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AN UPDATE OF POST-STROKE DEPRESSION AND THE USE OF SELECTIVE SEROTONIN REUPTAKE INHIBITORS IN POST-STROKE RECOVERY

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ABSTRACT

Advancements in acute stroke management have led to improved mortality rates. However, stroke remains a chronic lifelong condition and is one of the top three leading causes of disability in Singapore. Stroke management typically commences in an acute hospital for acute stabilisation, followed by inpatient rehabilitation and outpatient rehabilitation. With the trend towards early supported discharge of stroke patients, general practitioners (GPs) are crucial in providing comprehensive and evidence-based post-stroke care, which includes treating associated cardiovascular comorbidities as well as preventing complications and optimising quality of life. This article aims to provide GPs with current evidence on the use of selective serotonin inhibitors (SSRIs) in post-stroke recovery. It is important for GPs to be aware that post-stroke depression (PSD) is a common complication of stroke and significantly affects mortality and recovery. SSRIs have been commonly used for treatment of PSD. Early phase studies had suggested improvement of post-stroke motor outcomes with the use of SSRIs, although subsequent trials demonstrated conflicting results.

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INTRODUCTION

Post-stroke depression (PSD) is common after stroke and affects about 30 percent of stroke survivors.[1] However, PSD is often underdiagnosed. It has been suggested that the rate of diagnosed and treated PSD in routine clinical practice is 5 percent.[2] Hence, it is important to monitor stroke survivors for PSD. GPs are one of the best healthcare professionals to do so as they often continue to manage the chronic diseases of stroke survivors.

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This review covers the following areas: when to screen for PSD, the screening tools to consider, the evidence of SSRIs in prevention and treatment of PSD, as well as the evidence of SSRIs in post-stroke functional recovery. Lastly, the review will also cover the SSRI-related adverse events to monitor for and the practical considerations to take note of when prescribing SSRI in post-stroke patients.

WHEN TO SCREEN FOR PSD AND THE SCREENING TOOLS TO CONSIDER

To the best of our knowledge, there are currently no local recommendations on the optimal timing to screen for PSD. The Australian guidelines recommend assessment of stroke survivors with suspected depression using a standardised and validated scale by trained personnel.[3] Clinical practice guidelines issued by the Canadian Stroke Best Practices, United Kingdom (UK) the National Clinical Guideline for Stroke and American Stroke Association (ASA) recommend routine screening for PSD by healthcare professionals.[4-7]

There are variations in recommendations on the optimal timing to screen for PSD among different countries. The Australian guidelines do not make any recommendation about the ideal timing to screen for PSD.[3] The ASA acknowledges that the ideal timing to screen for PSD is unknown.[6] The Canadian guidelines advise screening for PSD at various stages throughout the continuum of stroke care, e.g., during follow-up appointments with GPs.[5] The UK guidelines recommend screening within six weeks of stroke, at the transfer of care into post-acute services and at six and 12 months post-stroke.[4]

As PSD is common, we suggest there is a need to consider routine screening of PSD and to do so at various stages along the continuum of care, e.g., during acute hospitalisation, upon transfer to rehabilitation unit/community hospital, and follow-up at the rehabilitation specialist/GP clinic. In a busy clinical setting, GPs can consider the use of questionnaires for screening of PSD. For stroke patients with aphasia or communication difficulties, observer rated screening tools can be considered.

Table 1 summarises some of the commonly used tools with good sensitivity and specificity for PSD screening.[5] Patients whose screening scores indicate either high risk for PSD or demonstrate severe/persistent symptoms of PSD should be assessed by a mental health professional.[4-6]

EVIDENCE OF SSRIS IN PREVENTION OF PSD AND TREATMENT

The recent Cochrane review, which reviewed the use of fluoxetine, sertraline, paroxetine, citalopram, and escitalopram, reported a reduction of depression in post-

stroke patients (RR 0.75) as well as a reduction in average depression scores with the use of SSRIs.[8] The EFFECTS and FOCUS trials that looked at whether a 6-month course of fluoxetine improved functional outcomes in patients with strokes showed a reduction in the onset of PSD.[9,10] Both the meta-analyses reported by Mead and Kalbouneh demonstrated fluoxetine and SSRI helped with treatment of PSD and its prevention, respectively.[11,12]

The jury is currently still out as to which antidepressant is most ideal for the prevention of PSD, as well as for the treatment of PSD. In general, the guidelines from Australia, Canada, and UK do not recommend the routine use of antidepressants for prevention of PSD due to the lack of high-quality evidence as well as risk of potential harm such as increased risk of seizures and bone fracture.[3-5] A statement from the ASA concluded that antidepressants might be effective in preventing PSD but recommended more research with representative samples of stroke survivors and additional studies to validate the ideal timing and treatment duration.[6]

