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Clinical Relevance and Ethical Aspects of Placebos

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In recent years, the topic of placebo has gained momentum. Basic scientists started elucidating the neurophysiological and neuropharmacological processes that mediate the placebo response. At the same time, questions arose about the purported power of placebos. In addition, the debate on the ethics of the use of placebos heated up after the publication of some recent surgical trials using invasive placebo surgery procedures. In this article, we discuss the clinical relevance and the ethical problems associated with the use of placebos. Although a recent meta-analysis questioned the power of placebo, good evidence exists that placebos can lead to important improvement in many clinical conditions. A part of the conflict on the ethics of the use of placebos in randomized clinical trials can be solved by distinguishing between ethical guidelines for good clinical practice and for clinical research. We will also discuss some of the difficulties in finding proper placebo controls in clinical trials involving neurosurgical procedures.

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It is surprising that placebo has remained, for such a long time, an unpopular and neglected topic. The genuine scientific interest in this powerful phenomenon emerged only recently. However, this interest initially was overshadowed by a vivid controversy over its potential (lack of) power and the ethical problems associated with its use in clinical trials. The ethics debate became very animated after the publication of a controversial placebo-controlled study on the efficacy and safety of stem cell implants for the treatment of Parkinson's disease (PD). In this study, invasive placebo surgery procedures were introduced. Whereas in the past, placebos mainly were associated with the oral administration of harmless sucrose tablets or mock procedures, this study dramatically changed the conceptualization of the placebo condition by including procedures, such as the drilling of intracranial burr holes and the extended postoperative administration of immunosuppressive drugs, to name a few.

In this article, we discuss the clinical relevance and ethical aspects of the use of placebos. Despite the negative results of a recent meta-analysis, there are good arguments to believe that placebos can exert powerful clinical effects, not only in

conditions of pain but also in PD and depression. Next, we will discuss the difficulties in providing a proper placebo control in neurosurgical pain treatment conditions, and we will consider alternatives to the classical placebo design. This discussion will be followed by a discussion of the ethical problems related to the use of placebos. However, we will begin with a historical overview of how the placebo concept changed over time.

A Brief Historical Account of the Modern History of the Placebo Effect

To better understand modern thinking about placebo, it is useful to start with an overview of how the attitudes toward placebo have changed throughout history. The word placebo is derived from Latin and literally means "I shall please." Until the term became introduced in modern medicine in the late nineteenth century, placebos were considered the equivalent to quackery. We can distinguish 3 phases in the modern history of the placebo effect.¹ During the first phase (pre-World War II), placebos were seen as morally acceptable and innocent management tools without curative or symptomatic consequences. They often were used as diagnostic tools to separate imaginary "psychological symptoms" from real medical problems. A positive placebo response was considered as a strong indication that the patient was hysterical or that the

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apparent disease or symptom was not real. The emphasis was clearly on the response of the single subject. Even today, placebos (*aqua pura*) are still sometimes used as a tool to unmask whether a patient's complaints are real or imagined. However, the idea that there exists something like a typical placebo responder is a misconception that can be rejected on the basis of studies that investigated the intraindividual variability of the placebo analgesic response. For instance, Liberman² investigated the effect of placebo on pain under 3 different situations (during delivery, postpartum pain, and experimental pain) and found that there was no correlation between the occurrence of a placebo response in these conditions. Other studies confirmed that there is no evidence relating personal characteristics such as age, sex, intelligence, race, social class, or ethnic or religious background to the occurrence of a placebo response.^{3,4} Even if some personal characteristics such as anxiety may influence the placebo response,⁵ placebo responsiveness may vary in the same individual according to health situation and clinical context.

The best predictors of placebo response are the expectancies or beliefs held by the patient regarding treatment efficacy and are critically influenced by the clinician's own beliefs.⁶ After World War II, the placebo became strongly associated with the double-blind randomized control trial (RCT). Until then, the evaluation of new therapies was strongly dependent on the personal opinions and preferences expressed by recognized leaders in the field. With the enormous expansion of biomedical research after World War II, efforts were undertaken to impose more scientific rigor in clinical research through the use of blind assessment and random assignment of subjects to an experimental or control condition. The need for blind assessment created the necessity for a control condition. As a result, placebo became a tool that allowed for the objective and unbiased evaluation of new therapies in the context of the RCT. The interest was no longer on how the individual responded to a placebo but how the group as a whole responded to it. However, there was still no real interest in the portrayal and the understanding of the placebo effect itself. The placebo effect was just something that needed to be controlled for to be able to distill the real pharmacological or physiological effects from the total mass of observed effects.

