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Placebos in Clinical Practice: an Ethical Overview

Placebos dans la pratique clinique : un aperçu éthique

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Abstract The use of placebos in clinical settings raises a host of important ethical issues. On the one hand, ethical guidelines tend to categorically prohibit the clinical use of placebos because they require deception. On the other hand, a growing series of empirical studies has revealed that placebos can be clinically effective and are still widely used by health professionals. In this article we provide a synthetic overview of the ethical debate discussing: 1) the ethics of deceptive placebos; 2) the ethics of placebos without deception, and 3) the ethics of eliciting placebo responses without administering a traditional placebo.

Keywords Ethics · Clinical medicine · Placebo · Deception · Open-label placebos

Résumé L'utilisation de placebos dans les milieux cliniques soulève plusieurs questions éthiques importantes. D'une part, les lignes directrices éthiques ont tendance à interdire catégoriquement l'utilisation clinique des placebos, car ils nécessitent la tromperie. D'autre part, de plus en plus d'études empiriques ont révélé que les placebos peuvent être cliniquement efficaces et qu'ils sont encore largement utilisés par les professionnels de la santé. Dans cet article, nous proposons un aperçu synthétique du débat éthique en abordant : 1) l'éthique de placebos avec tromperie ; 2) l'éthique de placebos sans tromperie et 3) l'éthique de déclencher des réponses placebo sans l'administration d'un placebo traditionnel.

Mots clés Éthique · Médecine · Placebo · Tromperie · Étude ouverte avec placebos

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Introduction

A placebo is a medical intervention believed to be inactive for the patient's condition but administered by a health professional as if it was an active treatment [1]. Depending on the circumstances and on the biomedical theory assumed, a placebo can be a pill, an injection, a diagnostic or even a surgical procedure [2]. Placebos are usually defined as "pure" if they are believed to lack therapeutic properties in general (e.g. lactose pills, saline injection, etc.), and "impure" if they are known to be effective for other conditions or under diverse modalities of administration (e.g. antibiotics for viral infections, over-the-counter analgesics, vitamins, etc.) (for a discussion of this distinction see [3,4]). Pure placebos are often described as "inert," but this is misleading because lactose pills or saline injections contain ingredients with biochemical properties and these "inactive" interventions can be effective in promoting placebo responses. The use of placebos in clinical settings raises a host of important ethical questions, the most important of which regards the use of "benevolent", "paternalistic" or "therapeutic" deception. Is it ever ethical to deceive patients for their own good? In this article we provide a synthetic overview of the ethical debate over the clinical use of placebos, focusing on their use as interventions in clinical practice as distinct from their use as control interventions in randomized, placebo-controlled trials. What follows is divided in four parts. First we reconstruct the historical debate over the use of placebos. Then, in section two, we review the main ethical arguments advanced to support or restrict the clinical use of deceptive placebos. Finally, we introduce the newer strands of the debate by discussing the ethics of placebos without deception and the ethics of eliciting placebo effects without administering physical placebos.

The origins of the placebo debate

In contemporary medicine the practice of administering inactive interventions has been relatively common until the

mid of the twentieth century. In 1803 Thomas Jefferson noted "one of the most successful physicians I have ever known has assured me that he used more bread pills, drops of colored water, and powder of hickory ashes, than of all other medicines put together" [5]. He famously defined this practice as the "pious fraud". Placebos were then conceived as inert substances unable to influence the pathophysiology of diseases. Accordingly, their primary functions were to provide "mental relief" or to ease the doctor's job by placating patients expecting treatment. Still in 1945, the first scholarly paper on this subject concluded that a placebo can smooth the "patient path", "cannot harm and may comfort", and that it was especially useful to treat "disappointed", hopeless, and incurable cases [6]. In the absence of ethical guidelines, placebos and therapies were both delivered by following the classical Hippocratic rule "help, or at least do not harm". Since placebos could "help" without harming, the benevolent deception required for their administration was frequently practiced, normally excused, and often considered one of the hallmarks of the doctor-patient relationship.

