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

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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 entire 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."

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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:
Number 10

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 ($T^2 = 6.76, p < .01$). 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

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 available, 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

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 non-responders, 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." 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 meaningful responses.

Number 7

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
got placebos. The difference between the two groups was words, language, meaningful utterances.

Another group, given open saline, is, after 15 min, given an injection of hidden naloxone (triangles); the pain returns; this is the replication of Levine, Gordon and Field. Then Benedetti adds another trick: after 15 min, he gives a hidden injection of proglumide, an opiate enhancer, and the pain drops even more (ridged circles). Benedetti manipulates placebo like a magician.

Number 5

15 newly admitted "neurotic" outpatients at the Johns Hopkins psychology clinic were invited to participate in a study. They presented an array of symptoms; all were pretty unhappy people. They were told that during their workup, they were going to be prescribed "sugar pills"; that is, pills "with no medicine in them at all." They were told such pills had helped many people in the past, and that the doctor thought that it would help them. They were told to take 3 a day at mealtimes. Fourteen of the patients returned in a week; on an array of measures, physician and patient scores, 13 were markedly better than a week earlier (one woman was worse; her husband had attempted suicide during the week). Placebos can help, can be deeply meaningful, even if you know that they are inert.

Number 4

Irving Kirsch and his colleagues took the unprecedented step of making a "Freedom of Information Act" (FOIA) request of the FDA for the studies used to approve the use of "SSRIs"
for depression. They analyzed data on 6 drugs from 38 studies with a total of 6944 patients randomized to drug or placebo treatment.

Table 1 shows the results of those studies. Mean improvement with drug treatment was a drop in the Hamilton scale score of 10 points; mean improvement with placebo treatment was a drop of 8 points.

Nearly 80% of the improvement from the drug was replicated by the placebo treatment, and the difference between drug and placebo was about 2 points on the Hamilton Scale. So: Placebos can improve a LOT of depression.

Number 3

Walsh and colleagues reviewed 75 published trials of various antidepressants: tricyclics, and SSRIs compared with placebo. The results of his study show that the effectiveness of drug treatment for depression has trended up substantially between 1981 and 2000, so that the proportion of patients responding to tricyclic antidepressants and to SSRIs had increased from about 40% to about 55%. Over the same period, the proportion of patients responding to placebo increased from about 20% to about 35%. The proportion responding was strongly correlated with the year of

Table 1  Mean improvement on Hamilton score for 6 SSRIs approved for use by the FDA. Overall average improvement for Drug groups 10.01; for control groups 7.82.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug group improvement</th>
<th>Placebo group improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine</td>
<td>8.3</td>
<td>7.3</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>9.88</td>
<td>6.67</td>
</tr>
<tr>
<td>Sertraline</td>
<td>9.96</td>
<td>7.93</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>11.54</td>
<td>8.38</td>
</tr>
<tr>
<td>Nefazodone</td>
<td>10.71</td>
<td>8.87</td>
</tr>
<tr>
<td>Citalopram</td>
<td>9.69</td>
<td>7.71</td>
</tr>
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publication of the study for both drug and placebo treat-
ment. 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".

However, the matter doesn’t seem too complicated to
me. Over the past generation, there has been a clear shift in
consciousness among doctors, patients, friends, and, gener-
ally, everyone, to the effect that depression can be treated
with drugs. This was simply not the case (or at least not
broadly shared) 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 clearly more enthusiastic about
electro-convulsive therapy (ECT) than it was about treat-
ment with imipramine or amitriptyline, which were said
never to be more effective than ECT.11

Today, while we practically never hear of ECT, we all
"know" that drugs are effective for depression; we read it
in the newspapers, in the scientific journals; we see it on
TV dramas, and, in the US at least, we see it in drug company
advertisements everywhere, both in professional media and
on TV commercials, blogs, Twitter and Facebook.

Antidepressant drugs are available in the drugstore, and,
in the form of St. John’s Wort, at the drug section of your
local supermarket. As we change our views of the effec-
tiveness of drugs, their effectiveness changes, as do their
placebo mimics in trials. Meanings change and so do meaning
responses. Placebos stay the same, always inert.

