

Placebo - More hatred than love

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ABSTRACT

A placebo is a sham medical intervention that can produce a placebo effect. Laboratory evidence supports the existence of several mechanisms of placebo effects in both healthy population and patients with a variety of medical conditions. The ethics of placebos have long been debated. However, accumulating ethical concern has arisen from the worldwide use of placebo in randomized control trials (RCTs), which may render their participants without early and optimal treatment. Although the pilgrimage of placebo is still on the way, refinement of controls in RCTs is worth paying new attention to.

Key words: Ethics, placebo, randomized control trials

Introduction

Placebo seems indispensable in modern clinical investigations. A placebo is a sham medical intervention that can produce a placebo effect. Common placebos are usually inert tablets or sham surgery based on false information.^[1] Since the publication of Henry K. Beecher's in 1955, the phenomenon has been considered to be clinically important.^[2] Placebo effects were shown to be genuine psychobiological events attributed to the overall therapeutic context.^[3,4] From a psychological point of view, many mechanisms might contribute to placebo effects, including expectations, conditioning, learning, motivation, memory, reward and anxiety reduction, etc.^[5,6]

Owing to the placebo effect, it is sometimes difficult to evaluate new treatments. Apparent benefits of a new drug may derive from the placebo effect but not from the drug per se. Therefore, modern clinical trials control for this effect by using a placebo, in which the subjects are blinded as to whether they receive a drug treatment

or a placebo. In this way, placebo-controlled trials might provide information about the real effectiveness of a drug.

The view of placebo effect was notably challenged when a systematic review of clinical trials in 2001 concluded that there was no evidence of clinically important effects, except perhaps in the treatment of pain and other continuous subjective outcomes.^[7] Since evidence-based medicine (EBM) is increasingly emphasized, placebo is still widely used in clinical trials other than in the treatment of pain and continuous subjective outcomes. Currently, international journals as well as clinical researchers are inclined to avoid or even ignore the ethical aspects of placebo. However, accumulating ethical concern has arisen from the worldwide use of placebo in randomized control trials (RCTs), because the investigators in a certain trial may render its participants without early and optimal treatment.

Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option. (Extracted from the Declaration of Helsinki)^[8]

A recent study, the European Cooperative Acute Stroke Study III (ECASS III) reported by Bluhmki *et al* and by Hacke *et al* supported the use of alteplase three hours

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after the onset of stroke symptoms, while together with other studies, ECASS III raised some concerns about thrombolytic studies.^[9,10] Despite repeated emphases of early treatment on acute ischemia, the control group in ECASS III failed to receive any treatment except the placebo. This is contradictory to the common sense “Time is brain”.^[11] The lack of evidence-based therapies should not justify the exclusion of empirical use of anti-platelet agents, or others. In this regard, it is almost always the case in China, since traditional Chinese medicine has been a routine for patients suffering from cerebrovascular ischemia.^[12] Another example of clinical trial that may raise ethical concerns is the one conducted by Kappos, *et al*, about oral fingolimod in treating relapsing multiple sclerosis (MS). This placebo-controlled trial revealed that fingolimod improved the relapse rate, the risk of disability progression, and end points on MRI.^[13] However, the longer the trial lasts, the longer the patients in the placebo group must go without treatment. In this context, the well-acknowledged and widely used therapeutic approaches should be considered first and foremost as controls, when RCTs are designed. Although placebos may be helpful in treating MS, the better-acknowledged ways such as interferon-beta and glatiramer acetate can potentially alleviate the sufferings of patients with MS^[14] and can readily serve as positive controls in that study. As a clinician, I feel suffocated when confronted with such ethically problematic studies. Where is the Hippocratic Oath? And where is Declaration of Helsinki. I hate the unreasonable use of placebos but cannot do anything. The sanctification of placebo is partly due to the repeated emphasis of RCTs as the gold standard of clinical trials. Thus for the time being, the ending of this sanctification seems incoercible. Dichotomy seems necessary in evaluating the role of placebo in scientific research; the need for placebo-controlled design cannot be denied at certain stage of drug development, whereas for larger phase IV studies, better alternatives should be considered.

I thus would like to propose some solutions to such an ethical conundrum. Ethically, the clinicians are always expected to provide their patients with the best choices of treatment other than placebo, and the best available treatment as a positive control other than placebos is preferable to the patients. In neurological field, for example, aspirin is widely accepted as a control in trials with regard to prevention or treatment of cerebral ischemic disorders,^[15] because its prophylactic as well as therapeutic effects on cardiovascular events are well established.^[16,17] Although the control group is a must in RCTs, an alternative way such as a delayed-start approach,^[18] can be utilized to avoid ethical issues that may arise. Delayed-start studies are designed primarily

to test the disease-modifying effect of a drug, whereas they can reduce the ethical concerns that patients in the placebo group must go without treatment until the end of the study. The control subjects enrolled in the aforementioned thrombolytic study should at least start to accept conventional medication therapies immediately after the time-window for thrombolytic studies. As an old Chinese saying goes, doctors ought to be parentally considerate. Similarly, clinicians should always bear in mind that no treatment equals killing for their patients. Clinicians/researchers need to understand the implications of offering no treatment in certain situations before enrolling experimental subjects. More importantly, a thorough explanation about the aforementioned possible implications should be performed by the clinicians.

