Author’s response to reviews

Title: The beneficial use of ultramicronized palmitoylethanolamide as add-on therapy to Tapentadol in the treatment of low back pain: a pilot study comparing prospective and retrospective observational arms

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Author’s response to reviews:

Dear Editor,

Thank you for your letter dated 3 September.

Enclosed is the revised version of the manuscript “BANE-D-17-00204R1” together with a point-by-point reply to reviewers. We have tracked the changes made in the text.

Thank you very much for your efforts in expediting the processing of our original paper.

Looking forward to hearing from you,

With kind regards,

Yours sincerely,

Marco Fiore

September, 10 2017
Reviewer #1:
Accept without revision
We want deeply thank the reviewer

Reviewer #2:

- Abstract - methods section line 11 - please remove "treated" as it is repeated

Line 11 The word “treated” was removed

- Methods:
the methods are well described. Inclusion and exclusion criteria are specified, and STROBE guidelines are used, and mentioned. The two arms are well described.

Actually, this is not a typical observational study since it is half retrospective and half prospective: as a reviewer, I'm not totally aware if specific tools and statistical methodologies should be applied in this case (the reason why I suggest additional opinion by an expert); however the methods used for the study are clear, and the statistical analysis appears to be appropriate.

Another study titled “Palmitoylethanolamide in Fibromyalgia: Results from Prospective and Retrospective Observational Studies” (Del Giorno et al 2015) used the same model for the same comparison.

However, a professional statistician with experience in the analysis of clinical study data was consulted. According to him the use of GLMM model is correct as long as the two groups are built independently. The limitation of the study is that the two groups were observed in different time periods, likely introducing extra confounding variables, however this is the limit of any other non randomized study.

- The only concern is the number of patients: it seems very low, probably configuring more a pilot investigation rather than an actual observational study (in the reviewer’s opinion) Further, there is no mention of registration on ClinicalTrials.gov: was the study included in any Registry? This aspect further argues towards the definition of "pilot study" rather than a trial.

The title has been changed from “The beneficial use of ultramicronized palmitoylethanolamide as add-on therapy to Tapentadol in the treatment of low back pain: Results from prospective and retrospective observational studies” to “The beneficial use of ultramicronized palmitoylethanolamide as add-on therapy to Tapentadol in the treatment of low back pain: a pilot study comparing prospective and retrospective observational arms”
Page 3, line 3, line 8; Page 4 line 16, Page 8 line 1 The word “pilot” has been added.

- Minor suggestions for the methods section: remove the daily mean dose of TP - it should be reported in the results, highlighting that the mean dose it is not statistically different between groups.

Page 4, line 56: “administered at a daily mean dose of 203.3 mg” and Page 4, line 58: “at a daily mean dose of 196.0 mg” have been removed

Page 5, line 55, the following has been added: “The mean daily dose of TP administered was 196.0 mg in the um-PEA-TP group and 203.3 mg in the TP group; no significant differences were observed between groups at baseline.”

- Results:

  lines 11-13: please remove the sentence "there was..(Figure 3)". You can only add "in favour of the prospective group" at the end of the sentence at line 7, avoiding repetitions.

Page 6, lines 11-13: the text "there was..(Figure 3)" has been removed; the following text: “with a significantly higher reduction in favor of the prospective group (p<0.0001) (Figure 3)” has been added at the end of line 7.

Page 6, lines 21-22: “There was a significantly higher reduction (p<0.0012) in the um-PEA-TP group compared to the TP group.” and “showing a further significant difference in the um-PEA-TP group compared to the TP group (p<0.0012).” have been added at the end of line 20.

- Line 42, page 6 - line 50, page 7: I suggest to erase this part..it is very long and confusing, and it is a repetition of data reported in the table.

Line 42, page 6 - line 50, page 7 This section has been removed

“Percentage of responder patients for each established MID and gold standard are presented in Table 2.” has been added at the end of line 40, Page 6

- Table 1: is the difference in the incidence of dyslipidemia and venous insufficiency statistically different? Is it somehow able to influence the study results and their interpretation? This should be probably discussed.

Many thanks for the suggestions, a further statistical analysis was performed to evaluate if the difference in the incidence of dyslipidemia and venous insufficiency is statistically significant. For the dyslipidemia there is no statistically significant difference between the two groups (p = 0.0510). This finding should be interpreted with the absence of clinical relationship between lipid plasma levels and Palmitoylethanolamid effect. To our Knowledge there is still no study that evaluates this possible interaction in clinical practice.
On the other hand there is a slight statistically significant association between chronic venous insufficiency and um-PA-TP ($p = 0.0429$). Chronic venous insufficiency (CVI) is often associated with venous skin ulceration that cause discomfort, pain and deteriorated quality of life (QoL).


The well-being caused by the um-PA-TP improves the physical state of the patient; this patient who start physical activity improves chronic vein insufficiency.


Of the improvement in the QoL could benefit the group with the largest number of patients with chronic venous insufficiency. Future studies are needed to evaluate a possible direct effect of Palmitoylethanolamide on chronic venous insufficiency.

- Tables and figures: when a statistically significant difference exists between groups, it should be evidenced with a marker (like * or **) in the figure/table, to help the reader's understanding.

Symbols “**” were added in Table 2 (not appropriate in Table 1, patient demographics)
In the case of Figures 2-5, statistical significance is determined in terms of the improvement seen over time, from baseline to the 24th week (study end). The degree of significance is stated in the respective figure legends.

Reviewer #3:

- There is no control group and I would recommend to the authors to do this prospective observational study with a true control group.

As this is a pilot study comparing prospective and retrospective observational arms we do not feel that a ‘true’ control group is warranted. In every case, doing as the reviewer suggests would, in essence, require repeating the study in its entirety.

- In the methods there should be more details in regard to the demographics and the exact diagnosis of the patients, the exact duration of their pain, whether or not they had previous surgeries and the various treatments they received before. Were the patients in any other medications? Did the dose of Ultramicronized -PEA decrease over time?
Many thanks for this observation. Unfortunately being an observational, and partly retrospective study, we collected what produced by every single physician during the medical visit. We did not have a case report form so it is not possible for all patients to answer each of the raised questions. Therefore, no comprehensive statistical analysis can be performed. Future studies are needed to evaluate each proposed issue.

Page 4 line 50-56. Um-PEA dosage was constant throughout the study

- Statistical analysis using GLMM can be improved.

Thanks, we would like to know what specific aspect of the GLMM needs to be improved.