Another factor that greatly influenced placebo research was the imposition of the principle of informed consent at the beginning of the 1970s. If the patient is told that he or she will receive either a real therapy or a placebo, there will naturally be speculation about the condition to which he or she has been assigned. This situation is very artificial and far from the natural daily clinical setting where high expectations of relief are offered to the patient. Knowledge that one has a chance of receiving placebo may introduce uncertainty and ambivalence on the part of the subject, leading to a reduction in the magnitudes of both the response to placebo and the active drug (see section "The Problem of Blinding"). Only starting from the early 1980s, we see for the first time a genuine scientific interest in the placebo phenomenon itself. Basic

scientists started to elucidate some of the mechanisms underlying the placebo response.⁷⁻¹¹ At the same time, a more critical attitude and more rigorous methodology succeeded in portraying the real power and limits of the placebo effect. Soon it became evident that much of what had originally been considered as placebo response was actually due to factors such as regression to the mean and natural course of the disease. This more critical attitude toward placebo recently culminated in a meta-analysis study concluding that placebos are lacking in power.¹² However, the results of this study have been heavily criticized for various reasons.^{13,14}

The Necessity of Placebo Controls in Clinical Trials

Whereas the potential harm in a placebo-controlled drug study is limited to the effects produced by withholding a standard medication that has been proven effective for the treatment of the disorder that is studied, surgical interventions carry risks that are far more larger. Therefore, everyone agrees that placebo-controlled trials of surgery can pose serious risks and should only be performed taking the greatest caution. One of the basic ethical principles of clinical research is indeed beneficence and nonmaleficence. Patients should not be exposed to possible risks if there is no hope for possible benefits. Because sham surgery seems to violate this principle (it is intrinsically without therapeutic effects and is potentially hazardous), one can ask the question if they are really necessary and if they cannot be avoided. However, a positive answer to this question would impose a double standard for clinical trials, a stringent one for drug research and a liberal one for surgical trials. This standard seems difficult to defend. In addition, too many surgeries are performed on the basis of anecdotic or insufficient evidence and they have not been submitted to the same sort of rigorous testing that is applied to pharmacological therapies.

In the mid-1990s, when reviewing the available literature on pain surgery,¹⁵ we were struck by the nearly complete absence of placebo controls in pain surgery, and we plead strongly in favor of such trials. In the meantime, the situation has not changed much and placebo-controlled procedures of pain surgery remain an exception rather than the rule. Our point of view is that sham surgery procedures are a prerequisite for the advancement of science and clinical medicine. Surgical trials using sham surgery procedures are particularly indicated when the outcome measures involve subjective reports such as pain, quality of life, and symptom improvement. As discussed further, the design of such trials highlights the potential conflict between individual (patient) and scientific (collective) ethics. Some critics have argued that it is difficult to justify the use of a placebo control when an effective therapy already exists because they entail potential risks for the study participants. However, the problem is that for conditions of chronic pain treatment, standard therapies are rarely available. That in these cases a placebo surgery is not only ethically acceptable but scientifically desirable is demonstrated by the following 2 examples.

Arthroscopic Surgery for Osteoarthritis of the Knee Joint

Numerous uncontrolled retrospective studies and RCTs without sham treatment in the control group have reported substantial pain relief after arthroscopic lavage and debridement for osteoarthritis of the knee joint (see references in Moseley et al¹⁶). To test the efficacy of this therapy, Moseley et al¹⁶ randomly assigned 180 patients to receive arthroscopic debridement, arthroscopic lavage, or placebo. Both patients and clinicians were blinded to group assignment. Patients in the placebo group also were anesthetized and received skin incisions and a simulated debridement. Outcomes were assessed at multiple times during a 2-year period. The results of this placebo-controlled study showed that at no point patients in the active groups did better than patients in the control group.

Cardiac Pacing for Vasovagal Syncope

Vasovagal syncope is a common clinical condition for which no effective pharmacological treatment exists. Because vasovagal syncope is preceded by a period of bradycardia, cardiac pacemakers were suggested as a potential treatment. This placement is an intervention requiring major surgery. To test the efficacy of cardiac pacing in this syndrome, 3 large randomized clinical trials were conducted in which patients were randomized to receive either a cardiac pacemaker or not (references in Connolly et al¹⁷). The results of these studies seemed to indicate that cardiac pacing is highly effective in reducing the likelihood of syncope in patients with recurrent vasovagal syncope (average risk reduction larger than 80%). Incited by these positive results, a large double-blind placebo controlled trial was undertaken.¹⁷ One hundred patients were implanted with a pacemaker and were randomly assigned to receive either active pacing or to have only sensing without pacing. The results of this study differed largely from those of the 3 open studies, showing no difference in the risk of recurrent syncope between the placebo and active pacing group. Interestingly, whereas in the open study more than 80% of the nonpaced patients had syncope by 6 months, only 41% of the patients in the placebo-pacing group in the later study had suffered a syncope by this time. The authors concluded that because of the lack of evidence of pacemaker therapy and the risks of complications, pacemaker therapy should not be recommended as first-line therapy.

