Using Placebo Medications in the Clinical Setting – An Intellectual Game or a Possible Reality?

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ABSTRACT

Prior to the development of the pharmaceutical industry and the advocacy of evidence based medicine in the late 20th century, placebo treatments were commonly used by physicians. In current clinical practice, neither a physician’s confidence in the efficacy of a specific treatment nor his personal ethical norms are any longer sufficient to initiate a given therapy.

We will discuss whether placebo treatments can be ethically used in clinical practice as an alternative to standard therapy, and propose an innovative conceptualization of the factors involved in the exclusion of placebo treatments from the clinical setting. Patient-related ethical and interpersonal arguments and physician-related legal and ideological arguments concerning placebo usage are presented. We describe current use of placebo treatments in the healthcare system and suggest that placebo therapy thrives and that its therapeutic efficacy is widely acknowledged. There is currently “underground” use of placebo medication, open label placebo trials, and innovative approaches to informed consent to facilitate ethical prescription of placebo therapy. Finally, using the specific example of treatment for depression, we demonstrate how the arguments against placebo use might be undermined, to retrieve the legitimacy of placebo therapy.

INTRODUCTION

Since ancient times, physicians have commonly used non-specific placebo treatments. An early example is the story of the Nehushtan in the Book of Numbers [21:8];

“And the Lord said unto Moses, Make thee a fiery serpent, and set it upon a pole: and it shall come to pass, that every one that is bitten, when he looketh upon it, shall live.” Subsequently, and until the 20th century, placebo continued to be an essential component in the treatment of patients. In 1807 Thomas Jefferson wrote in a letter to Dr. Casper Wistar: “One of the most successful physicians I have ever known, has assured me, that he used more bread pills, drops of colored water, and powders of hickory ashes, than of all other medicines put together. It was certainly a pious fraud” (1). The first clinical trial using a placebo arm took place in 1931 (2). Since then, and following the development of effective and specific interventions, and the intensifying implementation of the principle of informed consent, placebo usage was gradually eliminated from the clinical setting.

Nonetheless, in many randomized controlled trials a placebo arm is still considered the gold standard control method. An active control arm is another option, depending on the efficacy of standard treatment. Nussinovitch et al. (3) discuss in detail the ethical dilemma involved, and the essential question is: are we allowed to administer an inert pill to a sick patient when an efficient and approved drug already exists? Substantial literature addresses this dilemma. Emanuel and Miller (2) delineate strict guidelines for the use of placebos in clinical trials in their seminal paper in the New England Journal of Medicine. Additional guidelines were published by the European Agency for the Evaluation of Medicinal Products, as part of the International Ethical Guidelines for Biomedical Research involving Human Subjects, and a position paper regarding the matter was also published by the Israel Medical Association in 2004 (3). Discussing the interesting and complex role of placebo in clinical trial deserves a separate paper and is beyond the scope of the present manuscript.

In a sense, medical science defines evidence-based efficacy of drugs by “excluding the placebo effect.” However,
the question remains whether or not a valuable tool is lost to clinical practice when this exclusion is endorsed.

Placebo treatments are defined as “a treatment whose benefits (in the opinion of the clinician) derive from positive patient expectations and not from the physiological mechanism of the treatment itself” (4). It should be emphasized that the placebo effect is routinely used by physicians in the clinical setting. This is accomplished with the physician’s verbal suggestions, the patient’s faith in the treatment, professional confidence, or the physician’s white robe (5). In this paper we focus on placebo treatments (sugar pills, sham procedures, etc.) their potential use and relevancy to clinical practice.

The efficacy of placebo therapy has been asserted in various fields of medicine, including cardiology (6), surgery (7), neurology (8), and urology (9). In psychiatry the efficacy of placebo is known to be particularly significant, specifically in depression, schizophrenia, and anxiety disorders (10). Thus, clinical science employs placebo medications (inert pills) because its high efficacy was demonstrated in clinical trials to an extent that could not be ignored.

Nonetheless, the same placebo pills that are routinely used in clinical trials are strictly prohibited in the clinical setting. We address the following questions: 1) Should placebo medications be used in clinical practice? 2) Under what circumstances can we ethically offer placebo medications as an alternative to a standard, proven therapy?

We first present the arguments against use of placebos. Notwithstanding, we then describe current applications of placebo therapy in the clinical setting. Finally, we use the treatment of depression as a platform to discuss the legitimacy of placebo usage in the clinical setting.

