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# Placebo Response: A Consideration of its Role in Therapeutics

**Richard L. Kradin**

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**Abstract** Placebo effects are a potentially inherent element in all treatment responses, and as such, they play a critical role in determining what is "therapeutic." However, the placebo response is also an area of substantial controversy. In the present review, the scientific issues that influence placebo effects are elucidated. The evolution of the concept of placebo and how this has affected its historical importance in therapeutics is considered. The importance of placebo responses in psychiatry and psychotherapy is specifically examined, and recent progress in determining the cognitive and neurobiological bases of placebo effects is reviewed. Finally, it is argued that the placebo response is a cardinal mind–body pathway that promotes salutogenesis and that evidence suggests its relationship to central nervous system activities that are responsible for the concomitant development of positive affects and somatic procedural memories that govern states of mind/body well-being during maternal–infant attachment.

**Keywords** Placebo response · Placebo effects · Therapeutics · Reward system · Dopamine · Antidepressants · Child development

## Introduction

Virtually every year, one can read several new reports that suggest the possibility that our current views concerning what is evidence-based therapy need revision. A variety of popular therapeutic interventions that were once widely accepted often prove to be "nothing but" placebos when examined critically. Take, for example, a recent report showing that arthroscopic surgical removal of degenerated cartilage fragments is no more effective in providing long-term pain relief than a sham surgery in which the skin of the knee is incised and no further surgery is performed [1]. What appear to be perfectly rational approaches based on our current understandings of anatomy and physiology can be undermined by controlled experimentation. How is one to explain such remarkable findings, let alone predict them?

The placebo response is perhaps the greatest enigma of therapeutics. Once the primary mode of therapeutic healing, it has in modern times become a confounding factor in the quest to establish an evidence-based science of therapeutics, and a target of skepticism and derision [2]. Much of the obscurity that surrounds the placebo response is shared within the larger domain of so-called mind–body interactions. Despite the recognition that humans are privy to both mind and body, the mind/body split continues to plague our ability to integrate these different modes of experience.

As one begins to probe the science of therapeutics, particularly the phenomenology of placebo-associated effects, it becomes evident that much of what we take for granted concerning therapeutics is uncertain. Like the naïve young boy in Hans Christian Andersen's fairy tale "The Emperor's New Clothes," placebo effects may be all that stand between us and our illusions concerning what constitutes effective treatment.

## Definitions and Pitfalls in the Science of Placebos

One problem in the domain of placebo science has been defining the relevant terminology. In his recent text,

R. L. Kradin (✉)
Departments of Medicine and Pathology, and Center for Psychoanalytic Studies, Massachusetts General Hospital, Warren 253,
Boston, MA 02114, USA
e-mail: rkradin@partners.org

Benedetti [3••] suggested that the terms *placebo effects* and *placebo responses* may be used interchangeably, as they often are in practice. For reasons to be explained in detail, I take exception with this view, and in the present review, I have adopted the definitions explicated in my own recent text on this topic [4••]. Accordingly, a *placebo response* is defined here as: (1) a complex mind–body interaction (2) evoked within a therapeutic dynamic, in which (3) the offer to treat (4) a preexisting dysphoric condition with (5) an inert or ineffective intervention (ie, a *placebo*) (6) results in the restoration of well-being.

Whereas it is possible that "placebo-like" responses may develop in other contexts, for the purposes of critical analysis, the role of an interpersonal treatment dynamic is judged to be critical [5]. This eliminates reports of "placebo responses" in nonhuman animals [6] and excludes therapeutic responses that may occur outside the context of an offer to treat [7]. However, because an offer to treat may also include the administration of nonplacebos, only those treatment situations that include a known placebo can help operationalize the response for critical study.

Whether there are one or many placebo responses remains a matter of controversy. Benedetti [8] has suggested that there is a multiplicity of distinct placebo responses; this perspective follows from his conclusion that there is no meaningful difference between placebo responses and effects. Although this may be correct, I have suggested alternatively that that a unitary placebo response could mediate diverse placebo effects if a neural mechanism for salutogenesis is linked to various somatic states of well-being by procedural memories encoded during infant development [9]. Under this condition, a variety of learned cognitive and behavioral cues could yield a self-ordering of somatic physiology together with the mental experience of well-being.