These 2 examples emphasize the importance of including placebos in surgery trials. The open studies suggested that arthroscopic surgery and cardiac pacing were both effective therapies. The placebo-controlled studies, however, revealed that the presumed effects were based on a placebo response. The results of these studies point to the ethical consequences of these types of interventions. For instance, many of the patients with neurally mediated syncope that are selected for pacemaker therapy are young and otherwise healthy. Inserting a permanent pacemaker not only produces the typical risks that are associated with this surgical intervention but also exposes these patients to continued medical surveillance and discomfort for decades.

Clinical Relevance of the Placebo: An Example of Placebo Neurosurgery

Any treatment, ranging from psychological, pharmacological, complementary, and alternative medical interventions (eg, acupuncture) or surgical procedures carries a potential placebo effect.¹⁸⁻²² Contrary to the general belief that placebo effects only occur for conditions with an important psychological component like chronic pain, insomnia, and depression, robust placebo responses have been reported for conditions that are supposedly less prone to subjective effects, such as motor performance in patients with PD, growth hormone and cortisol hormone secretion, and even cutaneous cancer cell lymphoma expression.^{7,9,23,24}

It is important to understand the distinction between the *placebo* and the *placebo effect*. The term placebo generally is used to define both the intrinsically inert substance or intervention (for example, an inert sugar pill) and the resulting effect (for example, the resulting analgesic response). It is problematic that many of the contemporary definitions still hold the implausible claim that the placebo effect is brought about by the placebo agent per se, independent of its perception. What elicits the placebo effect is not the inert substance but the entire context in which it is administered. It is difficult to define the placebo and the placebo effect in a coherent and logical manner and therefore some authors have even suggested to abandon the concept and to replace it by the “meaning response.”²⁵ Meaning responses after the administration of inert or sham treatment can be labeled “placebo effect” when they are desirable and “nocebo effect” when they are undesirable.

One of the great misunderstandings in the placebo literature is that approximately 30% of subjects will respond to a placebo procedure or that 30% of any treatment effect is attributable to nonspecific or placebo effects. This figure derives from a misinterpretation of the results of a meta-analysis by Beecher.²⁶ Beecher reviewed the results of 15 clinical studies that included a placebo arm and that covered a wide variety of different conditions, such as postoperative pain, angina pectoris, anxiety, and the common cold. On average, symptoms were satisfactorily relieved in 35% of the patients. However, a large variability occurred in the occurrence of the placebo response in the individual studies. The results of Beecher’s study have been heavily contested because they didn’t take into account factors such as natural course of the disease or regression to the mean. Regression to the mean is a phenomenon that often is overlooked and that may explain a considerable amount of variance that normally is attributed to placebo or treatment effects.²⁷ It describes a tendency of extreme measures to move closer to the mean when they are assessed later. Let us consider the following fictive case. A patient presents to his physician and complains that for a couple of weeks, his low back pain has increased enormously and is no longer tolerable. The physician examines the patient and decides that this might be the appropriate moment to start with a trial of spinal cord stimulation (SCS). An SCS

system is implanted and the patient is asked to come back within a month for a first evaluation of the effect of SCS. At follow-up, the patient reports that his pain has improved significantly since he is using his stimulator.

Which may be the reasons for this patient's improvement in pain? When a particular patient shows clinical improvement, this may be either because of specific or nonspecific (placebo) treatment effects. Specific treatment effects are those that can be attributed to the specific content of the intervention. However, there is a third reason, which can explain clinical improvement, namely the natural history of the disease and regression to the mean. Many acute and some chronic pains resolve spontaneously and do not need a special intervention. In chronic pain, periods of severe pain intersperse with periods of less or minimal pain. Typically, chronic pain patients seek help when their symptoms are at their worst. This means that the most likely change that is going to take place next is an improvement in pain. This phenomenon has been described as regression to the mean. With regression to the mean is meant that a variable that is extreme when it is measured will tend, by chance, to be closer to its central tendency on a subsequent measure. Because subjects seeking treatment for pain do so when there is an increase in the pain, a mechanism of regression to the mean may occur when pain is assessed later. This regression may then be erroneously interpreted as a treatment effect. Therefore, comparison with a nontreated control group is necessary. Let us consider again our patient. In case a suspicious physician would have started placebo stimulation instead of real SCS, the patient would have been erroneously categorized as a placebo responder. In other words, regression to the mean may explain both presumed genuine treatment effects and placebo effects. An implication of this is that it is difficult or impossible to judge placebo effects in individual patients since we don't have information on the natural course of the disease.

Placebo Neurosurgery

In trying to establish the efficacy of a medical therapy, a major issue is to eliminate as much as possible the contribution of nonspecific factors. In pharmacological trials, this elimination can be readily accomplished by comparing in a double-blind manner an active drug with an inactive placebo. In the evaluation of invasive interventions such as neurostimulation techniques, this may be more difficult to achieve because finding a credible "placebo" may be difficult or impossible. An exception may be motor cortex stimulation since it produces an analgesic effect at stimulation intensities that do not evoke paresthesia or other sensory or motor effects.

