Time for the next stage of stroke recovery trials

Almost 10 years ago, the FLuoxetine for motor recovery After acute ischaemic stroke (FLAME) trial suggested that early prescription of daily 20 mg fluoxetine, a selective serotonin-reuptake inhibitor (SSRI), could substantially enhance upper and lower limb motor recovery, as measured with the Fugl-Meyer Motor Assessment Scale, in patients with moderate to severe ischaemic stroke. The rationale for using fluoxetine was that it would enhance spontaneous poststroke plasticity mechanisms, with beneficial effects on functional recovery. FLAME put fluoxetine in the spotlight as a recovery drug, but the study was a small trial (N=118) and did not generate robust evidence to change practice.1

Two almost identical phase 3 trials, the Assessment Of Fluoxetine In Stroke recovery (AFFINITY) trial and the Efficacy of Fluoxetine—a randomisEd Controlled Trial in Stroke (EFFECTS),1 reported in The Lancet Neurology, have examined the effects of fluoxetine on disability 6 months after stroke. The AFFINITY trial was an international, double-blind, placebo-controlled study done in Australia, New Zealand, and Vietnam (N=1280), whereas the EFFECTS trial was a national study done at 35 sites (N=1500) in Sweden. These two trials followed the larger Fluoxetine Or Control Under Supervision (FOCUS) trial2 done at 103 sites in the UK (N=3127). All three trials convincingly show that the use of 20 mg oral fluoxetine prescribed daily and starting 2–15 days after stroke has no effects on the modified Rankin Scale (mRS) compared with placebo, as shown by an identical common odds ratio in the AFFINITY trial: (0.94, 95% CI 0.76–1.15; p=0.53) and the EFFECTS trial (0.94, 0.78–1.13; p=0.42), and similar in the FOCUS trial: (0.95, 0.84–1.08; p=0.44). As expected, fluoxetine had a beneficial effect on mood and emotional control in both AFFINITY and EFFECTS, with a significantly lower proportion of patients with a new diagnosis of depression in the fluoxetine group compared with the placebo group in the EFFECTS trial.3 Daily use of fluoxetine might also cause harm, with an increased number of serious falls,4 bone fractures,5–7 epileptic seizures,5 hyponatraemia,5 and uncontrolled diabetes5 in the first 6 months poststroke. Therefore, the promising results from the FLAME trial have not been supported by the results from these three trials. The AFFINITY, EFFECTS, and FOCUS trials (combined N=5907) had high adherence and a low risk of bias, providing class I evidence that daily 20 mg oral fluoxetine should not be recommended for patients with a mild to moderate stroke having routine poststroke care. The differences and similarities between the results of all four trials of fluoxetine for recovery after stroke are shown in the appendix.

However, before closing the chapter on pharmacological enhancement of recovery after brain injury, it is worth revisiting why fluoxetine was considered a recovery drug in the first place. There is a wealth of evidence from animal models that fluoxetine specifically, and SSRIs in general, can increase the potential for activity-dependent plasticity in the adult brain, most probably through a reduction of extracellular concentrations of GABA and an increase in BDNF expression.5 There has also 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 experience.4 This crucial difference between drugs as enhancers of physical or behavioural training effects and drugs as restorative agents was not appreciated in the design of the FOCUS, AFFINITY, and EFFECTS trials. In these trials, there was no attempt to influence or even measure the physical or behavioural training that is so important for stroke recovery. It has been suggested6 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 patient level. However, the dose of usual care rehabilitation is likely to be insufficient in all three trials for this secondary analysis to be informative.6,8 The key clinical question, whether pharmacotherapy can modulate an adequate dose of physical or behavioural training to enhance stroke recovery, has yet to be addressed in a phase 3 trial.

Another contentious issue is the appropriateness of the outcome measures. In the FLAME trial, the mRS (a secondary outcome measure) showed a significantly greater improvement in the fluoxetine group than in the placebo group, and thus attempts to replicate this result in the larger trials are understandable. Therefore, FOCUS, AFFINITY, and EFFECTS used the mRS as the primary outcome. However, given its probable mechanism of action, fluoxetine was most likely to have an effect at
the level of impairment, and changes in impairment do not necessarily translate into reduced overall disability as assessed by the mRS. With this in mind, the Stroke Recovery and Rehabilitation Roundtable (SRRR) group has provided consensus recommendations to harmonise stroke recovery research with respect to stratified trial design, use of biomarkers, and outcome measures. The SRRR recommended additional validated performance tests beyond the use of the mRS for stroke recovery and rehabilitation trials. One hope is that careful selection of primary and secondary outcome measures might allow characterisation of those patients more likely to respond to treatments in different ways (eg, reduced impairment, improved activity, improved participation), leading to targeted trials with appropriate stratification. For example, in the case of motor recovery, 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 stroke. We note that several organisations have adopted these recommendations as important considerations when appraising grants.

AFFINITY7 and EFFECTS8 started before FOCUS9 concluded, but it is now not clear what their added value is. In a world of finite resources, these trials illustrate the need for a global agenda for stroke recovery research that allows optimal alignment to address complementary research questions. To improve stroke recovery research, the SRRR should help in designing and delivering improved and more robust translational trials that bridge the gap between preclinical and clinical fields. There is an important role also for the Global Alliance of Independent Networks focused on Stroke trials (GAINS) to improve communication, alignment, and complementary (not identical) design of phase 3 and 4 trials among the excellent national networks that already exist in stroke research worldwide. The results from the AFFINITY and EFFECTS trials should not signal the end of pharmacotherapy for stroke recovery, but rather the beginning of the next stage.

We declare no competing interests.

G Kwakkel, CGM Meskers, NS Ward
g.kwakkel@amsterdamumc.nl

Department of Rehabilitation Medicine, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam Movement Sciences, Amsterdam Neuroscience, 1081 HV Amsterdam, Netherlands (GK, CGMM), Department of Physical Therapy and Human Movement Sciences, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA (GK, CGMM); Department of Clinical and Motor Neuroscience, University College London Queen Square Institute of Neurology, London, UK (NSW), and Department of Neurology, National Hospital for Neurology and Neurosurgery, London, UK (NOW)