Journal of Medical Ethics, 1996; **22: 140–146**

Placebos in clinical practice and research

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Abstract

The main current application of placebo is in clinical research. The term placebo effect refers to diverse non-specific, desired or non-desired effects of substances or procedures and interactions between patient and therapist. Unpredictability of the placebo effect necessitates placebo-controlled designs for most trials. Therapeutic and diagnostic use of placebo is ethically acceptable only in few well-defined cases. While "therapeutic" application of placebo almost invariably implies deception, this is not the case for its use in research. Conflicts may exist between the therapist's Hippocratic and scientific obligations. The authors provide examples in neuropsychiatry, illustrating that objective scientific data and well-considered guidelines may solve the ethical dilemma. Placebo control might even be considered an ethical obligation but some provisos should be kept in mind: (a) no adequate therapy for the disease should exist and/or (presumed) active therapy should have serious side-effects; (b) placebo treatment should not last too long; (c) placebo treatment should not inflict unacceptable risks, and (d) the experimental subject should be adequately informed and informed consent given.

Placebo-controlled randomised clinical trials

Shapiro[1] defined placebo as "any therapeutic procedure (or that component of any therapeutic procedure) which is given deliberately to have an effect, or unknowingly has an effect on a patient, symptom, syndrome, or disease, but which is objectively without specific activity for the condition being treated". Since the earliest days of medical science, and certainly since the advent of chemotherapy, placebo effects have been considered more often a nuisance than a therapeutic tool. Both inert and active therapies were observed to produce effects beyond their predicted physiological properties. These rather surprising observations on the clinical consequences of the administration of placebos became known as "the placebo effect", comprising the total of unexplained consequences of administering placebos as well as active treatments. Due to, amongst other things, the unpredictability of placebo effects in individuals and patient groups, placebos came to play an irreplaceable role as "inactive" controls in randomised clinical trials (RCTs).

The first rather isolated placebo-controlled clinical trial took place in 1916 and was conducted by Macht who compared the analgesic action of morphine with that of physiological saline.[2] It was only in the 1940s and 1950s that the large-scale use of placebos in clinical research emerged, simultaneously with scientific knowledge pertaining to the placebo effect. The unabated need for placebo-controlled clinical trials is illustrated by several anecdotes in the development of presumedly therapeutic procedures. Surgical ligation of the internal mammary artery, once proclaimed to be efficacious for treatment of angina pectoris, might serve as an example. In the 1950s, considerable relief of symptoms was reported for patients with angina pectoris subjected to bilateral ligation of the internal mammary artery. In the early '50s, Italian clinicians Battezzati and colleagues[3] were the first to apply this technique, and the *Reader's Digest* published an enthusiastic report.[4] A year later promising results were also reported by American researchers who based their enthusiasm upon data from non-controlled trials.[5–7] It only took two double-blind placebo-controlled studies, involving 35 subjects, to disprove the presumed efficacy of this putative treatment. Fourteen subjects were placebo-treated (sham-operated) and 21 underwent a ligation of the internal mammary arteries under local anaesthesia.[8 9] The placebo procedure consisted of parasternal skin incisions without ligation, while the "active" treatment consisted of parasternal skin incisions followed by ligation of the internal mammary artery. It was demonstrated that internal mammary artery ligation did not increase cardiac muscle perfusion and had no effect on the pathophysiology of coronary artery disease. Although deception was obvious in these two placebo-controlled trials (patients were not informed about the possibility of sham operation),

Key words

Medical ethics; placebo; research; epilepsy; Alzheimer's disease; deontology.

the double-blind evaluation of the procedure's effect in 35 patients prevented wide-spread introduction of this non-efficacious surgical procedure.

Demonstration of safety and effectiveness of a drug is a legal requirement for marketing drugs in many countries. In the USA, evidence submitted to the Food and Drug Administration (FDA) to meet this requirement has to include results of "adequate and well-controlled investigations" capable of distinguishing "the effect of a drug from other influences, such as spontaneous change in the course of the disease, placebo effect, or biased observation". According to FDA regulation this usually implies standard clinical trial features such as (inactive) control groups, randomised assignment to treatment, and blinded outcome assessment. Difference in outcome among patients, concurrently randomised to therapy, should not be due to personal beliefs, secondary interests, and/or prejudices of patients, investigators or sponsors. FDA official Leber[10] stresses the necessity of RCTs. Even though Leber states that "[t]here is no alternative to the randomised controlled design – no ifs, ands, or buts!", he certainly does not take the RCT device as infallible. In any case, open studies, case series and studies relying on external or historical controls do not allow sound conclusions. Historical controls are highly unreliable, especially in regard to diseases with poorly known or highly variable natural courses such as insomnia, anxiety, depression and pain syndromes.[11–13] As Leber[10] argues, it is often impossible to show improvement to be unrelated to pharmacological effects of the administered agents without the inclusion of a placebo arm.