The cardinal placebo effect and its *sine qua non* is the subjective feeling of well-being. The subjectivity of this effect has led some skeptics to dismiss it as imaginary (ie, fictitious). However, advances in neuroscience demonstrating that hitherto subjective "black box" mental states are associated with neural activities that can be experimentally measured have recently challenged earlier distinctions between what is "subjective" and "objective." Positron emission tomography (PET) and functional MRI have demonstrated specific changes in the central nervous systems of patients reporting placebo responses, including changes in the activities of specific brain structures and neurotransmitters that are comparable, if not identical, to those seen in individuals responding to nonplacebo interventions [10, 11]. Such observations refute the notion that mental states have no material grounding. However, it is critical to recognize that the psychology of placebo responses is not isomorphic with neurological activities but instead represents an emergent property of the brain's complex activities that can in turn influence subsequent nervous system events.

## Why Does Skepticism Concerning Placebo Responses Persist?

Perhaps the greatest obstacle to the acceptance of placebo effects is in establishing a placebo as the cause of a salutogenic response by excluding other causal contributions. A variety of factors mimic placebo effects, including the normal waxing and waning of physiologic distress [12], regression to the mean, and bias in reporting [4••]. Because few clinical trials adequately control for these factors, skeptics are correct in insisting that there is no nonfalsifiable evidence—a cardinal criterion for accepting a scientific finding according to the logical positivist school of philosophy of science—to compel acceptance of placebo responses. However, few phenomena in medical science are held to such a degree of rigor.

Defining the conditions under which the placebo effects can be predicted is difficult and may even be, for reasons to be discussed, impossible. As Shapiro [13] showed, there is no psychological phenotype that corresponds to a placebo responder. Another obstacle to the predictability of placebo effects is methodologic. Although randomized, placebo-controlled trials currently constitute the gold standard for determining what is therapeutic, this design actually detracts from one of the major psychological factors that promote placebo responses: expectancy. In the naturalistic treatment setting, patients receiving a placebo believe that they are receiving a potent intervention, whereas in the randomized controlled trial (RCT), patients are informed that the chance of that occurring is 50%, depending on whether they are randomly assigned to the treatment or placebo arm of the trial [14].

Inconsistencies in reproducing placebo effects in the same individual are also well-recognized. Under comparable conditions, an individual may develop placebo effects on 1 day, but not the next [15]. This has prompted some skeptics to question the scientific veracity of these responses. However, it is possible, and indeed likely, that the central nervous system mechanisms that mediate placebo responses are sufficiently complex to be governed by probabilistic nonlinear dynamics, in which small changes in initial conditions greatly influence outcomes. Meteorologists confront similar limitations in making long-term weather predictions, and it can be reasonably argued that the complexity of the human nervous system exceeds that of the weather.

Controversies have surrounded placebo effects since the inception of the concept of a placebo. A challenge to

placebo effects was recently raised by Danish epidemiologists Hrobjartsson and Gotzsche [16]. These investigators argued, based on a meta-analysis of 130 trials that included placebo effects, that the evidence to support their potency was limited, and that placebo effects were most evident in trials that reported subjective improvements in pain relief. The implication was that placebo responses were primarily psychological (ie, limited to changes in mental states) and were not convincingly linked to physical changes.

The article generated a wide variety of pointed responses. Critics argued that the study was flawed in its design, as it included trials reporting highly diverse outcomes in a wide variety of conditions, a fact that may limit the accuracy of the conclusions derived from meta-analyses. In an editorial that accompanied the article, Bailar [17] argued that the placebo response was unlikely to be dismissed by most clinicians who have been convinced by their anecdotal experiences that placebo responses are common and at times potent.