**EXCLUSION OF PLACEBO TREATMENTS**

There are various arguments for opposing the use of placebo therapies in the clinical setting. We offer a novel conceptualization by dividing the arguments into four domains:

1. **Patient-related ethical argument**
2. **Patient-related interpersonal argument**
3. **Physician-related ideological argument**
4. **Physician-related legal argument**

**PATIENT-RELATED ETHICAL ARGUMENT**

First and foremost, it is considered unethical and unwise to prescribe non-specific placebo treatments when a specific approved and efficient treatment is available. In addition, effective prescription of placebo calls for total ignorance on the part of the patient regarding the true mechanism of action of the treatment. The physician in effect deceives the patient by violating the principle of full informed consent for treatment (11). This deception is necessary because an essential element in the efficacy of placebo is expectation. The patient’s expectation of an approved and efficient drug is in itself a component of the healing process. Part of the physician’s task is to provide information regarding the drug in a suggestive manner in order to convince the patient that he is being offered a specific, efficient, and approved treatment. This is not possible when administering placebo therapy.

An additional ethical dilemma encountered in placebo treatment is potential decline in the patient’s sense of autonomy. The patient’s right to choose a treatment is somewhat nullified, because if he is not fully aware of the nature of his options (12) or of the existence of additional specific and helpful treatments, he cannot make an informed decision.

**PATIENT-RELATED INTERPERSONAL ARGUMENT**

Prescription of placebo therapy can potentially threaten trust and negatively affect the doctor-patient relationship. Placebo usage “contravenes the pact of confidentiality in the doctor-patient relationship, which is the nucleus of the therapeutic dialogue” (13). This dialogue is crucial to the ongoing compliance of many patients and harming it might have long lasting effects on the patients’ health. In a recent survey Fassler et al. (14) found that 70% of patients wanted to be explicitly informed when receiving a non-specific intervention in the clinical setting, and 50% stated that they would be disappointed with their physician if they learned that they had been treated with pure placebo.

Interestingly, a recent study demonstrated that in randomized controlled trials the specific components of placebos (sugar, vitamin, etc.) were seldom described to the subjects (15). This might have spared the investigators a negative effect on subjects’ attitudes and cooperation if the composition of the placebos had been brought to their knowledge. Possibly, the simple fact that a physician/investigator prescribes an inert substance might threaten the trust of patients/subjects.

**PHYSICIAN-RELATED IDEOLOGICAL ARGUMENT**

Thomas suggests that physicians prefer to perceive themselves as caregivers that implement progress and are part of the scientific project (16). They are educated along the lines of evidence-based medicine and are
expected to treat patients accordingly. The scientific stance is expressed in relation to patients, as well as colleagues, as it is an important element in the physician's professional image and reputation. The modern physician believes in science, identifies with its values, and tends to renounce nonspecific treatments. In fact, prescribing placebo can be perceived as an irrational, nonprofessional therapy, identified more with alternative medicine then with medical science.

**PHYSICIAN-RELATED LEGAL ARGUMENT**

According to the Declaration of Helsinki (1964) every subject in a clinical trial should be treated with the most efficient treatment methods available (13). This is true in research, and more so in the clinical setting. The Israel Medical Association Code of Ethics addresses the use of placebo in clinical trials, but does not refer to placebo use in the clinical setting, probably because of the obvious exclusion of placebo treatments in clinical practice (3).

In the Israeli “Patients Rights Law” (1996) it is clearly stated in clause 5, “A patient shall be entitled to proper medical care, having regard both to its professionalism and quality, and to the personal relations incorporated in it.” Accordingly, the physician is obliged to provide the patient with the most efficacious treatment available. The prescription of placebo might contradict this legal obligation when an effective and specific treatment is already available. Furthermore, clause 13 requires the physician to provide the patient with full information regarding his treatment, including the essence, procedure, aims, and expected benefits and limitations of the treatment. Thus, the “pious fraud” of prescribing placebo treatments might turn out to be a violation of the Israeli law (17).

**LATENT PRESENCE OF PLACEBO TREATMENTS**

Placebo therapy is not acceptable in the clinical setting due to the arguments described above. Nonetheless, accumulating data regarding placebo “abuse” by medical staff members in clinical practice and ongoing attempts to authorize placebo therapy is reflected by:

1. Underground usage of placebo
2. Open label trials
3. Tailored informed consent procedures

**UNDERGROUND USAGE OF PLACEBO**

Thirty years ago the use of inactive substances to induce placebo effects was still commonplace in the clinical setting. Senior medical staff members can openly testify to the extensive use of placebo in the treatment of psychiatric patients. Nitzan and Lichtenberg have found that underground usage of placebo therapy is still quite common (18). Among Israeli physicians and nurses 60% reported using placebo pills and procedures; the majority of them (62%) as often as at least once a month. The circumstances in which placebo treatments were routinely used included: unjustified demand for medication, as an analgesic, a diagnostic tool, to calm a patient, for non-specific complaints, or to gain time until the next regular dosage of medication was scheduled. Similar findings were later published in Europe (19), where 90% (n=270) of general practitioners admitted to actively propose treatments with non-specific effects. In a survey among 1,200 internists and rheumatologists in the U.S., about 50% reported prescribing placebo treatments on a regular basis, most of them believing it to be ethically permissible (4). Only 2-3% percent reported using pure placebo (sugar pills, saline), while 38-41% reported using active placebos (over the counter analgesics, vitamins). Physicians who reported using placebo treatments usually described them to the patient as “a medicine not typically used for your condition but might benefit you,” or as “a medicine with no known effects for your condition.” In another study 231 (45%) interns reported using placebo treatments; most commonly to calm patients or as a supplemental treatment (20). Interestingly, it was a Canadian survey revealed that most psychiatrists agree with the therapeutic effects of placebos and seem to administer significantly more placebo medications compared with non-psychiatrists.

