Editorial Commentary



# Fluoxetine in stroke (FOCUS) trial—reasons to be cheerful about antidepressants in stroke?

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## Why study Fluoxetine for stroke recovery?

Despite substantial advances in prevention and treatment, stroke stubbornly remains the world's leading cause of death and adult disability (1). Stroke and the burden of stroke are increasing globally with a particular rise in the prevalence of people living with long-term stroke related disability (2). In this context, any treatment that can prevent or reduce stroke related impairments would be of substantial public health importance. Unfortunately, the stroke therapeutic toolbox has limited options. We have a robust evidence base to support hyperacute treatments such as intravenous thrombolysis and mechanical thrombectomy and we have effective secondary prevention strategies (3-5). However, to date, all putative neuroprotective or neurorestorative therapies have failed to deliver clinically important benefits.

Many in the stroke community had cautious optimism that trials of selective serotonin reuptake inhibitors (SSRIs) may offer the elusive positive result we had been waiting for. Certainly, all the initial signals were hopeful. SSRIs had shown convincing benefits in animal models of stroke (6), observational data were supportive (7) and early phase trials had results that trended in the right direction (8). The publication of the FLAME (Fluoxetine for motor recovery after acute ischaemic stroke) trial generated further excitement (9). FLAME suggested that the SSRI Fluoxetine could decrease stroke related disability. The body of SSRI-stroke trial evidence was collated by the evidence synthesis group Cochrane. The Cochrane Stroke Group concluded that while the accumulating data were encouraging, an adequately powered trial was needed before any treatment recommendations could be made (8).

## FOCUS design and headline results

Thus, a trial was designed—the Fluoxetine or Control Under Supervision (FOCUS) randomised controlled trial (RCT) (*Table 1*) (10). The trial was delivered within the UK National Health Service across a network of secondary care stroke centres. Participants were randomised relatively early after stroke to 6 months of fluoxetine (20 mg once daily) or matching placebo. Primary outcome was stroke related disability as measured by the modified Rankin Scale (mRS) (11). A series of secondary efficacy, safety and health economic measures were also collected. FOCUS conformed to all the characteristics associated with a good quality trial—there was double blinding, robust randomisation and all aspects of conduct and analysis were pre-defined in a published protocol.

Unfortunately, FOCUS continued the tradition of so many preceding stroke RCTS. Despite all the promise of the background evidence, the trial was convincingly neutral for the primary endpoint—after 6 months of treatment, stroke related disability did not differ between active and control arms. A reminder, if any reminder was needed, of the importance of well-designed and conducted RCTs—even when the weight of observational and pre-clinical data are supportive.

With all the caveats that come with analysis of secondary

 

**Table 1** Summary of FOCUS trial

| Domain | Details for FOCUS RCT |
|---|---|
| Patients | Adult stroke survivors within 15 days of stroke, with residual impairments not taking SSRI for depression (n=3,127), UK NHS setting |
| Intervention | Fluoxetine 20 mg, oral administration, given once daily for 6 months |
| Control | Matched placebo, oral administration, given once daily for 6 months |
| Outcomes | Primary: global disability at 6 months [modified Rankin Scale (mRS)] |
| | Secondary: survival; quality of life (stroke impact scale andEuroQol-5); mood (mental health inventory); fatigue (SF36); adverse events (events of specific interest: depression, fracture, cv events, seizures, metabolic abnormalities, bleeding, self-harm) |
| Study type | Multi-centre, parallel group, double-blind, randomised, placebo-controlled trial |
| Results | Primary: difference in mRS, odds-ratio 0.95 (95% CI, 0.84–1.08) |
| | Secondary (selected): incident depression: difference –3.78 (–6.3 to –1.3)<br>Fractured bone: difference 1.41 (0.38 to 2.43) |
| Author conclusions | *"Results do not support the use routine use of fluoxetine either for prevention of post-stroke depression or to promote recovery of function"* |

FOCUS, Fluoxetine or Control Under Supervision; RCT, randomised controlled trial.

outcomes, the authors described some interesting results from these data. The rate of new depression at 6 months was significantly lower in the group receiving fluoxetine but the rate of bone fracture was increased in the fluoxetine group. Despite concerns around metabolic disturbance and bleeding with SSRI treatment, there were no other significant differences in rates of adverse events between groups. Based on balance of risk, the authors' interpretation of the trial results was that the data do not support the use of fluoxetine to improve recovery or reduce depression.

## Exploring reasons for the FOCUS trial's unexpected results

So, why was the FOCUS trial neutral? We can confidently discount many of the common cited reasons for a non-significant finding. With 3,127 participants, the trial had sufficient power to detect a modest but clinically meaningful effect; the impressive retention (less than 1% lost to follow-up) suggests that attrition is not contributing; the baseline clinical and demographic features were matched between groups and representative of a contemporary stroke cohort.