Can placebo-controlled trials with neurostimulation procedures be performed in other conditions than motor cortex stimulation? Let us try to answer this question by describing one of the few placebo-controlled trials of SCS for pain treatment.²⁸ We will first briefly describe the design and the results of this study and then discuss a number of methodological issues with respect of how to evaluate placebo effects in neurostimulation procedures.

An Illustration: Spinal Cord Stimulation for Painful Diabetic Neuropathy

In Tesfaye et al's study,²⁸ 10 patients with diabetes, among whom 6 had type II diabetes, who did not respond to conventional pain treatment were scheduled for a placebo-controlled trial of SCS. All the patients had severe symptomatic neuropathy, and the mean duration of pain was 5 ± 2.1 years. An electrode was implanted in the spinal epidural space and pain relief was assessed after connecting the electrode in a random order to a placebo stimulator or to a percutaneously implanted electrical stimulator. The placebo stimulator had an identical appearance as the active stimulator but with a disconnected output. A series of lights on the placebo stimulator gave the impression of real activity. The authors used a randomized placebo-controlled crossover study design. In the immediate postimplantation period, 8 of the subjects had significantly better pain relief with the electrical stimulator than with the placebo stimulator and were therefore implanted with a permanent stimulation system. A statistically significant pain relief of both background and peak neuropathic pain was achieved until the end of the 14-month study period. Six of the patients used the stimulator as the sole treatment for their neuropathic pain. The authors also reported significant improvements in exercise tolerance on a treadmill. These results are in agreement with the first study on SCS for chronic low back using a placebo control.²⁹ In this study, Marchand et al reported that SCS was significantly superior to placebo SCS for both clinical and experimental pain.

The Problem of Blinding

The most appropriate way to test for placebo effects is to use double-blind placebo-controlled procedures. This leads us quickly to the crucial question whether clinical trials with neurostimulation techniques can be blinded. In the literature, only a few reports can be found on placebo-controlled trials for neurostimulation. These were mostly performed with respect to transcutaneous electrical nerve stimulation (TENS) and therefore didn't involve invasive procedures. In addition, the successfulness of blinding was rarely assessed in most of these trials. This is surprising because it can be easily accomplished at the end of the trial with some simple questions to the patient and the treating physician. Failure of blinding may lead to higher outcome expectancies in the active as compared with the sham treatment group. The study by Tesfaye²⁸ didn't mention anything about the successfulness of their blinding procedure, so it might be argued that the better outcome in the real stimulation group was due to the fact that higher expectancies were created in this condition. Another problem with the Tesfaye study is that the study was only performed in a single-blind manner. Therefore, the physician's knowledge about the treatment condition might have undeliberately influenced the results.

Deyo and colleagues³⁰ were one of the first to address the issue of blinding in neurostimulation procedures in an explicit way. These authors studied the effect of TENS in the treatment of chronic low back pain. Great care was taken to

incorporate in the study design as many features as possible to promote blinding: use of sham TENS units that were physically identical to real units, use of identical visit frequency, instructions and modifications in electrode placement in both the real and sham TENS group. At the end of the trial, both patients and clinicians were asked to guess actual treatment assignments. In the TENS group, every patient believed the unit was functioning properly. In the sham TENS group, most of the patients also believed they had functioning units, but their certainty was significantly less than in the active treatment group. Dropout rates and daily duration of TENS use was not different between the 2 groups. These findings suggest that the blinding was at least partially successful. However, some methodological problems with the placebo and the pain measurement used in their study have been raised (see Marchand et al³¹). In a subsequent study, Marchand and colleagues,³¹ measured both pain intensity and unpleasantness in the patients' home settings on different days and found that both TENS and placebo-TENS produced clinically significant results on low back pain ratings, but that TENS was significantly superior to placebo-TENS for pain intensity but not pain unpleasantness, at least at short-term. This difference between pain intensity and pain unpleasantness suggest that the placebo effect was mainly affecting the emotional component of pain. This is a good example of a study that could lead to the conclusion that the evaluated procedure, in this case TENS, was not superior to a placebo, while the apparent ineffectiveness is related to the methodological approach.

However, TENS is a noninvasive procedure and therefore the question still remains whether blinding can be achieved using more invasive procedures like SCS or thalamic stimulation. An attempt for a placebo-controlled study of the analgesic effect of deep brain stimulation (DBS) was done by Marchand and colleagues.³² Also here, great care was taken to maximize blindness. To assure blindness, 2 experimenters were involved in this study. The experimenter who was aware of the stimulation condition (real or placebo) was not involved in the outcome evaluation. Six patients with a DBS electrode participated in the study. The subjects had their stimulating devices implanted for an average of 6 years. In brief, the patients were told that new types of stimulation parameters were going to be tested. They were further told that some of these might be accompanied with paresthesia whereas others were not. They were asked to switch off their stimulator from the evening before the start of the sessions. All the patients reported moderate-to-very-severe pain at the beginning of the experimental session. The patients were shown the stimulation parameters that were going to be tested. Thereto, the stimulator was connected to an oscilloscope and whenever the experimenter changed one of the stimulator settings, this was accompanied with a visible change of the waveform on the oscilloscope. After showing these waveforms to the patient, the experimenter who put the stimulator in either the normal or placebo mode left the room and the second experimenter came in. The second experimenter was unaware of the experimental condition. After some baseline pain assessments, he turned on the stimulator

