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The mysterious placebo effect

Understanding it can help avoid flawed study designs.

BY CAROL HART

Mandrake root, powdered mummy, comb, spider web, ants, scorpions, bone, teeth, crab's eyes, viper's flesh, worms, and pearls. These are just a few of the ingredients from the premodern pharmacopoeia, some of which were still in use at the turn of the century. No one would question the fact that they worked as a placebo, if at all. But how many drugs in our current pharmacopoeia also might be ineffective? We rely on double-blind placebo-controlled trials to tell us, but the answers may not always hold true with clinical experience.

The word placebo ("I will please" in Latin) entered the English language by way of a peculiar mistranslation of the 116th Psalm that read, "I will please the Lord" rather than "I will walk before the Lord". In the medieval Catholic liturgy, this verse opened the Vespers for the Dead; because professional mourners were sometimes hired to sing vespers, "to sing placebos" came to be a derogatory phrase describing a servile flatterer. By the early 19th century, "placebo" had come to mean a medicine given "more to please than to benefit the patient" *(1).*

Outside the context of modern clinical trials, "placebo" has been a term reserved for characterizing the substandard practices of other less ethical or knowledgeable healers, if not outright quacks and frauds. Few doctors admit to knowingly using placebos *(1).* In fact, some off-label uses or suboptimal dosing of active medication may act only as a placebo, and the much-criticized but common practice of prescribing antibiotics for viral colds and flu is evidence that use of placebos still flourishes in contemporary medicine *(2).*

In recent decades, the reputation of placebos as a deceitful fraud has undergone considerable reconstruction. To alternative medicine practitioners, placebo response represents the mysterious self-healing forces generated by the mind–body connection. Mainstream physicians now urge their colleagues to make more effective use of placebo-based healing by more empathic and attentive interactions with their patients *(3).* Researchers still may be inclined to view placebo effects as a nuisance or as a background noise that complicates clinical trial design. Understanding the basis of placebo effects, however, can help in filtering out noise and avoiding flawed study designs.

Placebo as "noise"

Placebo effects can result simply from contact with doctors or other health care providers, perhaps a diagnosis or simple attention from a respected professional alleviates anxiety. As Hróbjartsson puts it, "Any therapeutic meeting between a conscious patient and a doctor has the potential of initiating a placebo effect" *(4).* The mere act of interviewing and examining a patient before enrollment in the study may have a placebo effect. Because of the near impossibility of obtaining a satisfactory control (no placebo) group, the effects of placebo administration alone (e.g., an inert pill or saline injection) are routinely overestimated by placebo researchers *(4).* Thus, it's rarely possible to know why some study participants get better with a placebo.

Several potential confounding factors exist that have nothing to do with the placebo itself (5):

[1]*Spontaneous improvement.* Particularly for disorders that have a wax-and-wane course, such as chronic pain conditions or mood disorders, patients may show

spontaneous improvement.

[1]*Fluctuation of symptoms, particularly regression to the mean.* Patients may enter treatment or a trial when signs and symptoms that have a high degree of variability (such as pain, depression, or cholesterol levels) have worsened, so improvement may occur without any intervention.

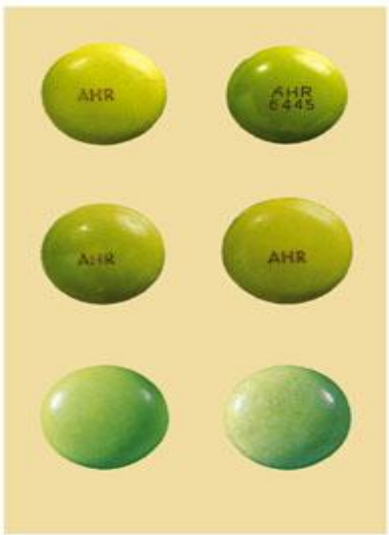
[1]*Beneficial effects of additional treatment and/or improved medical care provided during a study.* Some trials described as placebo-controlled are actually following an additive design—both the active treatment and the placebo group are receiving additional supportive therapies.

[1]*Scaling bias in measuring subjective outcomes.* Using a scale that has more grades for assessing improvement than for no improvement or worsening, presents a scaling bias.

[1]*Answers of politeness or experimental subordination.* The participant, knowing what the desired answer is, might report benefit when no benefit has occurred.

Placebo-related changes may be overestimated if there is little knowledge of the underlying natural history or the prevalence of symptoms under study. Louis Lasagna, dean of the Sackler School of Graduate Biomedical Sciences at Tufts University and one of the early researchers of the placebo effect, cites a study he did in which a placebo sedative was given to patients hospitalized overnight before scheduled surgery. More than two-thirds of the placebo-treated patients fell asleep within one hour, which might seem an impressive response, except that a similar rate was observed in a control group of hospitalized patients who received no treatment for insomnia.

