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Placebo effects and placebo responses: Filling the interstices with meaning.

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Abstract:

Reviews the book, "Placebo effects: Understanding the mechanisms in health and disease" by Fabrizio Benedetti (see record 2009-02085-000). Benedetti's book is a lucid and extensive review entrenched in the neuroscience of placebo research and heralding the importance of this area of study. Benedetti addresses his book to medical students, doctors, and nurses, who will surely find his compilation a useful source of timely information. He also addresses his book to social scientists, but they may find his exposition unbalanced, with only cursory allusions to relevant placebo studies from their purview. This latter crowd would be wide of the mark to take Benedetti for a rabid fan of neurobiological reductionism because his superb research and careful presentations suggest that he is keenly aware of other perspectives, including those of Anne Harrington, Daniel Moerman, and Irving Kirsch. Alas, the field is vast and the cover of Benedetti's book—depicting a structural brain scan, an electrophysiological trace, and molecule charts—may cue the intelligent reader to the author's choice of tenor. This choice was likely both strategic and pragmatic. With definitional imprecision of elementary terms continuing to present a major shortcoming, however, Benedetti must realize that many practitioners simultaneously construe placebos as a screening tool to unmask malingering, a method to control for psychogenic effects, and a compelling example of the power of the mind (Harrington, 2006). While Benedetti acknowledges that we should sort out ethical and practical conceptualizations regarding placebos in order to forge clear directions for future research, placebos—including their responses and effects—will likely remain a moving target until we refine an overarching approach to this burgeoning field. (PsycINFO Database Record (c) 2009 APA, all rights reserved)

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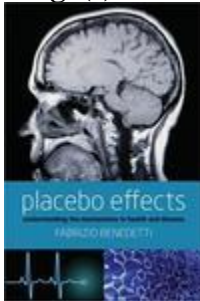
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Placebo Effects and Placebo Responses : Filling the Interstices With Meaning

Review By: [Amir Raz](#)
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Review of: Placebo Effects: Understanding the Mechanisms in Health and Disease
By: Fabrizio Benedetti, New York: Oxford University Press, 2009. 295 pp. ISBN 978-0-19-955912-1. \$59.95

Has your doctor discussed with you the value of placebos? Fabrizio Benedetti is a physician and a leading placebo researcher who answers this question in letter as well as in spirit in his recent book *Placebo Effects: Understanding the Mechanisms in Health and Disease*. Gradually emerging from the shadows of clinical trials, placebos have become the objects of rigorous scientific study over the past half century.

While these investigations have helped further our understanding of what placebo effects are and how they occur, placebo effects have also garnered confusion and bias. Benedetti's book is a lucid and extensive review entrenched in the neuroscience of placebo research and heralding the importance of this area of study. Investigators adopting the reductionist lens of neurobiology, however, cannot arrogate to themselves the entirety of placebo research; the sparse mention of findings from other fields of science—social science—has slightly marred our delectation of this wonderful book.

Imprecision regarding the definition of *placebo effect* is a crucial problem. Individuals typically imagine placebos as sugar pills, inert substances given to satisfy patients or serve as controls in a drug trial. If one expands on this notion, an inactive placebo becomes synonymous with ineffective or nonspecific medical treatment, including inert pills, sham surgeries, or saline injections. Thus, the *placebo effect* engulfs the psychobiological phenomena attributable to the placebo and treatment context while another term, the *placebo response*, designates the improvement occurring in the placebo group—which may be due to spontaneous remission or regression to the mean (Kirsch, 2003).

Many researchers and clinicians conflate placebo effects and placebo responses into one transposable term. Even Benedetti himself—although explicitly raising the issue of terminological confusion—is inconsistent throughout his exposition. He first defines placebo effect and placebo response one way (p. 5) before swapping the two definitions liberally (pp. 5–6) and finally deciding to “use the two terms interchangeably” (p. 31). Lack of uniformity underscores inherent ambiguity and fosters a climate of uncertainty. Moreover, it may adversely influence the direction and nature of research efforts. In addition, placebo-like effects often occur without the administration of an actual placebo, highlighting the central role of expectation and suggestion in placebo-related phenomena.

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Researchers attribute placebo effects to three different mechanisms (Hróbjartsson, 1996). Some effects, especially relating to the immune and endocrine systems, are due to conditioning types of processes. For example, Benedetti discusses studies involving rats showing that a flavored liquid had immunosuppressant effects after being repeatedly coadministered with an immunosuppressant drug.