After World War II, two factors conspired in changing the ethical debate over the clinical use of placebos. The first one was the rise of respect for autonomy as a basic principle in medical ethics. After the 1947 Nuremberg trial it was established that people have a right to refuse medical procedures [7]. In order to authorize or veto an intervention, however, patients need to be informed about it. Thus physicians have a duty to disclose to patients truthful information about their diagnosis, prognosis and the nature of prescribed treatments. With the emergence of honesty and transparent communication as a key value for health professionals, the "pious fraud" associated with the traditional use of placebos became increasingly questioned as inappropriate and unethical. The second factor was the series of scientific investigations that in last forty years have progressively uncovered the mechanisms of placebo responses. Collectively these studies have suggested that placebo responses are ubiquitous in research and clinical settings and may modulate both subjective and objective health outcomes in a number of conditions such as pain, recurring migraine, irritable-bowel syndrome, and Parkinson's motor disorders [8]. Thus, through placebo responses, the administration of a placebo may "help" patients by providing something more than just "mental relief".

More recently, the debate has been influenced by survey research regarding clinicians' and patients' attitudes toward the clinical use of placebos. These studies have revealed that deceptive placebos are still widely used across clinical settings, and especially in general practice. A 2008 study among U.S. internists and rheumatologists concluded that between 46% and 58% have recommended placebo treatments at least once [9]. Similarly, a 2013 survey among UK doctors found that 97% of the participants reported having used placebos and 77% use them at least once a week [10]. The only systematic review published so far (22 studies published between 1973 and 2009) concluded that between 41% and 99% of health professionals use deceptive placebos at least once a year [11].

Against this backdrop, the contemporary ethical debate over the clinical use of placebos is structured around two poles. On the one hand, the use of placebos is attacked because it involves deception. On the other hand, the use of placebos in defended by arguing that deception is justifiable given its benefits, or that the concept of deception does not apply. Since the primary moral issue associated with the clinical use of placebos regards deception, in the next section we begin by appraising the main arguments that have been used to justify or reject the clinical use of deceptive placebos.

The ethics of deceptive placebos

Current ethical guidelines tend to endorse a policy of "categorical prohibition" with respect to the clinical use of deceptive placebos. In 2006 the American Medical Association (AMA) released its placebo policy in the form of an official "Opinion" in which it stated "Physicians may use placebos for diagnosis or treatment only if the patient is informed of and agrees to its use" [12]. According to this position, using deceptive placebos in clinical settings without patients' consent is never permissible. Over the years several commentators have defended similar positions and therefore the AMA Code of Medical Ethics is not alone in advocating a categorical ban of deceptive placebos in clinical settings [1,13].

In general, two arguments can be used to justify a "categorical ban" of deceptive placebos. First, there are deontological or duty-based arguments. Scholars inspired by Kant's moral philosophy consider the morality of an action as being independent from its consequences. On Kant's view, to determine whether an action is moral (e.g. "to lie") we should ask whether it could be generalized as a universal maxim of conduct. This is tantamount to imagine a world in which everyone lies, and asking whether this world can be imagined without contradiction. Consider the case of deception. To be effective deception requires the trust of others. However, if everybody deceives everybody else, then nobody will eventually trust anyone. And without trust, no deception could be successful. Hence, to elevate deception at the level of a general maxim of conduct leads to contradiction. This means that deception is never morally permissible and that we have an absolute duty not to deceive others. Accordingly, supporters of deontological approaches tend to consider deceptive placebos as always unethical [14].

A traditional critique to deontological views is that clinicians' obligations to veracity may legitimately conflict with

their obligations of beneficence (or nonmaleficence). A typical example is when doctors must disclose bad prognostic news to highly vulnerable patients. While there are several ways in which the impact of bad news can be mitigated, sometimes a clinician may suspect that by disclosing the truth she will irremediably harm her patient. Though these cases may be rare, in such exceptional circumstances it is generally recognized that the clinician may justifiably opt for paternalistic deception [15]. For this reason absolute deontological positions are rarely upheld in medical ethics without important qualifications [14].

