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Maturitas

Boon or Bane: Using Antidepressants After Stroke

--Manuscript Draft--

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18 January 2021

Prof Leon Flicker
Editor, Maturitas

Dear Prof Flicker

Re: Boon or Bane: Using Antidepressants After Stroke

Thank you for inviting us to contribute an editorial for Maturitas. Please find attached the relevant manuscript.

I would like to take the opportunity to thank you for allowing us to include one figure, eight references and three co-authors (four in total) in this editorial.

I look forward to hearing from you.

With kind regards

Oswaldo P. Almeida (on behalf of the authors)

Boon or Bane: Using Antidepressants After Stroke

The results of the fluoxetine in motor recovery of patients with acute ischaemic stroke (FLAME) trial (n=118) showed that stroke survivors treated with fluoxetine had better motor function than their counterparts treated with placebo for 3 months [1]. Three large randomised placebo-controlled trials were subsequently designed to confirm these preliminary findings: the fluoxetine or control under supervision (FOCUS) trial (n=3127), the assessment of fluoxetine in stroke recovery (AFFINITY) trial (n=1280), and the efficacy of fluoxetine randomised controlled trial in stroke (EFFECTS) (n=1500) [2-4]. The three trials found that daily treatment with 20 mg of fluoxetine for 6 months after acute stroke does not improve functional outcomes, but increases the risk of bone fractures [2-4]. These findings raised significant concerns regarding the safe use of fluoxetine in this population, but need to be balanced against potential benefits, such as the prevention of depression.

The FLAME trial used the Montgomery-Åsberg Depression Rating Scale (MADRS) to assess depressive symptoms at study entry and after 3 months. The scores of participants treated with placebo increased significantly more than for those treated with fluoxetine. In FOCUS and AFFINITY, depression was defined as a new clinical diagnosis recorded during trial follow-up that required treatment with an antidepressant [2,4], whereas in EFFECTS the need for antidepressant use was not required [3]. The fluoxetine and placebo groups were well balanced for all relevant measures at the time of randomisation in the three trials. FOCUS and EFFECTS, but not AFFINITY, found that treatment with fluoxetine decreased the odds of depression among study participants. Such findings offer some reassurance that treatment with fluoxetine may prevent post-stroke depression (most participants were not depressed at randomisation), but fail to address the risk-benefit issue associated with the use of fluoxetine. For this reason, we pooled the unadjusted published data for these three trials to estimate the risk ratio of

depression and fractures, and respective 95% confidence limits (95%CL). We used a random effects restricted maximum likelihood (REML) model to summarise the depression and fracture data from the three trials, and calculated the absolute risk reduction (ARR) for depression and the absolute risk increase (ARI) for fractures associated with fluoxetine use. The number needed to treat (NNT) is the reciprocal of the ARR and the number needed to harm (NNH) is the reciprocal of the ARI. The risk benefit ratio (RBR) was calculated as the ARI/ARR . $RBR > 1$ indicates that treatment is associated with harm, and results < 1 with benefit.

The figure shows the unadjusted distribution of depression and fractures in the FOCUS, AFFINITY and EFFECTS trials: 6 months of treatment with fluoxetine was associated with a decreased pooled risk of depression and an increased risk of fractures. The ARR of depression associated with fluoxetine use was 3.37%, whereas the ARI of fractures was 1.76%. The NNT to prevent one case of depression was 30 and the NNH to cause a fracture was 56. The RBR was 0.52.

FIGURE

The mechanism linking fluoxetine to fractures in this population is most likely associated with its negative effect on bone density [5], higher risk of falls [2,4], or it could be due to increased activity among stroke survivors without depression. This increased risk should be an area of concern for the practicing clinician, despite fractures being a relatively uncommon clinical complication in this population. Indeed, the 6-month probability of new depression following a stroke was 10 times greater than new fractures. With 30 people with stroke requiring treatment with fluoxetine for six months for one person to avoid depression, the use of

