IS THE PLACEBO EFFECT REAL?

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Abstract

This review describes papers written addressing the placebo effect. The question is whether patients ever have done better because they are taking a placebo with no therapeutic value. The author finds a place in medicine and in health for placebos.

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The placebo effect has become a subject of interest among biomedical professionals in the last 3 decades. This interest in understanding the mechanism of action of placebos is important to them because of the role of the placebo in clinical research. Beecher described the placebo effect in 1955.(1) From an analysis of 15 trials with different diseases Beecher demonstrated that "35% of 1,082 patients were satisfactorily relieved by a placebo alone." Since then, the placebo gained popularity in biomedical research attained position of critical importance in clinical trials.(2-9)

The placebo effect was described as resolution of the illness when the patient is treated with an inert substance. Inert substance given to the patient as if it was real treatment is known as placebo. According to *Merriam-Webster's Medical Dictionary*, a placebo is “an inert or innocuous substance used especially in controlled experiments testing the efficacy of another substance (as a drug)”.

Typically, subjects in a placebo-controlled clinical trial are grouped either to receive the placebo or the active drug. In a randomized, blinded, placebo-controlled clinical trial, subjects do not know which group they are in. In properly designed clinical trials, placebos are physically identical to the active drug, but they lack the chemical structure of the active drug. Regardless, positive therapeutic effects can be observed with placebos, and the effects have been related to the trial subject's expectations.

THE CONTROVERSY

In spite of the need for placebos in clinical trials, a debate about the placebo effect continues in the biomedical literature. The arguments are either that the placebo effect is not real or that it is real. The disputers of the placebo effect argue that factors or reasons other than the placebo by itself are responsible for the apparent improvement in symptoms experienced by a patient. As example, a patient's symptoms could improve spontaneously due to the natural evolution of the disease.

When attacked by an illness, the human body calls its own internal defense system to deal with the offending disease process. The war that ensues between the body's defense system and the disease, and tissue destruction associated with the invasion of a body organ by the disease causing process manifests as the symptoms of the illness. The body defenses often overcome the offending disease process, and the patient heals spontaneously. Supposing that a patient with such a courageous defense system was enrolled in a placebo-controlled study, and was put on the placebo. Such spontaneous improvement due to the body's own defense system can be misconstrued to be placebo effect and really should suggest that the active drug was not helpful and perhaps completely unnecessary.

DISSENTERS

Hrobjartsson and Gotzsche (2001) found that such a misleading conclusion can occur when the research methodology is flawed, thus the emerging data does not help the researcher distinguish between the natural evolution of disease and placebo effect.(10)

According to Caroll, the reported improvement after fake knee surgeries by Moseley and colleagues are typical examples of flawed methodology reported as placebo effect.(11)

Moseley and colleagues randomly assigned 180 patients with osteoarthritis of the knee to receive arthroscopic débridement, arthroscopic lavage, or placebo surgery.(12) The patients in the placebo group received skin incisions and underwent a simulated débridement without insertion of the arthroscope. At the end of the study, 165 patients completed the trial. Upon analysis of the results, Moseley and colleagues did not find "any clinically meaningful difference between the placebo groups and the intervention groups."

Carroll argues that this lack of meaningful difference was not due to placebo effect of the surgery. Rather, the patients would have healed spontaneously without intervention anyway.(11)

In their study published in 1997, Kienle and Kiene claimed a host of other causes of false claims of placebo effect.(13) According to Kienle and Kiene, some causes of false placebo effects include "fluctuation of symptoms, regression to the mean, additional treatment, conditional switching of placebo treatment, scaling bias, irrelevant response vari-

ables, answers of politeness, experimental subordination, conditioned answers, neurotic or psychotic misjudgment, psychosomatic phenomena, misquotation".(13)

Turner, Deyo, Loeser, Von, and Fordyce reviewed the literature to examine the implications of placebo effects in pain treatment.(14) In this study, the authors reported that the placebo response rates varied greatly, and were often higher than the rates reported by Beecher in 1955. This increased power of the placebo in recent years is likely to relate to changes in the patient population over time. In fact, Walsh and colleagues observed an improved response to placebo antidepressants in published clinical trials over the past 20 years.(15) Walsh and his colleagues attributed this the fact that many patients received treatment for depression over the past several years, and depression in the population tends to be milder, briefer, and more responsive to treatment.(9) Other factors that could explain the placebo effect include anxiety, expectations, learning, and the regression towards the mean.(14)

