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Against the ''placebo effect'': A personal point of view

Daniel E. Moerman*

William E Stirton Professor Emeritus of Anthropology, University of Michigan-Dearborn, 6515 Cherry Hill Road, Ypsilanti, MI 48198, United States

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Summary The author reviews 10 of his favorite studies which are said to be about the ''placebo effect,'' but which, instead, show the significance of *meaning* in a medical context. ''Placebos,'' he argues, are inert substances which can't do anything. Yet it's clear that after the administration of such drugs, things *do* happen. The one (and maybe only) clear thing here is that whatever happens is not due to the placebo (that is what ''inert'' means). But placebos can be of various colors and forms which can convey compelling meaning to patients. They often represent medical treatment in compelling ways; they can be metonymic representations of the entire medical experience (a metonym is a representation where a part of something comes to represent it all, as in ''counting noses,'' where the nose represents the whole person, or a ''White House statement'' where the White House represents the Executive Branch of the US Government; here, the pill represents the whole medical experience). More precisely, they can be metonymic simulacra (a simulacrum is a sort of artificial object, like a statue rather than a man, or a placebo rather than an aspirin). Such objects are well known for their powerful abilities to contain and convey meaning; for example, a European cathedral ordinarily is constructed of thousands of metonymic simulacra, from the rose window to the altar. In this context, a placebo can repeatedly remind the patient of the medical encounter, its shadings and comforts. Placebos can convey the physicians innermost feelings about medication and treatment; and the clinician can by her simple presence enhance the effectiveness of a medical procedure (and a clinician is hardly a placebo, hardly inert).

Inert placebos can help us see the human dimensions of medical treatment; but calling these things ''placebo effects'' dramatically distorts our understanding of such treatments, by focusing on the inert, and avoiding the meaningful. Think ''meaning response,'' not ''placebo effect.''

I thought this would be easy. I would pick out my 10 favorite studies, the ones I've learned the most from over the years, and go thru them from 10 to 1. This turns out to have been more difficult than I had imagined it would be. But nonetheless, interesting, and, I will argue that in most of these, the results usually make more sense if we try to determine how a meaningful interaction occurred, rather than trying to understand the effectiveness of ... ''nothing.'' I will argue that there is never nothing going on here. Here's a good example:

* Tel.: +1 734 483 3283; fax: +1 734 480 1908.
E-mail address: dmoerman@umich.edu

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Number 10[1]

In an important study, 835 women who reported that they regularly treated headaches with over the counter analgesics were randomly placed in 4 groups: one group received unlabeled placebo, one received placebo marked with a widely advertised brand name, ''one of the most popular. . .analgesics in the United Kingdom widely available for many years and supported by extensive advertising'', one received unbranded aspirin, and one received branded aspirin.

They noted the amount of headache pain relief an hour after taking the pills. Results: First, aspirin was more effective than placebo. But brand name aspirin was more effective than generic aspirin, and brand name placebo was more effective than generic placebo.

In particular, 55% of headaches reported by branded placebo users improved after an hour (rated 2, 3 or 4 on the scale) while only 45% of 410 headaches were reported to be that much better by unbranded placebo users ($\Pi^2 = 6.76$, $p < .01$). Aspirin relieves headaches. But so does the knowledge that the pills you are taking are good ones, which you learned on TV. The difference here is to be attributed not to the placebo (which is, after all, inert) but to the brand name which clearly is not, enhancing the effect of both placebo and aspirin.

Note that saying that this is ''Smith's Aspirin'' is not a lie if, indeed, it is Smith's aspirin.

Both aspirin and placebo work better when they have a highly advertised brand name on them. That's NOT a placebo; that's *meaning*, something added to the tablets with WORDS.

Number 9[2]

Rick Gracely has described a phased experiment in which dental patients were told they would receive either placebo (which might reduce the pain of third-molar extraction, or might do nothing), naloxone (which might increase their pain, or do nothing), or the synthetic narcotic analgesic fentanyl (which might reduce their pain, or do nothing). 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 because of administrative problems with the study protocol, fentanyl was not yet a possibility, yielding the PN (''Placebo Naloxone'') group; it is worth noting that fentanyl is well known in medical circles as a very powerful drug, much more potent than morphine. In the second phase, clinicians were told that, now patients might indeed receive fentanyl, yielding the PNF (Placebo Naloxone Fentanyl) group. Placebo treated patients during the first phase of the study received no relief from it, and, after an hour, their pain reports increased significantly. In the second phase of the study, placebo treated patients experienced significant pain reduction from their inert treatments. The only apparent difference between the two groups was that the clinicians knew that no one in the first group would get fentanyl while the patients in the second group might (although no one reported on here actually did; they all received only placebo). It is not at all clear how physicians elicited these effects from their patients in a double blind trial. But they did; the clinicians were clearly more impressed by fentanyl than were the patients.

This study clearly shows how physician knowledge of the context in which placebos are administered can dramatically change the outcome.

Number 8[3]

In a landmark study in 1978, Levine and colleagues showed that pain relief brought on by prescribing a placebo could be reversed by administration of an opiate antagonist, naloxone or Narcan. The clear implication was that somehow, the brain produced endogenous opiates which led to the pain relief which was extinguished by the naloxone.

In this study, students were enrolled who had impacted third molars. Following third molar extraction, patients were told (twice) that they might receive morphine, placebo, or naloxone, an opiate antagonist.

Two hours following the initial anesthesia patients were told they would receive either morphine, placebo, or naloxone: 9 responded to the placebo and 14 didn't. At three hours (180 min) all these individuals were given naloxone as a second treatment. It had no appreciable effect on the nonresponders, but definitely eliminated the pain relief in the placebo responders.

This was not a perfect experiment; a lot went on which I haven't described, and the paper was very controversial. But, 18 years later, Fabrizio Benedetti said of this paper it marked the date that ''the biology of placebo was born.''[4] It is now generally recognized that this is the first study to show convincingly that inert treatment could stimulate the production of endogenous opiates in the brain. In a personal communication about this study, Howard Fields told me ''The first time we did this and did not have morphine as a possibility, there was no placebo effect. Once we truly blinded it, so that nobody really knew what they were getting, we started seeing robust effects from saline infusions.'' As in the previous study by Gracely, only when clinicians knew that patients might get morphine did patients have significant meaning responses.

Number 7[4]

This study by Fabrizio Benedetti was largely designed as a replication of the previous one by Levine, Gordon and Fields.

In this study, subjects induced pain by squeezing on a hand exerciser with a tourniquet on the upper arm creating intense pain.

When pain reports reach 7 on a scale of 10, an open injection of saline — presented as a helpful pain reliever in about 6 or 8 words — is given to the members of one group (see line with squares in Fig. 1); the outcome is compared to another group which receives a hidden injection of saline — the same injection, but with no words — in the other group (diamonds). That's the only difference between the two groups. Yet the open saline group shows a persistent decline in pain reports while the hidden infusion group shows a continued rise in pain. Let me qualify this: Does this show us that placebos have effects? No, *because both groups*