fibrillation, clinicians avoid prescribing SSRIs due to the possible risk of promoting QT prolongation and ventricular arrhythmia including torsade de pointes, which can be potentially life-threatening [54].

Previous research have indicated that SSRIs may have the potential to improve motor function, reduce disability (regardless of depression status) and enhance QOL post-stroke [31, 55]. These favourable effects could be attributed to the facilitation of motor output by the brain serotoninergic system [56] and modulation of inhibitory neural activity to promote motor learning [57]. However, findings from our study did not detect a significant association between SSRI therapy and stroke rehabilitation outcomes measured using FIM-motor, MBI and SAQOL-39g scores. Several reasons could be proposed to explain this discrepancy. Firstly, the use of SSRIs may only be useful in certain patient subgroups. For example, in the FLAME trial, patients were excluded if they had haemorrhagic stroke, severe neurological impairment (National Institutes of Health Stroke Scale, NIHSS score > 20), substantial premorbid disability, severe aphasia or depression [27]. The average baseline stroke severity of patients included in most other trials that demonstrated a positive effect of SSRIs on disability was moderate based on a systematic review [31]. It had been suggested that the likelihood of detecting a clinical benefit would be greater if studies included patients with moderate baseline stroke severity and excluded those with very mild or very severe stroke [58]. In contrast, our study was an observational study in a regular inpatient rehabilitation setting and with minimal patient selection by study investigators. In addition, as the mean acute hospital LOS of the patients in our study was 14 days, many patients were likely not started on SSRIs within the first week of stroke, which may have diminished the effectiveness of the therapy [59]. Secondly, the use of disability and QOL scales in our study may not be sensitive

Table 3 Rehabilitation outcomes of study participants and their associations with use of selective serotonin reuptake inhibitors using simple and multiple linear regression

Outcome	Non-SSRI group ($n=35$)			SSRI group ($n=22$)			Simple linear regression	Multiple linear regression[h]
	Baseline, mean ± SD	Discharge, mean ± SD	Mean change from baseline (95% CI)[a]	Baseline, mean ± SD	Discharge, mean ± SD	Mean change from baseline (95% CI)[a]	Regression coefficient (95% CI)	Regression coefficient (95% CI)
FIM-motor score[b]	47.4 ± 21.0	64.6 ± 21.8	17.20 (12.94 to 21.46)*	37.5 ± 18.7	60.9 ± 20.6	23.36 (16.82 to 29.91)*	6.16 (− 1.12 to 13.45)	− 1.44 (− 9.08 to 6.21)
Rehabilitation effectiveness (%)[c]	NA	NA	45.78 (35.40 to 56.16)	NA	NA	46.07 (33.99 to 58.14)	0.29 (− 15.59 to 16.16)	− 8.79 (− 23.90 to 6.33)
Rehabilitation efficiency (per 30 days)[d]	NA	NA	22.25 (15.72 to 28.78)	NA	NA	22.51 (15.09 to 29.93)	0.26 (− 9.65 to 10.17)	− 4.93 (− 15.79 to 5.92)
MBI score[e]	49.9 ± 31.4	73.5 ± 29.9	23.56 (17.05 to 30.06)*	36.1 ± 29.0	71.0 ± 27.4	34.91 (24.87 to 44.95)*	11.35 (0.21 to 22.50)*	− 0.76 (− 11.84 to 10.31)
Rehabilitation effectiveness (%)[c]	NA	NA	55.03 (42.75 to 67.32)[f]	NA	NA	58.95 (46.36 to 71.54)	3.92 (− 14.04 to 21.87)	− 8.53 (− 25.47 to 8.42)
Rehabilitation efficiency (per 30 days)[d]	NA	NA	27.52 (19.67 to 35.37)	NA	NA	32.42 (21.79 to 43.04)	4.90 (− 7.80 to 17.60)	− 4.27 (− 18.63 to 10.09)
SAQOL-39g overall score[g]	3.2 ± 1.0	3.6 ± 1.0	0.37 (0.18 to 0.56)*	2.8 ± 1.0	3.6 ± 1.0	0.82 (0.39 to 1.24)*	0.45 (0.05 to 0.85)*	0.15 (− 0.29 to 0.59)
Physical domain[g]	2.9 ± 1.4	3.6 ± 1.4	0.69 (0.42 to 0.97)*	2.5 ± 1.3	3.6 ± 1.2	1.07 (0.59 to 1.54)*	0.37 (− 0.12 to 0.87)	0.08 (− 0.47 to 0.64)
Communication domain[g]	3.8 ± 1.3	4.0 ± 1.3	0.20 (− 0.02 to 0.43)	3.4 ± 1.5	4.2 ± 1.1	0.83 (0.35 to 1.31)*	0.63 (0.16 to 1.09)*	0.29 (− 0.17 to 0.75)
Psychosocial domain[g]	3.1 ± 0.8	3.3 ± 0.9	0.14 (− 0.06 to 0.33)	2.8 ± 0.9	3.4 ± 0.9	0.59 (0.13 to 1.06)*	0.46 (0.02 to 0.89)*	0.14 (− 0.34 to 0.61)

