Indian Journal of Clinical Anatomy and Physiology 2020;7(4):412–416

Content available at: https://www.ipinnovative.com/open-access-journals

Indian Journal of Clinical Anatomy and Physiology

Journal homepage: https://www.ijcap.org/

Short Communications

Abdicating placebo

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ARTICLE INFO

Article history:
Received 23-12-2020
Accepted 29-12-2020
Available online 11-01-2021

Keywords:
Placebo
Placebo effect
Nocebo
Cancer research

ABSTRACT

The efficacy of the placebo ('I shall please') is variable, depending on both the type of disorder and the effectiveness of the treatment itself. The efficacy of the placebo is usually considered to be about 20–30% and produced by the effect of psychological variables, such as expectations, conditioning, etc. A phenomenon that is a placebo in a given science does not have to remain a placebo forever; it depends on the progress and advancement of scientific research, Recently use of placebo has taken myopic stance for ethical research in life style diseases or any other acute or chronic illness with some exceptions.

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1. History of Placebo

The first placebo-controlled clinical trial was completed in 1931. The study focused on Sanocrysin, a drug to treat tuberculosis, and the placebo in this case was distilled water. Variations in the placebo effect can be explained in part by differences in how clinical trials are managed and in how the patients are informed. Henry Beecher discovered the placebo effect as medicine in world war II, where he replaced morphine with saline. Pioneer in placebo research was Prof Louis C. Lasagna who evaluated various drugs in placebo controlled clinical trials. FDA gave its stand on the use of placebo by end of 2019, where its justified use in limited conditions is clarified.[1]

2. Character of Placebo

Placebo is mediator used in clinical trials which is inert, neutral substance (with no treatment properties). Its usage in clinical trials is based on additive model", the assumption that true ("net") drug efficacy can be calculated by subtracting the efficacy in placebo arm (placebo efficacy) from the efficacy in drug arm of trial.[2] From researcher's point of view, placebo effects should be minimized in order to improve scientific strength of clinical trials, No drug should get the approval unless it confirms being undoubtedly superior to placebo, in specified therapeutic areas particularly in cancer.

3. Placebo Effects

The placebo effect was first described by H.K Beecher, who suggested that about 35% of patients with a variety of conditions could be improved or cured by placebos.

The placebo effect is the positive response some participants experience after receiving a placebo. When present, this response has a perceptible and measurable beneficial effect that may be subjective (e.g., pain reduction) or objective (e.g., improved blood pressure).

The nocebo effect is the negative response some patients/participants experience after receiving a placebo. These effects range from minor discomforts (e.g., headache, nausea) to life-threatening complications (e.g., cardiac arrest).

The physical characteristics of a placebo medication, such as its colour, size, or quantity, may also contribute to its effectiveness.

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https://doi.org/10.18231/j.ijcap.2020.086
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Placebos have been used largely as a tool for reducing bias in clinical trials. Placebos have no effect on progression of cancer, they have been found to reduce associated symptoms of pain, loss of appetite, anxiety, and depression.[3,4]

4. Placebo Action

The theories most accepted for explaining psychological mediation of placebo effects are expectation and classical conditioning. Verbal and non-verbal interactions between the patient and the physician may affect the perception of treatment efficacy, which in turn may influence patient expectations, and clinical outcome. The expectation of relief is an important contributor to placebo response, there are various other psychological mediators, including motivation. The expectance theory postulates that placebo response is related to a patients' expectations of improvement, which are connected to the change that takes place Among all the emotions related to placebo, anxiety has been the major psychological mediator. Anxiety has been reduced with administration of a placebo treatment Side effects of placebos are usually similar to those of drugs which patients have previously taken, although they may elicit symptoms not previously encountered.[5]

