Editorial Commentary

FOCUS trial: results, potentialities and limits

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Background

In January 2019 *Lancet* has published the paper "Effects of fluoxetine on functional outcomes after acute stroke (FOCUS): a pragmatic, double-blind, randomised, controlled trial" (1). The main purpose of this prospective trial was to asses if fluoxetine [a selective serotonin reuptake inhibitor (SSRI) drug] could improve recovery after stroke.

Ischemic stroke is one amongst the most frequent causes of disability in the western world and currently large effort is dedicated to identifying the best medical strategies that can help patients to reach a full recovery from post-ischemic deficits (2). Depending on the area of ischemia, several types of damage can result. One of the potential areas of damage after the occurrence of an ischemic stroke is related to those cortical and sub-cortical pathways associated to the control of movement. In fact, hemiplegia and hemiparesis are generally recognized as the main deficits following events of stroke (3).

Previous studies have demonstrated that post-stroke rehabilitation helps to re-obtain motor functionality in a significant percentage of cases. Moreover, it has to be highlighted that post-stroke rehabilitation programs must deal with the full spectrum of health problems that arise from or predispose to the ischemic event, such as associated disability and the chronic diseases.

The wealth of data available in the literature offered the tools to design universally accepted guidelines in an attempt to incentivize the implementation of effective clinical practice in post-stroke rehabilitation (4). In particular, motor functions are targeted with dedicated rehabilitative strategies that span from physical to occupational therapy (5).

Neuroplasticity

In the past years, neuroimaging techniques have played a pivotal role in demonstrating the association between spontaneous recovery of neurological functions and mechanisms of intracerebral re-organization of the human brain in the aftermath of an ischemic event (5). In particular, it has been demonstrated that areas of ischemic brain damage can be replaced via mechanisms of neuronal cell migration or neurogenesis that takes place within the same affected site. The human brain is characterized by a certain degree of innate physiological and anatomical plasticity that can be held responsible for the patients' potential of recovery after a stroke. In this respect, the combination of training and specific exercise is considered the gold-standard treatment for post-stroke rehabilitation. In a number of studies carried out on primates it emerged that, as a result of an ischemic injury to the primary motor cortex of the hand area, a significant reduction of hand representation results, unless rehabilitative training is performed. Interestingly, rehabilitative exercise seems capable of preserving the area affected by the insult; it may be that training represents a stimulus towards the re-acquisition of impaired motor

skills and the maintenance of corticospinal cell function in the control of hand motoneurons (6,7). Even so, it must be noted that as many as 15–30% of patients hit by a stroke will still remain permanently disabled regardless of intensive task-specific training and tailored physical activity.

This is an extremely complex topic as it still remains unknown to what extent neuroplasticity can occur in the adult human brain; most likely, the level of extensive neural reorganization observed in children cannot feasibly be expected in adults. Therefore, it cannot be stressed highly enough how important it is to gain further knowledge in the comprehension of the mechanisms behind post-stroke neuroplasticity if novel rehabilitative strategies are to be designed and implemented. Interestingly, neuronal plasticity and intracerebral re-organization of the damaged human brain circuits can be modulated, not only with specific types of exercises, but also with the use of different drug classes (8). In particular, monoaminergic drugs seem to modulate brain plasticity after a stroke with an improvement of the residual neurological deficit and subsequent disability. In animal models, amphetamines proved able to enhance recovery from acute brain lesions, while drugs from other pharmaceutical classes such as neuroleptics or benzodiazepines showed opposite effects (8,9). An interesting class of drugs, under this scenario, is the SSRI, even though little evidence exists on their effects. In some studies, performed on animals, a neuroprotective action has been found together with the activation and promotion of hippocampal neurogenesis, whereas other studies have demonstrated that these drugs yield a neurotrophic effect (10,11). In these regards, it has been shown that neurotrophins not only play and essential role in the regeneration of nerves, but also play an important role in a number of biological processes, such as embryogenesis, organogenesis, the control of neural plasticity in adults, the regulation of synaptic activity and the synthesis of neurotransmitters.