The high placebo response rates reported for conditions such as depression are often explained as suggestibility or expectancy effects. Lasagna suggests an alternative explanation, “It’s not unusual to do a study comparing a standard antidepressant to placebo and find no difference between the two. I think that’s due at least partly to the fact that depression is an off-and-on disease, so these results are a reflection not so much of suggestibility as spontaneous fluctuations in symptoms.” Similarly, pain intensity varies spontaneously, so any treatment manipulation may be followed by a reduction in pain level simply by chance *(6).*

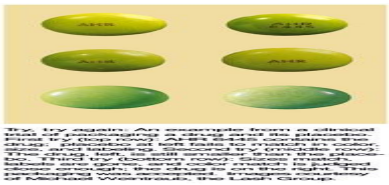


Try, try again: An example from a clinical trial of packaging a drug and its placebo. First try (top row): AHR 6445 contains the drug; placebo at left fails to match in color, size, and labeling. Second try (middle row): The drug, left, is still smaller than the placebo. Third try (bottom row): Sizes match, labels are gone, and color match is judged close enough; the drug is on the right. This packaging was accepted. Images courtesy of Michael Weintraub, the Lash Group.

When and why placebos heal

Some of the most striking case reports of placebo healing of cancer or other severe, progressive diseases are so poorly documented that both the diagnosis and the long-term outcome are open to doubt *(7).* All the same, an abundance of evidence from clinical studies and experimental psychology indicates that subjectively assessed disorders such as migraine headache, back pain, postsurgical pain, rheumatoid arthritis, angina, and depression may respond very well to a placebo (8, 9). Some objective signs also can respond significantly to placebos, including blood pressure, skin temperature, cholesterol level, and heart rate, and some skin conditions, such as warts and contact dermatitis, are reported to be affected by placebos *(9).*

Three major mechanisms have been proposed to explain placebo-evoked improvement: release of endorphins in response to the placebo stimulus (the “opioid model”), a learned response to medical intervention (the “conditioning model”), or a more consciously mediated response (the “meaning” or expectancy model) (4). Studies by Howard Fields,



Donald Price, and colleagues have shown that placebo-induced analgesia can be reversed by naloxone, an opioid antagonist *(6).* According to conditioning theory, previous benefits from taking pills or interacting with a white-coated doctor serve as the conditioning stimulus (comparable with the bell stimulus in Pavlov's famous experiments). Experiments in animals have evoked a conditioned response resembling a placebo, offering some confirmation for this mechanism *(10).* Studies also have shown that expectation powerfully influences how subjects respond to either an inert or active substance—for example, given sugar water but told that it was an emetic, 80% of patients in one study responded by vomiting *(11).* These three mechanisms are not exclusive, but all may be present to varying degrees in any clinical setting.

Placebos in clinical trials

Some so-called placebo effects can originate in study methodology—for example, poorly designed outcome measures or patient inclusion criteria. Trial design, in theory at least, can influence placebo effects. Leora Swartzman, associate professor of psychology at the University of Western Ontario, points out that the informed consent form can be an expectancy manipulation that will influence reports of both adverse effects and subjective improvement. This is particularly true in crossover trials, she said, when participants are informed that they will receive placebo at some point in the trial, as opposed to being told simply that they may receive a placebo at some point in the study.

The history of the placebo-controlled trial

The first known double-blind placebo-controlled trial was performed by W.H.R. Rivers in 1907 to investigate the influence of alcohol and other drugs on fatigue (1). A few placebo-controlled studies appeared during the 1920s and 1930s, but most of these were not blinded. Much of the credit for establishing double-blind placebo-controlled design as the gold standard for clinical trials goes to a pharmacologist named Harry Gold (1). In addition to conducting a number of trials, Gold lectured and published extensively on the double-blind placebo-controlled design in the 1940s and 1950s. In the 1970s, the FDA started recommending and now requires that safety and efficacy studies of new drugs use a double-blind design with placebo controls whenever ethical and feasible (1).

Some types of studies may be particularly liable to confounding because of placebo effects. The crossover design has the attractive advantage of using each patient as his or her own control, eliminating the problems created by variability among subjects. However, patients who receive active treatment in the first arm of the trial will have heightened placebo effects when the control is given; this appears to be a conditioning effect that occurs despite the use of a washout period to eliminate continuing pharmacologic effects *(10).*

Adverse responses to a placebo occur in almost every clinical trial and occasionally approach the levels reported for some newer, highly specific medications. Like therapeutic effects, adverse responses to a placebo may have many determinants, including negative expectations or conditioning that might result from a distrust of doctors, many failed treatment attempts, or the side-effect warnings included in the informed consent. Often, however, these adverse placebo effects may reflect spontaneous occurrences of common everyday complaints such as headaches, fatigue, insomnia, irritability, and nasal congestion *(12).*

