TIME FOR THE NEXT PHASE OF STROKE RECOVERY TRIALS

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Nine years ago, the FLAME trial¹ suggested that early prescription of daily 20 mg fluoxetine, a selective serotonin reuptake inhibitor (SSRI), could dramatically enhance upper and lower limb motor recovery measured with the Fugl-Meyer motor scale in patients with moderate to severe ischemic stroke. The rationale for using fluoxetine was that it would enhance spontaneous post-stroke plasticity mechanisms with beneficial effects on functional recovery¹. FLAME put fluoxetine in the spotlight as a 'recovery' drug but it was a relatively small trial (N=118) and did not generate sufficient evidence on its own to change practice¹.

In the present issue of the Lancet Neurology, two almost identical high-quality phase III trials, the AFFINITY² and EFFECTS³ trials, examined the effects of fluoxetine on disability 6 months after stroke. The AFFINITY trial is an international double-blind, placebo-controlled trial conducted in Australia, New Zealand and Vietnam (N=1280), whereas the EFFECTS trial is a national trial conducted at 35 sites (N=1500) in Sweden. (Table 1) These two trials followed the larger FOCUS trial conducted at 103 sites in the UK (n=3127)⁴. All three trials convincingly show that the use of 20 mg fluoxetine prescribed daily and starting 2-15 days after stroke has no effects on the modified Rankin Scale (mRS), as illustrated by an identical common odds for the AFFINITY (0.94, 95%CI:0.76-1.15;p=0.53)², EFFECTS trial (0.94,95%CI:0.78-1.13;p=0.42)³, and FOCUS (0.95,95%CI:0.84-1.08;p=0.44)⁴. As expected, there were beneficial effects on mood and emotional control in both trials^{2,3} with a significant lower proportion of new depressions in the EFFECTS trial³, it is also clear that daily use of fluoxetine may also cause harm with an increased incidence in number of serious falls², with more bone fractures of 2-3%^{2,3}, epileptic seizures², hyponatremia³ and uncontrolled diabetes³ in the first 6 months post stroke. So, the promising results from the FLAME trial¹ have not been supported. The AFFINITY², EFFECTS³ and FOCUS⁴ trials (combined N=5907) had high adherence and a low risk of bias, so we now have further class I evidence that the simple daily prescription of 20 mg fluoxetine cannot be recommended for patients with a mild³ to moderate² stroke undergoing routine post-stroke care. The differences and similarities between the results of all four trials are shown in Supplementary Table 1.

Before closing the chapter on pharmacological enhancement of recovery after brain injury however, it is worth revisiting why fluoxetine was considered a recovery drug in the first place.

In fact, there is a wealth of evidence from animal models that fluoxetine, and SSRIs in general, can increase the potential for activity-dependent plasticity in the adult brain, most likely through a reduction of extracellular levels of GABA and an increase in BDNF-expression⁵. There has been interest in the modulation of other neurotransmitter systems to promote recovery after brain injury but it has always been understood that drugs help only when combined with appropriate environmental experience⁶. This crucial difference between drugs as enhancers of physical or behavioural training effects rather than restorative agents was not appreciated in the design of the FOCUS, AFFINITY and EFFECTS trials. There was no attempt to influence or even measure the physical or behavioural training so important for stroke recovery. It has been suggested⁷ that the identical outcomes used in the FOCUS, AFFINITY and EFFECTS trials will allow for a combined secondary analysis to look for interactions with the amount of exercise therapy provided at an individual level. However, the dose of usual care rehabilitation is likely insufficient in all three trials for this to be revealing.^{6,8} The key clinical question, whether pharmacotherapy can modulate an adequate dose of physical or behavioral training to enhance stroke recovery, has yet to be addressed in a phase III trial.

Another contentious area is that of appropriate outcome measures. FOCUS⁴, AFFINITY² and EFFECTS³ used the mRS, the most commonly used outcome score in large stroke recovery trials, as the primary outcome score. In the FLAME trial¹, the mRS (a secondary outcome measure) showed a significantly greater improvement in the fluoxetine group, and so attempting to replicate this result further in the larger trials is understandable. However, given its likely mechanism of action, fluoxetine is most likely to impact at the level of impairment and so attempting to replicate the effect of fluoxetine on impairment seen in FLAME¹ would have been useful. Changes in impairment do not necessarily universally translate into reduced overall disability assessed by mRS. With this in mind, the recent Stroke Recovery and Rehabilitation Roundtable (SRRR) group published several consensus documents on how to harmonize stroke recovery research with respect to stratified trial design, using biomarkers and outcome measures⁸. With a shared vision, the SRRR group recommended a set of additional validated performance tests, beyond the use of the mRS for stroke recovery and rehabilitation trials⁹. One hope is that careful selection of primary and secondary outcome measures might allow characterization of those people more likely to respond in different ways (reduced impairment, improved activity and/or participation), leading to further targeted trials with appropriate stratification¹⁰. In the case of recovery of behavior for example, there is an urgent need to measure quality of movement in stroke recovery and rehabilitation trials to understand what patients learn and how they improve their motor performance after stroke⁹. We note that several organisations have adopted these recommendations as important considerations when appraising funding applications.

The current three almost identical trials arrived together. Whilst we acknowledge that AFFINITY² and EFFECTS³ would have been started before FOCUS⁴ concluded, it is now not clear what their added value is. It seems that the same lemon is squeezed not once, but twice more with necessarily diminishing returns. In a world of limited resources, it illustrates the need for a global agenda for stroke recovery research allowing the optimal alignment of trials to address complementary research questions. To improve stroke recovery research, we foresee a growing need for the role of SRRR in designing and delivering improved and more robust translational trials that bridge the gap between pre-clinical and clinical fields. In particular, there is an important role for the Global Alliance of Independent Networks focused on stroke

Trials (GAINS) (<https://www.globalstroketrials.org/>) to improve communication, alignment and complementary (not identical) design of phase III and IV trials between the excellent national networks that already exist worldwide in stroke research. We hope this does not signal the end of pharmacotherapy for stroke recovery, but rather the beginning of the next phase.

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