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Understanding and Harnessing Placebo Effects: Clearing Away the Underbrush

FRANKLIN G. MILLER*
National Institutes of Health, Bethesda, Maryland, USA

HOWARD BRODY
University of Texas Medical Branch, Galveston, Texas, USA

*Address correspondence to: Franklin G. Miller, PhD, Department of Bioethics, Clinical Center, National Institutes of Health, Building 10, Room 1C118, Bethesda, MD 20892, USA. E-mail: fmiller@nih.gov

Despite strong growth in scientific investigation of the placebo effect, understanding of this phenomenon remains deeply confused. We investigate critically seven common conceptual distinctions that impede clear understanding of the placebo effect: (1) verum/placebo, (2) active/inactive, (3) signal/noise, (4) specific/nonspecific, (5) objective/subjective, (6) disease/illness, and (7) intervention/context. We argue that some of these should be eliminated entirely, whereas others must be used with caution to avoid bias. Clearing away the conceptual underbrush is needed to lay down a path to understanding and harnessing placebo effects in clinical medicine.

Keywords: *clinical medicine, placebo effect*

I. INTRODUCTION

In medicine, conceptual clarity is generally taken for granted; it is seldom seen as requiring systematic investigation. Occasionally, however, we find ourselves trapped in a scientific and medical thicket not because we lack the facts, but because we are tripping over unclear or contradictory concepts and distinctions. In those situations, we have no choice but to pay explicit attention to conceptual clarification.

There is probably no medical phenomenon that has suffered more from lack of conceptual clarity than the placebo effect—a problem that persists despite the burgeoning scientific literature on this topic. This confusion is manifested in a number of distinctions that are ill conceived or that lead to common errors in reasoning. In addition to producing misunderstanding of

Table 1. Distinctions that create confusion around the concept of "placebo effect"

Verum	Placebo
Active	Inactive
Signal	Noise
Specific	Nonspecific
Objective	Subjective
Disease	Illness
Intervention	Context

the placebo effect, the use of these distinctions devalues the placebo effect, making it difficult to appreciate the potential clinical significance of promoting placebo effects in medical practice. In this paper, we will examine seven of these distinctions (Table 1). For some years, critics have suggested that the very term "placebo effect" be eliminated because of the confusion associated with it (Moerman, 2002); however, this label has become entrenched and is unlikely to be abandoned in the near future. Our goal is to clear away conceptual underbrush so that a path to a proper understanding of placebo effects opens before us. This task is especially timely given the wealth of new data on placebo effects, which we are currently in danger of misinterpreting or misclassifying (Guess et al., 2002; Benedetti, 2009).

As we address these distinctions one by one, a key reason why they interfere with proper understanding of and devalue the placebo effect will become evident. Medicine during the 20th century has tended to devalue and to dismiss the mind as contrasted with the body (Engel, 1988). Most of the seven distinctions implicitly or explicitly identify the placebo "side" of the distinction with the mind, and the contrasting "side" with the body. Today's science of the placebo demonstrates the power of mental factors, such as expectancy and conditioning, to affect bodily healing. The worldview typical of 20th century medicine simply cannot understand or accept attributing so much efficacy to the mind. The various distinctions then function as hidden ways to reassert the comfortable medical worldview by denigrating the placebo. In the process, however, the distinctions prevent us from fully grasping what today's neuroscience tells us about the placebo effect (Guess et al., 2002; Benedetti, 2009).

II. VERUM VERSUS PLACEBO

The first distinction is probably the least conceptually problematic but sets the stage for the devaluation of the placebo effect. The way that placebos are employed in clinical trials requires that there be a convenient term for whatever intervention is being compared to placebo and is *not* placebo. The common Latin label "Verum" (literally, that which is true) makes sense in that it denotes the treatment under investigation. Nevertheless, we should note that it implicitly bestows a negative connotation upon "placebo." If the

nonplacebo intervention is the *true* one, then it follows that the placebo must be false or fake. Of course, the placebo control is designed to be a fake intervention that mirrors the appearance of the verum; however, the response of patients who receive a placebo may represent a genuine therapeutic effect. By labeling the chemically potent medicine as "true" and the placebo by contrast as "false," one tempts the observer to conclude that any therapeutic effect produced by the placebo is just as false as the placebo itself is.

