The use of the placebo effect in clinical medicine – ethical blunder or ethical imperative?*

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ABSTRACT: *The current debate in medical ethics on placebos focuses mainly on their use in health research. Whereas this is certainly an important topic the discussion tends to overlook another longstanding but nevertheless highly relevant question, namely if and how the placebo effect should be employed in clinical practice. This paper describes the way the placebo effect is perceived in modern medicine and offers some historical reflections on how these perceptions have developed; discusses elements of a definition of the placebo effect; and suggests some conditions under which making use of the therapeutic potential of the placebo effect can be ethically acceptable, if not warranted.*

Introduction

The placebo effect keeps popping up – in the science pages of daily newspapers as well as in medical journals and academic volumes written by philosophers, anthropologists and other scientists.[1-11] Modern medicine with its focus on specific interventions seems to be at odds with this hard-to-grasp phenomenon that has accompanied medicine from its very beginning.[12] However, it can be projected that an increasingly sophisticated and individualized medicine will not only provide tailor-made diagnostic pathways and therapeutic solutions but will also find ways to consciously employ the placebo effect in order to maximize therapeutic effects.

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For the moment, however, the discussion on the use of placebos and/or the placebo effect is framed mainly by their use in health research and the – certainly valid – moral appeals not to use a placebo when there are therapeutic options available unless there are compelling reasons, and to make sure prospective study participants are well aware of the existence of a placebo arm. This debate inadvertently contributes to the overall reputation of the placebo effect as something to be weeded out, to be minimized, to be avoided; as something that stands in the way of "proper medicine". The placebo effect is thus a phenomenon still looking for its place in clinical practice. This paper will 1) describe the way the placebo effect is perceived in modern medicine and offer some historical reflections on how these perceptions have developed; 2) discuss elements of a definition of the placebo effect; and 3) suggest some preconditions for an ethically acceptable use in clinical medicine.

Perceptions of the placebo effect in clinical medicine

A look at the changing attitude in medicine towards placebos over the last fifty years reveals a rather radical shift. Whereas Henry Beecher's famous paper on "The Powerful Placebo"[13] reflects a certain degree of awe and wonder at the placebo phenomenon, the meta-analysis conducted by Hrobjartsson and Gotzsche in 2001 comes to the conclusion that placebo equals "no treatment".[14,a] Not only has the placebo to some extent become a symbol for an outdated, morally questionable practice implying deceit and paternalism; there seems to be no scientific rationale, and therefore no role for its use in a scientifically based clinical medicine. Employing the placebo effect – should it exist at all – for therapeutic purposes thus seems to have lost all justification, being at best a waste of time and resources distracting from the demands of clinical efficiency. From a mainstream intervention half a century ago (like handing out sugar pills to demanding patients without substantial pathology), the use of placebos has moved to the fringes of medicine, to "complementary" or "alternative" approaches.

The only role left for the placebo in current mainstream medicine is thus to serve as a negative control, as a foil against which effective, "real" treatment is being tested. For that purpose, as well, the use of placebos has come under criticism.[15,16] And indeed, well-known studies conducted in the past cannot stand up to current ethical standards: An example is the famous study on the therapeutic effectiveness of internal mammary artery ligation as a treatment for angina, where patients were not even told about the placebo arm and no IRB approval had to be obtained.[17]

Placebo-controlled trials today certainly take ethical considerations into account to a larger extent than in the 1950s. But still, the question remains under what conditions the use – or the forgoing – of placebo controls can be justified, in particular, when invasive procedures are involved, like drilling holes into the cranium in studies transplanting embryonic cells into the brains of Parkinson's patients.[18,19] Whereas it

a. I will not provide a methodological or conceptual critique of this paper here, which will be done elsewhere in this issue (cf. Porzsolt et al., pp. 119-132)

can be argued that a well-designed placebo-controlled trial honours the obligation towards future patients to find out as quickly and as reliably as possible if interventions are effective or not, critics consider invasive or risky interventions without any potential benefit unjustifiable.[20,21] Another issue that has been discussed in particular with regard to the latest revision of the Declaration of Helsinki concerns the question if placebo-controlled trials can be conducted in environments where no standard treatment exists (although it is available in richer countries); this would mean certain trials could be conducted in poor countries, but not in rich ones.[22,23,b]

Although the ethical problems related to placebo-controlled studies are likely to have contributed to the hesitancy of many physicians to explore ways to employ the placebo effect in clinical practice, some of these studies have shown that placebos were almost as good or even as good as the "active" medication or specific intervention under investigation. In a review of 75 randomized, placebo-controlled trials Walsh et al. found that on average a substantial 30% of patients suffering from depression responded to placebos (as compared to 50% for the active medication group with the greatest response).[24] A randomized, placebo-controlled study including 165 patients with osteoarthritis found that simulated arthroscopic surgery (where just the skin was incised and no instruments inserted) was as effective in moderately improving pain and function as arthroscopic lavage or debridement over a period of two years.[25] These findings in a very poignant manner raise the issue of what kind of active treatment should be reimbursed and under what conditions placebo treatment can be justified.