Serotonin-reuptake inhibitors trials and FOCUS

In a number of clinical trials, albeit small and preliminary, it is argued that the positive effects of SSRI stem from the capacity expressed by these drugs to enhance neurogenesis and the expression of neurotrophic/growth factors; in particular, such effects were observed in the area of the adult hippocampus. Arguably, this may account for the behavioral benefits seen with the administration of antidepressants in animals. Besides, the use of SSRI has been implicated in a number of other potential pathways, including: (I) neuroprotective effects resulting from anti-inflammatory properties (e.g., through the repression of microglia activation); (II) promotion of specific protein expression (hypoxia inducible factor-1 alpha, hemeoxygenaste-1); and (III) modulation of the adrenergic system via the upregulation of beta1 receptors (12-14).

Functional MRI (fMRI) research has shown that the administration of fluoxetine and paroxetine in single doses determined the over-activation of motor cortices when compared against placebo controls; such effects were demonstrated both in healthy individuals and patients affected by stroke (15). SSRIs allowed for neuro-behavioural outcome improvements by 52%, according to a meta-analysis of animal studies where the stroke model was reproduced (16). Furthermore, from a number of small clinical trials it emerged that fluoxetine enhanced motor recovery, even though it still remains unknown what its actual clinical efficacy would be. In particular, a previously published randomized study (17), the FLAME study, performed in 9 centers in France, in 113 patients with ischemic stroke and unilateral weakness [113 patients randomly assigned to fluoxetine (n=57) or placebo (n=56)] showed a superiority of fluoxetine compared to placebo in terms of functional independence and motor recovery. In the FLAME trial fluoxetine was administered 5 to 10 days after the onset of symptoms, showing improvements in motor functionality and independence at the third month. In particular, at 90 days the group randomized to fluoxetine showed a higher score (34.0 *vs.* 24.3; P=0.003) in the Fugl-Meyer Motor Scale (FMMS).

It is important to underline that the FLAME study had some, important, limitations; in particular, it was relatively small in terms of cohort size and with a short-term outcome (assessing 90-day). These biases determined uncertainty regarding the real value of fluoxetine following stroke. However, after the FLAME study, prescription of SSRI to post-stroke subjects, even patients without depression, significantly rose due to the hype determined by this study. In 2012 a newly published work, the Cochrane review of SSRIs for stroke recovery, found some degree of heterogeneity across the examined trials; the study examined 56 completed trials of SSRI versus control, extracting data for meta-analysis from 52 of these works (accounting for 4,059 participants). A significant part of these studies suffered from some methodological limitations, leading the authors of the Cochrane review to conclude that large, well designed trials were necessary to establish whether or not

SSRIs truly improved functional outcomes in patients with stroke (18).

Consequently, three big trials were designed in an attempt to solve these doubts, namely: the FOCUS (1), the AFFINITY (Assessment of Fluoxetine in stroke recovery) and the EFFECTS (Efficacy of Fluoxetine—a randomised controlled trial in stroke). Such studies adopted a multi-centre approach, enrolled parallel groups and consisted in placebo-controlled randomized trials. They all shared the common goal of determining whether a six-month routine administration of fluoxetine (20 mg per day) following an acute stroke carried some degree of improvement on the functional outcome of patients.

The first and largest among these studies, namely the FOCUS, has recently been published by *The Lancet* (1). In this work the authors have tried to overcome the limits of the FLAME trial in order to provide a complete analysis of causal relationships between fluoxetine and post-stroke evolution. In the FOCUS trial, 3,127 patients (mean age 71.4 years; 62% men) with a clinical diagnosis of stroke with focal neurologic deficits were recruited and assigned to treatment with either fluoxetine 20 mg or placebo daily for 6 months. Therefore 2 of the most significant limits of the FLAME trial (small cohort size and short follow-up) were solved in the FOCUS trial. All subjects were randomized 2 to 15 days after stroke onset (mean, 7 days) and most patients (90%) had ischemic strokes with a mean NIH stroke scale score of 6 at the time of study entry.

In the FOCUS trial, the primary endpoint was to study the effect to the modified Rankin Scale scores (mRS) at 6 months. The working hypothesis was that the use of fluoxetine could modulate brain plasticity with improvement of the residual neurological deficit and subsequent disability. By checking the results, no differences were found in the mRS at 6 months between the fluoxetine and placebo groups: functional independence occurred in 36% of fluoxetine recipients and 38% of placebo recipients, a nonsignificant difference. Both groups distributed similarly across the 6 mRS categories when examined at the end of the 6 months period and adjusted for minimization [odds ratio (OR), 0.951; 95% CI, 0.839 to 1.079; P=0.439]. Moreover, the non-adjusted findings offered similar results (common OR, 0.961; 95% CI, 0.848 to 1.089; P=0.531).

