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STROKE (H DIENER, SECTION EDITOR)

Serotonin Selective Reuptake Inhibitors (SSRIs) and Stroke

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Abstract

Purpose of Review The interest in SSRIs after stroke has increased in the past few years, with better knowledge of post-stroke depression and with the demonstrated capacity of some SSRIs to act on the functional recovery of non-depressed subjects.

Recent Findings Arguments for the action of SSRIs in favour of post-stroke neurological function recovery have improved through new elements: basic science and preclinical data, positive clinical trials and repeated series of stroke patient meta-analysis, and confirmation of favourable safety conditions in post-stroke patients.

Summary Global coherence is appearing, showing that SSRIs improve stroke recovery in non-depressed patients when given for 3 months after the stroke, with highly favourable safety conditions and a favourable benefit/risk ratio. Large series are still needed.

Keywords Ischaemic stroke · SSRIs · Recovery from stroke · Brain plasticity · Neuroprotection · Post-stroke depression

Introduction

Interest in serotonin selective reuptake inhibitors (SSRIs) after stroke has been renewed by a better knowledge of post-stroke depression and, above all, by their potential capacity to act on the functional recovery of non-depressed subjects.

Post-stroke depression (PSD), affects 30 to 50% of hemiplegic patients within 1 year of their cerebral infarction. In the first 3 months after a stroke, PSD is known to increase morbidity, worsening functional and vital prognoses as well as worsening quality of life. Post-stroke depression has a negative consequence on patients' recovery. [1, 2, 3••, 4].

Stroke remains a major public health issue worldwide and recovery of neurological functions remains a concern despite the positive effect of thrombolysis and thrombectomy. Half of the patients undergoing a thrombectomy score > 2 on the modified Rankin Scale after 6 months.

Several preclinical and clinical studies have shown that post-stroke brain plasticity could be modulated by external agents like SSRIs, through a specific effect independent of depression. A limited number of clinical trials have shown that SSRIs are active in patients' recovery after stroke and reduce the clinical deficit found at 3 months [5–7].

At the same time, our knowledge of SSRI side effects has improved through specific stroke population or non-specific wider population studies, with a better evaluation of the benefit/risk ratio, which appears to be highly favourable most of the time.

Moreover, SSRIs can be given in almost all patients with ischaemic stroke. They can be given early after the stroke with no particular restriction and with no requirement for major facilities. They can be of interest in developing countries.

In this paper, we will differentiate between (a) SSRIs and post-stroke depression and (b) SSRIs and post-stroke recovery in non-depressed patients.

SSRIs and Post-stroke Depression

The clinical consequences of post-stroke depression on functional recovery remain a major question. The diagnosis of post-stroke depression is, most of the time, not easy.

This article is part of the Topical Collection on *Stroke*

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Linguistic difficulties in aphasic patients with left hemispheric lesions, neglect and its cognitive consequences in patients with right hemispheric lesions, and preexisting memory disturbances often prevent or delay an appropriate diagnosis of depression. PSD is difficult to diagnose at the very acute period of the stroke and it has to be differentiated from the initial mood consequences of any acute neurological deficit. At least 2 weeks of continuous symptoms are generally necessary.

In fact, the scales used in this context are not designed for stroke patients and, most of the time, the diagnosis relies on the clinician's conviction. Specific randomised clinical trials on the effectiveness of SSRIs in PSD are relatively few, and most of them were performed some years ago.

A literature review of post-stroke-depressed patients reveals arguments concerning three main aspects, detailed in the remarkable synthesis by K. Satler [3••]: post-stroke depression has a negative impact on functional recovery, SSRIs are active on post-stroke depression, and SSRIs may improve stroke outcome in patients with depression.

Post-stroke Depression Has a Negative Impact on Functional Recovery

Several clinical studies show that, despite rehabilitation programmes, the functional status of patients with PSD remains at a lower level than that of non-depressed patients [8–14]. Co-occurrence of stroke and depression is associated with greater physical limitations than either condition on its own [15, 16].

So early identification and treatment of PSD may enhance functional recovery.

Moreover, post-stroke depression interferes with cognitive performance and depression may appear to be associated with definitive cognitive decline while, most of the time, cognitive disturbances may be mainly the transient consequences of depression.