AMK-THKH Ang Mo Kio-Thye Hua Kwan Hospital, *CI* confidence interval, *FIM* Functional Independence Measure, *LOS* length of stay, *MBI* Modified Barthel Index, *NA* not applicable, *SAQOL-39g* Stroke and Aphasia Quality of Life-39 generic questionnaire, *SD* standard deviation, *SSRI* selective serotonin reuptake inhibitor, *TTSH* Tan Tock Seng Hospital

*$p < 0.05$

[a]Paired t-test was performed to compare baseline and discharge scores (if applicable)

[b]MBI scores for 22 AMK-THKH patients were transformed to FIM-motor scores using crosswalk tables from a previous study [39]

[c]Calculated as a percentage u sing the change in score from baseline divided by the difference between maximum and baseline score

[d]Calculated using the change in score from baseline divided by the rehabilitation LOS, and multiplied by 30

[e]FIM-motor scores for 35 TTSH patients were transformed to MBI scores using crosswalk tables from a previous study [39]

[f]One patient was excluded from analysis as there was no difference between maximum (i.e. 100) and baseline score

[g]The SAQOL-39g overall score is a mean score and is calculated by adding up scores for all the items and dividing by the number of items. Domain scores are calculated in the same way. Overall, domain and item mean scores can vary from 1 to 5

[h]Adjusted for age, number of physiotherapy and occupational therapy sessions per day, number of speech therapy sessions per day and respective baseline score. Adjustment for baseline score is suggested, as estimates are generally more precise than without adjustment [49]

enough to quantify improvement over the short period of stroke rehabilitation. In our study, patients were admitted for a mean duration of 32 days. In comparison, the FLAME trial followed patients for 90 days [27]. Although impairment scales related to neurological (e.g. NIHSS) or motor function (e.g. FMMS) may be most responsive to change [58], these scales were not routinely administered to patients at the two rehabilitation centres in our study. Thirdly, there may be a time lag before the beneficial effects of SSRIs on improving disability or QOL become apparent. Results from an earlier meta-analysis showed that SSRI therapy should be sustained for at least 4 weeks to ameliorate disability after stroke [31]. Although the average duration of therapy in the SSRI group was 31 days, there were 8 (36.4%) patients who took SSRIs for < 4 weeks during rehabilitation. This would have made the detection of any treatment effect more difficult. Lastly, even though most published trials have reported that SSRIs are useful to aid recovery after stroke, the possibility of publication bias cannot be totally excluded. Based on findings from a Cochrane systematic review, the funnel plot for trials investigating SSRI therapy for the outcome of disability appeared asymmetric on visual inspection [55], suggesting that the publication of studies may have been dependent on the nature of their results [60]. While it is possible that studies that reported positive results for SSRI therapy are more likely to be published, asymmetry in funnel plots could also be due to selective outcome reporting, poor methodological quality leading to spuriously inflated effects in smaller studies, true heterogeneity and even chance [60]. In addition to the FLAME trial, the results of ongoing multi-centre trials, namely AFFINITY (Assessment oF FluoxetINe In sTroke recoverY) and EFFECTS (Efficacy oF Fluoxetine—a randomisEd Controlled Trial in Stroke), should be able to more robustly inform the efficacy of fluoxetine for stroke recovery [3].