5. Guidance on Placebo use

1. **The Food and Drug Administration (US, FDA)** have provided guidance on the use of placebos and blinding in clinical trials for oncology and hematologic malignancies. The guidance is required due to concerns over the ethics of using placebo treatments for these patient populations, as well as blinding and patient reported outcomes.
2. **ASCO (American Society of Clinical Oncology)** mentions The fastest way to improve access to new cancer treatments for all patients is the timely completion of well-designed, definitive clinical trials that provide evidence of the safety and effectiveness of a new drug and lead to marketing approval. In some circumstances, such clinical trials may require the use of placebo controls to provide convincing evidence of drug safety and clinical benefits.
3. Placebo-controlled trials indicates that the assay sensitivity, the ability of a trial to distinguish between an efficacious and non-efficacious treatment, is better in placebo controlled than in active-control trials, which are often non-inferiority trials. The FDA fears that a lack of assay sensitivity in active-control studies would result in the approval of ineffective drugs.
4. Well-controlled trials did not have to be placebo controlled– they could have active controls, or even historical controls– but the regulations stated clearly that "uncontrolled studies are not acceptable evidence to support claims of effectiveness.
5. **EU Guidance document** emphasizes conduct of clinical trial with well established comparator rather than with placebo (ICH E 10 Guidelines).
6. Outline the methodology to minimize risks to subjects.
7. Committee for Medicinal Products for Human Use recommends where feasible, threarm trials including experimental medicine, placebo and active control represent a scientific gold-standard and there are multiple reasons to support their use in drug development.[6]

6. Guidelines of the office for Human Research Protection on Placebo

The Office for Human Research Protection (OHRP) published guidelines in 2008 for the use of placebo and methods to minimize the risk associated with it. The guidelines state, "Placebos may be used in clinical trials where there is no known or available alternative therapy that can be tolerated by subjects." Placebo-controlled trials are controversial. Critics of such trials argue that if a proven effective therapy exists, a placebo should not be used.[8]

7. Ethics in Placebo Controlled Trials

Placebo-controlled trial or trials that include an untreated control group cite Article 11.3 of the Declaration of Helsinki: "In any medical study, every patient including those of control group, if any should be assured of the best proven diagnostic and therapeutic methods and no patient should suffer from unnecessary pain." It is therefore essential to provide best proven treatment to both control as well those receiving new therapy. Argument also proposed against placebo-controlled trials is that they potentially violate the concept of clinical equipoise when proven effective therapy is available. The use of placebo in children is more restricted than in adults, because children cannot consent. Placebo should not be used when it means withholding effective treatment, particularly for serious and life-threatening conditions.[9]

8. Alternative Medicine and Placebo

The conditions are precisely those that researchers believe are especially susceptible to inordinately strong placebo responses: back and chronic pain, fatigue, arthritis headache, allergies, hypertension (in some situations), insomnia asthma, chronic digestive disorders, depression, anxiety and erectile dysfunction. Persons with self-limiting diseases, such as the common cold and sprains and strains, also frequently use alternative medicine. In contrast to conventional medicine, with its measured objectivity, alternative medicine offers a charged constellation of expectations in terms of end results. It is believed that more than 90% of all alternative medicines are based on the

Table 1: Regulators response to placebo [7]

Always placebo control	Placebo control if disease is not life threatening	Placebo control for transient disorder	Always standard therapy if justified	Other specified indications
Discouraged or Not approved	Argentina Hungary Slovakia UK	Chile Czech Republic EMA	Cuba Czech republic Ghana Japan Kenya Malaysia UAE	Austria Argentina Germany Japan Turkey US

placebo effect. [10]

9. Trials in Cancer with Placebo (www.clinicaltrials.gov)

Placebo-controlled oncology trials are scientifically feasible, ethically justifiable, and may be necessary or desirable to meet regulatory standards for drug approval. Using cross-over or randomized withdrawal trial designs, requiring inclusion of state-of-the-art palliative care, and developing valid and acceptable surrogates for survival are critical strategies to address some of the ethical dilemmas associated with placebo-controlled trials. Many drug approvals were based on placebo controlled studies, Letrozole, Sorafenib, Marimastat, Erlotinib, Geftinib, Cetuximab, Prinomastat, Tipifarnib, Tamoxifen etc. Placebos may be used in a clinical trial that compares standard treatment plus a placebo, with standard treatment plus a new treatment.

Based on an interim analysis conducted during the study, sunitinib was approved by the Food and Drug Administration (US Food and Drug Administration) because it showed a significantly longer time to progression compared with placebo. [11]

100 Japanese and 660 non-Japanese patients were randomized to regorafenib (n = 67 and n = 438) or placebo (n = 33 and n = 222). Regorafenib had a consistent OS benefit in the Japanese and non-Japanese subpopulations, with hazard ratios of 0.81. [12,13]

In a meta-analysis, it is found a low response rate among the placebo-treated patients with advanced or metastatic DTC (differentiated thyroid cancer). [14]

9.1. Guidelines under Schedule Y (CDSCO)

Allow the use of placebo in Phase III studies when existing therapies are minimally effective or have serious side effects