SSRIs and Treatment of Post-stroke Depression

Imbalance and under-activity of the cerebral noradrenergic and serotonergic systems have been proposed as the rationale for PSD treatment. A number of studies have contributed to a better understanding of the phenomenon. Early meta-analyses reported a significant treatment response to antidepressants [1, 2] regardless of the scales used to assess outcome. Duration and time of treatment appear to be correlated with clinical benefit [2]. From 3 weeks onward, demonstrated effects were, generally, of increasing significance. As far as drug categories are concerned, there is strong evidence that heterocyclic antidepressants improve depression post-stroke. Side effects in elderly patients mean that these medications should be used with caution in that population. Based on the results of meta-analysis, there is also strong evidence that selective serotonin reuptake inhibitors are effective in the treatment of post-stroke depression [17–25].

Two studies with the SSRI fluoxetine showed a benefit in depressed patients [24, 25].

Several subsequent meta-analyses have confirmed the efficacy of antidepressant treatment in PSD as compared to placebo in patients with stroke [26, 27]. Some recent studies and reviews have tried to identify the best antidepressant among all the available drugs [28], and confirmed the efficacy of the SSRI escitalopram [29]. Among all antidepressants, SSRIs showed good efficacy with low rate of side effects and reduced risk [27]. In a global report [30•] providing an updated review of the pharmacological state of art of PSD, Paolucci concluded that "even if currently an antidepressant treatment can improve depressive symptoms, neither the optimal drug nor the optimal lengths of treatment, have been identified. Serotonergic drugs are preferable because of their better safety profile".

SSRIs and Stroke Outcome in Patients with Depression

The appearance of post-stroke depression adversely affects the rate of recovery and rehabilitation of stroke survivors. A study by Gainotti et al. [31] demonstrated that treatment with fluoxetine was associated with an improvement in functional recovery in addition to recovery from depression, a finding which is supported by other studies [32, 33]. The gain is greater when the treatment is started early—within 4 weeks after the stroke [33]. Moreover, another study demonstrated that patients with improvement of depressive symptoms were more likely to be independent 12 weeks after the stroke [34]. It is now accepted that there is strong evidence that pharmacological treatment of depression and improved functional recovery post-stroke are closely associated. However, a recent randomised placebo-controlled study of 478 patients with acute stroke showed no improvement of depressive symptoms 3 months after the stroke but the daily dose of escitalopram was only 10 mg [35].

The new SSRI vortioxetine might become an important option for PSD treatment as it has been shown to improve cognitive functions [27].

SSRIs Probably Also Prevent Post-stroke Depression

As a consequence of the negative impact of PSD on functional recovery, the question of early initiation of antidepressant drug therapy to prevent its development has been proposed. However, individual studies have given conflicting evidence.

Hackett's Cochrane review [1] included 14 trials involving 1515 participants. Data were available for 10 pharmaceutical trials (12 comparisons) with different antidepressants. There was no clear global effect of pharmacological therapy on the prevention of depression. However, arguments exist for a positive effect of citalopram.

In a systematic review and meta-analysis examining the evidence available from published randomised controlled trials (RCTs) evaluating the effectiveness of pharmacotherapy for the prevention of PSD, it was shown that the early initiation of antidepressant therapy, in non-depressed stroke patients, may reduce the odds for development of PSD. However, the optimum timing and duration for treatment and the identification of the most appropriate recipients for a programme of indicated prevention require additional examination [36].

SSRI and Stroke Recovery in Non-depressed Patients

Preclinical Data and Mechanisms of Action

Preclinical studies on animal models clearly show that the rate and extent of functional recovery after focal brain injury can be modulated by drugs affecting neurotransmitters in the central nervous system. This is the case for noradrenalin and for dopamine [5, 6, 37].

The role of antidepressant SSRIs was initially more controversial. Some studies detected little or no significant action on recovery but more recent studies have underlined that fluoxetine is active in rat stroke models [38, 39].

McCann et al. have analysed the preclinical animal data on antidepressant treatment in focal cerebral ischaemia, modelled with or without depression. They published a meta-analysis of data from experiments testing the efficacy of antidepressants versus no treatment in reducing infarct volume and in improving neurobehavioural or neurogenesis outcomes in animal models of stroke. From 44 publications describing the effects of 22 antidepressant drugs, they showed that antidepressants reduced infarct volume by 27.3% and improved neurobehavioural outcomes by 53.7%. There was little evidence for an effect of selective serotonin reuptake inhibitors on infarct volume. However, selective serotonin reuptake inhibitors were the most frequently studied antidepressant subtype and was shown to improve neurobehavioural outcome and increase neurogenesis [40•]. Various beneficial mechanisms were identified, including enhancement of neuroplasticity, antiinflammation-mediated neuroprotection, improvement of cerebral blood flow autoregulation, and modulation of the adrenergic neurohormonal system [41].