Based on our multiple linear regression analyses, the frequency of rehabilitation therapies (specifically number of physiotherapy and occupational therapy sessions per day) seem to be an important factor contributing to more favourable outcomes. Physiotherapy and occupational therapy were provided to all patients during rehabilitation in our study. However, the frequency of these therapies may differ depending on the condition, motivation and family support of each patient. Recovery after stroke is a complex process that occurs through a combination of spontaneous and learning-dependent processes [61]. These therapies provide task-specific and context-specific training in ADLs (e.g. walking, feeding, toileting, bathing) that facilitate motor learning and promote post-stroke independence [61]. Although there is no clear consensus for the optimal frequency of therapy, increased training is generally accepted to be beneficial for recovery during stroke rehabilitation [62–64].

Results from our study should be viewed in light of some limitations. Firstly, due to the observational nature of our study, our findings may have been affected by unmeasured confounding. Nonetheless, we had taken into consideration many known factors that could affect stroke recovery including premorbid condition, comorbidities, rehabilitation LOS, medication use and therapies received during rehabilitation. Secondly, the number of included patients in our study was small. Even though we performed a sample size calculation and enrolled more than the minimum target number of patients, the study is still inadequately powered for the subgroup analyses. Furthermore, post-hoc sample size estimation using results from our study showed that the minimum sample size required is 206 (103 in each group). Thirdly, as different disability scales (FIM-motor or MBI) were used in the two rehabilitation centres, not all study participants were administered the same instrument. However, we successfully converted between the scores using validated crosstalk tables [39]. Lastly, while there might be differences between self-reported and proxy-reported QOL [46, 65], our sensitivity analyses showed that results from separate multiple linear regression analyses obtained via self-report and proxy, respectively, were largely consistent.

5 Conclusion

This prospective observational pilot cohort study had evaluated the association between SSRI therapy and the rehabilitation outcomes of disability and QOL among multi-ethnic patients with first-ever stroke admitted to two rehabilitation centres in Singapore. Among the 57 enrolled patients, 38.6% were prescribed with SSRIs, mainly to aid motor recovery during rehabilitation. After adjustment for confounders, no significant association between SSRI therapy and stroke rehabilitation outcomes was found. However, findings from our study showed that physiotherapy and occupational therapy during rehabilitation enhanced post-stroke recovery, hence increasing the frequency of such therapies (as tolerated) should be considered for all stroke patients. Similar results were observed from our subgroup analyses (restricting to patients on fluoxetine in the SSRI group), which are in line with the FOCUS (Fluoxetine Or Control Under Supervision) pragmatic trial suggesting that fluoxetine does not improve post-stroke disability [66]. The results of other ongoing multi-centre trials, namely AFFINITY and EFFECTS, to investigate the effects of fluoxetine in patients with recent stroke, should provide more evidence

on any benefits of pharmacotherapy for functional recovery and enhancement of health-related QOL after stroke. Nonetheless, as a previously published meta-analysis had demonstrated an improvement in disability among Chinese patients who received SSRI therapy (but not among Caucasian patients) [31], while these multi-centre trials (FOCUS, AFFINITY and EFFECTS) are conducted in countries with predominantly Caucasian populations (i.e. United Kingdom, Australia, New Zealand and Sweden), future research should also be performed in Asian populations.

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Compliance with Ethical Standards

Conflict of interest The authors declare no conflict of interest.

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Ethical approval Approval for the conduct of this study was obtained from the National Healthcare Group Domain Specific Review Board (Reference Number: 2016/01206).

Informed consent Written informed consent was obtained from all individual participants (or their legally acceptable representative or designated proxy) included in the study.