III. ACTIVE VERSUS INACTIVE

Placebos are incorporated into randomized trials in order to control for various sources of bias in the evaluation of the treatments under investigation. Many of these sources of bias have nothing to do with the placebo effect, properly understood. Patients may improve because of the natural history of their condition, independently of the verum or placebo intervention; alternatively, they may report improvement because they think they should have gotten better after taking a treatment or to please the investigators (report bias). Another source of bias derives from the investigator, who might miscalculate or misclassify outcomes if he was aware which subjects had received placebo and which verum, regardless of whether any subject actually improves as a result of placebo administration. Once we have eliminated all these sources of bias, we are left with the one that *does* reflect a genuine placebo effect—people who receive an "inactive" placebo but believe that they are getting a medical treatment, and experience an improvement of symptoms as a result solely of their belief state. The latter source of bias makes sense only if it is possible that some subjects will indeed improve as a result of placebo administration. This constitutes a frank admission that a placebo is not necessarily *inactive*. Moreover, thanks to recent research on neural and biochemical pathways, we now possess much more knowledge of the mechanisms by which placebos may exert their activity in different conditions (Benedetti, 2009).

Yet there remains a clear, common-sense logic to the notion of placebo as inactive—that is, we typically *know* that ingesting 100 mg of lactose (or whatever the placebo pill or capsule is made of) cannot have a pharmacological impact on the condition under investigation in a randomized trial. But common sense here is misleading. The sugar pill or saline injection is inert only in the relative sense that there is no scientific reason to think that sugar or salt contained in the placebo intervention will have an effect on clinical trial outcomes. Yet some other aspect of the intervention, or of the circumstances in which it is administered, may be causally efficacious (as we will discuss under the intervention/context distinction).

Moreover, an intervention can be pharmacologically active and still serve very well as a control condition in a randomized trial. Some randomized trials

use "active placebos" designed to mimic the side effects of the verum treatment, as in studies of antidepressants that compare them with a sedating drug not thought to have any effects on depressive symptoms (Montcrieff, 2003). In sham surgery trials, the invasive placebo control obviously is not inert or inactive.

In sum, it is a confusion to define the placebo as inactive, and doing so devalues the placebo effect. A placebo intervention that triggers a genuine placebo effect cannot be inactive. Moreover, lack of biological activity is not required for a valid placebo control.

IV. SIGNAL VERSUS NOISE

This third distinction relating to signal and noise also highlights the relativity of the concept of placebo effects. In scientific measurement, a signal is the phenomenon under investigation and noise represents background factors that interfere with detecting the signal. From the standpoint of a typical pharmacologic clinical trial, aimed at evaluating treatment efficacy, the placebo effect represents noise. In this context, the distinction is sound. It is problematic, however, insofar as it leads to the inference that the placebo effect is *inherently* noise. What is considered noise with respect to conventional clinical trials becomes the signal to be detected and evaluated from the standpoint of studies designed specifically to investigate placebo effects and elucidate their mechanisms. Placebo effects are typically examined scientifically by comparing placebo interventions with no-treatment or natural history control groups.

Our ability to understand placebo effects has been expanded recently by a series of elegant experiments involving the open versus hidden administration of a drug such as an opiate without a placebo intervention (Colloca et al., 2004). In such studies, it has been shown that the analgesic drug, administered via a hidden IV infusion mechanism at an unknown time, produces about half the pain relief as the same drug given by means of open injection. Which is signal and which is noise—the response to the open or to the hidden drug administration? It depends on whether there is an interest in measuring the "specific efficacy" of the drug or the placebo response, which in these experiments is defined by the difference between the responses of subjects to the open and the hidden administrations. The investigator who dismisses the enhanced effectiveness of the openly administered drug as "noise" seems to ignore a possibility that ought to concern her as a scientist—the possibility that in her own drug studies, a certain proportion of the effectiveness of the study drug might be caused, not by its "bare" chemical components, but rather by the fact that the subject knows he is taking it. Hence care must be taken in using the signal/noise distinction, so as to avoid the erroneous presumption that the placebo effect is inherently noise.

V. SPECIFIC VERSUS NONSPECIFIC

The characterization of the placebo effect as "nonspecific" has had remarkable staying power despite its apparent lack of logic (Shepherd and Sartorius, 1989). Kirsch pointed out that if we administer a placebo in an experiment on asthma, and some subjects experience a positive placebo response, we expect them to say that their breathing is better, not that their pain has been relieved; whereas if the experiment is for treatment of headache, the opposite would be true. That hardly seems to reflect the actions of a "nonspecific" agent (Kirsch, 1986).

The placebo/nonspecific association is rather, we suggest, best seen as a historical artifact. Rosenberg has equated the rise of modern medicine during the 19th and 20th centuries with the dominance of a notion of *specific* diseases—and, by implication, specific therapies (Rosenberg, 2002). Prior to the rise of pathological anatomy and clinicopathological correlation as a mainstay of medical science around 1800, knowing about a disease meant knowing the peculiarities of the individual who suffered from it. Under the old humoral theory, deciding on proper treatment meant knowing the patient's history, idiosyncrasies, and constitutional predispositions in great detail.