There is also a small but continuous volume of research that focuses on the placebo effect in its own right. One important part of this research deals with the mechanism through which placebos work. It has been found, for instance, that response to fluoxetine treatment for depression and to placebo work through the same pattern of changes in brain metabolism.[26,27] Another Positron Emission Tomography (PET) study showed that a substantial dopamine release was triggered in Parkinson's patients in response to placebo.[28] The authors argue that the placebo effect encountered in the treatment of other medical disorders might be mediated by a placebo-induced dopamine release in limbic structures as well.[29] Already in the 1970s the neurobiologist Howard Fields and colleagues have pointed to the role of endogenous opioids for placebo analgesia.[30,31] They and others have also pointed to the role of conditioning, learning and expectation as explanatory mechanisms for the placebo effect, including effects like immunosuppression.[32,33,34] Different work has focused on the pharmacological properties of placebos, identifying time-effect curves as well as peak, cumulative, and carryover effects similar to those of active medications.[8] In addition, a meta-analysis has raised the question if a considerable portion (25%) of what is usually regarded as the effect of the tested drug is not actually a placebo response.[35]

Beyond the existing findings, the NIH has started to sketch out a research agenda for further work in the field. One element in the process was the meeting "The Science

b. Ethical issues of the use of placebos in health research are being dealt with extensively in other contributions to this issue (cf. for example the contributions by Idänpään-Heikkilä et al., pp. 23-28; Sugarman, pp. 29-35; and Zilgalvis, pp. 15-22.)

of the Placebo: Towards an Interdisciplinary Research Agenda" (2000), dealing with the meaning and mechanism of the placebo effect as well as with ethical implications.[36] Another element are two research grants that have been announced for 2002, one on the "Elucidation of the Underlying Mechanisms of Placebo Effect"[37] and another one on "The Placebo Effect in Clinical Practice"; an important aim of the latter program is "to understand what factors are necessary to elicit a placebo effect in clinical practice so that the benefits for the therapeutic intervention can be enhanced to improve health and promote wellness".[38] Existing results as well as the agendas for further research point to a potentially important role for the placebo effect in clinical medicine. The questions to be addressed are thus how to appropriately define the placebo effect and how to employ it in an ethically acceptable manner. Should it be possible to sketch out such conditions, it may even be argued that seriously exploring the therapeutic potential of the placebo effect is an ethical requirement.

Placebo vs. Placebo Effect

Every discussion on the existence of the placebo effect and its use and abuse should be based on a clear and consistent definition of the placebo effect. Unfortunately, even in papers with potentially considerable implications for health policy and allocation of research funds such a definition is not always provided.[14] In this paper, the following definitions shall be put forward for discussion. For one, the placebo effect has been defined by Brody as a "change in a patient's condition that results from the symbolic aspects of the encounter with a healer or with a healing setting, and not from the pharmacological or physiological properties of any remedy used".[39] This definition contains two important aspects: It does not make any claims concerning the curative power of the placebo effect or the duration of the evoked changes; much of that is still subject to research and may vary according to individual or situational factors. Secondly, it does not specify the medium – the "placebo" – by which the placebo *effect* is evoked; the definition goes beyond the "sugar pill" that many still associate with this notion and can include a whole range of unspecific interventions (like, for example, relaxation therapies) that may either alleviate symptoms in their own right or might contribute to maximizing the effects of a specific intervention (like taking a pain killer).

Some other important aspects are brought forward by a definition that can be found in the announcement of a NIH grant on the placebo effect in clinical practice: "Placebo effects can be defined as the positive physiological or psychological changes associated with the use of inert medications, sham procedures, or therapeutic symbols within a healthcare encounter. Placebos can also be active substances or real procedures that produce unexpected beneficial effects."[37] This definition introduces the notion of "positive physiological or psychological changes", thus allowing for the needed distinction between placebo and nocebo effects. It also acknowledges these changes can be physiological or psychological in nature, or – it might be added – a combination of both.