## Evolution of the Concept of Placebo

The notion of the placebo response has undergone substantial modifications with time. As Shapiro and Shapiro [15] noted in their seminal study of the topic, virtually all therapeutic effects in antiquity were attributable to placebo responses, as few of the apparently efficacious interventions detailed in ancient pharmacopoeia have proven to have therapeutic effects that exceed those of placebos. Only with the advent of the scientific method did it become possible to conceive of a therapeutic intervention as placebo. The word itself is derived from the Hebrew term *ethalekh* in Psalm 116, meaning "I will walk." However, St. Jerome's Vulgate translation rendered the Hebrew term *placebo,* changing its meaning to "I will please." Medieval Roman Catholic priests chanted this psalm as part of the Vespers Prayer for the dead, for mourners and for a fee. The Reformation in its polemical stance against the excesses of the Roman Catholic Church viewed the term *placebo* pejoratively, and this sense has continued to inhere to the term. This is affirmed by the first known reference to placebo in the 18th century as a "commonplace" treatment [4••].

The knowing administration of placebos was common among practitioners of medicine until the middle of the 20th century [18]. Until that time, physicians were convinced of the efficacy of placebos in select patient populations. However, as medical practice became increasingly evidence based, attitudes toward placebos soured. Richard Cabot, a major figure in early–20th century medicine, warned fellow physicians to avoid placebos, as their administration was unscientific and unethical.

A critical change in the status of placebos occurred when the RCT was established as the gold standard of therapeutic efficacy. As part of its design, placebos were adopted as the fundamental control, and therapeutic efficacy was defined as the ability of the tested intervention to outperform placebo. This indicates the uncomfortable fact that there had until then been no foolproof way to determine what was effective treatment. As a consequence, placebo effects achieved their current reputation as confounding factors in the analysis of controlled trials. Simply put, the higher the placebo response within a trial, the greater the difficulty is in establishing a new treatment as effective.

However, even the RCT is fraught with difficulties. Many clinical trials are inadequately blinded with respect to placebos such that patients and trial coordinators are too often aware of the differences between intervention and placebo arms [19]. Another rarely considered problem is how to assess placebo effects when a previously established therapeutic intervention is administered under conditions outside an RCT. The method of induction that is generally applied suffers from being based on limited population samples. In reality, it is virtually impossible to extend the findings of a randomized trial with accuracy.

## Placebos and Psychiatry

From the perspective of those primarily interested in placebo mechanisms, what is perhaps most noteworthy is that placebo effects are rarely absent in clinical trials and may range as high as 90%, particularly in clinical trials related to the psychopharmacology of anxiety and depression. Despite the inability to identify a phenotype for a placebo responder, Shapiro [13] did find that patients with anxiety and mild depression were prone to develop placebo effects. This has been established repeatedly in clinical trials. Placebo researchers Sapirstein and Kirsch [20] have argued that antidepressant effects may in fact be no greater than those of placebos, and whereas evidence seems to suggest that psychotropic medications outperform placebos, at least somewhat, when "active placebos"—drugs that produce interoceptive sensations that suggest an element of bioactivity—are used in antidepressant trials, the selective advantage of antidepressant medications may be lost [21••].

## Placebo Responses Differ Based on Disease

Another area that has not received sufficient attention is that of the differences observed in placebo rates in trials of different disorders [4••]. In the psychiatric literature, it is recognized that placebo effect rates are low in patients with obsessive-compulsive disorder as compared with patients

with other anxiety-based Axis I disorders [22]. Most studies suggest that placebo response rates in attention-deficit/hyperactivity disorder and schizophrenia are also substantially lower than those seen in anxiety and depressive disorders [23]. The reasons for these differences are not clear. They may reflect primary or acquired abnormalities in the hedonic mechanisms of patients with obsessive-compulsive disorder, altered defective reward pathways in attention-deficit/hyperactivity disorder [24], and cognitive defects in schizophrenia that limit the psychological capacity to construe meaning in therapeutic situations, the latter being strongly implicated by Moerman [25] in the development of placebo effects.