References

1. Murray CJ, Barber RM, Foreman KJ, et al. Global, regional, and national disability-adjusted life years (DALYs) for 306 diseases and injuries and healthy life expectancy (HALE) for 188 countries, 1990–2013: quantifying the epidemiological transition. Lancet. 2015;386(10009):2145–91.
2. GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015;385(9963):117–71.
3. 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;16:369.
4. Meschia JF, Bushnell C, Boden-Albala B, Braun LT, Bravata DM, Chaturvedi S, et al. Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014;45(12):3754–832.
5. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2018;49(3):e46–110.
6. Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014;45(7):2160–236.
7. Chollet F, Cramer SC, Stinear C, Kappelle LJ, Baron JC, Weiller C, et al. Pharmacological therapies in post stroke recovery: recommendations for future clinical trials. J Neurol. 2014;261(8):1461–8.
8. Gao XJ. Effects of fluoxetine on the depressive symptoms, self-care ability of daily life and neurological function in stroke patients. Chin J Clin Rehabil. 2005;9(16):12–3.
9. Robinson RG, Schultz SK, Castillo C, Kopel T, Kosier JT, Newman RM, et al. Nortriptyline versus fluoxetine in the treatment of depression and in short-term recovery after stroke: a placebo-controlled, double-blind study. Am J Psychiatry. 2000;157(3):351–9.
10. Yamakawa Y, Satoh S, Sawa S, Ohta H, Asada T. Efficacy of milnacipran on poststroke depression on inpatient rehabilitation. Psychiatry Clin Neurosci. 2005;59(6):705–10.
11. Whyte EM, Lenze EJ, Butters M, Skidmore E, Koenig K, Dew MA, et al. An open-label pilot study of acetylcholinesterase inhibitors to promote functional recovery in elderly cognitively impaired stroke patients. Cerebrovasc Dis. 2008;26(3):317–21.
12. Gladstone DJ, Danells CJ, Armesto A, McIlroy WE, Staines WR, Graham SJ, et al. Physiotherapy coupled with dextroamphetamine for rehabilitation after hemiparetic stroke: a randomized, double-blind, placebo-controlled trial. Stroke. 2006;37(1):179–85.
13. Bartolo M, Zucchella C, Capone A, Sandrini G, Pierelli F. An explorative study regarding the effect of l-deprenyl on cognitive and functional recovery in patients after stroke. J Neurol Sci. 2015;349(1–2):117–23.
14. Johansson BB. Brain plasticity and stroke rehabilitation. The Willis lecture. Stroke. 2000;31(1):223–30.
15. Gu Q. Neuromodulatory transmitter systems in the cortex and their role in cortical plasticity. Neuroscience. 2002;111(4):815–35.
16. Maya Vetencourt JF, Sale A, Viegi A, Baroncelli L, De Pasquale R, O'Leary OF, et al. The antidepressant fluoxetine restores plasticity in the adult visual cortex. Science. 2008;320(5874):385–8.
17. Ng KL, Gibson EM, Hubbard R, Yang J, Caffo B, O'Brien RJ, et al. Fluoxetine maintains a state of heightened responsiveness to motor training early after stroke in a mouse model. Stroke. 2015;46(10):2951–60.
18. Schneider CL, Majewska AK, Busza A, Williams ZR, Mahon BZ, Sahin B. Selective serotonin reuptake inhibitors for functional recovery after stroke: Similarities with the critical period and the role of experience-dependent plasticity. J Neurol. 2019. https://doi.org/10.1007/s00415-019-09480-0
19. Shin TK, Kang MS, Lee HY, Seo MS, Kim SG, Kim CD, et al. Fluoxetine and sertraline attenuate postischemic brain injury in mice. Korean J Physiol Pharmacol. 2009;13(3):257–63.
20. 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.
21. Schmidt HD, Duman RS. The role of neurotrophic factors in adult hippocampal neurogenesis, antidepressant treatments and animal models of depressive-like behavior. Behav Pharmacol. 2007;18(5–6):391–418.
22. Wang JW, David DJ, Monckton JE, Battaglia F, Hen R. Chronic fluoxetine stimulates maturation and synaptic