Secondly, there are consequentialist arguments aimed at justifying the categorical ban for precautionary reasons. Supporters of this view do not deny that deceptive placebos may have clinical benefits. Rather, they argue that deceptive placebos have a series of short and long-term effects that once factored in justify the categorical bad of their use. First, deception may irremediably undermine the trust between doctor and patient [15–18]. Discovering that a physician has lied about the nature of a medication may lead patients to feel angry and betrayed, thus compromising the doctor-patient relationship, the compliance with other therapies, and shared-decision making [15]. Deception may also undermine the trust between society and medicine. Condoning the use of deceptive placebos might lower the public trust in the moral integrity of health professionals, jeopardizing the *bona fide* grounding the social status of medicine [16,17]. Lastly, placebos may harm patients by inducing side effects (e.g. lactose pills given to lactose-intolerant patients); inducing psychological addiction; and increasing the risk of missing a diagnosis of serious illness because the placebo has temporarily relieved the symptoms [8,17,18]. Hence, according to this line of argument, given the limited benefits and the severe risks involved in using deceptive placebos, we should prohibit their use.

Not everyone, however, supports this conclusion. Motivated by recent discoveries on placebo responses, in the last years a growing series of scholars have argued in favor of the use of deceptive placebos. Usually, defenders of the clinical use of placebos pursue one or more of the following three strategies.

First, one can argue that paternalistic deception is justifiable whenever (a) the expected benefits are sufficiently great and (b) the infringement on patient's autonomy sufficiently negligible. The crux of this argument, then, is to construct a case for which the clinical utility of deceptive placebos justifies paternalistic measures. How can deceptive placebos be useful in clinical contexts? Scholars upholding this strategy usually back up their view by stressing the possible therapeutic and diagnostic utility of deceptive placebos in clinical settings [19–22].

As for therapeutic utility, empirical studies support the claim that for conditions like pain, depression, recurring migraine, and irritable-bowel syndrome, the effectiveness of deceptive placebos may sometimes match or surpass that of conventional medications [8,19,22]. Deceptive placebos may be a viable therapeutic option, especially when other conventional therapies have already proven ineffective [20,21]. Critics of this position object that the evidence about the therapeutic utility of placebos is inconclusive: placebo effects vary between individuals and they are far too unpredictable in their magnitude and duration to turn the use of placebos into a reliable therapeutic option [1,17,18,23].

Another possibility is to argue that deceptive placebos can have diagnostic utility [22]. For example, deceptive placebos can be used to distinguish patients with epilepsy from those who have pseudoseizures, which are attacks indistinguishable from epileptic seizures but that have a psychological origin. Standard diagnostic tests may be prohibitively expensive, as they require observing the encephalography of patients during actual seizures. Studies suggest that doctors can use deceptive placebos to induce seizures in patients with pseudoseizures, but not in patients with epilepsy [22]. This diagnostic technique is believed to be superior to standard clinical observation, which yields high risks of misdiagnosis. However, performing this test would be unethical under the AMA's placebo policy.

Arguments based on the clinical utility of deceptive placebos may provide a compelling case to reject the categorical position. If one agrees that medical paternalism is justifiable whenever the expected benefits clearly exceeds the expected harms, and if deceptive placebos may have high clinical utility, then one must conclude that using deceptive placebos might sometimes be justifiable. The strength of these arguments, however, depends both on the quality of the evidence supporting the case for the clinical utility of placebos as well as on the force of general ethical principles, as supporters of deontological views would still find these arguments unpersuasive.

A second argument used to attack the categorical prohibition is that deceptive placebos may not compromise autonomy and trust because a significant portion of patients considers their use adequate. At present, empirical evidence on patients' attitude toward the clinical use of placebos is scarce. However, a 1993 Swedish study found that 25% of interviewed patients agreed completely or for the most part that physicians ought to prescribe more often placebos on their own initiative, while 63% agreed that it is acceptable to administer a placebo to a dying cancer patient if there is little chance that she will discover the truth [24]. More recently, a survey in US patients found that "most respondents (50–84%) judged it acceptable for doctors to recommend placebo treatments… Only 21.9% of respondents judged that it was never acceptable for doctors to recommend placebo treatments" [25].

These findings may reinforce the arguments in favor of deceptive placebos in two ways. First, they can reinforce the case for paternalism by suggesting that "placebo deception" constitutes only a minor infringement of patient's autonomy. Second, they can mitigate the concerns about the effects of deception on trust. If a patient considers morally appropriate the use of deceptive placebos, then, when she discovers that her clinician had given her a placebo, she might not consider such deception a too severe breach of her trust. Perhaps some patients might even consider it as a sign of the doctor's commitment to their wellbeing. Similarly, if the vast majority of patients support the use of deceptive placebos, weakening the categorical ban would not compromise the social status of medicine.