## Psychological Factors in Placebo Responses

Several psychological factors have been implicated in the development of placebo responses. These include expectancy [26], meaning [27], hope [14], faith [28, 29], and belief [30] and have all been accorded a role in placebo responses. In his now-famous article "The Powerful Placebo," Beecher [31] suggested that placebo responses were dependent on the attitude that patients adopt toward caregivers. Studies have shown that perceived competence, concern, empathy, and trust by patients with respect to caregivers all increase the likelihood of positive therapeutic outcomes [5, 32]. Interestingly, many of these factors are identical to those that appear to promote an effective therapeutic alliance and holding environment within the practice of psychotherapy. The controversial claim that psychotherapy is a placebo effect may result from parallels between what constitutes an effective psychotherapeutic intervention and those practices that tend to promote placebo effects [4••, 33, 34]. These include increased time spent with patients, empathic concern, and a milieu of established trust between patient and caregiver. Increased concern for these factors may help explain the persistent desire of many Americans to seek out alternative/complementary practices in addition to or in lieu of traditional allopathic medicine despite the fact that most studies offer little evidence that these practices are superior to placebo interventions. Nocebo effects (ie, dysphoric responses to the offer to treat with a placebo) appear to parallel the "negative therapeutic reactions" seen in psychotherapies and may, as I have suggested, reflect defects in hedonic mechanisms [5].

## The Neurobiology of Placebo Responses

Recent studies have demonstrated specific changes in the central nervous system of patients reporting placebo responses. Among patients treated with a selective serotonergic reuptake inhibitor or placebo, those who reported therapeutic responses to the placebo also exhibited central nervous system changes by PET that were indistinguishable from those who had received selective serotonin reuptake inhibitors [11]. Mayberg et al. [10, 35] and Muller [36] have examined the functional neuroanatomy of placebo responses by functional MRI. Benedetti [37] demonstrated a critical role in opiate pathways in responses to placebo analgesia.

Another area of interest has been placebo-induced increases in dopaminergic activities as judged by PET scanning in patients with Parkinson's disease. De la Fuente-Fernandez et al. [38] linked expectancy with dopamine release in placebo responses seen in patients with Parkinson's disease, and sham placebo surgery has yielded increased levels of dopamine in the central nervous system and alleviated symptoms of the disease for prolonged periods, suggesting that placebo effects can be long lived [39].

What conclusions can be gleaned from these recent studies? Perhaps the most important is the long-awaited proof that placebo responses are associated with objective changes in physiologic activities, effectively dismissing critics who hold that placebo responses are imaginary. The second is that the effects observed are indistinguishable from those evoked by accepted therapeutic interventions, suggesting that comparable, if not identical, pathways are activated in these responses. The families of neurotransmitters that have been shown to be involved in placebo responses (ie, dopamine, serotonin, opioids) are the same as those recognized to play a role in salutogenesis and in central nervous system reward pathways [4••].

Finally, and perhaps most worthy of further exploration, is the finding that the structures and neurotransmitters involved in placebo responses are similar to those implicated in the early development of positive affects during attachment [40]. The possible link between placebo biology and that of psychosomatic development may prove to be a rich explanatory source for how an innate neurological capacity for salutogenesis is fostered or hindered by the psychology of early experience.

## Conclusions

Placebo effects are an ineradicable aspect of therapeutics. They contribute to the process of healing in ways that might best be termed *predictably unpredictable.* Whereas a great deal has been written about the positive contributions of placebo effects to healing, much with little scientific evidence to support the claims made, there is currently little clarity as to how to "harness" them in the service of healing. Certainly, factors that have been implicated in

positive therapeutic outcomes, including empathy, attention, positive expectations, the construal of meaning, faith, belief, and trust, also appear to promote placebo effects. These factors can also at times yield idiosyncratic effects based on what will almost certainly eventually prove to be the complex interactions between genes and environment. Undoubtedly, new insights into the neurobiology of subjectivity, as well as the application of new analytical approaches to complex neural systems, will eventually help unravel the mystery of placebo effects. Until then, the ancient Hippocratic maxim (Aphorisms 1) may be apropos:

"Life is short
Art is long,
Opportunity fleeting,
Experiment fallible,
Judgment difficult."

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