plasticity of adult-born hippocampal granule cells. J Neurosci. 2008;28(6):1374–84.
23. Greene J, Banasr M, Lee B, Warner-Schmidt J, Duman RS. Vascular endothelial growth factor signaling is required for the behavioral actions of antidepressant treatment: Pharmacological and cellular characterization. Neuropsychopharmacology. 2009;34(11):2459–68.
24. Lee JS, Jang DJ, Lee N, Ko HG, Kim H, Kim YS, et al. Induction of neuronal vascular endothelial growth factor expression by cAMP in the dentate gyrus of the hippocampus is required for antidepressant-like behaviors. J Neurosci. 2009;29(26):8493–505.
25. Russo-Neustadt AA, Beard RC, Huang YM, Cotman CW. Physical activity and antidepressant treatment potentiate the expression of specific brain-derived neurotrophic factor transcripts in the rat hippocampus. Neuroscience. 2000;101(2):305–12.
26. Coppell AL, Pei Q, Zetterstrom TS. Bi-phasic change in BDNF gene expression following antidepressant drug treatment. Neuropharmacology. 2003;44(7):903–10.
27. Chollet F, Tardy J, Albucher JF, Thalamas C, Berard E, Lamy C, et al. Fluoxetine for motor recovery after acute ischaemic stroke (FLAME): a randomised placebo-controlled trial. Lancet Neurol. 2011;10(2):123–30.
28. Winstein CJ, Stein J, Arena R, Bates B, Cherney LR, Cramer SC, et al. Guidelines for adult stroke rehabilitation and recovery: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2016;47(6):e98–169.
29. Engelter ST, Frank M, Lyrer PA, Conzelmann M. Safety of pharmacological augmentation of stroke rehabilitation. Eur Neurol. 2010;64(6):325–30.
30. Engelter ST, Urscheler N, Baronti F, Vuadens P, Koch J, Frank M, et al. Frequency and determinants of using pharmacological enhancement in the clinical practice of in-hospital stroke rehabilitation. Eur Neurol. 2012;68(1):28–33.
31. 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.
32. Hamilton BB, Laughlin JA, Fiedler RC, Granger CV. Interrater reliability of the 7-level functional independence measure (FIM). Scand J Rehabil Med. 1994;26(3):115–9.
33. Ottenbacher KJ, Hsu Y, Granger CV, Fiedler RC. The reliability of the functional independence measure: a quantitative review. Arch Phys Med Rehabil. 1996;77(12):1226–32.
34. Dodds TA, Martin DP, Stolov WC, Deyo RA. A validation of the functional independence measurement and its performance among rehabilitation inpatients. Arch Phys Med Rehabil. 1993;74(5):531–6.
35. Heinemann AW, Linacre JM, Wright BD, Hamilton BB, Granger C. Relationships between impairment and physical disability as measured by the functional independence measure. Arch Phys Med Rehabil. 1993;74(6):566–73.
36. Kidd D, Stewart G, Baldry J, Johnson J, Rossiter D, Petruckevitch A, et al. The functional independence measure: a comparative validity and reliability study. Disabil Rehabil. 1995;17(1):10–4.
37. Linacre JM, Heinemann AW, Wright BD, Granger CV, Hamilton BB. The structure and stability of the functional independence measure. Arch Phys Med Rehabil. 1994;75(2):127–32.
38. Shah S, Vanclay F, Cooper B. Improving the sensitivity of the Barthel Index for stroke rehabilitation. J Clin Epidemiol. 1989;42(8):703–9.
39. Hong I, Woo HS, Shim S, Li CY, Yoonjeong L, Velozo CA. Equating activities of daily living outcome measures: the Functional Independence Measure and the Korean version of Modified Barthel Index. Disabil Rehabil. 2018;40(2):217–24.
40. Young JH, Kyu PB, Suk SH, Kyoo KY, Bom PS, Jong PN, et al. Development of the Korean version of Modified Barthel Index (K-MBI): multi-center study for subjects with stroke. Ann Rehabil Med. 2007;31(3):283–97.
41. Heinemann AW, Roth EJ, Cichowski K, Betts HB. Multivariate analysis of improvement and outcome following stroke rehabilitation. Arch Neurol. 1987;44(11):1167–72.
42. Shah S, Vanclay F, Cooper B. Efficiency, effectiveness, and duration of stroke rehabilitation. Stroke. 1990;21(2):241–6.
43. The WHOQOL Group. The World Health Organization Quality of Life Assessment (WHOQOL): development and general psychometric properties. Soc Sci Med. 1998;46(12):1569–85.