Deceptive use of placebo

The two major ethical problems in the use of placebo involve deception when used either therapeutically or in research without adequate patient information and consent, and the potential conflict between the Hippocratic and scientific obligations of the therapist-researcher. Even though it remains inadmissible to use placebo for therapeutic or diagnostic purposes, most therapists do occasionally apply placebo in a deceptive but rather benevolent way. Use of placebo for therapeutic and diagnostic use is inadmissible since the patient may be withheld from an active treatment, may be denied his or her right to self-determination and finally, because there is no scientific ground for the application of placebo in diagnosis. Deception is certainly unacceptable when applying placebo as an inactive control in clinical research.

Park and Covi[14] demonstrated that deceipt may not be necessary in therapeutic application. They showed that in neurotic patients presenting signs of anxiety, placebo could be used openly as a therapeutic agent. Virtually all patients accepted the placebo and improved over a one-week treatment. Park and Covi[14] found that a number of patients even refused to believe they had received placebo. Alternatively, in discussing placebo use with patients, one might consider another ethically acceptable or preferable description of placebo: "Placebo is a medicine which does not act directly through known bodily mechanisms but which may work through the mind".

Although many authors[15] vividly defend consequentialist or utilitarian strategies and deceptive use of placebo, others point to the important unethical and non-scientific use of placebo in so-called therapeutic or diagnostic contexts. Goodwin *et al*[16] surveyed the knowledge of placebo action in 60 house officers and 39 registered nurses, and their patterns of placebo use. Most respondents underestimated or were unaware of the power of placebo effects, and the following unfortunate patterns of placebo use emerged: (a) to prove the patient "wrong" (ie, to expose a patient thought to be exaggerating, imagining or faking symptoms); (b) in disliked or "undeserving" patients (for example, alcoholic, psychotic or manipulative and demanding patients); (c) in situations where standard treatments either fail or make patients worse, (d) as a group activity to act out staff annoyance towards "difficult" patients.

Deception in the therapeutic use of placebo might be ethically acceptable in few well-defined cases, for example, when the physician is dealing with subjects with a history of substance abuse or when subjects have to be withdrawn from certain addictive agents. Indeed, in these cases, giving placebo without obtaining consent of the patient, will almost invariably contribute to the patient's well-being, and in addition does not imply that one withholds a possibly beneficial medical treatment. Other therapeutic usage of placebo in non-informed patients is regrettable, ethically unacceptable and illustrative of ignorance and prejudice. It needs to be stressed, however, that malingerers or drug addicts are not relieved more efficiently by placebo. Quite on the contrary, most studies suggest that such patients are less likely placebo responders. Also, complaining or "manipulative" patients are no more likely to respond to placebo than patients who are well liked by the hospital staff.[17]

In the scientific application of placebo, however, informed consent should be mandatory, implying that thorough information with regard to the rationale, the design, the eventual standard therapeutic procedures for the given disease, the randomisation procedure as well as the chance of being randomised to placebo should be communicated and discussed. Moreover, informed consent procedures require subjects to be informed about all risks and benefits associated with the trial and their right to withdraw at any time. Some authors disagree with this and oppose compulsory informed consent. Brewin[18] argues that "too much information may be as bad as too little". This author also suggests that some

investigators, once in possession of written informed consent, might become less concerned than they should about their ethical responsibilities. Still other authors perceive an incompatibility between informed consent and placebo control. Levine[19] warns us about subjects who are *thoroughly informed* of the expected therapeutic and adverse effects of pharmacologically active agents in placebo-controlled trials. In several clinical trials, subjects unblinded the study by correctly guessing their treatment assignment. Levine[19] proposes a modification in consent procedures that would eliminate or at least reduce this possibility without defeating the ethical purpose of informed consent. Levine suggests adding irrelevant side-effects in the provided information that are of the same order of importance as the actual expected side-effects. This is consistent with the ethical purposes of informed consent in that it entails disclosure of material risks.

Another poignant issue concerns the patient's ability to understand placebo-controlled trials. Do the patients really know what placebo means, do they realise that they have a certain chance of receiving placebo and why they will be on it? Stanley[20] reviewed the literature and concluded that irrespective of their condition and whether or not they were psychiatric patients, patients were fairly able to understand the risks and benefits of a proposed treatment and the purpose of a particular treatment or procedure.

