Is There a Moral Issue When Doctors Prescribe Placebos?

What guidelines need to be followed with their use?

BY NEIL BAUM, MD, AND DAVID F. MOBLEY, MD

A placebo is an inactive treatment, sometimes called a "sugar pill." A placebo may be given in a pill, capsule, liquid, or tablet form, or it may be an injection or a medical treatment or device. Whatever the form, placebos often look exactly the same as the real medical treatment that is being studied, with the only difference being that the placebo does not contain the active medication, treatment, or procedure.

The human body has an uncanny ability to heal itself. History has demonstrated that a little nudge from a shaman, witchdoctor, or a "real" doctor with the initials MD after his or her name initiates the healing process.

By definition, placebo interventions do not have any direct pharmacologic or therapeutic effects on the body. However, all treatments are delivered in a context that includes social implications, physical cues, verbal suggestions, and treatment history.

An example of the importance of context is the following story. Virtuoso violinist Joshua Bell, who is one of the best concert violin players in the world, wearing a baseball cap and sunglasses, played for 45 minutes, on a violin worth $3.5 million, at a Washington, DC subway station during rush hour. Over a thousand people passed by Bell; however, only seven people stopped to listen to him play, and only one person recognized him. Just a few nights before his performance in the subway station, he had played at the Kennedy Center and the cost of the tickets was $100.

This is no surprise; the social context in which a behavior occurs affects how it is interpreted. The same applies to the use of a placebo and who is prescribing the "drug" and under what circumstances and in what context the placebo is recommended. Joshua Bell played incognito in the Metro station as part of a social experiment about perception, taste, and the priorities of people. The experiment can be extrapolated to demonstrate the importance of the context in which an event or even a placebo is used for treating a medical problem or condition.

Placebo interventions do not have any direct pharmacologic or therapeutic effects on the body.

Two elements are involved in the context of using placebos.[1] The first element is the external context. In this context, the success of a placebo

Continued on page 120

Placebos (from page 119)

comes from verbal suggestions, such as stating in a positive fashion, "This is going to make you feel better"; the context of the place where the placebo is given, such as in a doctor's office; and, finally, social cues, including eye contact, body language, voice cues, and, of course, the doctor wearing a white coat and perhaps even having a stethoscope draped around his/her neck.

The second element is the internal context. This context consists of memories, emotions, expectancies, and appraisals of the meaning of the context for future survival and well-being. An example of the internal context of the patient's outcome expectations might include the use of self-talk such as, "I'm sure this 'medication' will make my pain go away."

All of these features, in both internal and external contexts, combine to make up the treatment context and are the "active ingredients" of placebo effects.

How Do Placebos Work?

We often ask, "How is it possible that a pill or medication that contains no active therapeutic ingredient, or even sham surgery, can result in improvement in the patient's condition?" Numerous studies have investigated the mechanism of action of placebos.

One study published in 2016[2] may have identified what goes on in the brain during a placebo effect. Researchers used functional magnetic resonance imaging to scan the brains of people with chronic knee pain. Then all the patients were given a placebo and had another brain scan. The researchers noticed that those patients who felt pain relief had greater activity in the middle frontal gyrus brain region, which makes up about one-third of the frontal lobe.

Although placebo interventions do not have any direct therapeutic or physiologic effects on the body, all treatments are delivered in a context that includes social and physical cues. These clues might include the healthcare provider wearing a white coat and verbal suggestions that the "drug" will be effective and relieve their symptoms and complaints. A substantial part of the therapeutic benefit patients

Studies have demonstrated that how the placebo is presented will affect the response.[3]

Continued on page 121

Placebos (from page 120)

receive when undergoing medical treatment is caused by their brain's response to the treatment when it interprets the context in which the placebo is presented.

Studies have demonstrated that how the placebo is presented will affect the response.[3] For example, a white tablet is less effective than a blue or green tablet. A capsule appears to achieve a greater placebo effect than a tablet. A placebo given multiple times a day is more effective than one given just once a day. Also, an injection of harmless saline (saltwater) is more effective than a tablet or a capsule.

Whether treatment consists of an active drug or a placebo, the clinical setting that surrounds treatment includes multiple types of context information that are perceived and interpreted by the patient's brain. The external context includes treatment, place, and social cues, along with verbal suggestions such as, "This will be very likely to help relieve your symptoms."

Placebo responses have been demonstrated to be effective in multiple clinical disorders, including pain relief, Parkinson's disease, overactive bladder, benign prostatic hypertrophy, and irritable bowel syndrome. Some cases of improvement may be related to the context in which the placebo is administered. A large part of the overall therapeutic response to drugs, surgery, psychotherapy, and other treatments may be due to the treatment context or the manner or atmosphere in which the placebo is administered.

