

The Placebo Effect: Ethical and Conceptual Issues

Summary: This project is devoted to ethical and theoretical inquiry relating to the placebo effect and the use of placebos in research and clinical practice.

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Background: Interest in the placebo effect emerged in the late 1940s, with the advent of placebo-controlled clinical trials. Henry Beecher’s classic 1955 article, “The Powerful Placebo,” brought the placebo effect, and the need to control for it in order to rigorously evaluate treatment efficacy, to the attention of the medical community. In the past decade, there has been a resurgence of scientific and popular interest in the placebo effect. Extensive laboratory research has been undertaken to elucidate neurobiological mechanisms of placebo effects. In addition, clinically-oriented research is beginning to investigate psychosocial factors that contribute to developing placebo responses in clinical practice and methods for eliciting therapeutic placebo responses. Ethical issues are posed by research on the placebo effect, which typically employs deception as an element of experimental design. Efforts to take advantage of the placebo effect in clinical practice also raise ethical concerns relating to compatibility with evidence-based medicine and informed consent.

While scientific knowledge about the placebo effect has grown dramatically, theoretical efforts to characterize this phenomenon remain primitive. In addition to the complexity of understanding mind-body interactions, understanding of the placebo effect is hampered by pervasive conceptual confusion and negative connotations tied to the history of characterizing placebos and placebo effects in medicine and the language employed for this purpose. The

prominent use of placebo-controlled trials to evaluate treatments has led to seeing the placebo effect as “noise” or bias that needs to be controlled for in order to detect genuine treatment efficacy. Within the prevailing understanding of evidence-based medicine, treatments are regarded as worthless if they are no better than placebos, casting a negative light on using treatments for the purpose of promoting placebo effects. Placebos are described as “inert” interventions in contrast to “active” drugs; and placebo effects are described as “non-specific,” in contrast to the specific effects of proven-effective treatments. In this context, it becomes difficult to understand how placebo interventions can produce clinically meaningful benefit.

Departmental Research Initiative: Miller’s extensive research on ethical issues relating to placebo-controlled trials (including pharmacological trials that withhold proven effective treatment, sham invasive procedure trials, and clinical trials of complementary and alternative medicine interventions) sparked an interest in the placebo effect, focusing on conceptual and ethical dimensions. An adequate understanding of the ethics of placebo-controlled trials depends on giving due attention to the methodological rationale for using placebo controls. One important reason is to control for the placebo effect, which is especially important in clinical trials to evaluate symptomatic treatments for a wide variety of medical conditions with subjective outcomes, such as relief of pain and psychic distress. A different line of ethical research concerned with the use of deception in human subjects research highlighted the problem of deception in research on the placebo effect and the issue of whether and how efforts to promote placebo responses in clinical practice can be undertaken without deception, consistent with informed consent. This interest in the placebo effect, from conceptual and ethical perspectives, led to undertaking a range of research initiatives relating to understanding the placebo effect, ethical analysis of issues posed by the use of placebos and efforts to promote placebo responses in research and clinical practice, and empirical investigation of clinical use of placebo interventions. To advance this research program, at the end of 2009 the Department hired Luana Colloca—a physician-neuroscientist, with extensive experience in conducting placebo experiments and an interest in bioethics—to join Miller in intensive research on the placebo effect. Her two-year position is funded by the National Center for Complementary and Alternative Medicine.

Conceptual and theoretical research on the placebo effect has given rise to a series of papers concerning approaches to characterizing and explaining placebo effects. Themes explored in this research program have included (1) identifying and dispelling confusions surrounding the concepts of placebo and placebo effects; (2) characterizing the type of healing involved in placebo effects, as distinct from spontaneous and automatic healing of the organism and technological healing produced by medical interventions; (3) evaluating the scope and limits of placebo responses in light of critical appraisal of relevant laboratory and clinical research; (4) applying philosophical perspectives to understanding placebo effects (Williams James on the power of belief and Charles Peirce’s theory of signs); and (5) explaining the generation of placebo responses from the perspective of the neuroscience of learning.

Ethical research on the placebo effect has focused on two areas. First, analysis of ethical issues relating to the use of deception in research on the placebo effect led to development of an “authorized deception” approach as an ethically superior alternative to the prevailing practice of deceptive research. Typically, in research that deploys deception, subjects are misled about the purpose of the study (to understand the placebo effect) and specific procedures (the use of placebo interventions deceptively described, for example, as a powerful pain-relieving agent). Subjects are not informed in advance about the use of deception but are “debriefed” at the conclusion of research participation. In the authorized deception approach, which has rarely been used, prospective subjects are informed that deception will be employed and that the nature of the deception will be revealed when study participation has been completed. The aim is to maintain the experimental control afforded by the use of deception while respecting the autonomy of prospective subjects by giving them a fair opportunity to decide whether they want to participate in research using deception. The issue of whether the authorized deception approach might compromise the scientific validity of research was identified and discussed, with the recommendation that evaluative research is needed to test the hypothesis that this approach could be deployed without biasing study outcomes.