Placebo-controlled trials are never appropriate when a highly effective or potentially curative therapy is available for a patient. An exception is unless the trial allows the patient to receive the new treatment/placebo in addition to the potentially curative therapy. [15]

10. Trials with vaccine (Recommendations of a WHO expert panel)

1. Placebos is acceptable when no effective vaccine exists
2. The vaccine under consideration is intended to benefit the population in which the vaccine is to be tested. – developing a locally affordable vaccine.
3. Of the 16 HPV vaccine randomized trials, only two used an inert saline placebo. Ten of the sixteen compared the HPV vaccine against a neurotoxic aluminium adjuvant, and four trials used an already-approved aluminium-containing vaccine as the comparison. Thus the placebo as comparator is not considered as standard. [15–17]

11. Trials in Sexual Dysfunction

Most of the drugs for Erectile dysfunction were evaluated on placebo controlled design where psyche constitutes the effect. Interesting finding was that the placebo response seems largely more important when the cause of ED is mainly due to psychogenic factors, as in post traumatic stress disorder. 12000 men diagnosed with erectile dysfunction (ED), placebo improved erectile dysfunction significantly. This is likely due to the emotional effect. 67% of the patients reported an improvement of erectile function with tadalafil (placebo: 20%), and 48% reported successful intercourse with tadalafil (placebo: 9%) ($p < 0.0001$). [18–20]

12. Trials in Neurology

The double-blind, placebo-controlled trial is considered the "gold standard" for clinical trials, in Amyotrophic lateral sclerosis, because it has the best chance of determining whether an active treatment is effective.

The placebo response rates in the treatment of acute headache episodes are higher than in headache prophylaxis, and invasive procedures, such as injections, have a higher placebo response compared with orally administered drugs.

Migraine constitutes a good model for the study of placebo response. It is a well-defined disease, affects a large population and a great number of clinical trials have been

performed, which have given homogeneous outcomes.[21–23]

13. Placebo in Psychiatry

1. Patients with panic disorder or mild to moderate depression get almost as much relief from placebo as from conventional treatment.
2. All placebo-controlled trials are increasingly questioned because they provide less-than-maximum therapy to patients, and the Declaration of Helsinki allows them only when inadequate or ineffective routine treatment options are available.[24,25]

14. Paediatric Hypertension

Placebo use can be considered ethical if the following conditions are met:

1. The potential subjects have asymptomatic, mild-to-moderate primary hypertension.
2. The potential subjects do not have hypertension-related target organ damage.
3. Placebo treatment of short duration (generally <4–8 weeks).
4. No standard of care exists in the community.[26]
5. Among the 1707 children in the 10 studies, no differences in the rates of adverse events reported between the patients who received placebo and those who received active drug.[27]

15. Conclusion

Placebo-controlled trials have high internal validity but may be difficult to apply to clinical practice; the situation is reversed for trials without placebo control. Placebos are rarely used in cancer treatment clinical trials. Placebo controls are ethically justifiable when they are supported by sound methodological considerations and their use does not expose research participants to excessive risks of harm. They are used when there is no standard treatment. or, they may be used in a clinical trial that compares standard treatment plus a placebo, with standard treatment plus a new treatment. The gold standard in clinical trial design is the double-blind randomized placebo-controlled study with two arms is legacy of past.

16. Source of Funding

None.

17. Conflict of Interest

The authors declare no conflict of interest.