It is interesting to note that in some cases, individuals who show the largest drug effects to real pharmacologic medications also show the largest placebo effects, which is one indicator that some drugs and placebos may share mechanisms of action within the central nervous system.[4]

Placebo treatments can also affect hormonal responses that are mediated through the hypothalamic–pituitary axis.

Placebos also have an impact on the immune system, particularly T lymphocyte proliferation and the release of interleukin-2 and interferon from peripheral lymphocytes. Relatively little is known about the brain mechanisms underlying such effects on the immune system, although recent work suggests that they are mediated by noradrenergic sympathetic efferents,[5] which require the hypothalamus and pituitary gland for their expression.

On the neuroendocrine level, there appears to be a relationship between placebos and the release of dopamine. One landmark positron emission tomography study of dopamine activity found that placebo administration increased dopamine binding in patients

Continued on page 122

Placebos (from page 121)

with Parkinson's disease, particularly in those patients who perceived an improvement in clinical status with placebo treatment.[6]

The take-home message is that the psychological context may have more pervasive effects on physiology than is generally recognized.

Although there is no single mechanism of action for the placebo effect, it is undeniable that in certain clinical settings, the placebo does have a place in the armamentarium of healthcare providers.

The Ethics of Using Placebos

There are two different options for delivering a placebo. The first is a placebo-controlled study. Such a study consists of two groups. One of the groups receives the medication that is undergoing study, which contains the active ingredient. The patients in this arm of the study do not know whether they are receiving the drug or the placebo. The second group receives the placebo. They, likewise, are not told whether they are receiving the placebo or the active ingredient. In this kind of study, the investigators and those who analyze the data are not aware which patients have received the placebo and which have received the active drug.

In a double-blind, placebo-controlled trial, the investigators do not know whether the subject has received the real drug or the placebo. (This is in contrast to a single-blind study, where the investigator may know whether the patient is receiving the placebo or the active medication, but the subject does not know.) Only after the study is completed and the data have been analyzed may the patient be informed whether he or she received the active drug or the placebo. Patients are informed both verbally and in a written consent prior to entering the study that some of them will receive the active drug and some will receive the placebo.

Patients first are screened to determine whether they fit the criteria to enter the study, and they sign an informed consent document that informs them that they may or may not receive the active drug. We believe that this is ethical and that there is no violation of patient confidentiality or breach of the Hippocratic Oath if a patient receives placebos in the situation of a clinical trial comparing an active drug to an inert pill, or a real procedure compared with a sham procedure.

An example of a sham procedure is giving a patient who has a torn meniscus in his or her knee a general anesthetic, making a small incision on the knee, and closing that incision with Steri-Strips or sutures. This sham procedure is compared with the patient who undergoes a procedure in which an arthroscope is inserted through small incisions and the torn meniscus is repaired.[7]

One of the most obvious ethical issues regarding placebos is their use when no comparison with a pharmacologic medication is involved and the patient is not informed that he or she is receiving an inert drug or medication. According to the World Medical Association's Declaration of Helsinki, which addresses ethical issues surrounding the use of human subjects in research, placebo use is acceptable when there is no proven acceptable treatment for the condition under investigation. This organization has declared that placebos are acceptable when "for compelling and scientifically sound methodological reasons" it's necessary to determine the experimental treatment's efficacy or safety, and when patients who receive a placebo "will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention."[8]

Historically, deception has been considered a major component of the use of placebos, and this remains one of the main ethical problems regarding their use. Traditionally, a full disclosure of potential side-effects is considered the most ethical and appropriate course of action regarding all medications prescribed, including placebos. In some cases, however, it is important to disclose the most critical information about possible adverse events in order to avoid undue patient distress.

More research may be needed, including opinions from ethicists, philosophers, and medical practitioners, to better understand the role of deception regarding the use of placebos.

A key premise underlying medical ethics discussion is the notion that the placebo effect necessitates patient deception. Indeed, the American Medical Association guidelines imply that placebo treatment necessarily entails a form of deception. The ethical issue that must be considered is whether that deception is ever justified. Recently performed experiments with open-label, transparently prescribed placebos have begun to challenge the notion that deception is necessary in eliciting the placebo effect.

Historically, deception has been considered a major component of the use of placebos, and this remains one of the main ethical problems regarding their use.

Focusing on disclosures where the truth is revealed to patients in placebo studies raises the question of whether deception is unethical. Blease, et al.[9] concluded that informing patients that they are receiving placebos fulfills current American Medical Association guidelines for placebo use, and proposed future research directions for harnessing the placebo effect ethically.