The Accepters

Brown posited that the medical professionals use "the placebo effect to enhance the care of patients".(16,17) Benson and Epstein argued that the placebo effect is a "neglected asset in care of patient".(17) Neuro-imaging has supported the contention of the reality of the placebo effect. In one study, by Dr Zubieta and colleagues (2005 cited in Kuehn, 2005) used magnetic resonance imaging and positron emission tomography scans to demonstrate that the activity on the endogenous opioid receptors mediated the placebo effect.

Conclusions

At the core of medical practice is the understanding that something that makes a sick person feel better is a good thing. This article had its genesis in a glass of orange juice with a colleague, who insisted on drinking out of a crystal goblet because the orange juice tasted better. That crystal goblet did not change the active ingredients or the taste of the orange juice, but did it cheer the colleague. Which made it a placebo according to the definition in *Webster's Revised Unabridged Dictionary* “A prescription intended to humor or satisfy”.

What is needed in clinical research is differentiation between effective and ineffective drugs, rather than assuming trial subjects are fooled, and hence stupid.

References

1.Beecher HK. The powerful placebo. JADA 1955;159:1602-6.

2.Alzheimer's Disease Cooperative Study. Effects of Rofecoxib or Naproxen vs placebo on Alzheimer disease progression: a randomized controlled trial. JAMA 2003;289:2819-26.

3.The Depakote Mania Study Group. Efficacy of divalproex vs lithium and placebo in the treatment of mania. JAMA 1994;271:918-24.

4.Varenicline Phase 3 Study Group. Efficacy of varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. JAMA 2006;296:56-63.

5.Krober MS, Bass JW, Michels GN. Streptococcal pharyngitis. Placebo-controlled double-blind evaluation of clinical response to penicillin therapy. JAMA 1985;253:1271-4.

6.Le Bars PL, Katz MM, Berman N, Itil TM, Freedman AM, Schatzberg AF. A placebo-controlled, double-blind, randomized trial of an extract of Ginkgo biloba for dementia. North American EGb Study Group. JAMA 1997;278:1327-32.

7.Placebo group. A randomized placebo-controlled trial of Saccharomyces boulardii in combination with standard antibiotics for Clostridium difficile disease. JAMA 1994;271:1913-8.

8.Schneider LS, Dagerman KS, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. JAMA 2005;294:1934-43.

9.Walsh BT, Seidman SN, Sysko R, Gould M. Placebo response in studies of major depression: Variable, substantial, and growing. JAMA 2002;287:1840-7.

10.Hrobjartsson A, Gotzsche PC. Is the placebo powerless? An analysis of clinical trials comparing placebo with no treatment. N Engl J Med 2001;344:1594-602.

11.Placebo effect. At http://skepdic.com/placebo. html.

12.Moseley JB, O'Malley K, Petersen NJ, Menke TJ, Brody BA, Kuykendall DH,Hollingsworth JC, Ashton CM, Wray NP. A Controlled trial of arthroscopic surgery for osteoarthritis of the knee. N Engl J Med 2002;347:81-8.

13.Kienle GS, Kiene H. The powerful placebo effect: fact or fiction? J Clin Epidemiol. 1997;50:1311-8.

14.Turner JA, Deyo RA, Loeser JD, Von Korff M, Fordyce WE. The importance of placebo effects in pain treatment and research. JAMA 1994;271:1609-14.

15.Brandon TH, Irvin JE, Hendricks PS, Sapir M, Schneider LS, Small GW. The increasing power of placebos in trials of antidepressants. JAMA 2002;288:449-50.

16.Brown WA. The powerful placebo: From ancient priest to modern physician. JAMA 1998;280:751-2.

17.Benson H, Epstein MD. The placebo effect. A neglected asset in the care of patients. JAMA 1975;232:1225-7.