Reviewer’s report

Title: Prospective, randomized, double-blind, placebo-controlled phase IIa clinical trial on the effects of an estrogen-progestin combination as add-on to inpatient psychotherapy in adult female patients suffering from anorexia nervosa

Version: 1 Date: 02 Sep 2017

Reviewer: Jennifer Jordan

Reviewer’s report:

1. Will the study design adequately test the hypothesis?

This is an ambitious study examining the potential impact of an oestrogen replacement treatment being trialled as a novel treatment for broad range of outcomes in 50 women with anorexia nervosa. The authors do not specify hypotheses, but rather exploratory aims.

The sample size is on the small size but justified by a power calculation taken from the Misra et al (2013) study which found that trait anxiety (but not eating disorder related variables) was improved after an oestrogen replacement therapy. In the current protocol, however anxiety is a secondary outcome and the study is not powered for neuropsychological changes (the primary outcome) - these authors state that there are no existing studies on which to base such a power calculation. I wonder if it might have been possible to look at clinically meaningful neuropsychological changes following other treatments in anorexia nervosa e.g. for cognitive remediation (e.g. see Tchanturia, K., Lloyd, S., & Lang, K. (2013). Cognitive remediation therapy for anorexia nervosa: current evidence and future research directions. International Journal of Eating Disorders, 46(5), 492-495)?

That aside, I consider the study design is suitable to achieve the aims of the study; to establish the magnitude of any effects on a range of outcomes being examined in this study.

2. Are sufficient details provided to allow replication of the work or comparison with related analyses: if not, what is missing?

The protocol provides sufficient detail to allow replication. The authors do not specifically mention this but I presume that the neuropsychological outcome will be based on examining change on each test rather than on a composite neuropsychological measure.

I note that St John's Wort is an exclusion criterion but I don't think that current antidepressant use was. I see that change in antidepressant use is listed as an outcome. An explicit statement about whether this is a contraindication or not at baseline would be useful in the inclusion/exclusion criteria.
The authors state that the protocol follows the SPIRIT guidelines however there are a number of details in the SPIRIT guidelines that are missing from this protocol. Please review and add details where appropriate in the manuscript or as a supplementary checklist.

3. Is the planned statistical analysis appropriate?

The statistics appear to be appropriate for this preliminary study, which aims to provide effect sizes data to inform future studies. I suspect this may end up being under-powered for variables other than anxiety but the data provided will still be useful.

4. Is the writing acceptable?

The protocol is well written overall.

General comments:

The authors clearly make the case for the need to trial novel biological treatments for anorexia nervosa, given the well documented biological dysregulation, morbidity and mortality associated with this serious condition. Traditionally oral contraceptives (OC) were prescribed with the purpose of ameliorating bone loss but impacts on other areas examined here (e.g. neuropsychological performance) have not been considered until very recently.

This is the first study trialling oestrogen replacement for AN for the purpose of comprehensively assessing improvement in 1) neuropsychological functioning 2) ED psychopathology and 3) HPA including stress hormones and appetite elated gut peptides. It seems that there have been at least three studies cited by these authors reporting a positive impact of OC on specific aspects such as verbal memory and other cognitive domains (refs 80-84), however some studies have produced contradictory results (their refs 83, 89, 90) which the authors suggest may be due to methodological differences. This novelty in this study is that it examines all these key but likely inter-related variables, addressing gaps in the literature not addressed by previous studies which just looked at one or two of these outcome variables. Examining the influence of gut peptides is a hot topic these days and this methodology seems to be widely used for assessing HPA axis functioning.

The authors' overview of the impacts of AN on biological systems is thorough and informative for the general reader. The choice of measures overall is appropriate. The choice of neuropsychological tests seems reasonable as these are well established tests and executive function deficits (especially mental flexibility) are well established. There are other tests that might have been more sensitive (see cognitive remediation studies again) however I realise that the assessment paradigm needs to be targeted in the context of the total assessment burden for participants.
Please check that the manuscript complies with the BMC Psychiatry submission guidelines for protocols e.g. in relation to the prescribed order of sections of the manuscript need for an abbreviation list, and the detail in the referencing style.

Small points:

The wording of the ethics statement could do with rephrasing (p 9 line 237) consider replacing "favourable opinion" with "approval". Similarly, "Next to female sex" would read better as something like "Other inclusion criteria were… (P9 line 242).

**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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If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

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