Alternative placebo treatment arms in trials: Implications may vary with differential results

Placebo is an inert substance given in the garb of a medicine, sometimes denoted as "sham treatment." Some people demonstrate a significant response to placebo, called placebo effect. This placebo effect is a significant phenomenon in medicine and research. In a classical 1955 paper, Beecher documented the therapeutic effect of placebo to the tune of 35.2 ± 2.2% of cases.[1] Though the figure is debatable due to deficiencies in study design, but many authors further worked on it and had equivocal results. Placebos have been reported to improve subjective and objective outcomes in patients with a wide range of clinical conditions, such as pain, asthma, high blood pressure, and even myocardial infarction.[2] New theories on placebo mechanisms have shown that placebo represents the psychosocial aspect of every treatment, and the study of placebo is essentially the study of psychosocial context that surrounds the patient.[3]

Labeling placebo as the inert substance is an old conceptual model of placebo. Contemporary theories capture the psychosocial context of treatment delivery, including the interaction between the patient, clinician, treatment, and the environment.[4] Expectations from the treatment being given and desire for pain relief, as well as classical conditioning, have been confirmed as important cognitive factors in a placebo response for analgesia.[5] Studies have also confirmed the involvement of the endogenous opioids in the placebo effect of pain relief by demonstrating that the placebo response can be reversed by naloxone.[6] Functional imaging studies have confirmed that the placebo response of pain relief is a measurable neurobiological event, as an activity has been documented in cortical areas directly associated with pain inhibition.[4] Others have also reported strongest placebo effects in studies of pain, nausea, asthma, and phobia.[7]

As placebos have shown significant effects, particularly in conditions requiring continuous subjective outcomes, and as placebos are used in almost all randomized controlled clinical trials (RCTs) to compare the effect of treatment arm with the placebo, and as different types of placebos (oral, parenteral, and topical) are used in different trials; Is there any possibility that different types of placebos will give a different effects and thus can affect the inference of results of different RCTs with same active drug, being conducted at different places, with different type/route of placebos? This possibility is always going to be there, since placebo is no more an inert substance, and this differential effect of different types of placebos has been explored in recent studies, at least in the fields of analgesia and migraine.

In a systemic review on migraine prophylaxis, sham acupuncture (proportion of responders, 0.38 [95% Confidence Interval: 0.30–0.47]) and sham surgery (0.58 [0.37–0.77]) were associated with a more pronounced reduction of migraine frequency than oral pharmacological placebos (0.22 [0.17–0.28]) and were the only significant predictors of response in placebo groups in multivariable analyses (P = 0.005 and P = 0.001, respectively). Network meta-analysis confirmed that more patients reported response in sham acupuncture groups than in oral pharmacological placebo groups (odds ratio: 1.88 [95% CI: 1.30–2.72]).[8]

A meta-analysis for deducing the effect of different placebos in osteoarthritis was conducted by Bannuru *et al*.[9] In this meta-analysis, placebo effects that were evaluated by using a network meta-analysis with four differential models showed that intra-articular placebo (effect size, 0.29 [95% credible interval: 0.09–0.49]) and topical placebo (effect size, 0.20 [credible interval: 0.02–0.38]) had significantly greater effect sizes than did oral placebo (effect size, 0.12 [credible interval: −0.09–0.33]). The authors concluded that all placebos are not equal, and differential placebo effects can substantially alter estimates of the relative efficacies of active treatments, and this important consideration should be kept in mind while designing the clinical trials and interpretation of the results.

While reporting a trial, specific treatment effect is reported, and overall treatment effect is seldom reported. This sometimes can lead to "efficacy paradox," where a treatment which has shown less effect as compared to placebo during trials may show more effect clinically. With differential placebo effect with alternative placebo arms, this "efficacy paradox" is going to be compounded, and should always be kept in mind while interpreting results of the clinical trials.

Rajiv Mahajan

Department of Pharmacology, Adesh Institute of Medical Sciences and Research, Bathinda, Punjab, India

Address for correspondence: Dr. Rajiv Mahajan, Department of Pharmacology, Adesh Institute of Medical Sciences and Research, Bathinda - 151 101, Punjab, India.
E-mail: drrajivmahajan01@yahoo.co.in

References

1. Beecher HK. The powerful placebo. J Am Med Assoc 1955;159:1602-6.
2. Hróbjartsson A, Gøtzsche PC. Is the placebo powerless? An analysis of clinical trials comparing placebo with no treatment. N Engl J Med 2001;344:1594-602.
3. Koshi EB, Short CA. Placebo theory and its implications for research and clinical practice: A review of the recent literature. Pain Pract 2007;7:4-20.
4. George SZ, Robinson ME. Dynamic nature of the placebo response. J Orthop Sports Phys Ther 2010;40:452-4.
5. Price DD, Finniss DG, Benedetti F. A comprehensive review of the placebo effect: Recent advances and current thought. Annu Rev Psychol 2008;59:565-90.
6. Benedetti F, Amanzio M. The neurobiology of placebo analgesia: From endogenous opioids to cholecystokinin. Prog Neurobiol 1997;52:109-25.
7. Hróbjartsson A, Gøtzsche PC. Placebo interventions for all clinical conditions. Cochrane Database Syst Rev 2010. Available from: http://onlinelibrary.wiley.com/enhanced/doi/10.1002/14651858.CD003974.pub3. [Last accessed on 2015 Aug 26].
8. Meissner K, Fässler M, Rücker G, Kleijnen J, Hróbjartsson A, Schneider A, *et al.* Differential effectiveness of placebo treatments: A systematic review of migraine prophylaxis. JAMA Intern Med 2013;173:1941-51.
9. Bannuru RR, McAlindon TE, Sullivan MC, Wong JB, Kent DM, Schmid CH. Effectiveness and Implications of Alternative Placebo Treatments: A Systematic Review and Network Meta-Analysis of Osteoarthritis Trials. Annals Int Med 2015 (online first). Available from: http://annals.org/article.aspx?articleid=2398908. [Last accessed on 2015 Aug 12].

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