For the treatment of PSD, there have been no specific local guidelines regarding the use of any specific antidepressant. Based on the Ministry of Health (MOH) clinical practice guidelines 2012, SSRIs are generally recommended as the first line for treatment of depression in adults as well as in the elderly due to better tolerance, safety in overdose, and favourable risk-benefit ratio.[13] The Australian guidelines have made a weak recommendation to consider the use of antidepressants, which include SSRIs.[3] The Canadian and ASA guidelines also recommend treatment of PSD with antidepressants.[5,7] UK guidelines state that antidepressant use may be effective in the treatment of PSD.[4] The guidelines from Australia, Canada, and ASA do not recommend any particular antidepressant as there is no evidence that particular antidepressants are more superior over others.[3,5-7] The UK guidelines state that SSRI reduces depression but no particular SSRI is more superior.[4] In terms of PSD antidepressant treatment duration, both UK and Canadian guidelines recommend continuation of antidepressants for at least four (UK) or six (Canada) to 12 months after therapeutic response has been achieved.[4,5] Based on MOH clinical practice guidelines, non-psychotic patients with first episode of depression should be treated with antidepressants for 6-9 months after remission of symptoms.[13]

EVIDENCE OF SSRIS IN POST-STROKE FUNCTIONAL RECOVERY

Since the publication of the FLAME trial in 2011, many doctors have been prescribing fluoxetine to post-stroke patients with the hope of enhancing motor recovery.

The FLAME trial results of 2011 showed improvement of the Fugl-Meyer Motor Scale (FMMS) in ischaemic stroke patients as well as a higher proportion of patients independent in living (modified Rankin Scale (mRS) 0-2) after a 90-day course of fluoxetine 20 mg daily.[14] The FMRICH trial showed improvement in FMMS, mRS, and Barthel Index (BI) in haemorrhagic stroke patients after prescription of fluoxetine 20 mg daily for 90 days.[15]

In contrast, the three large, recent trials (FOCUS, AFFINITY, and EFFECTS) conducted in patients with both ischaemic and haemorrhagic strokes showed no improvement in mRS.[9,10,16]

The Cochrane review concluded that there was no improvement in mRS and BI scores with the use of fluoxetine.[8] Three meta-analyses reported by Mead, Liu, and Kalbouneh independently reported no improvement in mRS with the use of fluoxetine or SSRI.[11,12,17] However, there were improvements in FMMS and BI reported by Liu and Kalbouneh.[11,17]

Although the current literature shows no improvement in disability with the use of SSRIs in stroke patients, there are a few possible explanations. First, mRS as a disability scale is relatively insensitive to changes in impairment. A study by Sreekrishnan et al showed that in a group of patients with intracerebral haemorrhage, BI might be more sensitive than mRS in measuring recovery.[18] Second, the stroke severity of the recruited patients in FOCUS, EFFECTS, and AFFINITY trials were mild to moderate. Hence, there might be ceiling effects that led to insignificant change on the mRS.

Third, there was heterogeneity in the studied trials. The meta-analyses by Mead, Liu, and Kalbouneh included different types of patients, different SSRI doses, and varying SSRI treatment duration.[11,12,17] Lastly, there might be variability of post-stroke functional recovery following SSRI administration due to either interindividual variability in stroke recovery or variable treatment response related to interindividual differences in motor network connectivity.[19] Studies had shown that several serotonin transporter gene polymorphisms might influence the efficacy of SSRIs.[11]

SSRIS-RELATED ADVERSE EVENTS

The adverse effects of SSRIs need to be taken into consideration when prescribing SSRIs in post-stroke patients. Moreover, these effects need to be monitored by the managing GP if he/she decides to prescribe an SSRI to the post-stroke patient.

SSRIs inhibit serotonin reuptake, which increases the amount of serotonin available to serotonin receptors.[20] Serotonin receptors mediate a variety of functions, such as sleep, appetite, sexual function, and cardiac conduction.[20] Therefore, most SSRI side effects are dose-related and are attributed to serotonergic effects.[20] Gastrointestinal (GI) disturbances are the most commonly reported side effects with SSRIs. Fluvoxamine in particular is associated with high incidence of GI side effects, whereas users of escitalopram and citalopram have fewer GI complaints [20,21] Nausea may also be reduced by coadministration with food. Although some SSRIs may cause some weight loss initially, weight gain is often reported after six months and with longer-term

use and more commonly with sertraline, fluoxetine, and paroxetine.[20]

