Reviewer’s report

Title: Youth Depression Alleviation with Anti-inflammatory Agents (YoDA-A): A Randomised Clinical Trial of Rosuvastatin and Aspirin

Version: 0 Date: 07 Oct 2019

Reviewer: Giovanni De Girolamo

Reviewer's report:

This is an important RCT on a topic of great interest, given the current paucity of effective treatments for youth depression. It should be published, but some issues should be solved and problems with the current manuscript should be tackled.

1. There was an impressive number of young people invited to join the study who declined to participate (N=500). Since the number is 4 times the number of enrolled subjects, they should explain this very high refusal rate, and possibly provide some info about the refusal sample (sociodemographic info, clinical characteristics, etc).

2. On page 14 they state that the sample size needed to power the study was N=270: if so, they started the trial with a sample which was exactly as half as the sample deemed as necessary. This questionable procedure should be explained in some ways, because starting a RCT being already aware at the start that the power will be not large enough to allow a meaningful answer to study questions raises interesting ethical issues.

3. On page 17 they report that while RESPONSE rates in the 3 groups were rather different, on the contrary REMISSION rates were surprisingly strikingly similar: they should comment this finding.
4. A MAJOR problem with the study, which has surprisingly been totally omitted, is that the experimental treatment was an ADD-ON to ongoing treatments. Needless to say, this may greatly confound the results, but the authors do not say anything about this. While they have done a lot of secondary analyses, they have not done any subgroup analyses stratifying between subjects taking or not taking ADs, undergoing or not undergoing psychotherapy, or doing combined treatment with AD + psychotherapy (if any). This info is of utmost relevance and these analyses should definitely be added, although the small sample can certain limit the conclusions to be drawn. In addition, it would be interesting to add a table with some info about the ongoing treatments: if possible, type of AD prescribed, mean dosage, type of psychotherapy, duration, etc.

5. Table 3 should be included as SUPPLEMENTARY table, because it is very long and does not provide any striking results.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
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Yes

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