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SEMINARS IN PAIN MEDICINE

# Making Space for the Placebo Effect in Pain Medicine

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**A broad view of the "placebo effect" incorporating neurobiology, individual psychology, epistemology, history, and culture deeply enriches our understanding of these complex and powerful forces and, indeed, urges us to abandon that narrow and logically inconsistent concept for a much more interesting one. We review some of the data and background for such a contention in a thoroughly interdisciplinary way showing how differently presented, but equally "inert," treatments (2 placebo tablets versus 4, for example) can have different effects; how the same inert treatment can act differently in different historical times and cultural places; and how crucial is the attitude of the clinician in shaping these intensely meaningful forces. These matters, which typically are left to chance, to ideology, or to market forces, should be embraced by the scientific community. We believe that fundamental insights into human biology remain to be discovered in this area.**
**Semin Pain Med 3:2-6 © 2005 Elsevier Inc. All rights reserved.**

**KEYWORDS meaning response, placebo, placebo effect, culture, history, pain**

The spring of 2001 saw the publication of an article about the placebo effect that briefly generated an extraordinary buzz with its claim that the effect did not exist. Using a meta-analysis of medical trials with 3 arms—treatment group, placebo group, untreated group—the authors, Hróbjartsson and Gøtzsche, argued that there were no differences between outcome in placebo and untreated groups. They concluded that there was "little evidence in general that placebos had powerful clinical effects," and certainly that there was "no justification for the use of placebo."[1] Although the scientific community faulted the report on a wide range of methodological and interpretive issues,[2] the study nevertheless received widespread and quite favorable media coverage. Indeed, an editorial that accompanied the original article (and was, for many journalists, the only source of their information about its content) said that the authors had shown that placebos were like the Wizard of Oz: a fraud "who was powerful because others thought he was powerful."[3]

The media reaction to the Hróbjartsson and Gøtzsche article is sociologically interesting, but it is also not without irony. Its publication coincided with a time in medical history when laboratory science had just begun to provide us with powerful new evidence that many people receive significant benefit when they are given inert treatments. The point that still remains imperfectly understood is that the inert treatments themselves are not responsible for that benefit. That is to say, the "active" ingredient responsible for the placebo effect does not lie in the placebo itself, but rather in the meaning—the cultural salience—patients project onto it.

In recent years, no one has demonstrated this fact in the laboratory more elegantly and persuasively than Fabrizio Benedetti in Turin, Italy. In one study of 4 different conditions (pain, anxiety, Parkinsonism, and heart rate), he treated some subjects openly with active drugs appropriate to the condition. A second set of groups received hidden infusions of the same drugs: there were no visual cues suggesting they were receiving relief from their conditions and no reassuring words. The openly treated groups responded significantly more to these active medications than did the surreptitiously treated ones.[4] Note that there were no placebos in this study; therefore, there could be no "placebo effects."

Why did these differences occur? Because, we suggest, only one group had the opportunity to note and "make meaning" out of the experience This is why one of us (D.M.) has long agitated for replacing the term "placebo effect" with the alternative term "meaning response."[5] Simply receiving an inert tablet, or an inert injection, can indeed be an inert experience. When, however, a patient receives a meaningful communication along with his or her inert tablet or injection, that is, a few words or an impressive visual display of medical competence, positive changes can happen.

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1537-5897/05/$-see front matter 
doi:10.1016/j.spmd.2005.02.008

This insight raises the further possibility that what we call "placebo effects" might regularly occur in setting in which no placebos (inert medications) are in play. In fact, there is good evidence for this. In one study, 835 women who regularly used over-the-counter analgesics for headaches were placed randomly into 4 groups: one group received unlabeled placebo; 1 received placebo marked with a widely advertised and widely-available brand name, "one of the most popular. . . analgesics in the United Kingdom and supported by extensive advertising"; 1 received unbranded true aspirin, and 1 received branded true aspirin. Each subject was asked to note the amount of headache pain relief experienced an hour after taking the pills.[6] The results showed, unsurprisingly, that aspirin was more effective than placebo. More surprising, perhaps, was the finding that brand-name aspirin was more effective than generic aspirin, and brand-name placebo was more effective (55% reporting improvement on a 2-, 3-, or 4-point scale) than generic placebo (45% reporting improvement). Aspirin relieves headaches, but so does the knowledge that one is taking pills whose efficacy one has learned to trust from television advertisements. In this study, a brand name itself turned out to have independent active properties, enhancing the effects of both placebos and true aspirin.