44. Hilari K, Lamping DL, Smith SC, Northcott S, Lamb A, Marshall J. Psychometric properties of the Stroke and Aphasia Quality of Life Scale (SAQOL-39) in a generic stroke population. Clin Rehabil. 2009;23(6):544–57.
45. Guo YE, Togher L, Power E, Koh GC. Validation of the Stroke and Aphasia Quality of Life Scale in a multicultural population. Disabil Rehabil. 2016;38(26):2584–92.
46. Hilari K, Owen S, Farrelly SJ. Proxy and self-report agreement on the Stroke and Aphasia Quality of Life Scale-39. J Neurol Neurosurg Psychiatry. 2007;78(10):1072–5.
47. Beninato M, Gill-Body KM, Salles S, Stark PC, Black-Schaffer RM, Stein J. Determination of the minimal clinically important difference in the FIM instrument in patients with stroke. Arch Phys Med Rehabil. 2006;87(1):32–9.
48. van der Putten JJ, Hobart JC, Freeman JA, Thompson AJ. Measuring change in disability after inpatient rehabilitation: Comparison of the responsiveness of the Barthel index and the Functional Independence Measure. J Neurol Neurosurg Psychiatry. 1999;66(4):480–4.
49. Guideline on adjustment for baseline covariates in clinical trials. Website: Committee for Medicinal Products for Human Use, European Medicines Agency 2015. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-adjustment-baseline-covariates-clinical-trials_en.pdf. Accessed 18 Sep 2018.
50. Cifu DX, Stewart DG. Factors affecting functional outcome after stroke: a critical review of rehabilitation interventions. Arch Phys Med Rehabil. 1999;80(5 Suppl 1):S35–9.
51. Sze KH, Wong E, Or KH, Lum CM, Woo J. Factors predicting stroke disability at discharge: a study of 793 Chinese. Arch Phys Med Rehabil. 2000;81(7):876–80.
52. Bagg S, Pombo AP, Hopman W. Effect of age on functional outcomes after stroke rehabilitation. Stroke. 2002;33(1):179–85.
53. Ursin MH, Ihle-Hansen H, Fure B, Tveit A, Bergland A. Effects of premorbid physical activity on stroke severity and post-stroke functioning. J Rehabil Med. 2015;47(7):612–7.
54. Nachimuthu S, Assar MD, Schussler JM. Drug-induced QT interval prolongation: Mechanisms and clinical management. Ther Adv Drug Saf. 2012;3(5):241–53.
55. Mead GE, Hsieh CF, Lee R, Kutlubaev MA, Claxton A, Hankey GJ, et al. Selective serotonin reuptake inhibitors (SSRIs) for stroke recovery. Cochrane Database Syst Rev. 2012;11:cd009286.
56. Jacobs BL, Fornal CA. Serotonin and motor activity. Curr Opin Neurobiol. 1997;7(6):820–5.
57. Pinto CB, Saleh Velez FG, Lopes F, de Toledo Piza PV, Dipietro L, Wang QM, et al. SSRI and motor recovery in stroke: reestablishment of inhibitory neural network tonus. Front Neurosci. 2017;11:637.
58. STAIR-II. Recommendations for clinical trial evaluation of acute stroke therapies. Stroke. 2001;32(7):1598–606.
59. Guo Y, He Y, Tang B, Ma K, Cai Z, Zeng S, 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.

60. Sterne JAC, Egger M, Moher D. Chapter 10: addressing reporting biases. In: Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions version 5.1.0 (updated March 2011). The Cochrane Collaboration; 2011.
61. Langhorne P, Bernhardt J, Kwakkel G. Stroke rehabilitation. Lancet. 2011;377(9778):1693–702.
62. Langhorne P, Wagenaar R, Partridge C. Physiotherapy after stroke: more is better? Physiother Res Int. 1996;1(2):75–88.
63. Kwakkel G, Wagenaar RC, Koelman TW, Lankhorst GJ, Koetsier JC. Effects of intensity of rehabilitation after stroke. A research synthesis. Stroke. 1997;28(8):1550–6.
64. Karges J, Smallfied S. A description of the outcomes, frequency, duration, and intensity of occupational, physical, and speech therapy in inpatient stroke rehabilitation. J Allied Health. 2009;38(1):E1–10.
65. von Essen L. Proxy ratings of patient quality of life: factors related to patient-proxy agreement. Acta Oncol. 2004;43(3):229–34.
66. FOCUS Trial Collaboration. Effects of fluoxetine on functional outcomes after acute stroke (FOCUS): a pragmatic, double-blind, randomised, controlled trial. Lancet. 2019;393(10168):265–74.