And finally it points to the fact that the "vehicle" of the placebo effect, the placebo, is not necessarily an inert substance or procedure, but can be an active substance as well, producing "unexpected beneficial effects".

It may even be that the usual dichotomy between "active" substance and "placebo" is not adequate, given that placebos can produce effects, and given that part of the effect of the "active" substance might be due to a "placebo" effect. A treatment with placebo should thus not be considered as absence of treatment, but just as absence of a specific, "active" intervention.[26] But instead of thinking if one or the other should be employed it may be more appropriate to ask how the placebo effect can be used to optimally enhance a given therapy – "placebo enhanced therapy" instead of "placebo or therapy". One thought experiment would be to ask if a pain killer with considerable side effects could not intermittently be replaced by a placebo, assuming that patients are conditioned to the pain reducing effect of taking a white pill. Another question would be if the effect of the pain killer could be enhanced by patients applying a relaxation technique after taking the pill and consciously focusing on the reduction of symptoms – a sensation that they might eventually learn – at least to some extent – to evoke at will. These ideas raise, of course, a whole bunch of methodological and ethical questions: Would the placebo also produce side effects? Which patient groups could be used for such an experiment without risk? Would informing the patients about the study design, particularly the intermittent drug regime, reduce the effect? But instead of continuing to pit "active" treatment against "placebo" and/or "no treatment", it might be interesting to explore how the effects of the "symbolic aspects of the encounter with a healer or with a healing setting", as Brody put it,[39] or, more broadly, how "contextual factors" add to the effects of known "active" substances or interventions. It will be an interesting test case for modern medicine if and how it will be able to integrate the placebo effect concept and make constructive use of it in an ethically acceptable manner.[12] Given the considerable populations of patients that medicine cannot provide with a cure nor with sufficient symptom reduction, like chronic pain patients, it may well be that medicine cannot afford to simply neglect the therapeutic potential of the placebo effect.

Ethical blunder or imperative?

If we think today of a physician who is at her wit's end in the treatment of a difficult patient with a non-life-threatening disease and who hands out an inert pill to this patient, telling him that this is the newest cure for his problem in order to finally get him out of the office, this would quite clearly have to be considered an ethical blunder. On the other hand, if the physician would, with the informed consent of her patients, run a well-designed clinical trial exploring possibilities to systematically enhance the effect of a specific intervention by evoking the placebo effect, such an initiative may well be considered not only ethically acceptable, but even laudable.

So under what conditions does the clinical use of the placebo effect have to be regarded as ethically unacceptable? Certainly, any use of the placebo effect that involves the deceit of patients is inappropriate.[40] This can happen when the response to a placebo is used as a diagnostic tool in order to distinguish supposed "malingerers" or

"hysterics" from the patients suffering from a "real" disease; such attempts at identifying the etiology of symptoms seems to be profoundly misguided. Another unacceptable practice is to offer an inert substance pretending that the patient is receiving active treatment. Such practices, that exclude the patient from important decisions regarding his or her treatment, are likely to lead to a disturbed patient-physician-relationship, even if the patient does not discover the deceit immediately. They also reflect a paternalistic attitude that presumes that the physician understands the patient better than the patient him- or herself does, and that the physician is *ex officio* best suited to judge what therapeutic measures are most appropriate without having to consult with the patient. Another problematic moment is the neglect of superior treatment approaches or the forgoing of a continued search for a satisfying diagnosis, because the physician might be precociously convinced that a placebo would be the best treatment for a particular patient whose symptoms the physician does not consider as serious. At least as problematic is the withholding of available treatment, especially if for the purpose of saving money that would otherwise need to be spent for costly "active" interventions. And finally there is the danger of overlooking possible nocebo responses[41] and of underestimating the risk and burden that can come with "placebo" interventions, particularly in the case of sham surgery.[c]

Figure 1

Ethical blunder	**OR**	**Ethical imperative?**
- Deceit		- Informed Consent
- Mistrust		- Trust
- Paternalism		- Respect for patient's autonomy, empowerment
- Withholding or neglecting superior treatment option		- Best therapeutic concept
- Exploitation		- Care, support

But not every use of the placebo effect in clinical practice has to become a victim of these pitfalls. It is conceivable to use the placebo effect in a way that is transparent and informs the patient of the respective therapeutic concept, including placebo components; that builds on and honours a trustful patient-physician-relationship; that respects the patient's autonomy, tolerating and even encouraging a patient's informed choice; that carefully develops an appropriate and promising therapeutic concept for the patient, based on acknowledged standards of care; and that reflects an attitude towards the patient that is characterized by genuine concern, the wish to care and to support.