Spiemann et al. [42••] give an accurate update of possible mechanisms involved in SSRI action in stroke patients.

a. Neuroprotection

It is well established that inflammatory pathways contribute to late-stage ischaemic-brain injury and thus to a deterioration of neurological outcome [43, 44]. Some animal studies have shown that the reduction of inflammation by SSRIs through inhibition of microglia and neutrophil granulocytes has a neuroprotective effect on neurons [41, 42••, 43]. In fact, rats undergoing middle cerebral artery occlusion (MCAO) had reduced infarct volume and less-severe neurological deficits after intravenous application of fluoxetine compared to untreated control rats. The effect was present even 9 h after ischaemia [40•]. As discussed by the authors, it might be concluded that the antiinflammatory action of fluoxetine contributes to neuroprotection in acute ischaemic stroke by inhibiting late stages of post-ischaemic inflammation [40•].

b. Neurogenesis

Neurotrophins regulate the ability of neural pathways and synapses to undergo morphological changes in response to environmental, behavioural, emotional, physical, and neurophysiological stimuli.

In animal studies, SSRIs have been shown to enhance neurogenesis and expression of neurotrophins in the hippocampus [45]. Correlations between SSRI-induced neurotrophin expression in the hippocampus and beneficial change in behaviour have also been shown in the mouse [46]. Several animal studies have indicated that SSRI-mediated stimulation of neurogenesis may contribute to structural and functional recovery from cerebral ischaemia and that newly generated neurons may migrate from neurogenerating brain areas toward damaged regions [39, 47–50].

c. Cortical Excitability

Motor cortex excitability is increased due to a post-stroke decrease in motor intracortical inhibition in the affected hemisphere [51, 52]. In a randomised, placebo-controlled trial in 20 patients with unilateral stroke, citalopram was shown to reduce motor cortex excitability measured using transcranial magnetic stimulation. This was paralleled by improvement in neurological status assessed by NIHSS [53]. In a small, double-blind clinical trial in patients with motor lacunar deficit, Pariente et al. [54] showed that a single dose of 20 mg fluoxetine was followed by an over activation of motor cortices. This single dose administration was correlated with a hyper excitability of motor cortices measured with TMS [55]. In subsequent studies of 3 months treatment with paroxetine 20 mg o.d. against placebo, it was shown that motor cortices of subjects under treatment exhibited significant hypoexcitabilty. So, strong arguments exist to demonstrate that SSRIs act on cortex excitability. A possible link between the observed decrease in cortical excitability and improved motor cortex recovery might be a beneficial effect of balanced bihemispheric motor cortex excitability on synaptic plasticity.

d. Reestablishment of Inhibitory Neural Network Tonus

Modulation of inhibitory pathways by SSRIs has been suggested. This modulation might be the rational basis for intracerebral reorganisation and reestablishment of excitatory-inhibitory control [56].

One hypothesis for the motor rehabilitation induced by fluoxetine is that the blockage of serotonin (5-HT) reuptake due to SSRI administration increases the availability of this neurotransmitter in the synaptic cleft, thus enhancing signal transmission [57–59] and consequently increasing the excitatory input of glutamate and activating the NMDA receptors leading to a cascade of intracellular events [59].

Nevertheless, the authors have also shown that this acute stimulation of excitatory activity is followed by an increase in inhibitory activity. Studies exploring the effects exerted by SSRIs on motor cortex plasticity show that SSRIs can also enhance inhibitory activity [60]. Inhibition in the motor cortex was observed after citalopram. Citalopram produced transient enhanced GABAergic interneuronal control over corticospinal neurons.

e. Cerebral Blood Flow Regulation

In mice undergoing cold laser-induced ischaemia in the medial frontal and somatosensory cortices, daily application of fluoxetine reduced extravasation and infarction size and improved cerebral blood flow regulation by normalising the lower boundary of cerebral mean arterial pressure [61]. An increase in the expression of haem oxygenase-1 (HO-1) was also observed, with increased CO production and a regulation of vascular tone independent of nitric oxide synthase-related pathways. An increase in hypoxia-inducible factor-1alpha (HIF-1alpha), which activates various genes whose products are essential to oxygen homeostasis, was also increased in the ischaemic-brain region [62].