SSRIs can increase the risk of GI bleed, particularly in patients older than 65, and in patients receiving other medications associated with increased bleeding risk such as anticoagulants and antiplatelets.[21] This is relevant to ischaemic stroke survivors, especially those who are elderly and are prescribed antiplatelet or anticoagulant therapy for secondary stroke prevention.[21] It has been shown that co-prescription of aspirin or warfarin together with a SSRI increases the risk of upper GI bleed, with an absolute risk of 6 percent and 4 percent respectively.[21] While the Cochrane review in 2019 showed increased incidence of GI adverse events in subjects treated with SSRIs,[22] a more recent Cochrane review in 2021 reported no significant increase in GI side effects and bleeding.[8] Kalbouneh et al also reported that SSRIs did not significantly increase risk of bleeding.[11]

SSRIs could potentially increase the risk of de novo haemorrhagic stroke, especially when antiplatelets or anticoagulants are concurrently prescribed,[21] although the evidence is mixed. A recent large study showed no significant association between pre-intracerebral haemorrhage SSRI use and intracerebral haemorrhage risk,[23] while a meta-analysis by Jensen et al concluded there is insufficient high-quality data to support withholding SSRIs to reduce the risk of intracerebral haemorrhage.[24] In the EFFECTS, FOCUS, and AFFINITY trials, there was no significant increase in the occurrence of new stroke, thrombotic event, or bleeding event.[9,10,16] If the patient is taking warfarin or direct oral anticoagulant (DOAC), citalopram or escitalopram has been recommended as the SSRI of choice due to a lower potential for interference with warfarin and DOAC metabolism.[21]

Sexual dysfunction is another frequently reported effect of SSRIs, in particular, paroxetine and escitalopram.[25] Alternatives include a trial of other SSRI types or to use non-SSRI antidepressants such as mirtazapine.

Compared to other classes of antidepressants, SSRIs carry the highest risk of hyponatremia, especially in the initial weeks of treatment, likely associated with the syndrome of inappropriate secretion of antidiuretic hormone (SIADH).[26] Post-stroke patients taking fluoxetine had twice the odds of developing hyponatremia compared to patients on placebo.[17] More cases of hyponatremia were also found in the fluoxetine group in the EFFECTS trial using a serum sodium cut-off level of <130 mmol/L.[9] There was no difference between fluoxetine and placebo groups reported in FOCUS and AFFINITY trials based on a cut-off level of <125 mmol/L.[10,16]

SSRIs, especially citalopram, can prolong the QT interval by antagonising myocyte potassium channels, which may lead to fatal tachycardias.[27] The risk of QT prolongation with citalopram appears to be dose-dependent, with increased vulnerability in those with cardiac disease and other QT-prolonging risk factors. This could be a consideration in post-stroke patients, especially those with multiple cardiac co-morbidities.

Observational studies have reported an overall 1.62-fold increase in fracture risk among adults with or without a previous stroke when prescribed with a SSRI.[28] In studies that looked at the use of SSRIs in post-stroke recovery, it was shown that patients who received SSRIs had higher risk of bone fractures (RR 2.35) and seizures (RR 1.40).[8] There were also significantly more falls with injury in the fluoxetine group demonstrated in the AFFINITY trial (3 percent vs 1 percent).[16] There was no significant difference in the number of falls with injury between fluoxetine and placebo groups in the FOCUS trial (7.67 percent vs 6.01 percent).[10]

Table 2 shows the drug-specific characteristics and a comparison of the common adverse effects of the different SSRIs.[20,21]

Table 1. Post-stroke Depression Screening Tools

Assessment Tool	Number of Items	Response Format	Score Range	Interpretation of Scores
Geriatric Depression Scale	30	Yes/No responses	0-30	0-10 = no to minimal risk of depression 11-20 = mild depression 21-30 = moderate to severe depression
Hospital Anxiety and Depression Scale	7 (depression subscale) 7 (anxiety subscale)	Multiple-choice response options	0-21 (depression subscale) 0-21 (anxiety subscale)	Using the depression subscale, 0-7 = no to minimal risk of depression 8-9 = high sensitivity for depression ≥10-11= high specificity for depression
Patient Health Questionnaire 9	9	Multiple-choice response	0-27	0-9 = no to minimal risk of depression 10-27 = presence of depression
Beck Depression Inventory	21	Multiple-choice response	0-63	0-9 = no to minimal risk of depression 10-18 = mild depression 19-29 = moderate depression 30-63 = severe depression
Centre for Epidemiological Studies Depression Scale	20	Multiple-choice response	0-60	0-15 = no to minimal risk of depression 16-60 = presence of depression
Stroke Aphasic Depression Questionnaire-10	10	Observer rating of observed behaviour	0-30	0-14 = no to minimal risk of depression 15-30 = presence of depression
Aphasia Depression Rating Scale	9	Observer rating based on interview & observation	0-32	0-8 = no to minimal risk of depression 9-32 = presence of depression

