27-Feb-2018

Dear Dr. Kaptchuk

Thank you for sending us this paper and giving us the chance to consider your work.

We sent it out for external peer review and discussed among the editorial team.

We do not consider it suitable for publication in its present form, but if you are able to amend it in the light of our andreviewers' comments, we would be happy to consider it again.

The reviewers' comments are at the end of this letter.

The editors' comments are listed below:

1. Editors thought that your paper covered an interesting and engaging topic and would like to work towards publication. The comments here are intended to strengthen your manuscript, develop the ideas presented, and allow greater depth to the discussion.

***Response*:** Thank you for the positive feedback.

2. Do the cited trials represent the totality of the evidence base, or are they selected examples? It would be helpful to get a sense of the overall picture.

Response: This has been made clear in the text.

3. If there are additional examples of open-label trials (whether published or in progress) that you can cite, please do add them.

Response: We've added a recently published trial.

4. We usually look for analysis articles to have a strong line of argument - what would that be here?

Response: We agree. We've re-threaded the paper around the question as to whether open-label placebos can help resolve ethical issues around harnessing placebo effect. In this spirit, we have re-titled the piece. We hope BMJ is ok with this.

5. Editors thought that the section on conditions likely to be responsive to open label placebos could be better substantiated and developed - what are the key factors of a condition or symptom being responsive to open label placebos, and

what evidence supports your opinion?

Response: We've expanded the discussion within the boundaries of space limitations.

6. We also thought that the section on future uses could be further developed as well - what might a future research agenda look like and how can barriers to greater use or study of open label placebo be addressed?

Response: We have strengthened this section within the restrictions of space.

7. As part of The BMJ's patient partnership strategy, we encourage authors to involve patients as co-authors or contributors, or at the very least to think about how the debate presented in the article might play out in the patient community. Perhaps you could reflect on this in the manuscript if you are aware of patients' views on this work?

Response: We now have an entire paragraph describing a large US patient survey (n=853) and a UK patient focus group (n=58) describing patient attitudes towards open-label placebo.

We hope that you will be willing to revise your manuscript and submit it within 4-6 weeks. When submitting your revised manuscript please provide a point by point response to our comments and those of any reviewers. We also ask that you keep the revised manuscript within the word count of 1800-2000 words.

Response: Done

Please note that resubmitting your manuscript does not guarantee eventual acceptance, and that your resubmission may be sent again for review.

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If accepted, your article will be published online at bmj.com, the canonical form of the journal. Please note that only a proportion of accepted analysis articles will also be published in print.

I hope you will find the comments useful. Please don't hesitate to contact me if you wish to discuss this further.

Response: Very helpful.

Please also accept my apologies for the long delay in getting your manuscript through the review process - I'm very sorry for any inconvenience caused.

Response: No problem.

Yours sincerely

Navjoyt Ladher
nladher@bmj.com

**IMPORTANT INFORMATION TO INCLUDE IN A RESUBMISSION

Key messages
This is a box at the end of the article containing 2-4 single sentence bullet points summing up the main conclusions.

Response: Done

Instead of returning a signed licence or competing interest form, we require all authors to insert the following statements into the text version of their manuscript:

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Please state any competing interests if they exist, or make a no competing interests declaration.

Response: Done

Reviewer(s)' Comments to Author:

Reviewer: 1

Recommendation:

Comments:
The review by Kaptchuk and Miller represents a very nice synopsis of the paradoxical clinical responses to open-label placebos. I have a few suggestions that if addressed, could make the article clearer.
Response: Thank you.
Major edits:
1. Indicate for all the trials described under the 'Open-label placebo studies', the nature of the TAU. For example, for the LBP study mention that both opioid and non-opioid were used by the patients enrolled in the trial.
Similarly, provide (when possible) the TAU treatments which were used for the IBS and depression patients. Finally, clarify that OLP were given on top of the TAU (OLP+TAU) for the all the three OLP clinical trials.

Response: We have clarified this discussion. On the specific of the inclusion criteria of LBP, I have not added further details because of space restraint.

2. Indicate the main endpoints and results for the IBS, LBP and depression studies.

Response: We have clarified this discussion. In order to add more recent evidence for OLP we have included only studies with 65 more patients. Other studies such as depression (n=20) and the sinusitis study (n=20) have been eliminated from the discussion as they do not provide significant evidence.

3. On Page 3, line 12: Report the reference for the depression, allergic rhinitis and ADHD studies. The ADHD reference is not reported. To my knowledge, the ADHD placebo studies published so far are trials in which a partial reinforcement has been adopted. Namely, the ADHD children received a reduction of total intake of amphetamine by using placebos as adjuvants (also called dose–extension placebos) rather than OLP+TAU. This point is not trivial and the studies with approaches in which placebos are given as adjuvants to reduce the main intakes of targeted drugs should be reported under another paragraph rather than under the 'OLP+TAU'category.

Response: Good catch. Thank you for raising this issue. We agree that the issue is not trivial. We have removed all mention of the ADHD study as it is, as you state, a "partial reinforcement study" and relies on conditioning. It is not an OLP study..

4. Consider discussing the case of 'dose-extending placebos' (i.e. ADHD study in children). Placebos given in the context of a partial reinforcement trial represent a potential important line of research given that a full disclosure of OLP can be adopted. This aspect can provide a rationale for use of placebos in medicine and therefore reserve to be mentioned in this paper. A place for mentioning this can be under the 'Implication for clinical practice' paragraph.

Response: We believe that "dose-extending placebos" methodology are not relevant to a short analysis of OLP. Dose extending studies actually rely conditioning and involved an entirely different set of issues. If the space limitation were different, we would of course discuss the similarities and differences.