and started with the evaluation of the analgesic effect of thalamic stimulation. Subjects also had to rate the intensity of the paresthesia. The findings were quite surprising. All 6 patients reported feeling paresthesia during the placebo session and a significant positive correlation was found between the placebo paresthesia and pain relief. Patients with the highest perceived placebo paresthesia reported the highest pain relief scores. The experimenter "guessed" correct treatment condition in only 3 of the 6 patients, indicating that blinding was successful.

Parallel Groups or Crossover Design?

Another question is whether parallel groups or a crossover design should be used. Both the studies of Tesfaye and colleagues²⁸ and Marchand and colleagues²⁹ used a randomized crossover design. This means that the same patients received both treatments, be it in a randomized order. In a parallel group design, 2 groups of patients would have been used, one group receiving real stimulation, the other receiving placebo stimulation. For 2 reasons, a parallel group design seems preferable. First, a parallel group design reduces the chance for unblinding of the study condition. If a patient first receives conventional SCS, the stimulation-induced paresthesia is readily perceptible for most of the patients. If these patients then receive sham stimulation in the second phase, they may become unblinded with respect to their treatment condition. A second reason why a parallel group design is preferable is that it reduces the likelihood for carry-over effects. The importance of carry-over effects was elegantly demonstrated by Suchman and colleagues.³³ These authors compared the magnitude of placebo responses in double-blind crossover studies. When a placebo was given in the first phase of the study, ie, before the subjects had received the active drug treatment, there were no significant differences between subjects taking a placebo and subjects taking nothing. However, when the subjects received the placebo in the second phase of the study, ie, after they had received the active drug treatment, subjects in the placebo condition showed significantly greater responses than subjects receiving no treatment. In other words, a carry-over effect had occurred in these patients.

These carry-over effects can be explained by conditioning effects. Using a crossover design, Charron and colleagues³⁴ compared the effects of instructions on the response to a placebo (saline injection) on experimental and clinical pain in patients suffering from low back pain patients. The subject received 2 saline injections on 2 different days. In one of the sessions, participants were told that they were receiving a strong analgesic whereas in the other session they were told that the injection was a nonactive saline control. Interestingly, when the placebo session was performed after the control session, the placebo effect on low back pain was substantially reduced and only observed in perceived relief. Variations in expectation could not account for the large difference in placebo analgesia between clinical and experimental pain. The important reduction in placebo analgesia in low back pain after the single preexposure to the ineffective

control treatment suggests the additional involvement of a conditioning effect that may counteract the pro-analgesic effects of expectations. This underscores the importance of previous experience on pain relief and attests of the remarkable flexibility of pro- and antianalgesic processes affecting the magnitude of placebo effects.³⁴

Ethical Considerations of Placebo

There has been a lively debate around the ethics of the placebo-controlled trial. On the one hand, the proponents of “placebo orthodoxy” argue that methodological considerations make placebo-controlled trials necessary. On the other hand, those who embrace “active-control orthodoxy” hold that placebo orthodoxy sacrifices ethics and the rights and welfare of patients to presumed scientific rigor.³⁵

In 2000, a revision was made to the Declaration of Helsinki, which supports the active-control orthodoxy by reinforcing a clear stance for prohibition against offering placebo instead of proven effective therapy. However, recently the World Medical Association issued a “Note of Clarification” that allows for a limited use of placebo controls, marking some departure from the revision of October 2000.³⁶ This note states that placebo-controlled trials may be ethically justifiable despite the availability of proven effective treatments in 2 circumstances: (1) when for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method or (2) when a prophylactic, diagnostic, or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.

Opponents of placebo-controlled trials pay little attention to the power of the placebo response. Given the fact that a large number of patients who are administered placebos show clinically meaningful improvements, the design and conduct of clinical trials could benefit substantially from a profound understanding of the placebo, its underlying mechanisms, and its interaction with test therapies. Conversely, the design and conduct of clinical trials might lead to a better understanding of the placebo. The placebo-controlled trial confronts us with the following dilemma: on the one hand, it is unethical to use placebo controls if effective treatments exist but, on the other hand, placebo-controlled studies form the most reliable way to determine the efficacy of an experimental therapy. The situation gets even more problematic for surgical placebo procedures because they seem to be a violation of the fundamental ethical principles of beneficence and nonmaleficence. Horng and Miller³⁷ argued that 3 key ethical criteria need to be fulfilled in cases of placebo surgery: (1) placebo surgical procedures have to be compatible with the ethical requirement to minimize risk; (2) the risks associated with placebo surgery should be reasonably and justifiable in relation to the potential value of the scientific knowledge that can be gained; and (3) the subjects should give their informed