A recently passed law, Cures Act 2021, which went into effect in 2021, entitles patients to their medical records. Transparency is going to be necessary regarding the patient's diagnosis, any medications that have been prescribed, and the discussions that have transpired between the doctor and the patient. Consequently, it will no longer be possible for a doctor to prescribe a placebo without disclosing that the use of an inert substance has been recommended to the patient.[10]

Continued on page 124

Placebos (from page 122)

Current Ethical Guidelines on the Use of Placebos

The following rules might serve the physician as guidelines for the justified use of placebo in clinical practice:

- The intentions of the physician must be benevolent: his or her only concern is the well-being of the patient. No economic, professional, or emotional interest should influence the decision. If the physician does what is in the best interest of the patient—and that may be the use of a placebo—there is no ethical breach on the part of the physician.
- The placebo, when offered, must be given in the spirit of relieving the patient's suffering, and not merely mollifying him, silencing him, or otherwise failing to address his distress. It is important always to keep the patient at the center of the ethical decision of using a placebo. The best advice for a physician is this: always to do what is in the best interest of the patient and you will be standing on firm ground.
- As soon as a placebo has been proven ineffective, it should be withdrawn immediately. In these circumstances, not only is the placebo useless, but it also undermines the subsequent effectiveness of other medications by undoing the patient's conditioned response and expectation of being helped.
- The placebo cannot be given in place of another medication that the physician reasonably expects to be more effective. Administration of placebo should be considered when a patient is refractory to standard treatment, suffers from its side-effects, or is in a situation where standard treatment does not exist.
- The physician should not hesitate to respond honestly when asked about the nature and anticipated effects of the placebo treatment he is offering. The physician must reveal the use of a placebo if the patient asks.
- If the patient is helped by the placebo, discontinuing the placebo, in absence of a more effective treatment, would be unethical.

We have seen that in almost any clinical trial, there is a positive response in the placebo arm, almost regardless of the condition being treated, and that the difference between placebo response and active drug response often is negligible. In a 12-week trial, this is often true. In a one-year trial, however, the placebo arm almost always reverts back to baseline symptoms or results. In other words, it is common for placebos to have an effect in the short term, but not for the long-term.

We have seen that in almost any clinical trial, there is a positive response in the placebo arm, almost regardless of the condition being treated, and that the difference between placebo response and active drug response often is negligible.

Bottom Line: The placebo can be of service to physicians in many clinical situations. Therefore, it should not be denied its rightful place in medical treatment as long as ethical guidelines have been followed.

Acknowledgment: The authors wish to thank Dr. Drew Chastain, Professor of Philosophy at Loyola University in New Orleans, who was the inspiration for this topic. **PM**

References

[1] Wager TD, Atlas LY. The neuroscience of placebo effects: connecting context, learning and health. Nat Rev Neurosci. 2015;16:403-418.

[2] Tétreault P, Mansour A, Vachon-Presseau E, Schnitzer TJ, Apkarian AV, Baliki MN. Brain connectivity predicts placebo response across chronic pain clinical trials. PLoS Biol. 2016;14(10), e1002570.

[3] Khan A, Bomminayuni EP, Bhat A, Faucett J, Brown WA. Are the colors and shapes of current psychotropics designed to maximize the placebo response? Psychopharmacology. 2010;211(1):113-122.

[4] Benedetti F, Amanzio M, Baldi S, et al. The specific effects of prior opioid exposure on placebo analgesia and placebo respiratory depression. Pain. 1998;75:313-319.

[5] Exton MS, Gierse C, Meier B, et al. Behaviorally conditioned immunosuppression in the rat is regulated via noradrenaline and ß-adrenoceptors. J. Neuroimmunol. 2002;131:21-30.

[6] De La Fuente-Fernandez R, Stoessl AJ. The placebo effect in Parkinson's disease. Trends Neurosci. 2002;25:302-306.

[7] Katz JN, Brownlee SA, Jones MH. The role of arthroscopy in the management of knee osteoarthritis. Best Pract Res Clin Rheumatol, 2014;28(1):143-156.

[8] WMA declaration of Helsinki-ethical principles for medical research involving human subjects. World Medical Association. www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/.

[9] Blease C, Colloca L, Kaptchuk TJ. Are open_label placebos ethical? Informed consent and ethical equivocations. Bioethics. 2016;30:407-414.

[10] Porter AS, O'Callaghan J, Englund KA, Lorenz RR, Kodish E. Problems with the problem list: challenges of transparency in an era of patient curation. J Am Med Inform Assoc. 2020;27:981-984.

Dr. Baum is Professor of Clinical Urology, Tulane Medical School, New Orleans, Louisiana, and author of The Three Stages of a Physician's Career—Navigating From Training to Beyond Retirement (American Association for Physician Leadership, 2017); email: doctorwhiz@gmail.com.

Dr. Mobley is Associate Professor of Urology at Weill-Cornell in Houston, Texas.