f. Modulation of the Autonomic Nervous System

Even if the mechanism remains to be answered, upregulation of beta 1-adrenergic receptors in the caudate–putamen and the somatosensory regions of the frontal cortex of rats has been shown with citalopram and fluoxetine using quantitative receptor autoradiography [63]. These results were replicated with multiple dosages of the study drugs, demonstrating reproducibility. Additionally, another study in rats demonstrated that acute peripheral administration of SSRIs induced changes in autonomic cardiovascular function mediated by inhibition of sympathetic activity, presumably via a central mechanism [64].

g. Genetic and Epigenetic Correlates

Genetic and epigenetic correlates are probably multiple through the expression and synthesis of mediators and neurotrophic factors but they are still under evaluated. However, correlations are known to exist between genetic characteristics and repair capacities in the central nervous system. It has been shown that fluoxetine may exert an antidepressive effect by increasing the level of brain-derived neurotrophic factor (BDNF). In a recent study, Jin et al. [65], in a model using male C57BL/6 J mice and photo thrombosis of the left anterior cortex combined with isolated-housing conditions, confirmed that fluoxetine could improve the depression-like behaviours of PSD mice and upregulate the expression of BDNF in the hippocampus. Hey demonstrated the epigenetic mechanisms involved in regulation of BDNF expression induced by fluoxetine.

Moreover, gene polymorphism could help to better detect responders in the future. In a recent post hoc analysis of the EMOTION study, Lee et al. [66] gave insights into the genetic control of serotonin transporter (SERT), which regulates levels of synaptic serotonin. Functionally relevant polymorphisms of SERT genes include STin2, a variable number tandem repeat (VNTR), and the serotonin transporter-linked polymorphic region (5 HTTLPR). In the EMOTION study, among escitalopram users, neurological function in subjects with STin2 12/10 had improved significantly more than that in STin2 12/12 carriers at 3 months. After adjustment for age, initial NIHSS and depression, STin2 12/10 independently predicted a good clinical outcome (mRS 0–1) at 3 months. S Tin2 VNTR polymorphisms may be associated with post-stroke neurological recovery after SSRI therapy.

Stroke Recovery: SSRI Clinical Trials and Meta-analysis

Motor Function 1. Early clinical trials

Some clinical trials with SSRIs were initially reported. Most of them included small numbers of patients and all had results suggesting a positive effect on recovery after stroke. In an early trial [67], fluoxetine and maprotiline were tested against placebo for 3 months in patients with hemiplegic stroke enrolled 1–6 months after the stroke. The patients in the fluoxetine group ($n = 16$) had a better outcome. Acler and colleagues [53] confirmed this finding in ten patients in the active-treatment group versus ten in the placebo group. In a double-blind, placebo-controlled crossover trial, Zittel and colleagues [68] investigated the effects of a single dose (40 mg) of citalopram in eight patients with chronic stroke. Dexterity was significantly improved. In a double-blind placebo-controlled study by our group, Pariente and colleagues [54], by combining clinical motor testing and functional MRI motor assessment in patients recovering from post-stroke hemiplegia ($n = 8$), showed that a single dose (20 mg) of fluoxetine improved hand motor function.

2. Neurological Function Efficacy Trials

a. FLAME trial [69]:

The FLAME Trial tested the efficacy of fluoxetine in motor recovery of patients with ischaemic stroke.

In a double-blind, placebo-controlled trial, 118 non-depressed patients (18–85 years old) who had suffered an ischaemic stroke with hemiplegia or hemiparesis and had Fugl-Meyer motor scale (FMMS) scores of 55 or less were randomly assigned, to fluoxetine (20 mg once per day, orally) or placebo, for 3 months starting 5–10 days after the onset of stroke. The primary outcome measure was the change on the FMMS between day 0 and day 90 after the start of the study drug.

FMMS improvement at day 90 was significantly greater in the fluoxetine group than in the placebo group. The drug was well tolerated and the number of patients who were independent (mRS 0–2) after 3 months of treatment was higher in the fluoxetine group.