Minor comments:

5. Page 2, Line 20, Current status of placebo concept: Mention oxytocin and vasopressin among the neurotransmitters that have been explored as CNS systems involved in placebo effects.

Response: We believe that the relationship to oxytocin and vasopressin to placebo effects needs further confirmation before can mention easily is passing.

6. Page 2, Line 48: Consider reframe 'This is the first..' as 'One of the first well-controlled OLP RTC was conducted'. Park and Covi were the first ones using OLP in a clinical context.
Citation: NONBLIND PLACEBO TRIAL: AN EXPLORATION OF NEUROTIC PATIENTS' RESPONSES TO PLACEBO WHEN ITS INERT CONTENT IS DISCLOSED. PARK LC, COVI L. Arch Gen Psychiatry. 1965 Apr;12:36-45.

Response: Park and Covi was an observational study on 14 "neurotics" and not an RCT. More importantly, this paper was part of a series three papers examining the validity of new research methodologies being developed in the early sixties. Their research question was what would happen if patients were told they were being observed for research, randomized or might get placebos. It had nothing to do with trying to see if placebos could be administered honestly as a therapeutic modality in clinical practice. Frank Miller has written on Park and Covi in "Clinical research before informed consent." *Kennedy Institute of Ethics J* 2014; 24: 141-57 and Ted Kaptchuik has a forthcoming paper in *Prospective of Biology and Medicine* that examines this issue in detail.

7. Page 3, Line 27: Replace 'unclear' with 'yet under-investigated'.

Response: We think “unclear” is more clear than “yet under-investigation.”

Additional Questions:
Please enter your name: Luana Colloca

Reviewer: 2

Recommendation:

Comments:
The paradox of “open-label placebos”, reviewed by Irving Kirsch

This is a nice overview of open-label placebos. I have only a few suggestions that I think should be considered.

Response: Thank you.

The section describing open-label placebo studies should mention the seminal work of Park and Covi (1965), in which the idea of giving placebos openly was first proposed, along with data on 14 patients with whom it was tried.

Response: Please see our comment to reviewer #2.

In discussing hope as a mechanism for therapeutic change, Jerome Frank’s book Persuasion and Healing might be cited. Also, doesn’t the concept of hope overlap with both expectancy and desire? Hopelessness implies that a desired outcome has no chance of happening, whereas hope implies a belief that it is at least possible. Further, Vase et al (2013) have provided evidence that initially weak expectancies can produce some reduction in pain, which then reinforces the expectancy, which in turn enhances pain reduction. Finally, predictive coding is a Bayesian approach to understanding the effects of “prior experience and expectations” (Büchel et al, 2014, Neuron). Therefore, if expectation and classical conditioning cannot “adequately explain therapeutic benefit associated with OLP trials,” then neither can predictive coding.

Response: Thank you for these valuable suggestions. Given our space and citation limitations, we have decided to save these suggestions for a future publication. In fact, we have shortened the discussion on expectancy to save space, increase clarity and avoid complexity.

Additional Questions:
Please enter your name: Irving Kirsch

Reviewer: 3

Recommendation:

Comments:
This is a well-written, timely, and informative review of the rapidly evolving literature on OLPs. The presentation is brief—yet still fully conveys the critical points that I would want to see covered. The manuscript is already in great shape and below I provide a small number of comments/suggestions. I realize the requirement for brevity in a paper of this style. As such, the points raised here are not necessarily for inclusion in this manuscript. Rather, the authors can view the comments as ideas to consider in their current and future scholarship.

Response: Thank you.

The authors suggest some conditions that are likely to be more responsive to OLP. At this time, do we have any idea as to what other situational variables might moderate/enhance the effectiveness of OLP? For example, the type of placebo treatment given or the length of time the treatment lasts? This data might not yet exist.

Response: This is an excellent question. At this point there is insufficient research to provide reasonable answers.

I was glad to see the authors discuss the psychological mechanisms that may be involved in the success of OLPs. The discussion of hope and cognitive dissonance were particularly valuable. The authors may also wish to consider the involvement of the need for personal control (for reviews, see Leotti, Iyengar, & Ochsner, 2010; Patall, 2012; Thompson & Schlehofer, 2008). Substantial research and theory suggest that personal control is a vital human motive. Personal control is adaptively advantageous, the loss of control leads to hopelessness, and perceiving oneself as regaining control over stressful events reduces anxiety, inhibits the activation of threat-related brain processes, and improves both mental and physical health outcomes. Given the interactive nature of the OLP intervention and the focus of the intervention on self-healing rather than healing from external agents, personal control may be an important psychological mechanisms involved.

Response: This is valuable suggestion. To our knowledge, there is not direct research linking “personal control” to placebo effects in patients. I think this would be a valuable avenue of investigation and applies to OLP, but we prefer not to raises mechanism that have not already been extensive discussed in the placebo literature.

If the authors wish to consider additional references, it could be useful to cite the

work of C. R. Snyder on the psychology of hope (e.g., Snyder, C. R. [2002]. Hope theory: Rainbows in the mind. Psychological Inquiry, 13(4), 249-275.).

Response. This is a great suggestion. We have already read the article and decided that it would be best used in an expanded discussion of possible psychological mechanisms of placebo.

Finally, it may be too soon for this point (this is up to the authors), but if practitioners began using OLPs, it would be valuable to develop training materials for the delivery of OLP and to perhaps navigate the potential complications one might be faced when initially administering OLPs to patients.

Response. Thank you for the suggestion. We added this idea to the "going forward" section.

Additional Questions:
Please enter your name: Andrew Geers

Job Title: Professor of Psychology