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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.
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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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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

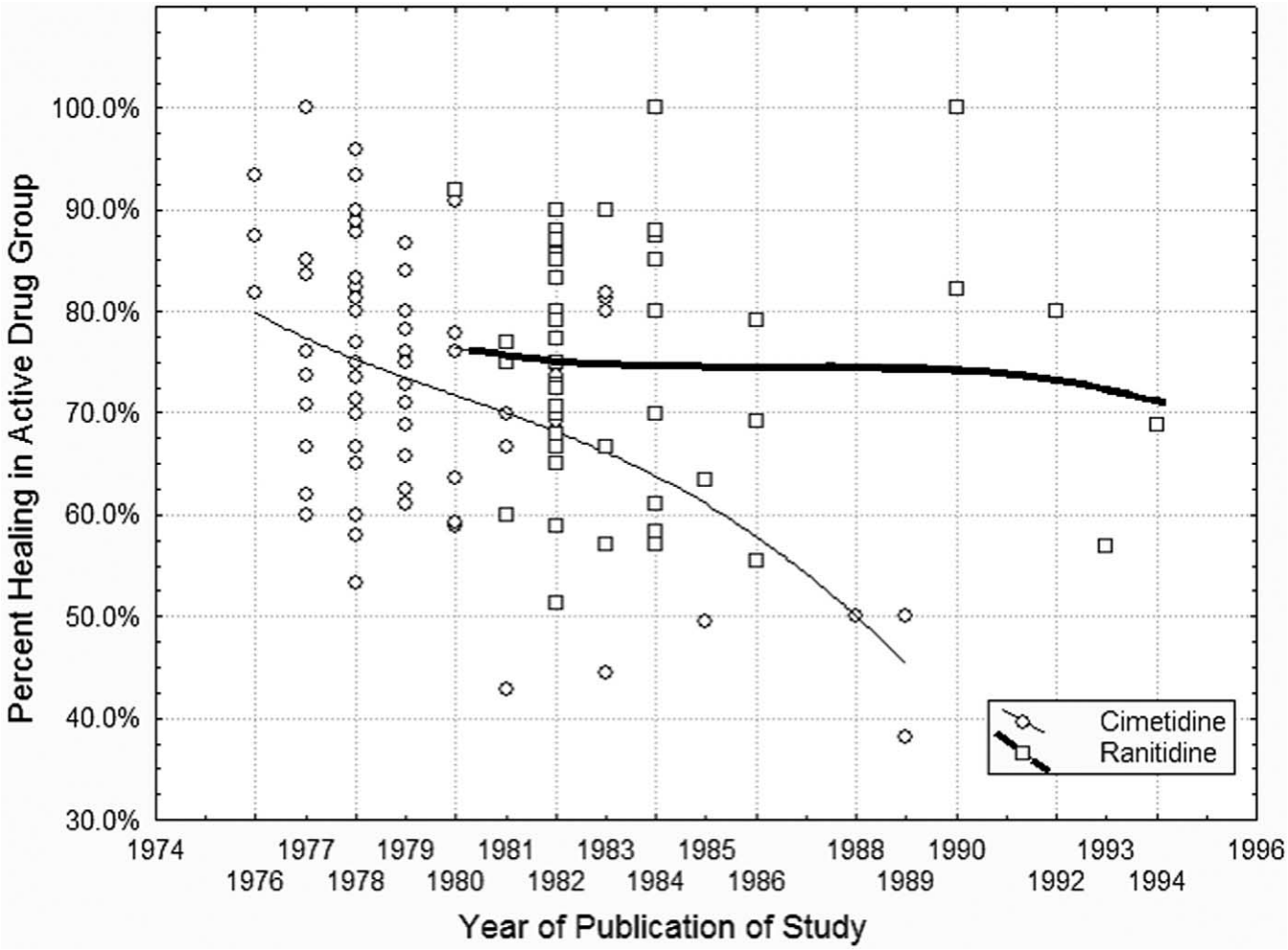

Figure 1 The figure shows the outcome in drug treatment groups in 117 studies performed between 1974 and 1998 using H-2 receptor antagonists for the treatment of peptic ulcer disease (PUD). Cimetidine (circles) became available for study in 1975, whereas ranitidine (squares) became available a few years later in 1981. Overall, no significant differences were found in these studies between the effectiveness of these 2 drugs. However, when plotted against the date of publication of the study, it is clear that cimetidine effectiveness dropped after the introduction of the "new, better" drug, ranitidine. Cimetidine hadn't changed, nor had the biology of PUD. However, doctor knowledge had changed.

can suppose that a patient with Parkinson's disease, on being told he was receiving his ordinary Parkinson's drug (even though he instead received an inert substance), used relevant parts of his brain to decode that sentence. The decoding process in turn served (in a way we are not yet able well to describe) to active the patient's striatum, producing endogenous release of dopamine. Similarly, a patient with depression, on being told she was getting her depression medication (even though she got an inert substance) presumably used relevant areas of his brain to make sense of that information, and that "sense" served to activate the striatum, brainstem and some other areas.

