Reviewer's report

Title: Evidence for placebo effects on physical but not on biochemical outcome parameters. A review of clinical trials

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Reviewer: A. Jon Stoessl

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General

The authors have performed 2 meta-analyses of studies in which the placebo effect was assessed. They conclude that in peripheral organs, the placebo effect is more likely to be detected when a “physical” outcome measure is used, as opposed to biochemical measures, which seem to be resistant to placebo effects (or possibly even negatively impacted). For the first dataset, the authors identified 34 studies in 17 different conditions from 1689 double blind randomized trials investigating chronic stable clinical conditions in which at least one peripheral outcome parameter was reported. Of these, another 5 trials were excluded because of insufficient data. They then determined the significance of changes from baseline within the placebo group of each trial. In this analysis, significant placebo effects were found for a variety of physical parameters, such as blood pressure, pulmonary flow rates, urinary flow rates or residual volume, but not for biochemical measures such as hormone levels, enzymes, inflammatory proteins, HbA1c or cholesterol. Interestingly, the ESR was subject to placebo effects in a study of rheumatoid arthritis. In studies with ‘physical’ outcome measures, a significant placebo effect was seen in 8/16 trials, in contrast to only 1/18 trials with biochemical outcome measures. The effect size for studies with physical outcome measures was approximately 1/3 of the value seen in the best active treatment arm.

In order to confirm their findings with an independent dataset, the authors then examined the studies included by Hrobjartsson & Gotzsche in their meta-analysis comparing the effects of placebo against no treatment. Whereas Hrobjartsson & Gotzsche had concluded that there was no evidence for a placebo effect, Meissner and her colleagues, selecting 26 trials with peripherally measured outcomes, found a significant placebo effect when the analysis was restricted to physical outcomes, but if anything a negative effect of placebo when biochemical outcome measures were examined.

This is an interesting report that lends further support to the importance of placebo effects, even in conditions other than neuropsychiatric disease, where these are widely recognized. It is of particular interest that the widely publicized analysis of Hrobjartsson & Gotzsche does in fact reveal significant effects of placebo when subjected to the subgroup analysis applied by Meissner and her colleagues. The authors suggest that their ability to detect ‘physical’ but not biochemical placebo effects reflects visceral reward learning, dependent upon contingent feedback to cortical areas involved in autonomic control. It may seem somewhat arbitrary to differentiate between physical and biochemical outcomes and in the case of neuropsychiatric disease, it is clear that at least some of the effects of placebos are mediated by neurochemical changes – e.g. dopamine release in the case of Parkinson's and pain, opioid release in the case of pain. Thus the crucial difference is that the majority of the biochemical measures were taken in conditions where the time course may be protracted and where there may not be any associated feedback – thus, patients do not know what to expect in response to therapy and it is this expectation that is critical to the placebo effect.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

No major compulsory revisions required.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

1. There is an error in Table 2 (supplemental material on the first dataset): Ref. 19 is a study on hypertension, not diabetes. The same mistake occurs in Fig. 1. Also in Table 2, Ref. 36 should refer to diabetes, not hypertension. Many of the entries on Figure 2 do not match up with the references or entries.
in Table 3. Similarly Ref. 63 (Table 3) refers to hyperprolactinemia, not diabetes, whereas the converse is true for Ref. 67.

2. Pg. 10, 2nd paragraph, first line should read “The meta-analysis of all 26 (not 29) trials…”.

Discretionary Revisions (which the author can choose to ignore)

1. Although not explicitly stated in the paper, the authors presumably chose to exclude neurological and psychiatric disorders precisely because they are recognized to be highly susceptible to placebo effects, even when objective outcome measures (both physical, such as motor scores or electrophysiological recordings and biochemical, such as measures of neurotransmitter release) are used, and because one might expect a more tenuous link between expectation and ‘peripheral’ outcomes.

2. While the authors have found one explanation for why Hrobjartsson & Gotzsche failed to validate a placebo effect in their meta-analysis, there are numerous other reasons that the conclusions of the Danish investigators should be viewed with caution. First, they included in their analysis studies performed in subjects with questionable ability to generate expectation. Secondly, the degree of expectation was low (placebo was compared to either no treatment alone, or to at most a single active treatment arm out of 3 arms). Thirdly, binary outcome measures (improved or not) were used, thus a graded degree of improvement would not be detected.

3. The analysis of changes compared to baseline is fraught with difficulty in the absence of a no treatment group, as apparent benefit could occur in the absence of a true placebo effect, reflecting regression towards the mean. The authors are aware of this and attempted to account for this confound by analyzing the second dataset, but cannot confidently exclude this possibility in the first dataset. A more robust approach to the analysis might be to apply analysis of covariance with baseline values as the covariate, rather than to simply rely on change from baseline.

4. The authors’ choice to include acute or post-surgical conditions in the second dataset may make the interpretation of their results difficult, as the magnitude (and mechanism) of the placebo effect may differ between acute and chronic conditions. In this dataset, they chose to include one trial in which subjects had high normal blood pressure. Although this condition may be highly sensitive to regression towards the mean, it would probably be associated with a negligible placebo effect, as subjects would have very little motivation to ‘improve’. Another potential bias is derived from the authors’ decision to restrict their analysis to “the parameter or measurement with the largest effect size during the treatment period” in situations where numerous parameters or time points had been measured.

5. The authors suggest that negative effects of placebo in the second dataset might be related to dietary factors. Another possibility is that participation in a study where patients feel they have a low likelihood of deriving benefit, or even more so, should they become unblinded and find that they have been receiving placebo, might lead to negative placebo effects. Whether or not this is more likely to occur with biochemical outcomes is not clear. The significance of the negative placebo effects on biochemical outcomes is in any event questionable. In the first dataset, there is a very large study (N>900) of cholesterol in which there was no effect of placebo.

Which journal?: Appropriate or potentially appropriate for BMC Medicine: an article of outstanding merit and interest in its field

What next?: Accept for publication in BMC Medicine after minor essential revisions

Quality of written English: Acceptable

Statistical review: No

Declaration of competing interests:

I declare that I have no competing interests.