The placebo effect is produced on the premise that the subjects believe the effectiveness of placebo. This is different from the practice in RCTs in which the subjects are informed of the possibility of accepting only a sham medical intervention. Informed consent for a study is usually required to be considered ethical, including the disclosure that some patients are to receive placebos only. In this case, the subjects do not know whether they might be getting a real treatment or a sham one, and thus might suspect the efficacy of the medical interventions even before the trials.^[19] As a result, placebos do not work as strongly in clinical trials, as in basic research. This may explain the insignificant clinically important effects as summarized by the said review.^[7] What’s worse, the deception involved in the use of placebos creates conflicts between the Hippocratic Oath and the honesty of the doctor–patient relationship.^[20,21] The purpose of the clinical trials should be explained in detail in the process of obtaining informed consent from the participants, while it is not always the case, especially in low-income countries. For patients in low-income countries, the participation in clinical trials is intriguing simply because poor patients have the chance of getting free treatment, or they can get rewards for attending the research. This may lead to selection bias as well as ethical debates because the poor participants have no better choice than attending the trials. The honest relationship between doctors and patients is further worsened because of the notion of the patients that they are utilized.

In summary, although the ethics of placebos have been debated frequently in history,^[21] even in the revision process of the Declaration of Helsinki, placebos have given rise to ethical debates much more often than ever before. As the pilgrimage of placebo is still on the way, refinement of controls in RCTs is worth paying close attention to.

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References

1. Lanotte M, Lopiano L, Torre E, Bergamasco B, Colloca L, Benedetti F. Expectation enhances autonomic responses to stimulation of the human subthalamic limbic region. *Brain Behav Immun* 2005;19:500-9.
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. Finniss DG, Kaptchuk TJ, Miller F, Benedetti F. Biological, clinical, and ethical advances of placebo effects. *Lancet* 2010;375:686-95.
4. Miller FG, Kaptchuk TJ. The power of context: Reconceptualizing the placebo effect. *J R Soc Med* 2008;101:222-5.
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. Mechanisms of placebo and placebo-related effects across diseases and treatments. *Annu Rev Pharmacol Toxicol* 2008;48:33-60.
7. Hróbjartsson A, Gøtzsche PC. Placebo interventions for all clinical conditions. *Cochrane Database Syst Rev* 2004;CD003974.
8. Declaration of Helsinki and World Medical Association. Available from: <http://www.wma.net/en/30publications/10policies/b3/index.html> [Last accessed on 2010 Nov 18].
9. Bluhmki E, Chamorro A, Dávalos A, Machnig T, Sauce C, Wahlgren N, *et al*. Stroke treatment with alteplase given 3.0-4.5 h after onset of acute ischaemic stroke (ECASS III): Additional outcomes and subgroup analysis of a randomised controlled trial. *Lancet Neurol* 2009;8:1095-102.
10. Hacke W, Kaste M, Bluhmki E, Brozman M, Dávalos A, Guidetti D, *et al*. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med* 2008;359:1317-29.
11. Saver JL. Time is brain--quantified. *Stroke* 2006;37:263-6.
12. Wu B, Liu M, Liu H, Li W, Tan S, Zhang S, *et al*. Meta-analysis of traditional Chinese patent medicine for ischemic stroke. *Stroke* 2007;38:1973-9.
13. Kappos L, Radue EW, O'Connor P, Polman C, Hohlfeld R, Calabresi P, *et al*. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. *N Engl J Med* 2010;362:387-401.
14. MacLean HJ, Freedman MS. Multiple sclerosis: Following clues from cause to cure. *Lancet Neurol* 2009;8:6-8.
15. Hennerici MG. PERFORM Study Investigators. Rationale and design of the Prevention of Cerebrovascular and Cardiovascular Events of Ischemic Origin with Terutroban in Patients with a History of Ischemic Stroke or Transient Ischemic Attack (PERFORM) Study. *Cerebrovasc Dis* 2009;27:s28-32.
16. Pignone M, Alberts MJ, Colwell JA, Cushman M, Inzucchi SE, Mukherjee D, *et al*. American Diabetes Association; American Heart Association; American College of Cardiology Foundation. Aspirin for primary prevention of cardiovascular events in people with diabetes. *J Am Coll Cardiol* 2010;55:2878-86.
17. Yang X, Zeng X, Wu T. Chuanxiong preparations for preventing stroke. *Cochrane Database Syst Rev* 2010;1:CD006765.
18. Olanow CW, Rascol O, Hauser R, Feigin PD, Jankovic J, Lang A, *et al*. A double-blind, delayed-start trial of rasagiline in Parkinson's disease. *N Engl J Med* 2009;361:1268-78.
19. Vase L, Riley JL 3rd, Price DD. A comparison of placebo effects in clinical analgesic trials versus studies of placebo analgesia. *Pain* 2003;104:714-5.
20. Miller FG, Wendler D, Swartzman LC. Deception in research on the placebo effect. *PLoS Med* 2005;2:e262.
21. Newman DH. *Hippocrates' Shadow*. New York: Scribner; 2008. p. 134-59.

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