By checking the other results, fluoxetine recipients had a significantly lower rate of new depression compared to placebo recipients (13% *vs.* 17%) but a significantly higher rate of bone fractures (2.9% *vs.* 1.5%). The increased risk of bone fractures associated with fluoxetine treatment was unexpected because, even if previous observational studies have suggested this might be an issue (19,20), randomized controlled trials of SSRI had not confirmed it. This could be explained because previous RCT of fluoxetine have been small, with short treatment periods, and predominantly carried out in much younger patients who have much lower risks of falls and fractures.

Moreover, of the variables used in the minimization of data, no significant differences between subgroup were observed. The indicators of survival and independence at 6 months (P=0.3259), delay from onset to randomization (P=0.9507), presence of motor deficits (P=0.1530), and presence of aphasia (P=0.1234) were all statistically comparable.

Secondary end-points included scores on the Stroke Impact Scale (SIS) which included multiple functional measurements (including strength, hand ability, mobility, motor functionality, daily activity, physical function, memory, etc.), as well as European Quality of Life-5 Dimensions-5 Levels (EQ5D-5L) score, Mental Health Inventory (MHI-5) score, and vitality from the Medical Outcomes 36-Item Short Form Survey (SF-36) score. The difference in MHI-5 scores was 76 (95% CI, 60 to 88) with fluoxetine compared to 72 (95% CI, 56 to 88) with placebo (P=0.01), though this difference was not sustained through follow-up. Comparatively, both vitality scores (P=0.6726) and EQ5D-5L scores (P=0.5866) were not significant statistically.

The difference between the results of the FOCUS and FLAME trials can be explained in different ways. The first difference is the patient population: in fact, patients selected for the FLAME trial reported ischemic stroke only, whereas FOCUS patients also underwent intracerebral hemorrhage. Ischemic and hemorrhagic strokes differ in terms of pathophysiology and may be characterized by different long-term cerebral and functional implications. Hemorrhagic strokes predispose to the irritating effects of blood on the cerebral parenchyma, whereas ischemic strokes may imply localized or diffuse cerebral vascular pathology. Previous studies have demonstrated that intracerebral hemorrhage is burdened by a higher risk of death compared with ischemic stroke and about 50% of the subjects with intracerebral hemorrhage die in the first 30 days after an acute event (21). Other studies have showed that patients with ischemic strokes display higher survival rates when compared to patients who undergo hemorrhagic strokes; the reason for this can be sought in the fact that hemorrhagic stroke acts not only via direct cellular damage

but also through high intracerebral pressure or vascular spasms. This translates into different neuroplasticity levels in subjects who have suffered ischemic or hemorrhagic events (22).

The second difference is the timings of outcome assessment: in FLAME, patients were treated for 3 months whereas in the FOCUS 6 months, with outcomes assessed at the completion of the treatment period has. It is possible to speculate that the benefit could be present only after 3 months (unfortunately, no information is available regarding functional outcomes in the FOCUS at the end of the 3-month period). This could be explained with the fact that neuroplasticity can have different pathways and effects according to the time-point analysis: effects could be visible in the short term and not in the long term and also the contrary (23). However, the fact that there were no benefits in the use of fluoxetine at the end of the 6-month period suggests that any potential benefit at the end of the 3-month period is non-persistent.

The third point was the presence/absence of background therapies: all patients in FLAME underwent physiotherapy in the course of the treatment timeframe, whereas this was not the case with the FOCUS. In this respect, it must be noted that physiotherapy could play an additive effect by reinforcing the effects from the SSRI, since it has been demonstrated that both approaches determine an effect to the neuroplasticity of the brain (4,5,8,9).

Conclusions

In conclusion, the results from the FOCUS showed, quite inexpertly, that fluoxetine 20 mg administered daily for 6 months following acute stroke does not provide any sort of improvement in terms of functional outcomes. Moreover, despite a reduction in the occurrence of depression, an increment in the frequency of bone fractures is observed. It would be important also to understand the discrepancy between the results of the FOCUS trial and the myriad of small studies which suggest that fluoxetine would be effective. However, it is important to remain prudent before coming to definitive conclusions: more data from the ongoing AFFINITY and EFFECTS trials are needed to properly balance the benefits of enhanced mood against the risks of adverse effects. These trials are expected to show their results by the year 2020. At that point we will have enough data to draw definitive conclusion.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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