The modern notion of specific diseases, by contrast, gave rise to a medical paradigm in which diseases were seen as having existence apart from patients. One could now largely ignore the subjective experiences of the individual patient and make an *objective* diagnosis through physical signs, chemical changes, and (later) imaging studies. Rosenberg explains, "Now disease was equated with specificity and specificity with mechanism" (Rosenberg, 2002, 243). Objective medical science led to an understanding of the underlying physical and chemical mechanisms by which disease was produced, without which knowledge scientific therapy could not be determined.

As this history unfolded, a nonspecific remedy came to connote one administered in ignorance of the underlying disease mechanism, and apart from an accurate (specific) diagnosis—regardless of whether the remedy produced an outcome positive for the patient. In short, to administer nonspecific remedies was to practice unscientific medicine. This negative connotation of nonspecific nicely paralleled the belief that a placebo could alter only *subjective* complaints (that were unreliable for determining a specific diagnosis) but could not affect *objective* bodily processes (that is what the disease truly consisted of).

Rosenberg proceeds to point out the irony and paradox of the modern model of diagnosis and therapeutics. Medicine is always and inevitably caught in a tension between generalizations and individual cases. In actuality, no disease exists completely apart from the (unique) individuals who suffer from it, and no "case" of a disease is exactly like every other case in every particular. By trying to act as if diseases were purely objective, and that

patient (and physician) subjectivity could be completely eliminated by science, medicine commits excesses of reductionism and gives rise to the complaints of lack of humanism and overreliance on technology that characterized the late 20th century (Rosenberg, 2002). Furthermore, by biasing scientific medicine in favor of technological interventions targeting specific disease processes, this reductionism leads to downplaying any therapeutic benefit deriving from the context of the clinical encounter—an issue that we discuss further below.

The randomized controlled trial also operates within this prevailing medical paradigm. It focuses exclusively on aggregate outcomes in groups of patients and treats results in the placebo arm as "nonspecific" effects that need to be factored out in order to detect "specific" treatment efficacy. Sullivan (1993, 227) aptly summarizes the orientation of scientific medicine: "Medical scientists set themselves apart from the doctor-patient relationship in order to obtain a knowledge that is stripped of personal elements. This allows the development of a context-independent expertise and therapeutic technology that can be delivered by a profession to its patients."

Finally, Benedetti has recently reviewed the extensive scientific literature showing that a variety of underlying neural and biochemical mechanisms can be demonstrated for placebo effects in many different organ systems (Benedetti, 2009). Given the specificity of these mechanisms of placebo effects, it follows that placebo effects are no longer nonspecific in any meaningful sense. In any event, the specific/nonspecific distinction says much more about our prejudices about what counts as "real" medical knowledge than it does about the workings of placebos. This distinction also needs to be cleared away to make progress in understanding and harnessing the placebo effect.

VI. OBJECTIVE VERSUS SUBJECTIVE OUTCOMES

Each of the next three distinctions has some validity in elucidating placebo effects. They nevertheless pose conceptual problems to the extent that they portray as absolute dichotomies phenomena that actually exist as overlapping categories. More importantly, they also have an evaluative dimension in which the first component of the distinction has been traditionally seen as superior to the second. Because the placebo effect is associated with the inferior component, these distinctions further contribute to devaluing the placebo effect.

The objective/subjective distinction is already implicit in other distinctions, especially the specific/nonspecific distinction, as we have noted. The strongest and most consistent evidence of placebo effects, both in clinical trials and laboratory experiments, comes from studies of conditions with subjective outcomes, most notably pain (Benedetti, 2009). Pain is an inherently

subjective experience, though it is typically expressed in behavior detectable by others. With the advent of brain imaging technology, objective neural correlates of pain experience can be investigated under experimental conditions. A great deal has been learned about the neurobiological mechanisms of placebo analgesia in recent years, including release of endogenous endorphins and other neurotransmitters. Similarly, the nocebo effect in the area of pain—the obverse of the placebo effect derived from expectations of experiencing increased pain—seems to be mediated by cholecystokinin (Benedetti et al., 2007). It follows that even with respect to pain, placebo effects are not purely subjective. Moreover, reduction in pain from a placebo effect may also lead to improvement in objective outcomes. For example, relief of angina or arthritic pain produced by a placebo intervention can be associated with objectively measurable functional improvement, such as the ability to walk or undergo other forms of physical exertion.