Conflict between Hippocratic and scientific obligations

The therapist-researcher is subject to two fundamental ethical obligations, a Hippocratic one and a scientific one. The therapist's Hippocratic obligation obliges him/her to apply all existing knowledge for the best possible treatment of individual patients. On the other hand, in agreement with the researcher's scientific obligations it is unethical to produce unsound scientific data. Thus, it is the duty of the researcher to acquire new knowledge so that future patients might benefit, and to communicate accurately this knowledge to the scientific community in order to contribute to the collective benefit. However, these two obligations may on certain occasions be in contradiction to the execution and design of placebo-controlled RCTs. According to certain people, randomisation by itself means that patients are no longer treated purely for their own good but are used at best for the benefit of future sufferers from their condition, at worst merely to satisfy scientific curiosity, and that they risk being treated inappropriately. It is thought that some kind of sacrifice is being demanded of them and that they should either be given a full explanation or else not randomised.

The primary question is whether it can be ethically justified to deprive a certain percentage of patients in placebo-controlled trials of their "right to receive" treatment of acknowledged efficacy merely in order to verify whether or not other active treatments exist. Withholding treatment of proven efficacy clearly violates the therapist's commitment to individual patient welfare. However, the conflict between therapist and researcher more often is emotionally, rather than scientifically, based. Patients can be allocated to standard therapy control groups, or to placebo groups when no standard therapy exists, without violation of Hippocratic commitment; developing new treatments of an already (partially) treatable disease need not necessarily be dangerous to the subject. Some therapists stress the pragmatic viewpoint of the RCT: only the application of an accepted treatment as control arm can answer the question whether the new treatment improves on a standard method. The use of placebo-controlled RCT designs is the only way to minimise the number of ineffective drugs and therapeutic procedures. The conviction that ignorance may cause patient harm may not only be used as a justification for research but in addition renders research an ethical obligation. The important ethical difficulties associated with the widespread application of a new treatment without a trial, and consequently potentially without specific effects but with varying degrees of side-effects, is far greater than those associated with the trial itself. The optimal and therefore often placebo-controlled and ethically founded RCT meets the duties of benefiting society and increasing knowledge without jeopardising the well-being of the experimental subjects.

There are many examples of marketed compounds without scientifically demonstrated efficacy and, in addition, several companies market so-called alternative medicines without needing to meet rigorous drug regulatory requirements for proof of efficacy. Recently, Pope[21] correctly stated that forty different compounds for treatment of Alzheimer's disease are available in Europe without any proven efficacy. The Ginkgo biloba case is an example where rigorous scientific standards of efficacy are not met.[21–25] In 1988, 5·24 million prescriptions for Ginkgo biloba extract involved a cost of DM 370 million to former West German health insurance. In 1992, sales were comparable with total costs of approximately DM 368 million. The drug, licensed under the 1986 drug law which does not require scientific evidence from controlled trials but merely positive therapeutic "experiences", is promoted for treatment of disorders as diverse as peripheral arterial disease, memory impairment, vertigo and impotence. Kimbel,[25] writes that "[t]he obvious discrepancy that Ginkgo biloba extracts are among the most prescribed medicines in France and Germany but not licensed in Anglo-American and Scandinavian countries suggests widely differing standards of acceptance. Would it not be advisable to base any therapeutic conclusions on the criteria of

leading regulatory agencies – ie, evaluation of all published and unpublished studies and use of established standards for clinically relevant efficacy?"

Acceptability of placebo-controlled randomised clinical trials

One definitely needs to be fully informed about current biomedical knowledge with regard to the disease at hand in order to be able to make ethical decisions correctly. Some examples pertaining to the development of new agents against depression, schizophrenia, epilepsy and dementia will illustrate this necessity.

DEPRESSION

With the advent of a variety of potent anti-depressive agents, one might be tempted to conclude that placebo-controlled trials should be considered ethically unacceptable. However, we believe that the difference in improvement rates between drug-treated and placebo-treated non-endogenous patients is not big enough to make placebo control unethical.

Endogenous depressions have placebo response rates around 30 per cent, while neurotic or reactive depressions have rates approaching 70 per cent.[26] The more severe depressions (Hamilton Depression score above 20) have placebo response between 30 and 40 per cent, whereas those with less severe illness (Hamilton score below 14) have placebo response rates greater than 50 per cent. Brown *et al*[26] found no difference between baseline clinical and demographic characteristics of placebo responders and non-placebo responders in a large group of patients with major depression, illustrating the limited predictability of placebo response. Quitkin *et al*[27] analysed the heterogeneity of placebo responses in 144 depressive patients (DSM-III criteria) randomly assigned to placebo medication in four double-blind antidepressant drug trials. Half of the patients were rated as improved for at least one week: 23 per cent with abrupt improvement; 27 per cent with gradual improvement. Gradual improvement was observed later in the course of treatment, more resembled drug response, and was more likely to persist than abrupt improvement. The authors attributed gradual improvement to spontaneous remission.