References

1. Guijarro C. A history of the placebo. *Neurosci Hist*. 2015;3(2):68–80.
2. Arnstein P, Broglio K, Wuhrman E, Kean MB. Use of Placebos in Pain Management. *Pain Manag Nurs*. 2011;12(4):225–9.
3. Skierka AS, Michels KB. Ethical principles and placebo-controlled trials – interpretation and implementation of the Declaration of Helsinki's placebo paragraph in medical research. *BMC Med Ethics*. 2018;19(1):24. doi:10.1186/s12910-018-0262-9.
4. Ćurković M. Ethical overview of placebo control in Psychiatric research - Concepts and challenges. *Psychiatria Danubina*. 2015;27(2):118–25.
5. Meissner K, Kohls N, Colloca L. Introduction to placebo effects in medicine: mechanisms and clinical implications. *Philos Trans R Soc Lond B Biol Sci*. 2011;366(1572):1783–9. doi:10.1098/rstb.2010.0414.
6. Cancer Clinical Trials for Drug and Biological Products Center for Drug Evaluation and Research (CDER), August 2019.
7. Available from: www.cancer.net/research-and-advocacy/clinical-trials/placebos-cancer-clinical-trials.
8. Daugherty CK, Ratain MJ, Emanuel EJ, Farrell AT, Schilsky RL. Ethical, Scientific, and Regulatory Perspectives Regarding the Use of Placebos in Cancer Clinical Trials. *J Clin Oncol*. 2008;26(8):1371–8. doi:10.1200/jco.2007.13.5335.
9. Gupta U, Verma M. Placebo in clinical trials. *Perspect Clin Res*. 2013;4(1):49. doi:10.4103/2229-3485.106383.
10. Kaptchuk TJ. The Placebo Effect in Alternative Medicine: Can the Performance of a Healing Ritual Have Clinical Significance? *Ann Intern Med*. 2002;136(11):817. doi:10.7326/0003-4819-136-11-200206040-00011.
11. Placebos and Blinding in Randomized Controlled Cancer Clinical Trials for Drug and Biological Products Guidance for Industry; 2019.
12. Yoshino T. Randomized phase III trial of regorafenib in metastatic colorectal cancer: analysis of the CORRECT Japanese and non-Japanese subpopulations. *Investig New Drugs*. 2015;33:740–50.
13. Available from: https://xtalks.com/placebo-controlled-oncology-clinical-trials-falling-out-of-favor-with-fda-1557/.
14. Valero ML, Guillén-Grima F, Zafon C, Juan C, Galofre. The placebo effect in thyroid cancer: a meta-analysis. *Eur J Endocrinol*. 2016;174:465–72.
15. Use of Placebo in vaccine trials, WHO; 2013.
16. Rid A, Saxena A, Baqui A, Bhan A, Bines J, Bouesseau MC. Placebo use in vaccine trials: recommendations of a WHO expert panel. *Vaccine*. 2014;32(37):4708–12.
17. Office for science and society, Placebos Used in Vaccine Trials Do Not Please Everyone, 2020 .
18. Rakel D. Placebo Responses Among Men With Erectile Dysfunction Enrolled in Phosphodiesterase 5 Inhibitor Trials: A Systematic Review and Meta-analysis. *JAMA Netw Open*. 2020;3(3):e201423. doi:10.1001/jamanetworkopen.2020.1423.
19. de Araujo A, da Silva F, Salvi F, Awad MC, da Silva E, Damião R. The management of erectile dysfunction with placebo only: does it work? *J Sex Med*. 2009;6(12):3440–8.
20. Incrocci L, Slagter C, Slob AK, Hop W. A randomized, double-blind, placebo-controlled, cross-over study to assess the efficacy of tadalafil (Cialis) in the treatment of erectile dysfunction following three-dimensional conformal external-beam radiotherapy for prostatic carcinoma. *Int J Radiat Oncol Biol Phys*. 2006;66(2):439–44.
21. Available from: https://www.massgeneral.org/neurology/als/research/placebo-trials.
22. Benatar M, Wuu J, Andersen PM, Atassi N, David W. Randomized, double-blind, placebo-controlled trial of arimoclomol in rapidly progressive SOD1 ALS. *Neurol*. 2018;90(7):565–74.
23. Macedo A, Baños JE, Farré M. Placebo response in the prophylaxis of migraine: A meta-analysis. *Eur J Pain*. 2008;12(1):68–75. doi:10.1016/j.ejpain.2007.03.002.
24. Shorter E. A Brief History of Placebos and Clinical Trials in Psychiatry. *Can J Psychiatry*. 2011;56(4):193–7. doi:10.1177/070674371105600402.
25. Kirsch I. Placebo Effect in the Treatment of Depression and Anxiety. *Front Psychiatry*. 2019;10:407. doi:10.3389/fpsyt.2019.00407.
26. Flynn JT. Ethics of Placebo Use in Pediatric Clinical Trials. *Hypertens*. 2003;42(5):865–9. doi:10.1161/01.hyp.0000095616.91352.2e.

27. Smith PB, Li JS, Murphy MD, Califf RM, Benjamin DK. Safety of placebo controls in pediatric hypertension trials. *Hypertens*. 2008;51(4):829–33.

Cite this article: Chaudhry S. Abdicating placebo. *Indian J Clin Anat Physiol* 2020;7(4):412-416.

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