1 fluoxetine for the prevention of depression should not be dismissed. Systematic review
2 evidence indicates that antidepressants may be similarly useful in preventing depression after
3 a stroke [6], and longitudinal data from other sources suggest that antidepressants may have no
4 lingering effect on the risk of fractures in later life, as other competing risk factors for fractures,
5 such as history of past fractures and frailty, are likely to override small detrimental effects
6 associated with the use of antidepressants [7].
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17 We would suggest that the potential increase in the risk of fractures associated with the use of
18 fluoxetine is overshadowed by its ability to prevent depression after stroke, although these are
19 but two among numerous clinical outcomes that clinicians must consider when making
20 decisions about how best to manage these patients. Instead of refraining from using fluoxetine
21 (or another antidepressant [8]), it may be more helpful to consider alternative strategies to
22 reduce the risk of fractures in this population, such as addressing factors associated with falls
23 (e.g., sedatives and polypharmacy) and the early introduction of measures to manage
24 osteopenia and osteoporosis. Weighing up risks and benefits associated with interventions, as
25 well as managing competing risk factors associated with undesirable health outcomes,
26 continues to be core business for competent clinicians.
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Drafting of the manuscript: Almeida.

Critical revision of the manuscript for important intellectual content: Almeida, Jones, Hackett and Hankey.

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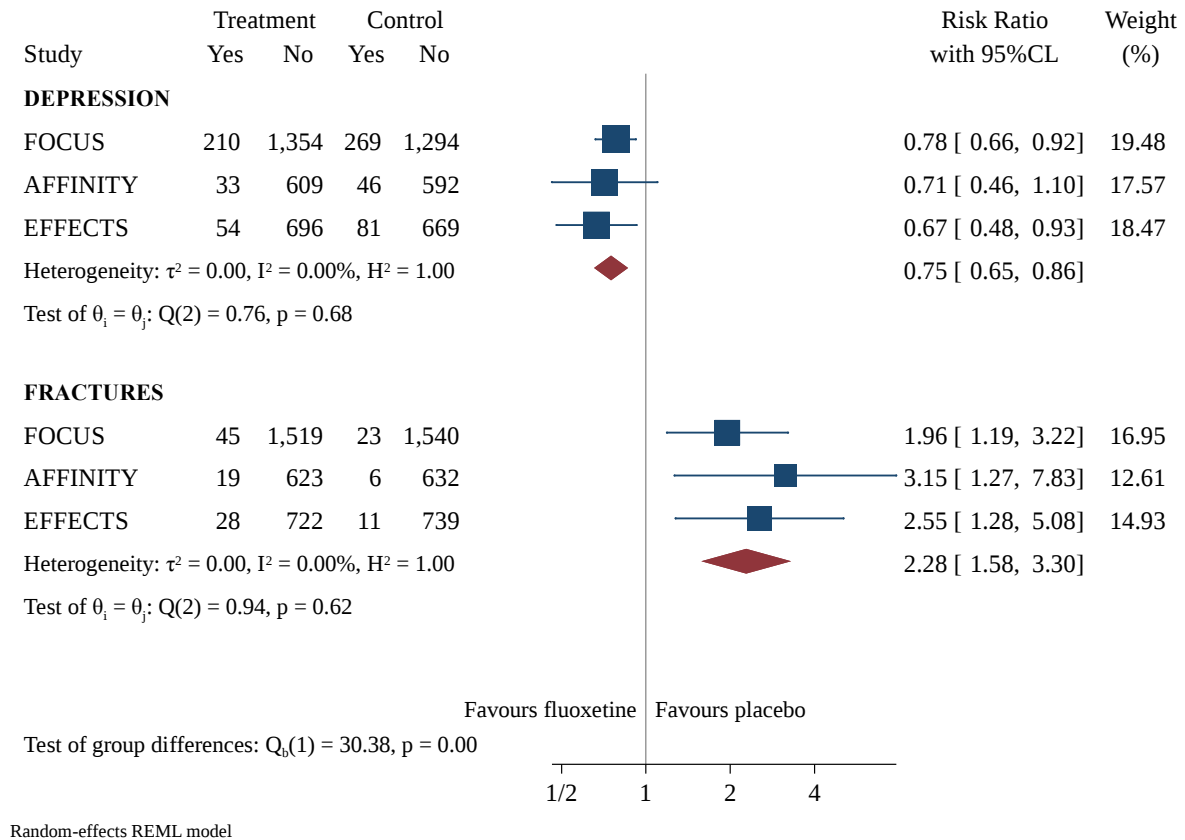


Figure 1. Forest plot showing the unadjusted effects of fluoxetine use for 6 months on the risk of post-stroke depression (new depression since randomisation) and fractures.

Declaration of interests

The authors declare they have no conflicts of interest.