The ability of placebo interventions to produce objective biological outcomes in laboratory experiments has been abundantly demonstrated. The clinical significance of placebo effects, however, remains in question. What types of patient outcomes are reasonable to expect from credible placebo interventions? Can placebos generate cures, slow the progression of disease, or change the course of disease so that symptoms are brought under control? To date, very little reliable evidence exists that placebo interventions can have such lasting disease-modifying effects (Miller et al., 2009). Accordingly, one hypothesis concerning the scope and power of the placebo effect is that it works to change the illness experience of patients rather than affecting the course of disease.

VII. DISEASE VERSUS ILLNESS

The distinction between disease and illness is important (Eisenberg, 1977). Patients may have detectable disease without any symptoms that make them feel sick or disabled. Conversely, they may feel ill without the presence of any disease that is detectable by medical diagnosis. Biomedicine has been justly criticized for its almost exclusive focus on disease as an (objective) biological phenomenon, with relative neglect of the patient's (subjective) illness experience (Kleinman, 1988). Interest in the placebo effect and enhancing placebo responses in clinical practice offers one perspective on redressing the balance. Nevertheless, the distinction between disease and illness should not be understood as an absolute dichotomy. One obvious overlap lies in symptoms that cause distress, which straddle the disease/illness divide. They often consist of experiential effects of pathophysiological processes, as in pain or wheezing related to inflammation.

Are placebo effects limited to amelioration of the symptomatic manifestations of disease? Earlier commentaries suggest that the placebo effect can alter illness but never disease (Spiro, 1986). The information we now have available about both known and hypothesized neural pathways, which include

catecholamine/cortisol and psychoneuroimmune pathways, renders implausible the hypothesis that the placebo effect always stops short of an impact on an underlying disease process (Eskandari and Sternberg, 2002). Clearly, the answer lies in further empirical investigation. To declare that the placebo effect solely influences illness experience seems at this stage premature.

VIII. INTERVENTION VERSUS CONTEXT

A fruitful way of characterizing placebo effects is to see them as deriving from the context of clinical interventions (Miller and Kaptchuk, 2008). This has again been made vivid by the experiments comparing open and hidden administration of drugs. The context of receiving a known effective analgesic agent, for example, powerfully affects its ability to relieve pain. In general, when placebo interventions produce therapeutic benefit, the benefit cannot be attributed to the inherent (chemical) properties of the intervention. Rather, it is the simulation or ritual of treatment and the associated context that produces clinical improvement by some psychological mechanism such as expectation or conditioning. Di Blasi et al. (2001) suggested that placebo effects should be renamed "context effects."

Though useful, the intervention/context distinction carries over some connotations from the biomedical orientation to placebo reflected in the first four distinctions discussed above. (This is not surprising because it contains vestiges of the specific/nonspecific distinction.) Biomedical therapeutics emphasizes technological interventions to treat disease. Here is where the power of medicine resides. The treatment context is essentially a vehicle for delivering the technological intervention. Furthermore, the minimal standard of therapeutic value is superiority to placebo, making the placebo effect itself of no therapeutic interest.

Interest in the placebo effect as a clinically significant phenomenon demands a gestalt shift in biomedicine. What has been relegated to the background of context needs to be placed in the foreground as a target of scientific investigation and therapy. To the extent that medicine has already begun to embrace this gestalt shift, and now regards research into the context of therapy as worthy of scientific attention, then the intervention/context distinction can be employed with a minimum of confusion. However, to the extent that medicine continues to resist the gestalt shift, and continues to try to relegate discussion of therapeutic context to the background and to second-class status, then the intervention/context distinction will help to perpetuate negative stereotypes relating to the placebo effect.

IX. CONCLUSIONS

Table 2 summarizes our assessment of the seven distinctions.

Table 2. Summary of the assessment of the seven distinctions

Distinction	Recommendation
Verum/placebo	Retain; be aware of negative connotation
Active/inactive	Eliminate
Signal/noise	Use with caution
Specific/nonspecific	Eliminate
Objective/subjective	Use with caution; reevaluate in light of new research
Disease/illness	Use with caution; reevaluate in light of new research
Intervention/context	Retain and explore further; be aware of possible negative connotation

Eliminating some of these distinctions, and using the remaining ones with appropriate care and understanding, will do much to clear away the underbrush that has thus far hindered our understanding of placebo effects and appreciation of their potential clinical significance. We hope for several good results once the path ahead is clear of obstacles. The recent wave of very promising research into underlying placebo-effect mechanisms should be complemented by clinically oriented translational research, aimed at understanding how to improve the context of medical care, so that physicians can learn new strategies to enhance dimensions of the context to optimize therapeutic outcomes. Instead of being relegated to the "art of medicine," the placebo effect can become a therapeutic target guided by scientific research, thus bringing it within the orbit of evidence-based medicine.

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