consent. Let us try to apply these criteria to the previous example of the arthroscopy study.¹⁶ First, the possible risks involved for the patients in the sham surgery group in this study were relatively small and derived from the anesthesia and discomfort associated with the small skin incisions. Second, the small risks to which the patients were exposed largely outweigh the gained scientific benefit. Because the results showed that arthroscopic surgery is not better than that of the placebo group, the results of this study show that this frequently used and costly intervention lacks efficacy. Not having conducted this study would have meant that thousands of patients would continue to be submitted to the hazards of a surgical intervention that is without therapeutic effects. Finally, the patients had to write in their diary that they realized that they might get sham surgery and that the placebo surgery will not benefit their clinical condition.

The Distinction Between Ethical Principles of Clinical Research and Ethical Principles of Clinical Practice

One of the reasons for the harsh opposition against the use of placebo (surgery) finds its origin in the fact that the opponents fail to accept that the ethical principles for clinical research and clinical practice are not identical. According to the ethical guidelines for good clinical practice, doctors should not expose patients to risks if there is no prospect of possible benefit for the patient. This implies that surgery can only be considered when it involves the possibility of clinical benefit. This is in contrast with the ethics of clinical research. The RCT that is used in clinical trials is not a form of an individualized therapy. Clinical trials are designed in the first place to give unambiguous answers to important clinical questions using scientifically sound methods and not to serve the optimal interest of the patients enrolled in the trial. Clinical research is therefore intrinsically plagued by finding the delicate balance between providing unequivocal scientific answers and protecting participants from possible harm. As mentioned earlier, one of the main ethical principles in research involving patients is that it is based on the principle of beneficence and nonmaleficence. One can judiciously ask the question where lies the beneficence for participants in case of clinical research. An answer to this question can be found in Rawls thinking about ethical dilemmas in modern society.³⁸ Just like many ethical dilemmas of a fair society cannot be solved by referring only to the “now” (the actual situation) position, medical dilemmas can not be resolved when considering them at the point of sickness but only when considering them in what is called the “original position.”

Imagine we were to consider in the original position which of the 2 societies we would wish to join. In the first society, a physician is simply placed under the obligation of providing the patient with the treatment he believes the most efficacious. In this society, no controlled trials are possible and consequently, medical progress is slow and not very efficient. In the second society, treatments are only accepted if a consensus about their efficacy is reached through controlled trials. In this society, patients not always get what the physician

consider as the best treatment but standard care will be much better than in the first. It is therefore likely that one would choose, when placed in the original position, for the second society. From the prospective patient's point of view, the best position is guaranteed by the second society until the individual gets ill, at which point he would make the choice for the first society. This would represent an unfair switch of behavior since it implies that the patient seeks an advantage that only others can provide and that he is unwilling to repay.³⁹ Therefore, when judged not at the point of sickness but from the patient's interests in the original position, clinical trials fulfill the requirement of beneficence and non-maleficence. In the original position, the interests of society and of the individual overlap. The only conflict that remains is that the persons administering the drugs and the patient are not in the original but in the "now" position. This requires that an acceptable trade-off is found between current (best treatment of current patients) and future (treating potentially large numbers of future patients) demands.

Alternatives to the Classical Placebo-Controlled Design

Because of the ethical problems related to the use of placebos, some alternatives to the classical placebo-controlled RCT design have been proposed. These are discussed below.

The Active-Control Trials

One alternative to the placebo-controlled trial is the active-control trial showing that a new treatment is equivalent or not inferior to a known effective treatment. In essence there are 2 ways of showing that a new treatment is efficient. Either it can be shown that the new treatment is superior to the control treatment or it can be shown that the new treatment is equivalent or not inferior in relation to a known effective treatment.⁴⁰ However, it is argued by Fleischhacker and colleagues⁴¹ that a comparison between a test drug and placebo is the most powerful method for demonstrating efficacy because replacing placebo with an active control drug can hamper the interpretation of the findings. If the test drug and the standard control show matching effects in the absence of a placebo group, it cannot be determined whether they were both either effective or ineffective. Consequently, in active control trials it has to be assumed that the active control drug is effective to interpret a result where the test drug showed to be not inferior. In other words, it must be assumed that if the study did in fact include a placebo group the placebo would have been inferior to the active control. If this assumption is incorrect, the study has a poor ability to distinguish between treatments, or low so-called assay sensitivity.⁴¹ If assay sensitivity cannot be assured active control trials are often uninformative in that they can neither demonstrate the efficacy of a new treatment nor provide a valid comparison to control treatment.⁴⁰