**OPEN LABEL TRIALS**

Placebo treatments administered in open label trials have demonstrated therapeutic value in treating psychiatric patients (21, 22). Importantly, in this scenario full informed consent can be obtained and the physician continues to foster patient trust.

Recently, Kaptchuk et al. (23) reported that in a two group (placebo pills vs no treatment), open label, randomized controlled trial, placebo pills administered without deception demonstrated efficacy in treating IBS (irritable bowel syndrome). In another open label prospective study placebo pills were found to be efficacious in the short-term treatment of some children with ADHD (24). ADHD behavior remained the same when stimulant medication dose was reduced, while remaining under treatment with placebo pills, but to deteriorate when
reduced without placebo treatment. It seems that some patients are willing to use open-label placebo, and that there is growing evidence concerning the efficacy of this type of treatment in various pathological conditions.

TAILORED INFORMED CONSENT PROCEDURES

The ethical problem with placebo is not that the patient is receiving an ineffective treatment, but rather that the doctor is deceiving the patient, concealing information and violating the principle of informed consent. Some caregivers have attempted to bypass this ethical conundrum with unique creative thinking concerning the concept of informed consent. Kihlbom (25) developed the construct of Negative Informed Consent, suggesting that “it is possible to exercise your autonomy without having the amount of and the kind of information that are assumed in the standard requirement of informed consent to medical treatment.” Kihlbom suggests that “if I, as a patient, choose to let you, as the physician, determine my treatment, and I have well founded beliefs that you will choose the treatment that best promote my values, and that the risks of the treatment you will choose is in accordance with my attitudes towards different kinds of risks, I will exercise my autonomy, not waive my right to exercise it... the norm of informed consent to medical treatments ought to be relaxed in contexts where substantive patient-doctor relationships of confidence or trust are established.” Shaw further suggested that using negative informed consent, “where a patient abdicates access to information to some extent,” facilitates perfect conditions for ethical use of placebos (26). According to Shaw the first step in offering effective placebo treatment would be to inform the patient that he is being offered a pill that “will hopefully make him better.” In case the patient asks for more information Lichtenberg and colleagues suggested alternative phrasing: “I would like to offer you a pill which I believe can help lessen your suffering. I do not know exactly how it works. I have other pills to offer whose mechanism is clearer, but I am not sure that they will work better for you, and they may also entail more serious side effects” (12). If asked about side-effects or the specific mechanism of action the physician can add that “this pill has few side-effects, but studies have shown that the more I tell you about how it works, the less effective it will be.”

When specifically discussing placebo treatment for mild to moderate depression the physician can honestly inform the patient that the placebo treatment might be useful and that it possibly acts via its influence on specific neural circuits in the brain (27).

Lichtenberg et al. also developed guidelines that delineate the conditions under which placebo usage might be appropriate in the clinical setting (12).

PLACEBO TREATMENTS AND DEPRESSION – A PRISM TO THE POSSIBLE FUTURE USE OF PLACEBOS

Using the example of SSRI vs placebo pills for depression, we challenge the arguments against placebo therapy. We focus on the ethical and interpersonal patient-related arguments, and attempt to undermine them on the basis of current evidence based medicine. We briefly address physician-related arguments, however a sociological and cultural discussion is beyond the scope of this paper.

Depression is one of the most common debilitating psychiatric disorders (28). Some recent meta-analyses have clearly indicated that antidepressant’s (AD) have a minor advantage over placebos (29-32), or no advantage at all in treating mild to moderate depression (33). Kirsch et al. (33) used the Freedom of Information Act to obtain data from the U.S. Food and Drug Administration (FDA) instead of the published scientific literature. They based their meta-analysis on reviews of all placebo-controlled clinical trials, positive or negative, submitted by pharmaceutical companies for the approval of the six most widely used ADs. Most of the trials had negative results, and placebos were found to be 82% as effective as the AD. The efficacy of AD becomes more significant as the severity of the depression rises, and this can be attributed to one of the following: 1) the advantage of AD over placebo in treating severe depression, 2) weakening of the placebo response in severely depressed patients, 3) the high doses required to treat severely depressed patients.