Could the outcome assessment have biased results? There is ongoing debate amongst stroke trialists around the optimal method to describe and analyse stroke related disability (12). The FOCUS trialists assessed their primary outcome of mRS using both dichotomisation (disabled and non-disabled) and shift across ordinal grades. Reassuringly, results were the same for both approaches. Outcome assessment was by postal questionnaire and additional telephone assessment was used where needed. Purists may argue that face to face assessment is more valid but in a pragmatic, large scale trial any measure that offers comprehensive data capture is acceptable (13). The previously published FLAME trial (9) demonstrated treatment benefit on a detailed stroke impairment scale, while FOCUS used a more global assessment of disability. Arguably the FOCUS approach is the more meaningful of the two. Health services are unlikely to invest in a therapy that offers subtle changes in function but that doesn't translate into any change in daily function (14).

Two factors that are worthy of considering are ethnicity and adherence. Until FOCUS much of the trial evidence had originated from Chinese populations. FOCUS had less than 1% participants of Chinese ethnicity and so a question remains around potential effects in this group. Adherence (active and placebo) was not perfect, around two thirds of participants took at least 150 days of study drug. However, these figures are comparable or better than SSRI compliance in real world treatment settings (15). Perhaps the most convincing, if disappointing, reason for the neutral finding is that the SSRI didn't have any neurorestorative or neuroprotective properties.

 

## Fluoxetine and prevention of depression

Accepting all of this, there may still be reasons to be cheerful about SSRI in stroke. The data describing lower rates of incident depression suggest that the drug is, at least, having the desired biological effect. The loss of between group effects at 12 months (6 months after treatment discontinuation) further confirms that the mood changes are likely to be a real effect of the drug. An intervention that reduces stroke related depression could prove to be incredibly important in stroke care. Rates of depression following stroke are substantial, current estimates are that at any one time around a third of people living with stroke have depression and over a 5-year time horizon one in two will have an episode of clinical depression (16). Despite these figures, the psychological aspects of stroke care have tended to be overlooked in favour of physical impairments and the assessment and treatment of post stroke depression is inconsistent and reactive (17). Although not designed as a mood trial, the FOCUS data are of an order of magnitude larger than the pooled results of all previous RCTs of pharmacological mood therapy in stroke (18). Indeed, FOCUS is one of the largest RCTS of antidepressant therapy in any patient group (19).

While the benefits of this depression prevention are real, we should not ignore the risk of fracture. For many reasons people living with stroke are at high risk of falls and fractures (20). A treatment that potentially improves mood but leads to a disabling event such as a fractured femur is not particularly appealing. Based on the risk, benefit trade-off the FOCUS trialists do not recommend use of fluoxetine for prophylaxis of depression. This difficult risk, balance is not unprecedented in stroke medicine. The IRIS trial, one of the largest stroke secondary prevention trials, found that the thiazolidinedione pioglitazone reduced vascular events but at the cost of increased fracture (21). Some have argued that pioglitazone may still have a role in stroke care, if patients at high risk of recurrent events and lower risk of fracture could be identified and targeted for treatment (22). It seems plausible that the same argument could hold for fluoxetine and incident depression. Of course, this kind of precision medicine approach demands that we understand risk factors and natural history of posts stroke psychological problems and at present, our understanding of both is limited (23).

## Where now for Fluoxetine and stroke

The FOCUS trial provides salient lessons for future pre-clinical and clinical research. The pre-clinical data supporting SSRI and stroke were compelling but, with hindsight, the experimental conditions may not have completely aligned with the 'messy reality' of clinical stroke. In this regard, moves to conduct pre-clinical research using methodological approaches that are closer to clinical trials are welcome. Experts groups such as the Stroke Recovery and Rehabilitation Roundtable are bringing together pre-clinical and clinical researchers to raise standards and harmonise activity in stroke research and we look forward to the outputs from these collaborations (24). Indeed, other fields in the clinical neurosciences, such as dementia, could also learn from this approach (25).

FOCUS is not the final chapter in the SSRI-stroke story. Two other major trials of SSRI in stroke (AFFINITY and EFFECTS) are recruiting and should report results soon (26). The trials have similar interventions and outcomes and so as well as presenting individual results, an individual patient level meta-analysis is also planned. Given the size of FOCUS, it seems unlikely that these other trials will change the general neutral finding for SSRI and stroke related disability, but they may provide important additional information on issues such as ethnicity and depression. The harmonised approach across the trials is a model for future large scale international stroke research (27) and that is something to be happy about.

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## Footnote

*Conflicts of Interest*: The author has no conflicts of interest to declare.