It is important to recognize that these effects can be of impressive magnitude that they can make a real difference and be of real clinical significance. In commenting on an earlier and similar study addressing only pain,[7] Price[8] noted that although the increase in pain relief in that study was by itself probably not clinically significant, it was important nonetheless: "Both pain research scientists and the pharmaceutical industry go to the ends of the earth to make improvements of this magnitude [to existing drugs]. Adding one or two sentences to each pain treatment might help to produce them."

The idea that one does not need to deceive to produce a placebo effect—that, in fact, a clinician can produce one by honestly informing a patient of a pending, effective treatment—helps explain something else: why it is that a physician's enthusiasm for a treatment turns out to be a critical variable in determining its effectiveness on a patient's condition. Gracely et al[9] have described a phased experiment in which dental patients were told they would receive one of the following: (1) placebo (which might reduce the pain of third-molar extraction, or might do nothing), (2) naloxone (which might increase their pain, or do nothing), (3) fentanyl (which might reduce their pain, or do nothing), or (4) no treatment at all. Subjects were all recruited from the same patient stream, with consistent selection criteria by the same staff.

In the first phase of the study, clinicians (but not patients) were told that there had been administrative problems with the study protocol and therefore that it was not possible after all to give any of the patients fentanyl (the only "true" active analgesic in the study). In the second phase, clinicians were told that the problems had been cleared up and that some patients would now indeed receive fentanyl. The results showed that all the placebo-treated patients during the first phase of the study—during which the clinicians all "knew" there was no chance they might be getting an effective treatment—received no relief from it. After an hour, their pain reports had increased significantly. In the second phase of the study, however, when the clinicians "knew" that some patients might now be getting an effective treatment, a significant proportion of the placebo-treated patients began to experience substantial pain reduction. Current methods of analyzing the nuances of honest and convinced versus skeptical and deceptive communications are not yet sophisticated enough to help us understand how, in a double blind trial, physicians elicited these different effects from their patients. Clearly, however, they did.[9]

The principle demonstrated here seems to generalize to contexts outside of pain relief. The healing rates of drug groups in endoscopically controlled trials of 2 antisecretory drugs, plotted by year of publication of the study suggest that, as new drugs are introduced into the market (often with considerable fanfare by marketers, and corresponding interest from the medical community), the older ones become less effective (see Fig. 1). The reason for these findings presumably (in that preinternet era) is that, as treatments were judged "old," physicians became less enthusiastic about them and their efficacy waned.[10]

## Brain Matters

A lot of current research in the field is focused on clarifying brain signatures of different placebo effects. In a recent article, Petrovic and his colleagues[11] showed that placebo and opioid analgesia share a neuronal network, that is to say, in a study that used experimental pain (heat applied to the back of the hand), both opioid (remifentanil) and placebo analgesia were shown to activate the rostral anterior cingulate cortex, with a secondary involvement of the brainstem. Imaging studies have also begun to identify the neurological substratum of placebo effects working on subjects with Parkinson's disease[12] and depression,[13] although some of the work here is less thoroughly developed and more controversial. In at least one of the depression studies, drug response in brain activity was somewhat more general than placebo response: "active fluoxetine treatment was associated with additional and unique changes in the brainstem, striatum, and hippocampus."[13] The implications of these differences are unclear: some have speculated that it could account for why it is that, while placebo treatment of depression is often very nearly as effective as is treatment with selective serotonin reuptake inhibitors, there is often substantially less evidence of side effects with placebos.

However, in the end, such brain images are likely to find their deeper significance only when researchers begin to relate them back to what we know about the processes that create them: words, visual cues, cultural constructs.[14] In other words, understanding the ways in which the brain mediates placebo effects is likely to require us to probe more deeply into the way in which language and other kinds of meaningful communication have their own brain signature[15] that in turn acts to engage other kinds of brain pathways capable of having downstream effects on the body. Thus, we