In any event, most caregivers would agree that placebo treatments can be useful in treating mild to moderate depression. Thus, the availability of approved and efficient antidepressants does not unequivocally exclude the usage of placebo from the ethical point of view. Moreover, in addition to its efficacy, placebo treatment has less side
effects (36), and is less expensive for the patient. Using placebo therapy in clinical care apparently respects the principles of beneficence and non-malfeasance (13).

Thus, it seems that the deception involved and the lack of informed consent are the main ethical obstacles that the physician encounters when considering the option of treating depressed patients with placebos. Theoretically these hurdles can be bypassed using negative informed consent. However this concept is yet to be considered acceptable or valid by most physicians and medical institutions.

Surprisingly, few attempts were made to elucidate the viewpoint of laypeople or depressed patients regarding the placebo therapy. Without being asked they are deprived of the right to “not know” or “know less” and consequently enjoy the benefits of a safe and possibly useful treatment for depression. In an open label trial, using placebos in the treatment of ADHD, children and parents were generally receptive of the treatment (37). Fassler and colleagues (14) conducted a survey in an attempt to investigate the attitudes of patients and physicians regarding placebo use in clinical practice. In their study most of the patients were open to the option of being treated with nonspecific treatments such as placebo, although 70% of the patients wanted to be explicitly informed when receiving placebo or other nonspecific treatments.

In the 2011 annual meeting of the EPA, we presented two surveys on the acceptability of placebo usage in the treatment of depression. In the first survey, conducted among 344 healthy students from five academic institutions in Israel, 70% of the study population expressed consent to receive placebo therapy as a first line treatment were they to suffer from mild to moderate depression. Most of the subjects did not feel that taking placebo medication would negatively affect their sense of autonomy or doctor-patient relationship. Similar results were found in a complementary study conducted among depressed patients. It seems that under certain conditions many depressed patients might opt to waive their right for complete information in order to receive a possibly useful and safe treatment (38).

The physician-related legal argument seems unequivocal at first glance. Nonetheless, Loftus and Fries have already speculated whether “the purpose of informed consent in its rigid and routinely demanded version is not protection of subjects, but rather protection of investigators and sponsoring institutions from lawsuits based on the charge of subjects deception should a misadventure result” (39). These authors acknowledge the essential right of people to “determine what is done to their minds and bodies,” but they question the current legalistic ritual associated with informed consent as the best way to ensure that this human right is protected (40). A good example presented is the explicit suggestion of adverse events required by the law as part of informed consent; causing many subjects to experience these effects by what is known as the nocebo effect (41). The law is out there, but it can always be creatively and innovatively interpreted.

Broader discussion of the physician-related ideological argument is needed. There is tremendous influence of the zeitgeist on medical education and on our clinical conduct. Our attitudes and openness to non-specific treatment such as placebo are dictated by the spirit of the times, economic interests, and a strong hegemony of physicians who perceive placebo treatments as a deception rather than a “pious fraud.” Marinker claims that “general practitioners remain life-long prisoners of their early medical education, and that perhaps postgraduate training should be a process of liberation and unlearning” (42).

Part of the definition of a placebo treatment is that at the time of its use it is believed to be a non-specific treatment for the condition for which it is prescribed. In the future, as science progresses, non-specific treatments might reveal a specific mechanism of action. This is already supported by promising basic science research that has been executed in the last decades on the neural mechanisms of placebo treatments (43). These scientific achievements might possibly direct the “lost placebo ship” back to its home harbor in the clinical setting. Alternatively, the cultural and ethical discussion regarding placebo treatments will advance, develop, and perhaps expand the bounds of medical practice; eventually turning placebo therapy to a legitimate clinical method - though restricted to specific situations delineated with clear guidelines - but implemented when appropriate and in the service of patient well being.

**CONCLUSIONS**

“Doctors should always bear the moral responsibility to act in their patients’ best interests” (13). We described various arguments that oppose the use of placebo medications in the clinical setting. Yet, it seems that these arguments are not always as firm as they seem, and are usually contextual to a specific doctor-patient-disorder interaction. We shed light on some controversial aspects of placebo usage in treating mild to moderate depression, and hope to advance its discussion among physicians and other health care workers.
Forty years ago, in a BMJ editorial, it was suggested that “there must be occasions when an appropriately prescribed placebo will be less harmful and perhaps more beneficial than a complex and incompletely understood drug” (44). Ultimately, the responsibility for choosing the appropriate remedy at the proper time rests on the shoulders of the caregiver; in accord with Balint’s view of the physician himself as the most widely used drug in medicine (16).

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References
17. Patients rights law, 1996.
39. Loftus E, Fries JF. Informed consent may be hazardous to your health. Science 1979; 204:211.
46. Emanuel EJ, Miller FG. The ethics of placebo-controlled trials—placebo is not a blank check. JAMA 2001; 286:1583-1585.