Even if individual suggestions for the clinical of the placebo effect would need to be reviewed in detail by a case-by-case approach, the conditions described above sketch out a preliminary outline for a framework of preconditions for an ethically

c. It can be presumed that sham surgery today is practised only in the context of surgical trials. For a discussion of this separate issue, see the following references.[42,43,44,45]

acceptable use of the placebo effect in clinical medicine, which can serve as a basis for an urgently needed discussion on these matters.

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REFERENCES

1. Benson, H., Epstein, M.D. (1975) The Placebo Effect. A Neglected Asset in the Care of Patients, *Journal of the American Medical Association* **232**: 1225-1227.
2. Ernst, E., Herxheimer, A. (1996) The power of placebo, *British Medical Journal* **313**: 1569-1570.
3. Harrington, A. (ed.) (1997) *The Placebo Effect. An Interdisciplinary Exploration*, Harvard University Press, Cambridge, MA.
4. Meyer, P. (2003) Placeboanwendung – Die ethischen Perspektiven, *Medizinethische Materialien* **140**: 1-35.
5. Shapiro, A.K., Shapiro, E. (1997) *The Powerful Placebo: From Ancient Priest to Modern Physician*, Johns Hopkins University Press, Baltimore.
6. Spiro, H.M. (1986) *Doctors, Patients, and Placebos*, Yale University Press, New Haven.
7. Stolberg, S.G. (1999) Sham surgery returns as a research tool, *The New York Times* 4/25/99.
8. Turner, J.A., Deyo, R.A., Loeser, J.D., Von Korff, M., Fordyce, W.E. (1994) The Importance of Placebo Effects in Pain Treatment and Research, *Journal of the American Medical Association* **271**: 1609-1614.
9. Wall, P.D. (1992) The placebo effect: an unpopular topic, *Pain* **51**: 1-3.
10. Weijer, C. (2002b) Placebo trials and tribulations, *Canadian Medical Association Journal* **166**: 603-604.
11. White, L., Tursky, B., Schwartz, G.E., eds. (1985) *Placebo: Theory, Research, and Mechanisms,* Guilford Press, New York, pp. 306-323.
12. Biller, N. (1999) The Placebo Effect - Mocking or Mirroring Medicine?, *Perspectives in Biology and Medicine* **42**(3): 398-401.
13. Beecher, H.K. (1955) The Powerful Placebo, *Journal of the American Medical Association* **159**: 1602-1606.
14. Hrobjartsson, A., Gotzsche, P. (2001) Is the placebo powerless? An analysis of clinical trials comparing placebo with no treatment, *New England Journal of Medicine* **344**: 1594-1602.
15. Rothman, K.J., Michels, K.B. (1994) The Continuing Unethical Use of Placebo Controls, *New England Journal of Medicine* **331**: 394-398.
16. Michels, K.B., Rothman, K.J. (2003) Update on Unethical Use of Placebos in Randomised Trials, *Bioethics* **17**: 188-204.
17. Cobb, L.A., Thomas, G.I., Dillard, D.H., Merendino, K.A., Bruce, R.A. (1959) An evaluation of internal-mammary-artery ligation by a double-blind technique, *New England Journal of Medicine* **260**: 1115-1118.
18. Freed, C.R., Greene, P.E., Breeze, R.E., Tsai, W.Y., DuMouchel, W., Kao, R., Dillon, S., Winfield, H., Culver, S., Trojanowski, J.Q., Eidelberg, D., Fahn, S. (2001) Transplantation of embryonic dopamine neurons for severe Parkinson's disease, *New England Journal of Medicine* **344**: 710-719.
19. Freeman, T.B., Vawter, D.E., Leaverton, P.E., Godbold, J.H., Hauser, R.A., Goetz, C.G., Olanow, C.W. (1999) Use of placebo surgery in controlled trials of a cellular-based therapy for Parkinson's disease, *New England Journal of Medicine* **341**: 988-992.
20. London, A.J., Kadane, J.B. (2002) Placebos that harm: sham surgery controls in clinical trials, *Statistical Methods in Medical Research* **11**: 413-427.
21. Weijer, C. (2002a) I need a placebo like I need a hole in the head, *Journal of Law, Medicine & Ethics* **30**: 69-72.