## References

1. GBD 2015 Mortality and Causes of Death Collaborators. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016;388:1459-544.
2. Feigin VL, Norrving B, Mensah GA. Global burden of stroke. Circ Res 2017;120:439-48.
3. Lees KR, Bluhmki E, von Kummer R, et al. Time to treatment with intravenous alteplase and outcome

 

in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. Lancet 2010;375:1695-703.
4. MacIsaac RL, Khatri P, Bendszus M, et al. A collaborative sequential meta-analysis of individual patient data from randomized trials of endovascular therapy and tPA vs. tPA alone for acute ischemic stroke: ThRombEctomy And tPA (TREAT) analysis. Int J Stroke 2015;10 Suppl A100:136-44.
5. McArthur KS, Quinn TJ, Higgins P, et al. Post-acute care and secondary prevention after ischaemic stroke. BMJ 2011;342:d2083.
6. McCann SK, Irvine C, Mead GE, et al. Efficacy of antidepressants in animal models of ischemic stroke: a systematic review and meta-analysis. Stroke 2014;45:3055-63.
7. Mortensen JK, Larsson H, Johnsen SP, et al. Impact of prestroke selective serotonin reuptake inhibitor treatment on stroke severity and mortality. Stroke 2014;45:2121-3.
8. Mead GE, Hsieh CF, Lee R, et al. Selective serotonin reuptake inhibitors (SSRIs) for stroke recovery. Cochrane Database Syst Rev 2012;11:CD009286.
9. Chollet F, Tardy J, Albucher JF, et al. Fluoxetine for motor recovery after acute ischaemic stroke (FLAME): a randomised placebo-controlled trial. Lancet Neurol 2011;10:123-30.
10. FOCUS trial collaboration. Effects of fluoxetine on functional outcomes after acute stroke (FOCUS): a pragmatic, double-blind, randomised, controlled trial. Lancet 2019;393:265-74.
11. Quinn TJ, Dawson J, Walters M, et al. Reliability of the modified Rankin Scale: a systematic review. Stroke 2009;40:3393-5.
12. Bath PM, Gray LJ, Collier T, et al. Can we improve the statistical analysis of stroke trials? Statistical Reanalysis of Functional Outcomes in Stroke Trials. Stroke 2007;38:1911-5.
13. McDermid I, Barber M, Dennis M, et al. Home-time is a feasible and valid stroke outcome measure in national datasets. Stroke 2019;50:1282-5.
14. Harrison JK, McArthur KS, Quinn TJ. Assessment scales in stroke: clinimetric and clinical considerations. Clin Interv Aging 2013;8:201-11.
15. Coupland C, Dhiman P, Morriss R, et al. Antidepressant use and risk of adverse outcomes in older people: population based cohort. BMJ 2011;343:d4551.
16. Hackett ML, Pickles K. Part I: frequency of depression after stroke: an updated systematic review and meta-analysis of observational studies. Int J Stroke 2014;9:1017-25.
17. Robinson RG, Jorge RE. Post-stroke depression: a review. Am J Psychiatry 2016;173:221-31.
18. Hackett ML, Anderson CS, House A, et al. Interventions for treating depression after stroke. Cochrane Database Syst Rev 2008;(4):CD003437.
19. Cipriani A, Furukawa TA, Salanti G, et al. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. Lancet 2018;391:1357-66.
20. Dennis MS, Lo KM, McDowall M, et al. Fractures after stroke: frequency, types and associations. Stroke 2002;33:728-34.
21. Kernan WN, Viscoli CM, Furie KL, et al. Pioglitazone after Ischemic Stroke or Transient Ischemic Attack. N Engl J Med 2016;374:1321-31.
22. Viscoli CM, Kent DM, Conwit R, et al. Scoring System to Optimize Pioglitazone Therapy After Stroke Based on Fracture Risk. Stroke 2018. [Epub ahead of print].
23. Kutlubaev MA, Hackett ML. Part II: Predictors of depression after stroke and impact of depression on stroke outcome: an updated systematic review of observational studies. Int J Stroke 2014;9:1026-36.
24. Bernhardt J, Hayward KS, Kwakkel G, et al. Agreed definitions and a shared vision for new standards in stroke recovery research: The Stroke Recovery and Rehabilitation Roundtable taskforce. Int J Stroke 2017;12:444-50.
25. Ritchie CW, Terrera GM, Quinn TJ. Dementia trials and dementia tribulations: methodological and analytical challenges in dementia research. Alzheimers Res Ther 2015;7:31.
26. Mead G, Hackett ML, Lundström E, et al. The FOCUS, AFFINITY and EFFECTS trials studying the effect(s) of fluoxetine in patients with a recent stroke: a study protocol for three multicentre randomised controlled trials. Trials 2015;16:369.
27. Doubal FN, Ali M, Batty D, et al. Big data and data repurposing - using existing data to answer new questions in vascular dementia research. BMC Neurology 2017;17:72.

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