The FLAME trial showed that, in patients with ischaemic stroke and moderate to severe motor deficit, the early prescription of fluoxetine with physiotherapy led to enhanced motor recovery after 3 months.

b. Citalopram randomised clinical trial [70••]:

In this randomised, placebo-controlled clinical trial, 144 patients with acute ischaemic stroke were studied for 3 months. Patients with depression were excluded throughout the study. In the treated group, the patients received oral citalopram 20 mg (once daily). The primary outcome was set to a 50% reduction in the 3-month NIHSS compared with the baseline.

The primary outcome of the study was achieved in 57 patients (79%) in the citalopram group while 39 patients (54%) in the placebo group ($P < .001$) achieved the primary outcome, with risk ratio and number needed to treat of 2 (CI = 1. 2–3) and 4 (CI = 2. 5–8.6), respectively. Citalopram was well tolerated in both groups.

The above two trials showed an improvement in the clinical score of patients treated with SSRI for 3 months after the stroke as compared to placebo.

The mechanism of action of SSRI remains to be clearly ascertained but cannot be related to an antidepressive effect in non-depressed patients. An effect on mood is likely even in non-depressed people. However, it is unlikely that SSRI acted only through its antidepressant property as patients were not depressed. A single dose of fluoxetine improved hand motor function and increased activity in the motor cortex compared with placebo in patients recovering from stroke, showing a specific motor effect, whereas a mood effect is unlikely after a single dose [54]. A specific effect on the recovery process and brain plasticity is likely.

However, an SSRI-mediated motivation and/or an SSRI-mediated attention effect cannot be completely excluded.

c. Long-term effect:

In the two trials discussed above, treatment was stopped after 90 days and no indications are given on the long-term condition of patients or on long-term effects.

In a subsequent study with citalopram, a population of post-stroke-depressed patients was treated for 3 months. Patients treated with antidepressants had made a better recovery from disability by 1 year after stroke (i.e., 9 months after antidepressants were stopped) than patients who did not receive antidepressant therapy. This effect was independent of depression and suggests a permanency of drug effect [71]. These results should be taken with caution as they concern a population of stroke-depressed patients where PSD improvement can be the main factor.

d. SSRI use before the stroke:

The influence of prestroke SSRI use on functional outcomes and stroke recovery was investigated by Etherton et al. SSRI use before acute ischaemic stroke had no correlation with the NIHSS admission score, the length of stay, or rate of symptomatic haemorrhage. On multivariate regression analysis, SSRI use was associated with a lower likelihood of discharge to home despite the absence of significant increase in length of stay or in NIHSS score [72].

Effect on Other Specific Neurological Functions

1. Cognition and Language

In the cognitive domain, Jorge et al. found that the administration of the SSRI, escitalopram, in individuals with subacute stroke improved performance on the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), independently of its effects on depression [73].

Very few clinical trials have specifically concerned recovery from aphasia. The SSRI fluvoxamine has been examined in post-stroke aphasia in a double-blind, randomised crossover trial. Ten subjects with fluent aphasia were administered either fluvoxamine or a calcium blocker as a control, and the fluvoxamine group showed significant improvements on naming, reduced perseverations, and better mood after 4 weeks of treatment, compared to controls [74].

In a recent study, the report of 2 series of patients [75••] identified 2 variables at onset that were strongly associated with good recovery of naming in the first 6 months after

stroke: (1) damage to left posterior superior temporal gyrus (pSTG) and/or superior longitudinal fasciculus/arcuate fasciculus (SLF/AF) and (2) selective serotonin reuptake inhibitor (SSRI) use.

Lesion load in left pSTG and SLF/AF was associated with poorer naming outcome.

Preservation of these areas and use of SSRIs were associated with naming recovery, independently of lesion volume, time since stroke, and depression.

Moreover, patients with damage to these critical areas showed better naming outcome if they took SSRIs for 3 months after stroke. Those with preservation of these critical areas achieved good recovery of naming regardless of SSRI use [76].

2. Visual deficit (clinical observation)

In a single illustrative clinical case, Milton et al. reported a 22-year-old woman who demonstrated improved compensation of her stroke-induced hemianopsy after the initiation of a selective serotonin reuptake inhibitor (SSRI) several months after the stroke. When treatment was stopped, hemianopsy appeared again and disappeared when treatment was reinstalled. This case shows that the brain modulation can occur (even if unlikely) late after the stroke and in the visual system [77].