22. Cox, P. (1999) Codes of medical ethics and the exportation of less-than-standard care, *Int J Appl Philos* **13**: 177-185.
23. Lurie, P., Wolfe, S.M. (1997) Unethical trials of interventions to reduce perinatal transmission of the human immunodeficiency virus in developing countries, *New England Journal of Medicine* **337**: 853-856.
24. Walsh, B.T., Seidman, S.N., Sysko, R., Gould, M. (2002) Placebo Response in Studies of Major Depression: Variable, Substantial, and Growing, *Journal of the American Medical Association* **287**: 1840-1847.
25. Moseley, J.B., O'Malley, K., Petersen, N.J., Menke, T.J., Brody, B.A., Kuykendall, D.H., Hollingsworth, J.C., Ashton, C.M., Wray, N.P. (2002) A controlled trial of arthroscopic surgery for osteoarthritis of the knee, *New England Journal of Medicine* **347**: 81-88.
26. NIH News Release: Placebo, Antidepressant May Lift Depression Via Common Mechanism, http://www.nih.gov/news/pr/may2002/nimh-01.htm (accessed on September 29, 2003).
27. Mayberg, H.S., Silva, J.A., Brannan, S.K., Tekell, J.L., Mahurin, R.K., McGinnis, S., Jerabek, P.A. (2002) The functional neuroanatomy of the placebo effect, *Am J Psychiatry* **159**: 728-737.
28. De la Fuente-Fernández, R., Ruth, T.J., Sossi, V., Schulzer, M., Calne, D.B., Stoessl, A.J. (2001) Expectation and dopamine release: mechanism of the placebo effect in Parkinson's disease, *Science* **293**: 1164-1166.
29. De la Fuente- Fernández, R., Stoessl, A.J. (2002) The biochemical bases for reward. Implications for the placebo effect, *Eval Health Prof* **25**: 387-398.
30. Levine, J.D., Gordon, N.C., Fields, H.L. (1978) The mechanism of placebo analgesia, *Lancet* **2**: 654-657.
31. Fields, H.L., Price, D.D. (1997) *Toward a Neurobiology of Placebo Analgesia. In: Harrington, A. (ed.) The Placebo Effect. An Interdisciplinary Exploration*, Harvard University Press, Cambridge, MA.
32. Ader, R., Cohen, N. (1975) Behaviorally conditioned immunosuppression, *Psychosom Med* **37**: 333-340.
33. Ader, R. (1993) Conditioned responses in pharmacotherapy research, *Psychol Med* **23**: 297-299.
34. Ader, R. (2000) Classical conditioning in the treatment of psoriasis, *Cutis* **66**: 370-372.
35. Kirsch, I., Sapirstein, G. (1998) Listening to Prozac but Hearing Placebo: A Meta-Analysis of Antidepressant Medication, Prevention & Treatment 1:Article 0002a, http://www.journals.apa.org/prevention/volume1/pre0010002a.html (accessed on April 10, 2003).
36. Engel, L., Wilentz, J. National Conference Explores the Placebo Effect, http://www.nih.gov/news/NIH-Record/01_23_2001/story03.htm (accessed on September 29, 2003).
37. NIH Guide: The Placebo Effect in Clinical Practice, http://grants.nih.gov/grants/guide/rfa-files/RFA-AT-02-001.html (accessed on September 29, 2003).
38. NIH Guide: Elucidation of the Underlying Mechanisms of Placebo Effect, http://grants1.nih.gov/grants/guide/rfa-files/RFA-AT-02-002.html (accessed on September 29, 2003).
39. Brody, H. (1995) Placebo, in: Reich WT, ed. Encyclopedia of Bioethics, Simon & Schuster Macmillan, New York, pp. 1951-1953.
40. Bok, S. (1977) The Ethics of Giving Placebos, *Scientific American* **231**: 17-23.
41. Barsky, A.J., Saintfort, R., Rogers, M.P., Borus, J.F. (2002) Nonspecific medication side effects and the nocebo phenomenon, *Journal of the American Medical Association* **287**: 622-627.
42. American Medical Association: Code of Ethics. E-2.075 The Use of Placebo Controls in Clinical Trials, http://www.ama-assn.org/ama/pub/printcat/8424.htm (accessed on April 10, 2003).
43. American Medical Association: Code of Ethics. E-2.076 Surgical "Placebo" Controls, http://www.ama-assn.org/ama/pub/printcat/8425.htm (accessed on April 10, 2003).
44. Macklin, R. (1999) The ethical problem with sham surgery in clinical research, *New England Journal of Medicine* **341**: 988-992.
45. Brody, B. Criteria for legitimate placebo controlled surgery trials, http://public.bcm.tmc.edu/pa/knee-drbrody.htm (accessed on April 10, 2003).