Second, research on ethical issues concerning the use of placebo treatments in clinical practice was prompted by an empirical study of this issue, described below. A recently published paper focused on available scientific evidence relating to two key questions: (1) can the use of placebo treatments produce clinically significant benefit? and (2) can placebo treatments be effective without the use of deception? A follow-up policy-oriented project is planned to examine the advantages and disadvantages of validating treatments in clinical practice (such as acupuncture, vertebroplasty, and some herbal treatments) that are no better than placebo controls but demonstrated to be superior to no-treatment or usual care interventions. Additionally, Miller has collaborated with investigators at Harvard in a pilot clinical trial aimed at determining whether open label-placebo, described to patients with irritable bowel patients as a pill with no medication in it along with positive expectation for promoting placebo responses, can produce superior outcomes to a no-treatment control group. Further collaborations in clinically-oriented placebo research are anticipated. Finally, research also is underway on exploring ethical issues relating to the nocebo effect—the tendency opposite to the placebo effect, but working by similar psychological mechanisms, of clinical communication and interventions to inadvertently cause negative health outcomes.

The department conducted empirical research on physicians’ use of placebo treatments. Questions relating to placebo use were nested within a questionnaire survey of a random sample of 1200 U.S. internists and rheumatologists regarding their attitudes on research evidence relating to complementary and alternative medicine. The physicians were asked to indicate which of several placebo treatments they had used in the past year, defined as “a treatment whose benefits derive from positive patient expectations and not from the physiologic mechanism of the treatment itself.” Fifty-five percent of the physicians reported having recommended at least one of a list of interventions as a placebo treatment during the past year: 41% recommended use of over-the-counter analgesics, 38% vitamins, 13% sedatives, and 13% antibiotics. Only 5% reported using pure placebos, such as sugar pills and saline injections.

When asked about their frequency of recommending a therapy “primarily to enhance patient expectation,” 46% reported doing so at least 2-3 times per month. Of those physicians who reported recommending one or more placebo treatments in the past year, 68% described this recommendation to their patients as “a medicine not typically used for your condition but may benefit you.” A companion survey of the attitudes of patients to the use of placebos and promoting the placebo response in clinical practice is being developed, in collaboration with the Division of Research, Northern California Kaiser Permanente. Data collection is planned to begin in September 2010. The National Center for Complementary and Alternative Medicine has provided financial support for both of these surveys.

Impact of research: The Department’s research has contributed to an improved understanding of the placebo effect and of ethical issues relating to the use of placebos in research and clinical practice. In addition to contributing to the medical and bioethics literature, the research of the Department on placebos has generated substantial attention in the news media, especially publication of the survey of physicians on use of placebo treatments. Journalists have also requested interviews on the nature of the placebo effect and the use of deception in placebo research. As a direct impact of the Department’s work on deception in placebo research, two psychologists recently published a study evaluating the authorized deception approach in connection with a placebo analgesia experiment (Martin AL, Katz J. *Pain* 2010;149:208-15). Healthy subjects were randomized to either the standard or authorized deception approaches to the consent disclosure. No differences in study outcomes between the two groups were observed, thus supporting the hypothesis that authorized deception is a methodologically sound method for conducting deceptive research while respecting subject autonomy. A recent experiment of the placebo effect in Parkinson’s disease adopted authorized deception (Lidstone SC et al. *Arch Gen Psychiatry* 2010;67:857-65), which suggests that this approach may become more widely used in research on the placebo effect.

Publications:

Daugherty C, Ratain M, Emanuel E, Farrell A, Schilsky R. Ethical, Scientific, and Regulatory Perspectives Regarding the Use of Placebos in Cancer Clinical Trials. *Journal of Clinical Oncology*. 2008;26(8):1-8.

Hornig S, Miller F. Placebo-Controlled Procedural Trials for Neurological Conditions. *Neurotherapeutics*. 2007;4:531-6

Miller FG. William James, faith, and the placebo effect. *Perspectives in Biology and Medicine* 2005;48:273-81.

Miller FG, Wendler D, Swartzman L. Deception in research on the placebo effect. *PLoS Medicine* 2005;2(9):e262.

Miller FG, Rosenstein DL. The nature and power of the placebo effect. *Journal of Clinical Epidemiology* 2006;59:331-35.

Miller FG, Kaptchuk. Deception of subjects in neuroscience: an ethical analysis. *Journal of Neuroscience* 2008;28:4841-43.

Miller FG, Kaptchuk TJ. The power of context: reconceptualizing the placebo effect. *Journal of the Royal Society of Medicine* 2008;101:222-25.

Miller FG, Colloca L. The legitimacy of placebo treatments in clinical practice: evidence and ethics. *American Journal of Bioethics* 2009;9(12): 39-47.

Miller FG, Colloca L, Kaptchuk TJ. The placebo effect: illness and interpersonal healing. *Perspectives in Biology and Medicine* 2009;52:518-39.

Finniss DG, Kaptchuk TJ, Miller FG, Benedetti F. Placebo effects: biological, clinical, and ethical advances. *Lancet* 2010;375:686-95.

Miller FG, Colloca. Semiotics and the placebo effect. *Perspectives in Biology and Medicine*, in press.

Miller F, Wendler D. The ethics of sham invasive intervention trials. *Clinical Trials*. 2009;6:401-2.

Tilburt JC, Emanuel EJ, Kaptchuk TJ, Curlin FA, Miller FG. Prescribing “placebo treatments” in clinical practice: results of a national survey of U.S. internists and rheumatologists. *BMJ* 2008;337:a1938.