Meta-analysis A first Cochrane Database review identified 56 completed trials of SSRI versus control, 52 of which (4060 participants) could be used for meta-analysis. Significant benefits of SSRI were detected on both of the primary outcomes: reduction of dependency at the end of treatment and disability score. For neurological deficit, depression, and anxiety, statistically significant benefits of SSRIs were also noted [41]. The authors concluded that "SSRIs appeared to improve dependence, disability, neurological impairment, anxiety and depression after stroke, but there was heterogeneity between trials and methodological limitations in a substantial proportion of the trials".

A systematic review and meta-analysis of randomised controlled trials [78] was performed to validate current evidence on the effects of antidepressants and other CNS drugs (antiAlzheimer drugs, antiParkinson drugs, central nervous system (CNS) stimulants, and piracetam) on post-stroke outcomes (motor function, cognition, disability, dependence, and quality of life). SSRIs had statistically significant effects in improving gross motor function, reducing disability and enhancing post-stroke quality of life, but insufficient evidence was found for their use in improving cognition or dependence.

Taking decrease of NIHSS as the primary outcome, and improvement of the Barthel index and functional independence (modified Rankin Scale score 0–2 at the end of follow-up) as the secondary outcome, Gu et al.'s meta-analysis of 8 trials with 1549 patients compared with placebo, showed that decrease in NIHSS was greater in SSRI-treated patients. Early SSRI treatment also improved performance measured on the Barthel scale [79].

Ongoing Trials Clinical investigations using SSRI for recovery of patients with stroke are still continuing. The FLAIR phase III trial with fluoxetine in the USA is in progress The LIFE phase IIb trial with SNRI levominalcipran in Europe has stopped but was never published. The FOCUS, AFFINITY and EFFECTS trials studying the effect(s) of fluoxetine in patients with a recent stroke should give results soon [80].

Safety: Side Effects and Drug Interactions

The safety of SSRIs should be considered carefully as it could put a limitation on their use. SRI drugs were introduced later than other antidepressants, in the 1980s, and showed a better tolerability profile due to their absence of (or their low) affinity for cholinergic or histaminergic receptors [30•].

Specific Pharmacological Actions Today, there are six SSRIs available (fluoxetine, paroxetine, fluvoxamine, sertraline, citalopram, and escitalopram) and each has secondary pharmacological actions other than serotonin transporter (SERT) blockade. In particular, fluoxetine acts as a 5HT2C antagonist, paroxetine has mild anticholinergic action, and sertraline shows dopamine transporter inhibition and σ1 binding. Moreover, fluvoxamine has more potent capacities of σ1 binding; citalopram has mild antihistaminic properties, which are not observable in escitalopram, a pure active S enantiomer of citalopram. SSRIs differ among themselves in the grade of inhibition of cytochrome-P450 isoforms, important for drug–drug interactions (sertraline and citalopram). However, drug–drug interactions are minor for sertraline and citalopram [30•].

Safety Overview SSRIs can have some relatively frequent side effects, such as gastrointestinal symptoms, headache, sexual dysfunction, and insomnia.

The Cochrane database review performed by Mead et al. showed a non-significant excess of seizures, a non-significant excess of gastrointestinal side effects and a non-significant excess of bleeding in patients allocated SSRIs [41].

Globally, good tolerance of SSRI is underlined in various studies and meta-analyses [79]. No difference has been found in the incidence of adverse events (diarrhoea, insomnia, hepatic enzyme disorders, seizure, or intracranial haemorrhage) between treated and placebo groups. Specific studies have shown that prestroke SSRI exposure has no effect on haemorrhagic complications and outcome following thrombolysis in ischaemic stroke [81]. This was confirmed in a subsequent retrospective study [82]. However, subgroup

analysis suggested an increased risk of intra cranial haemorrhage in patients taking both SSRI and oral anticoagulants. Conversely, SSRI use was not associated with an increased risk of bleeding or transfusion in patients undergoing cardiac surgery [83].

Specific Issue: Intracranial Bleeding As serotonin is involved in platelet aggregation, a possible increased risk of bleeding complications, including intracerebral bleeding—probably as a result of inhibition of platelet aggregation, has been discussed.

While a recent meta-analysis confirmed this risk, it also defined it to be very low ('… 1 additional intracerebral bleeding episode per 10,000 persons treated for 1 year …') [84]. Moreover, Howland did not confirm this issue [85•].