Although placebo use may not always be advisable (for example, in depressed patients at significant risk of suicide, with psychotic features, or with severe functional impairment), Brown's[28] suggestion to apply placebo in an open manner in mild to moderate depression might hold some merit. He proposes to inform the patients about the fact that their condition tends to respond to placebo (he defines placebo adequately), and that in an attempt to treat them, they will receive placebo for a period of six weeks after which the need for other treatment will be evaluated. The authors provide, of course, possibilities for escape in case of deterioration of the symptomatology and/or increased risk for complications such as suicide.

SCHIZOPHRENIA

Several authors have questioned the ethical acceptability of short-term placebo treatment of chronic schizophrenics.[29] Even though double-blind placebo-controlled trials provide the most reliable evaluation of antipsychotic agents, some clinicians fear that subjects exposed to placebo or inactive new agents might suffer lasting *harm* when the trial leads to relapse. Sixty-six per cent of patients given placebo and only eight per cent of those given fluphenzine decanoate relapsed during a trial that showed no differences between groups – neither in any clinical or social variable measured at the end of seven years follow-up, nor in the number of relapses after the trial.[29] Placebo-controlled clinical trials of antipsychotic agents can still be acceptable on condition that escape treatment is provided by applying well thought-through exit criteria within reasonable time after relapse.

EPILEPSY

The first guidelines of the *International League Against Epilepsy* on the development of anti-epileptic agents state that new agents cannot be introduced unless it has been proved that patients with intractable epilepsy become seizure-free or experience an appreciable (for example, 25 or 50 per cent) reduction in seizure frequency.[30] The placebo-controlled add-on design is the appropriate clinical trial to identify such agents. In this type of clinical trial, the patient's baseline medication is maintained but in addition, either placebo or the new investigational drug is introduced. However, research on new anti-epileptic drugs with similar efficacy as drugs already marketed but with fewer or no side-effects should also find a place. The placebo-controlled add-on design is obviously not the best approach in this latter case. Equally active anti-epileptic agents with fewer side-effects might be missed since side-effects are difficult to assess in add-on designs due to drug interactions and difficulties in analysing individual drug actions. Determination of the activity of a compound may also be impossible in add-on designs when the agent tested influences the blood levels of concomitant agents.[31] Add-on trials may overestimate the toxicity of the test compound, especially if toxicity of the new compound is similar and additive to that of concomitant drugs. Finally, placebo-controlled add-on trials are often expected to yield an unlikely 50 per cent reduction in subject seizure frequency, whereas Schmidt[32] found only 15 per cent reduction with co-administration of a marketed drug.

Since epileptic seizures can result in serious discomfort or lasting disability, the sometimes more appropriate placebo-controlled, single-drug designs

face adverse ethical judgment. (Of course, certain seizure types such as primary generalised tonic-clonic seizures are imminently more dangerous than, for example, simple focal seizures without secondary generalisation; also, patients who only present seizures during sleep are less likely to develop complications). We argue that placebo application in clinical epilepsy research can be considered ethically acceptable under certain conditions and in the following trial designs: (a) placebo-controlled add-on designs in intractable epilepsy; (b) developmental drug monotherapy versus placebo in pre-surgical video-EEG or video-invasive neuroelectrophysiological monitoring (in order to be able optimally to observe epileptic seizures in this patient population, the baseline medication is withdrawn in the pre-surgical work-up; following this short observation period, the efficacy of the new developmental drug can be compared against that of placebo); (c) active control designs with attenuated form of the active control (in this design, an active control group is used but the administered dosage of the classical anti-epileptic agent is too low to be really effective); (d) placebo-controlled design in *de novo* patients presenting with a first-ever epileptic seizure.