**Number 2**12,13

Brain imaging has had a significant effect in placebo stu-
dies, making clearer to people just what is going on; I’m not
convinced that the imaging studies showed us a whole lot
we didn’t know before, but I believe they converted a lot
of people previously skeptical. Such images are indeed very
compelling: I will consider only two of many that have been
published, mostly since about 2000.

Parkinson’s disease has long been known by clinicians
to be susceptible to influence by inert treatments. Imaging
studies by a group from British Columbia have shown a neuro-
logical basis for this common clinical observation. Using PET
scanning, the authors showed substantial increase in occu-
pancy of D2 receptors with dopamine in the striatum after
an injection of saline solution to a Parkinson’s patient pre-
sented as his standard medication; the increased dopamine
crowds out the radioactive dye.12

In a somewhat more complex study, regional glucose
metabolism in PET scans of fluoxetine (Prozac in the US) has
been shown to overlap the metabolic pattern of placebo in
depressed patients. The active regions in fluoxetine respon-
ders overlap the area where activity was evident in placebo
responders.13

Although the clinical response of drug and placebo
patients was very similar in this study, drug response in brain
activity was somewhat more general than placebo response.
This may help to account for why it is that, while placebo
treatment of depression is often very nearly as effective as
is treatment with SSRIs, there is often substantially less evi-
dence of unwanted side effects with placebo.9 These studies

![Figure 3](https://via.placeholder.com/150)

**Figure 3** When the clinician is present for the injection, patients report less pain. Note in particular that there are no placebos anywhere in this study, hence no "placebo effects." Reprinted with permission from Ref. 14.

underscore the vital reality of meaningful treatment in seri-
ous illnesses.

**Number 1**14

Finally, Benedetti and his group have reported on a cli-

dical experiment where surgery patients were treated with
four different drugs appropriate to their conditions; how-
ever, half the patients received their drugs openly, with an
injection by a clinician, while half received equivalent doses
of the same drugs by hidden infusion through an intravenous
line.

One of the four groups was given tramadol. Patients
receiving the medication openly, who were told they were
about to receive it (the lower line in Fig. 3), reported more
pain relief than those who received equivalent amounts of
drugs secretly (upper line).

Pain researcher Don Price, in an accompanying editorial,
described this study as "assessing placebo effects without
placebo groups."15 As much as I respect Don Price, this is an
unfortunate use of language. There were no placebos here;
both groups got tramadol. So obviously, there weren’t any
"placebo effects." What differentiated the separate groups
in this study were human interaction and words.

Benedetti has replicated his open/hidden drug exper-
iment in three other areas: diazepam in anxiety state,
stimulation of the subthalamic nucleus in Parkinson’s
patients, and administration of beta-blocker (propranalol)
or muscarinic antagonists (atropine) in healthy volunteers.
In all these cases, when the treatment was given openly, it
was more effective than when given secretly.16

In his discussion of these cases, Benedetti and his col-
leagues write this: "It is probably wrong to call placebo
effect the difference between open and hidden treatments,
since no placebos are given. Meaning response is perhaps
more appropriate, in order to make it clear that the crucial factor is not so much the inert treatment per se but rather the meaning around the medical treatment... Therefore, it might be time to limit the use of the term placebo effect to those situations in which inert (dummy) medical treatments are given. However, it is worth noting that even if a placebo is given, there is no such thing as a placebo effect, since this term deflects our gaze from what is really important (the meaning and the meaning-induced expectations) and aims it at what is not (the inert pills and, in general, the inert medical treatments).”

Conclusions

I, of course, agree fully with Benedetti. A placebo, unless made by an incompetent pharmacist, is inert. That means it doesn’t do anything. But we often find that things do happen to people after placebos are administered. The one thing we can know for sure is that these effects are NOT due to the placebo. But as these long past favorite studies of mine (plus others) show, the meanings of drugs or other treatments to patients, clinicians, families, friends, community, are supremely important here.

It is long past time to give up on a flawed notion, the “placebo effect” or the “placebo response.” People don’t respond to placebos. They respond to what placebos, drugs, clinicians, and others mean and when there are no placebos in the study, they respond to the person who brings it to them.

People respond to what we know, think, and feel... People respond to what we are told, believe and know... People respond to their various cultural backgrounds... They respond to language, to caring, to culture, to community, to history. In a word, they respond to meaningful phenomena.

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References