Specific Issue: Mortality in Stroke Patients Using SSRIs There has been widespread discussion on possible higher mortality in stroke patients using SSRIs for depression.

Very inconsistent results have been reported. In the South London Stroke Register, it was observed that a treatment with SSRI after stroke was associated with higher mortality, independently of depression at 3 months [86]. Similarly, in an 8-year cohort from the National Health Insurance Research Database of Taiwan, use of SSRIs independently increased the risk of stroke across age strata [87]. Conversely, in the Danish Stroke Registry study, SSRI treatment carried out in the early phase of consecutive first-ever ischaemic stroke patients was associated with lower 30-day all-cause mortality [88]. In another study evaluating patients over time, SSRI use after ischaemic stroke was associated with a lower risk of new cardiovascular events [89]. Lastly, in a study of 870 veterans with PSD, SSRI treatment was associated with longer survival and, in particular, SSRI treatment both before and after the stroke was protective compared with no SSRI treatment during the year following the stroke [90].

Finally, a retrospective observational cohort study of patients with obsessive compulsive disorders (OCD) showed that SSRI use was associated with decreased risk of stroke [91].

It is noteworthy that an important methodological issue for these observational studies is that the risk of stroke among SSRI users may be confounded by indication for prescription, as SSRI were given mostly for depression and it is known that chronically depressed subjects have a higher risk of stroke.

Post-stroke Epilepsy A specific question needing to be addressed concerns the risk of seizure and epilepsy in recovering stroke patients under SSRI.

Animal preclinical studies have given conflicting and unclear results. SSRIs are considered as convulsants, particularly when given daily, but some studies have reported that SSRIs are potential anticonvulsants [92, 93].

Several studies have shown that in non-stroke, depressed patients, the risk of epilepsy/seizures is significantly increased for all classes of antidepressant [94]. The effects of SSRIs on post-stroke epilepsy in a population-based, nationwide study were investigated in a population of 4688 patients with stroke [95]. The incidence of epilepsy in the SSRI group was significantly higher than in the comparison group.

Despite the findings of previous meta-analyses, it is possible that the risk of epileptic fits is slightly higher in post-stroke patients.

Gastrointestinal Bleeding Risk The risk of gastrointestinal bleeding has been shown to be increased in long-term prescriptions of SSRIs [96]. From several observations, it appears likely that aspirin-SSRI association in patients with stroke increases the risk moderately [97].

Interaction with Clopidogrel Higher risk of subsequent ischaemic events has been dreaded in patients who start clopidogrel while treated with a cytochrome P450 (CYP) 2C19-inhibiting selective serotonin reuptake inhibitor (SSRI) (fluoxetine, fluvoxamine).

A cohort study of adults who initiated clopidogrel while being treated with either an SSRI that inhibits CYP2C19 (fluoxetine and fluvoxamine) or a non-inhibiting SSRI showed that CYP2C19-inhibiting SSRI was associated with a slightly increased risk of ischaemic event but with no difference in terms of bleeding. CYP2C19-inhibiting SSRIs (fluoxetine and fluvoxamine) may be associated with a slight decrease in the effectiveness of clopidogrel when initiating clopidogrel treatment [98].

Cardiotoxicity Regarding the possible association between antidepressants, SSRIs and cardiac toxicity, in particular prolongation of corrected QT interval (QTc), the effects of citalopram and other SSRIs at therapeutic doses on QTc are not likely to be of clinical relevance unless other known risk factors are present [99].

Conclusion

SSRIs were identified to be active in the treatment of PSD, with favourable safety conditions and good tolerance compared to other antidepressants.

Arguments for action of SSRIs in favour of post-stroke neurological function recovery have increased progressively in the past few years through: new basic science and preclinical data, positive clinical trials, and repeated meta-analysis.

However, no large scale clinical data and no definite argument for a long-term clinical benefit in terms of independence and disability are available at the time of writing.

Nevertheless, it is worth underlining that SSRIs are associated with highly favourable safety conditions and a favourable benefit/risk ratio. They could be given to all ischaemic stroke patients with no need for particular facilities. This is a major difference with acute phase de-occlusion techniques. Most SSRIs are relatively inexpensive as they are not covered by active patents.

Compliance with Ethical Standards

Conflict of Interest Marianne Barbieux-Guillot reports grants from "Groupement interrégional de Recherche Clinique et d'Innovation Sud-Ouest Outre-Mer", outside the submitted work.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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