The Balanced Placebo Design

The so-called balanced placebo design overcomes some of the flaws associated with the placebo-controlled trial and the

active control trial. In this design, subjects are assigned randomly to 1 of 4 groups. The subjects in the first group are told they will receive a drug, and they do receive it; the subjects in the second group are told they will receive a drug, but instead they receive placebo; the subjects in the third group are told they will receive placebo and do receive it; and those in the fourth group are told they will receive placebo but instead they receive a drug.^{14,42} The balanced placebo design has several advantages: it provides a baseline from which to evaluate drug and placebo effects, and further provides a direct measurement of the drug effect with the placebo component eliminated. However, the problem with the balanced placebo design is that it involves deception. Therefore, this design has only been used in studies with healthy volunteers and not in clinical trials.⁴²

The Hidden-Administration Design

Benedetti and colleagues⁴³ recently introduced an innovative study design that unlike the balanced placebo design bypasses the need for deception and further allows for measurements that cannot be performed in the balanced placebo design. The design consists of two conditions that are similar to 2 conditions in the balanced placebo design. In the first condition, the patient knows the details of the therapy, why it is being performed, and what outcomes to expect because an open treatment is administered in full view and the patient is informed what is going on. In the other condition, a hidden medical treatment is machine administered with the patient completely unaware that the therapy is being given. In other words, the main difference between open and hidden treatments is the knowledge that a medical procedure is performed. These 2 groups are comparable with the conditions "told drug/get drug" and "told no drug/get drug" in the balanced placebo design. As such the hidden versus open administration design provides a measurement of the placebo component of treatment administration by subtracting the drug effect (hidden administration) from the drug response (open administration). Consequently the placebo effect reflected as the knowledge that a treatment is being administered, can be studied without placebo groups.⁴³ The last 2 conditions of the balanced placebo design "told drug/get no drug" and "told no drug/get no drug" are not present in the open versus hidden administration design but these could easily be added. The open versus hidden administration design represents an innovative alternative to the classic placebo-controlled trial to understand the crucial psychosocial factors involved in any therapy, such as the patient-provider interaction, awareness of treatment and expectancies.⁴³

Conclusions

Placebo and nonspecific treatment effects form an integral part of nearly all therapeutical interventions. Often, their contribution to the therapeutic outcome is grossly underestimated. Any improvement observed after the initiation of a pain treatment procedure may reflect specific or nonspecific treatment effects or may be the result of regression to the

mean. The only way to find out the relative contribution of each of these factors is to make use of double-blind and placebo-controlled procedures. Although “blinding” may be inherently difficult in the context of some pain neurosurgical interventions, with the necessary care and imagination, a satisfactory degree of blinding can be reached. The ethics debate can be resolved by considering placebos from the perspective of the ethical guidelines for clinical research instead of those for good clinical practice.

