

Dear Dr. Ladher,

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We appreciate your invitation to submit a revised manuscript in response to your comments and queries. We hope we have been sufficiently responsive.

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Our responses are embedded in your letter below.
Best wishes,

Ted Kaptchuk

04-Jul-2018

Dear Dr. Kaptchuk

Manuscript ID BMJ.2018.044026 entitled "Open-label placebo: Can honestly prescribed placebos evoke meaningful therapeutic benefits?"

Thank you for letting us consider your resubmitted manuscript, which we discussed at our editorial meeting on 21 June 2018 (Present: Cat Chatfield, Navjoyt Ladher, Robert Redelmeir, Paul Simpson).

We are pleased to make a provisional offer of publication if you are able to revise it to address the points made by the editors set out below.

Thank you for this opportunity.

1. Thank you for revising your paper in response to comments from reviewers and editors. Editors found your paper thoughtful and interesting. We just have a few small suggestions for additional revisions prior to acceptance.

Thank you for the positive remarks.

2. In some places we felt that there was a leap between the evidence presented and the resulting conclusions. Please go through the article and soften and signpost areas of speculation using more cautious language - particularly in the sections on neurobiological topics and also where you say "but OLP could be helpful for symptom management of cancer-related nausea, pain, hot flashes or, as we have seen, fatigue" (this needs to be referenced and softened)

We have softened the language around cancer and added references.

We have added words like "speculate," "probably," "suspect," and "but more research is required" in different places to indicate caution.

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3. We felt the conclusion could be more specific and clearer. It would be helpful to break down the conclusion that more research is needed into the component steps - what are the research questions of interest? How might this field move forward? What other actions might be helpful?

Instead of expanding the conclusion we have expanded the section "Moving OLP

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research forward.” We have moved some of the original conclusion to this discussion and expanded the entire discussion to more specific and concrete as to steps that are needed.

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4. There was also a concern about whether the studies presented here represent the totality of the evidence base. Are there other negative studies that should be mentioned?

We have added this sentence:

▲ To our knowledge, three smaller OLP pilot or feasibility clinical studies exist -- two studies with allergic rhinitis (n=25, n=45)^{two citations} and one with depression (n=20)^{citation} -- suggesting similar potential benefits.

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We could have added these three sentences instead:

▲ Three much smaller OLP trials add little to the clinical evidence. Two trials treating allergic rhinitis (n=25, n=45)^{two citations} showed significant benefits. In one feasibility study in depression (n=20)^{citation} those receiving OLP had greater improvement than TAU with a medium sized effect (d=0.54) but the difference was not statistically significant.

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In the interest of the word count, we decided to add the shorter version. If the editors prefer the longer version, we're fine.

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5. What is the message for patients at this stage? Could you elaborate on how doctors and patients might discuss this research and discuss what it means for current clinical practice?

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We have moved parts of our previous conclusion to the section: “Moving OLP research forward” and also elaborated on these issues.

6. You say: “Placebo is usually a pejorative term used to denigrate therapies deserving rejection” - we were not convinced that that is the common perception of placebo, particularly in a research context. Perhaps this phrasing could be amended?

We have deleted the phrase “pejorative” and rephrased the sentence.

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7. Could you be clearer about how this paper advances on what you describe in your earlier NEJM article? <https://www.nejm.org/doi/full/10.1056/NEJMp1504023>
The NEJM article was a general discussion of what we know about placebo effects and their implications for clinical practice. It contained only a single sentence on OLP. This current paper is focused entirely on OLP and presents data from the full range of OLP studies reported to date.

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8. You say: “OLP research is disruptive.” Please could you elaborate on what this

means and adds?

We have deleted the work “disruptive” in the conclusion and just explain what OLP does.

Again, thank you for your consideration.
Best wishes,
Ted Kaptchuk

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