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Declaration of interest

The authors declare that they have no conflict of interest.

Letter

We congratulate Lee and colleagues for their article “Effects of various statins on depressive symptoms: A network meta-analysis”, published in June 2021 in the *Journal of Affective Disorders* (Lee et al., 2021). In this paper, they included 13 randomised controlled trials with the aim of determining the “optimal statin” for the treatment of depression. They found that only atorvastatin, compared to placebo, significantly reduced depressive symptoms (mean difference [MD]= -3.46, 95% confidence interval [95% CI]: -5.26 to -1.67). All other statins (simvastatin, lovastatin, pravastatin, and rosuvastatin) failed to produce a significant benefit. Lee et al. also reported that atorvastatin was specifically more efficacious in reducing depressive symptoms compared to simvastatin (MD= 2.29, 95% CI= -4.45 to -0.13) and pravastatin (MD= 3.31, 95% CI= -5.75 to -0.88), whereas no differences emerged from any of the other comparisons. They noticed a “low similarity of included studies” and that a single study (Sparks et al., 2005) was responsible for the large treatment effect seen for atorvastatin. They concluded that “in this first network meta-analysis, atorvastatin, with high intensity and a lipophilic effect, was identified as the optimal choice of statin for treating depression”.

Through their ability to express several potentially useful neurobiological effects in depression (especially, anti-inflammatory), as well as their well-established safety profile, statins are ideal candidates for drug repurposing in depression – as confirmed by promising results from *in vitro*, animal, and clinical studies (De Giorgi et al., 2021a). Accordingly, our previous meta-analysis published in March this year showed that statins can be efficacious in depressed patients when given in addition to antidepressant treatment after as little as two months (standardised mean difference [SMD]= -0.48, 95% CI= -0.74 to -0.22), with acceptability, tolerability, and safety that are comparable to placebo (De Giorgi et al., 2021b).

In the same article, we conducted a network meta-analysis to compare and rank the antidepressant efficacy of different statins. In contrast to several previous analyses, including that of Lee et al., this analysis included only those 5 trials that involved a homogeneous population of depressed participants. In view of the low number of trials and participants included, we defined our network meta-analysis as “exploratory”, thus advising that its results should not be considered conclusive. We found no differences between individual statins, but only simvastatin (SMD= 0.92, 95% CI= 0.41 to 1.43) and lovastatin (SMD = 0.77, 95% CI = 0.22 to 1.32) appeared significantly better than placebo in relieving depression, whereas the positive trend of atorvastatin and rosuvastatin was not statistically significant. We therefore hypothesised that our results could reflect statins’ (theoretical) differential capacity to cross the blood-brain barrier according to their lipophilicity – respectively, simvastatin > lovastatin > atorvastatin > rosuvastatin. In line with this finding, a small (300 patients with comorbid depression and acute coronary syndrome) observational study by Kim and colleagues had shown a higher antidepressant response in those who used a lipophilic statin compared to all other statins (odds ratio [OR]= 2.91, 95% CI= 1.21–6.99) (Kim et al., 2015). Consistent with this, a very large (4,607,990 depressed individuals) cohort study reported an antidepressant effect for simvastatin (OR= 0.93, 95% CI= 0.89-0.97), whereas atorvastatin seemed to increase the risk of depression (OR= 1.11, 95% CI= 1.01-1.22) (Redlich et al., 2014). Again, our interpretation should be considered tentative: although some evidence indicates a degree of central inflammation in depressed patients (Enache et al., 2019), others have suggested that peripheral inflammation may play a more crucial role (Bullmore, 2018). Still, it is noteworthy that the two ongoing trials investigating the antidepressant effects of statins in depression (Husain et al., 2019; Otte et al., 2020) have chosen to use simvastatin in preference to others.

Overall, it is perhaps unsurprising that the findings from the network meta-analysis by Lee and colleagues differ from our own. As mentioned, they included 13 trials of which only 5 involved patients with depression, while the remainder were in non-depressed populations of participants with hypercholesterolaemia (3 studies), coronary syndromes (1 study), multiple sclerosis (1 study), Alzheimer’s disease (1 study), traumatic brain injury (1 study), and healthy volunteers (1 study). Correspondingly, 4 out of 5 studies on depressed participants included an antidepressant treatment in addition to a statin, whereas all other studies compared statins alone. Although a certain degree of heterogeneity is to be expected in most meta-analyses, and can be dealt with via appropriate statistical methods, pooling such clinically heterogeneous trials is methodologically challenging. An excess of clinical heterogeneity certainly leads to significant statistical heterogeneity, and therefore potentially inaccurate or misleading conclusions (Chess and Gagnier, 2016). Indeed, Lee et al. do report high heterogeneity ($I^2 = 83.1\%$) in their study. Therefore, we suggest that their strong conclusion that “atorvastatin...[represents] the optimal choice of statin for treating depression” should be received with caution at this stage.

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