However, defenders of the categorical position may reply with two counter-arguments. First, one can observe that, even if some patients would not consider the use of deceptive placebos as a severe infringement of their autonomy, many will. Since it is impossible to anticipate with confidence the preferences of every single patient, we should adopt the more cautious position and restrict the use of deceptive practices as much as possible. Secondly, as noted by Bok, often we tend to appraise the moral consequences of a deceptive act differently depending on the perspective that we assume: the one of the deceiver, or the one of the deceived [16]. If this is true, then patients may agree that physicians should use placebos in certain circumstances, but may nonetheless consider a deception as a breach of *their* trust if they found out that *they* are the ones that have been deceived. Interestingly, the above-mentioned US study found also that most of the "respondents valued honesty by physicians regarding the use of placebos and believed that non-transparent use could undermine the relationship between patients and physicians" [25]. This suggests that while not every patient considers the use of deceptive placebos as a breach of trust, some will, and most patients would still consider this practice to be problematic when the deception is uncovered.

The last strategy is to argue that some ways of administering placebos do not qualify as "deceptive" [19-21]. Scholars pursuing this line of argumentation usually start by questioning the definition of "deception" assumed at the outset of the discussion. Deception is then normally defined as "intentionally causing someone to have a false belief that the deceiver believes to be false" [26]. Consider, however, the following way of introducing a placebo: "I am prescribing you a pill which research suggests can be of benefit to you. In your circumstances I have reason to believe that it will work, with a minimum of side effects" [21]. It is claimed that this disclosure is "not transparent"–because it does not openly inform the patient that the pill is a placebo– and yet it is also "not deceptive"–because the statement is not factually false: placebos can be clinically helpful and the physician may genuinely believe so. Therefore, one can agree with the categorical ban on deceptive placebos while at the same time arguing that there are ways of administering placebos that are not deceptive. This argument, however, is problematic. As Cabot [26] observed about the use of misleading practices in medicine "a true impression, not certain words literally true, is what we must try to convey", and what counts as "deceptive" may be dependent on the norms and expectancies associated with a particular social settings [18]. Today patients may reasonably expect that all the medicines that doctors prescribe to them have been tested and approved for their specific efficacy. To contravene this widely shared expectation counts as deception, even if the words uttered by the clinician are sufficiently vague as not be literally false.

Placebos without deception

Recent empirical studies on placebos "without deception" have questioned the widely-shared assumption that placebos require deception to be effective [27–29]. In a pilot trial, patients with irritable bowel syndrome were randomized to receive either no treatment or a placebo pill that was honestly described as containing no active medication (an "open-label placebo", or OLP). Patient were read a script about placebo responses and informed about the rationale of the study. Perhaps surprisingly, patients who received OLPs reported statistically significant improvements with respect to the control group [27]. Similar results have been replicated in other pilot studies for recurring migraine [30] and depression [31], suggesting that "taking a pill" may have beneficial effects even if that pill is not deceptively presented as an effective medication.

Yet, though OLPs may not involve deception, their use in clinical settings raises a series of ethical concerns. First, evidence concerning their effectiveness is not conclusive, and the results of the few studies of OLPs are not free of potentially important biases, owing to the fact that the patients in the no-treatment comparison groups knew that they were not receiving any treatment intervention. Before considering OPLs a viable therapeutic option further studies are needed, including a better understanding of their underlying mechanisms of action. For example, it is still unclear whether OLPs are as effective as deceptive placebos or whether they imply a trade-off between honesty and effectiveness. Second, there are concerns of transparency relating to the way in which an OLP can be honestly presented to a patient in a way that does not unethically manipulate her expectations for the sake of promoting the placebo effects [23].

In light of these concerns, one promising way of using OLPs may be that of incorporating them as part of a therapeutic regime based on deliberate pharmaco-conditioning. In

these therapeutic protocols an OLP is paired with an active medication until the administration of the OLP alone induces a conditioned placebo response that mimics the effects of the medication. Evidence from pilot studies in psoriasis [28] and ADHD [29] suggests that OLPs based on pharmaco-conditioning may be effective in maintaining therapeutic responses while reducing the side effects of active medications. If further studies confirm these findings, then OLPs used in therapeutic regimes based on pharmaco-conditioning might represent the least controversial way of incorporating placebos in real clinical settings.