Culture Matters

The larger empirical and conceptual challenges for both medicine and biobehavioral science here could hardly be more profound, inviting questions about the way in which brains operate in cultural worlds and are changed by those worlds. However, one modest and empirically tractable way into some of the larger issues may be through the investigation of variability in placebo responsiveness. It is widely (and incorrectly) believed that placebo effects occur approximately one third of the time in any individual circumstance. In fact, one study that examined the 4-week endoscopically verified healing rates in 117 control groups in trials of antisecretory medications for peptic ulcer disease showed that the placebo response ranged from 0 to 100%.[10] What accounts for such enormous variability?

We know some of the factors that seem to trigger variation in response to placebos designed to treat the same disorder. They are all differences at the level of "meaning."[4] Thus, color makes a difference: red pills tend to be interpreted as stimulants and blue pills as tranquilizers. Large pills and very small ones are perceived as more potent than aspirin-sized tablets. Greater numbers of pills are perceived as more potent than

fewer. In a very subtle meta-analysis, de Craen[16] showed that in some 80 studies of several antisecretory medications for duodenal ulcer, a significant difference existed in the endoscopically verified healing rates for those who took 2 placebos per day (36%) compared with those who took 4 per day (44%), a difference of 8%. Moreover, inert injections are more effective than inert pills. When sumatriptan was first introduced for treatment of migraine, it was only available in the form of an injection; today, it is still available that way, but also as tablets and nasal spray. De Craen[17] did another meta-analysis of 35 trials and compared placebo treated patients who took pills or injections. This difference is modest (about 7%) but it is statistically significant ($P^2 = 9.4$, $P = 0.002$).

There is, however, an intriguing twist to this last claim. In studies performed in Europe, the difference between relief reported from injections as opposed to pill disappeared (27% oral versus 25% subcutaneous placebo relief rate) whereas in the United States it did not (22% oral versus 34% subcutaneous placebo relief rate).[15] Injections work better than pills, but only in the United States. National cultures also are part of what gets "into the head" and down into the body. This has been clearly shown in work with peptic ulcers, for which meta-analysis shows that the mean placebo healing rate in a 4-week, endoscopically verified ulcer is 59% in 6 German studies and only 7% in 3 Brazilian studies. When one compares the 6 German studies to 5 studies from Germany's northern low-country neighbors in Denmark and the Netherlands, the German placebo healing rate is 59% compared with the Danish and Dutch rate of 22%. These differences in healing rates are not generic cultural phenomena, let alone "racial" phenomena. They seem, rather, to be related to differences in culturally specific conceptualizations of illness in different cultures seem to have different real impacts on health and healing.[8] Evidence for this is found in the fact that these differences vary by illness: although there is a very high placebo response rate for ulcers in German clinical trials, the response rates in trials testing drugs for hypertension are lower in Germany than in other Western nations.

Further evidence is found in the fact that variations in placebo responses can be seen, not only between different cultures, but across time as attitudes and understandings change. Walsh and his colleagues[18] recently published a meta-analysis that reviewed 75 trials of tricyclic and SSRI antidepressants. They found that overall effectiveness of drug treatment for depression has trended up over time, so that the proportion of patients responding to tricyclic antidepressants and to selective serotonin reuptake inhibitors increased from about 40% to approximately 55%. During the same period, the proportion of patients responding to placebo also increased from approximately 20% to about 35%. The proportion responding was strongly correlated with the year of publication of the study for both drug and placebo treatment. The authors conclude that "Some factor or factors associated with the level of placebo response must therefore have changed significantly during this period. Unfortunately, we were not able to identify these factors."[18]

Had they consulted an historian or anthropologist, they might have felt able to say more. Over the past generation, there has been a growing consensus among doctors, patients, friends, and, generally, everyone, that depression is best treated with drugs. This was not the case 20 or 25 years ago. As recently as 1970, for example, Goodman and Gilman's *Pharmacological Basis of Therapeutics*, one of the standard reference sources, was far more enthusiastic about electro-convulsive therapy than it was about treatment with imipramine or amitriptyline.[16]

Today, however, we all "know" that drugs are effective for depression; we read it in the newspapers, in the scientific journals; we see it on television dramas, and in drug company advertisements everywhere, both in professional media and on direct-to-consumer advertisements. Antidepressant drugs are available in the drugstore, and, in the form of St. John's wort, in the drug aisle at one's local supermarket. As we change our views of the effectiveness of drugs, their actual effectiveness changes.

Conclusions

What we know, understand, think, and feel; what we are told and believe; the relationships we have with our clinicians—our doctors, nurses, and probably receptionists and parking lot attendants—can very directly affect our response to medical treatment, and, in particular, analgesic treatment. These matters are, these days, largely left to chance, or to ideology, or to market forces, but are still rarely subject to robust science. There is much to be learned here that is not only of enormous intellectual interest but that also might lead to material improvements of the quality of medical care for pain and other disorders; making room for the placebo in pain studies may complicate matters, but there is too much at stake to do anything else.

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