Reviewer’s report

Title: The impact of depression and anxiety treatment on biological aging and metabolic stress: study protocol of the MOod Treatment with Antidepressants or Running (MOTAR) study

Version: 0 Date: 29 Jul 2019

Reviewer: Martino Belvederi Murri

Reviewer's report:

The study protocol described the motar study, comparing antidepressants and running for patients with anxiety or depressive disorders. Several mechanisms of efficacy are being measured (biological and psychological). Another important point of originality of this study is to take in account patient preference re. allocation to treatment. Given the wide variability in patients' preferences and beliefs re. efficacy, I think this adds very useful information, although this choice brings along some problems as well.

Some issues indeed may complicate the interpretation of findings.

First, the study has already been carried out since several years (2012-2019). The publication of the study protocol before starting recruitment might have been more useful (it might have allowed some adjustments).

Second, another important limitation, in my opinion, is the likely imbalance between the two groups in terms of contacts with psychiatrists. If I understood correctly, the antidepressant group will see a psychiatrist during at least 4 additional visits. It will be hard to disentangle the relative effect of contacts and treatment at study end. Adding further contact also in the running group may also have allowed the use of a clinician-rated instrument and a more fine-grained clinical assessment.

Third: authors stated they adopted a "pragmatic" approach for the study design. However, various approaches have been used to encompass patient preference into clinical research while attempting at reducing bias. It would be important to compare and discuss differences/implications with other designs. E.g. "partially randomized patient preference" design (PRPP). Here, participants are interviewed re. their treatment preference before enrollment, then only those without a clear preference are randomized. Lambert et al Journal of Clinical Epidemiology Volume 53, Issue 2, February 2000, Pages 163-166). Another interesting example is the "Doubly Randomized Preference Trial" approach (Zoellner et al., Am J Psychiatry 176:4, April 2019). The adopted design, together with the inclusion of various psychiatric disorders, increases the risk of having findings that are difficult to interpret. There is a consistent risk that treatment groups will be unbalanced also in terms of diagnoses (anxiety vs. depressive disorders), as well as personality and other "hidden" unmeasured features. Also, it is unclear what is the proportion of the subsample of patients who will be (have been?) randomly allocated (e.g. 20-40% of the total or using a cutoff based on preference). Also, what is the rationale for this choice, and was it decided a priori?

Fourth: why biological aging was chosen as the primary outcome instead of a clinically important one (e.g. remission?). In my opinion "pragmatic" trials are far more interesting for their clinical implications and translation potential, while the "real world" implications of telomere length are by far more unclear. The risk of mortality associated with telomere length, for instance, is significant but relatively weak (Mons et al., Am J Epidemiol. 2017 Jun 15;185(12):1317-1326.; Darrow et al.,
Psychosom Med. 2016 Sep;78(7):776-87). I suggest the authors pre-specify how they will derive "biological aging" from the two indices (telomere length and telomerase activity).

Minor issues
- It is unclear how patients who will undergo neurobiological assessments are selected. Also, in my opinion, the paragraph dedicated to MRI assessment is overlong relative to other parts (e.g., no description of HRV and several other indices), considering that only a subset of participants will be assessed. Also, please add few details on HPA axis measurements (how many per day? How many days?).
- Authors should provide more details on the type of matching between study participants and healthy participants.
- Do participants receive any type of incentive? (economic, other)
- Eligibility: how is current physical activity recorded? Is past use of antidepressants or psychotropics recorded? This may be important for post-hoc analyses. Please add details on suicide exclusion (e.g., instrument used, criteria for ideation or attempt) and pregnancy.
- What are the contra-indications to running therapy? I argue a cardiologist visit/EKG may have been necessary for all participants, considering the inclusion of people aged up to 70 yo.
- What is the size of running groups? Will it be outdoors or indoors?

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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