References

- Kaptchuk TJ: Intentional ignorance: A history of blind assessment and placebo controls in medicine. *Bull Hist Med* 72:389-433, 1998
- Liberman R: An experimental study of the placebo response under three different situations of pain. *J Psychiatr Res* 33:233-246, 1964
- Averbuch M, Katzper M: Gender and the placebo analgesic effect in acute pain. *Clin Pharmacol Ther* 70:287-291, 2001
- Shapiro AK, Shapiro E: *The Powerful Placebo*. Baltimore, The Johns Hopkins University Press, 1997
- Staats PS, Staats A, Hekmat H: The additive impact of anxiety and a placebo on pain. *Pain Med* 2:267-279, 2001
- Moerman DE, Jonas WB: Toward a research agenda on placebo. *Adv Mind Body Med* 16:33-46, 2000
- Benedetti F, Pollo A, Lopiano L, et al: Conscious expectation and unconscious conditioning in analgesic, motor, and hormonal placebo/nocebo responses. *J Neurosci* 23:4315-4323, 2003
- Colloca L, Lopiano L, Lanotte M, et al: Overt versus covert treatment for pain, anxiety, and Parkinson's disease. *Lancet Neurol* 3:679-684, 2004
- Fuente-Fernandez R, Ruth TJ, Sossi V, et al: Expectation and dopamine release: mechanism of the placebo effect in Parkinson's disease. *Science* 293:1164-1166, 2001
- Fuente-Fernandez R, Stoessl AJ: The biochemical bases of the placebo effect. *Sci Eng Ethics* 10:143-150, 2004
- Petrovic P, Kalso E, Petersson KM, et al: Placebo and opioid analgesia—imaging a shared neuronal network. *Science* 295:1737-1740, 2002
- Hrobjartsson A, Gotzsche PC: Is the placebo powerless? An analysis of clinical trials comparing placebo with no treatment. *N Engl J Med* 344:1594-1602, 2001
- Kaptchuk TJ: Is the placebo powerless? *N Engl J Med* 345:1277-1279, 2001
- Kupers R: Is the placebo powerless? *N Engl J Med* 345:1278-1279, 2001
- Kupers R, Gybels JM: Evaluation of pain surgery, in Gildenberg PL, Tasker R (eds): *Textbook of Stereotactic and Functional Neurosurgery*. New York, McGraw-Hill, 1998
- Moseley JB, O'Malley K, Petersen NJ, et al: A controlled trial of arthroscopic surgery for osteoarthritis of the knee. *N Engl J Med* 347:81-88, 2002
- Connolly SJ, Sheldon R, Thorpe KE, et al: Pacemaker therapy for prevention of syncope in patients with recurrent severe vasovagal syncope: Second Vasovagal Pacemaker Study (VPS II): a randomized trial. *JAMA* 289:2224-2229, 2003
- Gracely RH, Dubner R, Wolskee PJ, et al: Placebo and naloxone can alter post-surgical pain by separate mechanisms. *Nature* 306:264-265, 1983
- Horvath P: Placebos and common factors in two decades of psychotherapy research. *Psychol Bull* 104:214-225, 1998
- Kleinhenz J, Streitberger K, Windeler J, et al: Randomized clinical trial comparing the effects of acupuncture and a newly designed placebo needle in rotator cuff tendinitis. *Pain* 83:235-241, 1999
- Long DM, Uematsu S, Kouba RB: Placebo responses to medical device therapy for pain. *Stereotact Funct Neurosurg* 53:149-156, 1989
- Quitkin FM: Placebos, drug effects, and study design: A clinician's guide. *Am J Psychiatry* 156:829-836, 1999
- Duvic M, Olsen EA, Omura GA, et al: A phase III, randomized, double-blind, placebo-controlled study of peldesine (BCX-34) cream as topical therapy for cutaneous T-cell lymphoma. *J Am Acad Dermatol* 44:940-947, 2001
- Pollo A, Vighetti S, Rainero I, et al: Placebo analgesia and the heart. *Pain* 102:125-133, 2003
- Moerman DE, Jonas WB: Deconstructing the placebo effect and finding the meaning response. *Ann Intern Med* 136:471-476, 2002
- Beecher HK: The powerful placebo. *J Am Med Assoc* 159:1602-1606, 1955
- McDonald CJ, Mazzuca SA, McCabe GP Jr: How much of the placebo 'effect' is really statistical regression? *Stat Med* 2:417-427, 1983
- Tesfaye S, Watt J, Benbow SJ, et al: Electrical spinal-cord stimulation for painful diabetic peripheral neuropathy. *Lancet* 348:1698-1701, 1996
- Marchand S, Bushnell MC, Duncan GH, et al: The effects of dorsal column stimulation on measures of clinical and experimental pain in man. *Pain* 45:249-257, 1991
- Deyo RA, Walsh NE, Martin DC, et al: A controlled trial of transcutaneous electrical nerve stimulation (TENS) and exercise for chronic low back pain. *N Engl J Med* 322:1627-1634, 1990
- Marchand S, Charest J, Li J, et al: Is TENS purely a placebo effect? A controlled study on low back pain. *Pain* 1993;54:99-106
- Marchand S, Kupers RC, Bushnell MC, et al: Analgesic effects of normal and placebo thalamic stimulation. *Pain* 105:481-488, 2003
- Suchman AL, Ader R: Classic conditioning and placebo effects in crossover studies. *Clin Pharmacol Ther* 52:372-377, 1992
- Charron J, Rainville P, Marchand S: Direct comparison of placebo effects on clinical and experimental pain. *Clin J Pain* 2005 (in press)
- Emanuel EJ, Miller FG: The ethics of placebo-controlled trials—a middle ground. *N Engl J Med* 345:915-919, 2001
- Miller FG, Brody H: What makes placebo-controlled trials unethical? *Am J Bioeth* 2:3-9, 2002
- Hornig S, Miller FG: Is placebo surgery unethical? *N Engl J Med* 347:137-139, 2002
- Rawls JA: *Theory of Justice*. Oxford, Oxford University Press, 1972
- Senn SJ: Ethics of clinical trials from bayesian perspective: Society's role is important. *BMJ* 326:1456-1457, 2003
- Ellenberg SS, Temple R: Placebo-controlled trials and active-control trials in the evaluation of new treatments. Part 2: Practical issues and specific cases. *Ann Intern Med* 133:464-470, 2000
- Fleischhacker WW, Czobor P, Hummer M, et al: Placebo or active control trials of antipsychotic drugs? *Arch Gen Psychiatry* 60:458-464, 2003
- Kirsch I, Scoboria A: Apples, oranges, and placebos: Heterogeneity in a meta-analysis of placebo effects. *Adv Mind Body Med* 17:307-309, 2001
- Benedetti F, Maggi CA, Lopiano L, et al: Open versus hidden medical treatments: The patient's knowledge about a therapy affect the therapy outcomes. *Prevention & Treatment* 6: 2003. Available online at <http://journals.apa.org/prevention/volume6/toc-jun-03.html>. Accessed February 14, 2005