Table 2. Comparison of SSRIs

SSRIs	Licensed dose for depression	Drug-specific characteristics	Common class adverse effects					
			Anti-Cholinergic effects	Postural Hypotension	Nausea/ Vomiting	Sedation	Cardiac conduction disturbance	Sexual dysfunction
Citalopram Hydrobromide	20mg/day; maximum dose 40 mg/day	Considered the best tolerated SSRI. One of the safest in potential for liver injury Higher incidence for hyponatraemia	-	-	++	-	+	+++
Escitalopram	10 mg/day; maximum dose 20 mg/day	One of the safest in potential for liver injury Higher incidence of hyponatraemia	-	-	++	-	+	+++
Fluoxetine hydrochloride	20 mg/day; maximum dose 60 mg/day	Slower onset of action. More potential drug-drug interactions. May affect glycaemic control. Serious allergic and skin reactions. Higher incidence of hyponatraemia. Seizures.	-	-	++	-	-	+++
Fluvoxamine maleate	Initial dose 50 mg/day; maximum dose 300 mg/day	Excellent safety profile in the elderly.	-	-	+++	+	-	+++
Paroxetine hydrochloride	20 mg/day maximum dose 50 mg/day	More potential drug-drug interactions. Worse withdrawal syndrome. Higher incidence of restless leg syndrome. May cause weight gain.	+	-	++	+	-	+++
Sertraline hydrochloride	50 mg/day, maximum dose 200 mg/day	Higher incidence of restless leg syndrome. Highest incidence of extrapyramidal side-effects.	-	-	++	-	-	+++

+++ high incidence/severity
++ moderate
+ low
-very low/none

PRACTICAL CONSIDERATIONS OF PRESCRIBING SSRIS IN POST-STROKE PATIENTS

A range of SSRI formulations are suitable for patients with swallowing difficulties, which can be common after stroke. Most SSRIs are available in film-coated tablets, including escitalopram, fluvoxamine, paroxetine, and sertraline. Most fluoxetine brands are available in capsule forms. The capsules can be opened, and the contents mixed with water, although admittedly there is no supportive data on this mode of adminstration.[29] The film-coated tablets can be crushed and/or dispersed in water and fed via feeding tube, or crushed and given with soft food, though this method of administration is also not officially licensed. Crushed sertraline and paroxetine tablets may have a local anaesthetic effect on the tongue,[30] so dysphagic patients who require these tablets to be crushed when taken orally will need to be reminded of such an effect.

When symptoms of PSD are in remission after a treatment course of at least six months, SSRIs should be gradually weaned over a period of several weeks to months instead of abrupt cessation, to mitigate the risks of relapse as well as withdrawal symptoms. Withdrawal symptoms happen more commonly after discontinuation of prolonged SSRI treatment with SSRIs that have shorter half-lives, such as paroxetine.[20] Common withdrawal symptoms associated with discontinuation syndrome include dizziness, paraesthesia, headache, anxiety, agitation, tremor, sweating, confusion, and nausea.

CONCLUSION

As PSD is common, we suggest a need to consider routine screening of PSD at various stages along the continuum of care of stroke patients such as at their follow-up visits with the GP. Stroke survivors should be screened for PSD and patients at risk should undergo a more detailed assessment. Based on the guidelines from Australia, UK, and America, referral to a mental health professional is recommended for patients at risk.

After confirmation of PSD diagnosis, treatment with an antidepressant should be considered bearing in mind the patient's characteristics, PSD symptom severity, safety, and potential side effect profile of the antidepressant. While current evidence does not fully support the use of SSRIs in preventing PSD and improving disability, it does appear that antidepressants with serotonergic action do have the potential to ameliorate PSD.

In general, SSRIs are a well-tolerated and effective treatment for depressive symptoms. Close monitoring for side effects such as bone fracture, seizure, and GI disturbance is recommended. Proton pump inhibitors can be considered when prescribing SSRIs in the elderly or in patients on antiplatelet or anticoagulant therapy, to mitigate GI effects. Bone health perhaps should also be considered and optimised prior to starting SSRI in stroke survivors as they are more susceptible to fractures. It would be important for the GP to consider the individual patient's needs and susceptibilities to specific side effects in prescribing an appropriate SSRI for the post-stroke patient.

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