We suggest that monotherapy designs b and c should always be preceded by more than one placebo-controlled add-on design indicating probable anti-epileptic efficacy of the test compound. Monotherapy trials were proposed to overcome the deadlock of no-difference outcome,[33] and have actually been used in the recent development of the anti-epileptic agents vigabatrin and felbamate. The acceptability of the designs rests upon a variety of factors such as type, frequency and onset time of seizures, investigational circumstances (for example, pre-surgery investigation of patients), preset safeguards such as escape criteria, duration of treatment, and (tentative) anti-epileptic efficacy of the test drug. Preset escape criteria are mandatory in design (b) trials. Bourgeois *et al*[34] used as primary efficacy parameter the time required to reach either a certain number of seizures or a fixed number of seizure-free days, whichever first. After a predetermined number of seizures or, for example, one (secondarily) generalised seizure, patients returned to the preregistration treatment schedule. This protocol was considered justified in the case of felbamate because of its promising clinical profile and strong interaction with other antiepileptics. In favour of a placebo-controlled design instead of an active-controlled design was the lack of sensitivity of the latter.[35]

In design (c), the test compound is compared against attenuated active control. The active control (a marketed anti-epileptic) can be administered in different doses (the lowest dose is not considered efficacious and such doses should be seen as pseudoplacebos) or at one fixed low dose. Patients with sufficient seizure control but side-effects can be enrolled in this type of trial. Although the exact percentage of seizure-free patients suffering side-effects is unknown, one could still find it unethical to run the risk of losing seizure control only in the hope that an adverse effect would disappear. Therefore, inclusion criteria eliminating patients with severe epilepsy and escape criteria are again mandatory. Treatment failure, the primary efficacy variable in these trials, is defined by specific exit criteria relating to either seizure frequency or seizure severity.

Placebo-controlled designs could be considered in *de novo* patients presenting with a first-ever seizure, provided that development of epilepsy is not too imminent as it might be in patients with epileptiform electroencephalographic elements or in those with predisposing structural lesions. As early as 1881, Gowers noted that seizures apparently beget seizures, an observation that remains controversial up to the present.[36] According to some authors but not to others, one of the most decisive factors in long-term seizure remission might be the number of pretreatment seizures.[37 38] This consideration also holds for non-*de novo* patients in whom additional seizures could change the prognosis of the disease. Only a trial with a placebo arm and an active anti-epileptic arm would be reliable in helping to resolve the issue of the risk of epileptogenesis after a first-ever epileptic seizure.

ALZHEIMER'S DISEASE

With recent FDA approval of tacrine as a drug against Alzheimer's disease, one might question the acceptability of placebo-controlled clinical trials. For several reasons we argue that placebo-controlled clinical trials in dementia are not only acceptable but ethically and scientifically preferable: (a) cholinesterase inhibitors such as tacrine cannot nearly be called standard therapy as only 23 per cent of Alzheimer patients benefit from tacrine treatment[39]; the clinical relevance of the therapeutic efficacy, at best only symptomatic and very limited, could even be doubted; (b) cholinesterase inhibitors are not devoid of side-effects since some 30 per cent of patients develop transaminitis, a reversible increase in liver transaminases, and some 15 per cent develop gastrointestinal complaints[39 40]; (c) placebo treatment does not inflict unacceptable risk on the patient suffering from this slowly progressing neurodegenerative disorder; (d) investigating new anti-dementic agents in cholinesterase inhibitor-controlled designs could lead to false positive findings (type II errors) when applying equipotency or no-difference outcome criteria; (e) cholinesterase inhibitor-controlled designs would require larger patient populations in order to reach sound conclusions: (f) cholinesterase inhibitor treatment as an active control arm would definitely unblind the study because of the high frequency of transaminitis.

Conclusion

Since it is inadmissible to perform ill-designed clinical trials and to market compounds or employ treatments without specific effect (efficacy not exceeding that of placebo) and/or with serious side-effects, properly controlled RCTs form the only scientifically valid tool. Nature of the disease process, duration of the study period, therapeutic-toxic ratio of the agent tested, availability and appropriateness of alternative therapy, and many other considerations all play a role in clinical trial design. Even though the placebo-controlled RCT remains the gold standard in therapy development, the need for and acceptability of placebo control has to be evaluated case by case, considering and reconciling both scientific and ethical issues. Often, placebo control might even be considered an ethical obligation but some provisos should be kept in mind: (a) no adequate therapy for the disease should exist and/or the (presumed) active therapy should have serious side-effects; (b) placebo treatment should not last too long; (c) placebo treatment should not inflict unacceptable risks on the patients, and (d) the experimental subject should be adequately informed and informed consent given.

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News and notes

First International Conference on DNA Sampling

This first international conference on DNA sampling will be held in Montreal, Quebec, Canada from September 6–8 this year.

The conference will provide a forum for interdisciplinary discussion on: DNA sampling and banking; patenting and commercialisation; legal status of human genetic material and information; models of consent and confidentiality; policy and ethical concerns; and genetic epidemiology and diversity.

The conference is being organised by the Research Center in Public Law (CRDP), Faculty of Law, Université de Montréal, in collaboration with the Health Law Institute, University of Alberta, Quebec Network of Applied Genetic Medicine, Quebec Health Research Fund.

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