Characterizing placebo effects as classical conditioning, however, requires caution because the extrapolation from animal models to humans may be tenuous. Evidence suggests that human conditioning—being but one way to create response expectancies—may be of interest only secondarily (Kirsch, 1985). Even when verbal suggestion is unable to reverse the effect of a saline injection on hormone levels following repeated injections of an active drug (Benedetti et al., 2003), the powerful context of an injection remains present, rendering results compatible with the response expectancy model. While these considerations hardly advocate a dismissal of the conditioning model, they do underscore the care required in defining and categorizing experimental results of placebo effects.

The promise of positive results in placebo analgesia—the oldest and most effective area of placebo research—often overshadows other areas of placebo research. Administration of a placebo with patient expectation of pain relief typically activates the endogenous opioid system. Conversely, administering active analgesics via hidden administration—that is, without the patient’s awareness—significantly reduces their effectiveness (pp. 71–72). Although Benedetti’s exposition spans topics ranging from Parkinson’s disease to cardiovascular pathologies and sports medicine, the pain model resurfaces as a source for informing the entire presentation, perhaps at the expense of insight into other and more recent areas of placebo research.

A third approach to placebo effects—the one scantily acknowledged in Benedetti’s book—draws on social science and pertains to concepts such as the meaning shrouding a response and the context surrounding the medical encounter (Moerman, 2002). The meaning model attempts to explain why red placebos stimulate whereas blue placebos calm, why more placebos work better than few, and why more expensive placebos work better than cheaper ones. Although many researchers as well as practitioners view placebo analgesia as the dominant paradigm to explain placebo effects, the meaning model is arguably the most comprehensive and overarching. Moreover, in placebo analgesia, the expectation of relief actually triggers endogenous opioids.

Active placebos—substances recommended solely by their salient side effects—can play a prominent role in exploring the meaning model of placebo effects. The common lack of side effects following the ingestion of an inactive placebo can lead to “unblinding” in clinical studies: Subjects may suspect receiving the control substance, which decreases expectation and greatly neutralizes potential placebo effects (Stone, Kerr, Jacobson, Conboy, & Kaptchuk, 2005). The use—or lack thereof—of active placebos may reveal decreased drug efficacies and increased placebo effects (Moncrieff, Wessely, & Hardy 2004). Furthermore, the use of inactive placebos insufficiently controls for the portion of the response in the treatment group attributable to the experiencing of side effects, thus potentially inflating drug efficacies and undermining placebo effects (Moncrieff et al., 2004).

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The power of side effects to independently influence a patient's experience underscores the psychosocial aspect of placebo effects. People typically construe side effects as evidence of the potency of a substance or drug (Thomson, 1982), and physiological effects reinforce the treatment context. But what if the active placebo is actually efficacious? Could active placebos be veridical drugs? The definition of *placebo* becomes even more problematic as scholars and practitioners obfuscate the line delineating effective from ineffective medication. Thus, active placebos prove useful for exploring the full extent of placebo effects, even if ethical concerns prevent many researchers from using active placebos in studies.

One persistent obstacle to elucidating the psychosocial component of placebo effects is a bias toward reductionism in medicine and neuroscience. Benedetti broaches with his readers the importance of the psychosocial context around any therapy (p. vii), but before long his exposition thrives almost exclusively on neurobiological mechanisms. Ample psychological and behavioral evidence points to the powerful and unique role of suggestion and expectation in eliciting placebo effects (e.g., Marlatt & Rohsenow, 1981). The prevailing tendency, nevertheless, is to try to understand the psychological aspect of placebo effects strictly in terms of "anatomy, physiology, cells and molecules" (p. vii). Unfortunately, reducing neuroscience to biology remains a tall order sidelining considerable psychosocial insights.

Scholars and educators stand to benefit from Benedetti's excellent tome. The increasing prominence of placebos bodes well for the future of medical care, and Benedetti's book communicates the powerful and diverse healing potential of placebos. The abridged term *psychosocial*—used throughout the book to describe placebo effects—speaks to their ability to tie disciplines together and to chart a common ground among the social and medical sciences.

Benedetti addresses his book to medical students, doctors, and nurses, who will surely find his compilation a useful source of timely information. He also addresses his book to social scientists, but they may find his exposition unbalanced, with only cursory allusions to relevant placebo studies from their purview. This latter crowd would be wide of the mark to take Benedetti for a rabid fan of neurobiological reductionism because his superb research and careful presentations suggest that he is keenly aware of other perspectives, including those of Anne Harrington, Daniel Moerman, and Irving Kirsch.

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