Swartzman suggests that several validated instruments for measuring expectancy might be useful in assessing and controlling for within-group variance in side-effect reporting or subjective outcome measures. She cites several studies that have measured specific personality traits or behavioral factors and shown, for example, that lower levels of hostility predicted improved compliance and reduced side-effect

reporting in a trial of an antihypertensive medication. “Negative affectivity” (which includes neurotic or hypochrondriacal features) predicted adverse placebo responses in a double-blind study of the antidepressant moclobemide *(13)*

The fact that trial participants know they have a one-in-two or one-in-three chance of receiving a placebo also has an impact on the perceived benefit from both the active treatment and the placebo. Two sequential trials examined the efficacy of acetaminophen for postpartum pain. The first study compared acetaminophen with a placebo, whereas the second study compared acetaminophen with naproxen. The reported efficacy of acetaminophen was smaller in the first trial than in the second, presumably because the women in that study knew that they might receive a placebo and had diminished expectations of pain relief as a result *(13).* When participants do not know they are receiving placebos—as in uncontrolled case reports of treatments later shown to be ineffective—placebo response rates have run as high as 70% or 82% *(2).*

The nocebo phenomenon: “Nothing to fear but fear itself”

Therapeutic response to an inert substance is thought to follow from expectations or conditioning that associate benefit with similar interventions. But it is also possible to have negative expectations that trigger symptoms or illness in response to an innocuous stimulus—called a nocebo in this context. Voodoo death (if it is not a myth) would be an extreme example of the nocebo phenomenon, but the power of negative expectations has been observed in various experiments; for example, subjects who are given a sugar solution but told it is an emetic often respond by vomiting (11). Adverse effects in response to a placebo are common but would not be considered an example of the nocebo phenomenon, unless the individual reporting the effects was known to have negative expectations, as well as a negative outcome (11).

When a placebo does not please—Alternative trial designs

The placebo-controlled trial is fast becoming a victim of its own success. When effective treatments exist for progressive or life-threatening disorders, it is no longer ethical to run a trial in which the control arm receives no treatment. From the U.S. Food and Drug Administration’s (FDA’s) perspective, a placebo-controlled trial is not actually a requirement. As Robert Fenichel, supervisor of the Medical Office for the Division of Cardio-Renal Products at the FDA’s Center for Drug Evaluation and Research puts it, to gain approval for a new drug, “You don’t have to run against a placebo, but you have to beat placebo.”

Fenichel gives the example of thrombolytic therapy after a heart attack. Past trials have shown different survival rates in both the placebo and the active treatment arms, reflecting overall advances in care for these patients over the years. However, the difference in mortality rates between the placebo and active treatment arms has tended to be relatively constant, around 2% or 2.5%. Given the consistent difference in mortality, it is no longer ethical to run an investigational thrombolytic against a placebo. One alternative is a “putative placebo trial”, in which the new drug is compared with a standard thrombolytic; in that case, the difference between the two is compared with that 2% or 2.5%. If the confidence limits for the trial put the investigational drug within that range compared with the mortality rate observed in the control arm, then it is assumed to have beaten the placebo.

Fenichel points out that this is not the same as a so-called “equivalence trial” in which the new drug is run against a standard treatment with the assumption that demonstrating equal efficacy would meet the requirement for beating the placebo. Because the aim is to show that no difference exists between the two arms, errors in study design or shoddy methodology will favor a finding of equivalence. In other

words, you might fail to see a difference between the two arms not because the drugs are equivalent but because the study wasn't good enough to detect a difference. "So the FDA has not viewed this trial design favorably," Fenichel commented.

A third design—the dose control trial—attempts to demonstrate efficacy by comparing two doses of the investigational compound. If the higher dose is clearly better, then the drug has been shown to be active. But as Fenichel pointed out, there are hazards with this design. It may take a very large trial to show the differences between two active doses. If the trial fails to show such a difference, then the results are open to two interpretations—either that both doses are effective or that neither is—and another trial would be needed to resolve the question.

The much-criticized but common practice of prescribing antibiotics for viral colds and flu is evidence that placebo use still flourishes in contempo-rary medicine.

An appreciation of the importance and ubiquity of placebo effects offers various spin-off benefits for physicians and researchers. The difficulty of defining or predicting improvement in placebo controls illustrates how little we know about the natural history of most disorders and the possibility for spontaneous improvement. Understanding how differences in methodology, patient selection, and study design can influence observed placebo response can be valuable in eliminating potential confounders. Clearly, too, the expectations of the patient and the quality of the interaction with the health care provider can have a powerful impact on outcomes, particularly for more subjective complaints and disorders such as conditions involving chronic pain.

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