Placebo effects without physical placebos

Compelling evidence from "open-hidden" experiments demonstrates that placebo responses may occur without the provision of a physical placebo. In this kind of experiments patients receive an effective medication (e.g. an analgesics) either by a clinician who explains the expected effects of the therapy (open administration), or through an automatic procedure such as an infusion machine (hidden administration) [8]. Both the open and the hidden groups receive the same amount of medication, and the only difference is the "informational context" surrounding its delivery. Using this design, in a randomized study researchers administered four common painkillers to post-operative patients, finding that the dose of analgesic needed to reduce the pain by half was significantly greater in the hidden administration groups for all four drugs [32]. Thus, the same dose of a proven analgesic had different effects depending on it being administered in an open or in a hidden way. In general, open-hidden experiments demonstrate that, through placebo responses, the same dose of a drug may have different effects depending on other contextual variables such as the bedside presence of a nurse or the way in which it is verbally described [6,8,27].

Since various components of the healing context may trigger significant placebo responses, it has been argued that physical placebos are unnecessary, as the same benefits can be achieved in ways that are less controversial [4,18,23]. For example the AMA–in the same "opinion" mentioned above–observes, "Physicians can avoid using a placebo, yet produce a placebo-like effect through the skillful use of reassurance and encouragement. In this way, the physician builds respect and trust, promotes the patient-physician relationship, and improves health outcomes" [12]. The possibility of eliciting placebo responses without placebos hints at an intriguing series of new empirical and ethical challenges, two of which deserve to be mentioned here.

First, clinicians' words can have both positive and negative placebo-like effects. In the latter case, it is now customary to speak of nocebo effects [8]. Nocebo effects follow the same logic of their placebo counterparts, and verbal cues may thus induce both placebo and nocebo responses [8]. For example, to tell subjects that a painful stimulation will be delivered shortly results in an amplification of the pain or in the perception of pain even when no painful stimulus is present [33]. The existence of nocebo effects poses an interesting set of ethical issues for the practice of information disclosure and informed consent [4,34,35]. How should clinicians describe the side effects of prescribed therapies in a way that is both respectful of patient's autonomy and does not promote negative nocebo responses?

Second, the possibility of modulating placebo and nocebo responses through communication raises the issue of how clinicians should present to patients low-risk therapies that are presumed to operate only through placebo responses. A typical example under this respect is the case of acupuncture. A series of high-quality randomized trials found that real acupuncture is only marginally more effective than sham acupuncture performed with retractable needles [36]. However, both real and sham acupuncture were almost twice as effective of conventional therapies for low-back pain. These findings suggest that placebo responses may represent a crucial component of acupuncture effectiveness. Since presenting the treatment as a placebo might reduce its effectiveness, how should physicians introduce this kind of treatments in a way that is honest and yet not counter-therapeutic?

These questions suggest that the future of placebo studies may increasingly focus on other aspects of the clinical encounters rather than on the provision of physical placebos. More empirical research and ethical discussions are needed to chart this vast and largely unexplored territory.

Conclusions

The use of placebos in clinical contexts is fraught with ethical issues. Over the last forty years scientific discoveries and ethical debates have revolutionized the way in which the role of placebos has been traditionally understood in clinical medicine. The current ethical debate over the clinical use of placebos revolves around the question of whether it is permissible for clinicians to deceive patients for their own good. While today some scholars and guidelines support a categorical prohibition of deceptive placebos for deontological or precautionary reasons, others have argued that using deceptive placebos is sometimes justifiable given their therapeutic and diagnostic value, low impact on mutual trust, or because they do not require deception. Alongside the main debate, recent studies on placebos without deception and on placebo responses without physical placebos are moving the traditional debate toward new directions, each of which raises its own distinctive set of ethical challenges.

Conflict of Interest: The opinions expressed are the views of the authors and do not necessarily reflect the policy of the National Institutes of Health, the Public Health Service, or the U.S. Department of Health and Human Services. The authors declare that there are no conflicts of interest.

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