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FOCUS: RESEARCH AND CLINICAL ETHICS

Deceit and Transparency in Placebo Research

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Studies designed to elicit the full strength of the placebo effect differ from those in which the placebo effect represents a nuisance factor to be accounted for in order to establish the efficacy of a treatment. In the latter, informed consent is the rule; in the first, while consent may be informed in some narrow sense of the word, deception is common. However, the trickery of placebo experimentation goes beyond straightforward lies to include the use of crafty ambiguities, half-truths, and deliberate omissions in scripts read to the subjects of these studies. As words come to resemble therapeutic agents in their own right, it is only to be expected that researchers would methodically exploit verbal effects to evoke the responses they are looking for. Even experiments in which placebo is disclosed as placebo have used language in leading and misleading ways. Such studies are conducted in the hope of yielding results that might translate into clinical practice, but it should be noted that good clinical practice has a placebo value of its own — that is, confers a benefit over and beyond the specific effects of treatments — even if nothing like a sugar pill is administered.

CUES, SUGGESTIONS, AMBIGUITIES

In 1955, a paper that has since been cited well over 1,000 times calculated that some 35 percent of the subjects in a sampling of clinical trials responded to placebo as to a medication [1]. While this figure has been challenged in recent years for conceptual sloppiness and other inaccuracies [2], clearly the placebo effect must be accounted for in clinical trials of proposed medications if the results are to mean anything. The author of the paper in question, Henry Beecher, was himself an advocate of the placebo-controlled trial. In another paper — one that has not attracted the notice received by “The Powerful Placebo” — Beecher urged the practice of informed consent in medical studies [3]. A half-century ago, neither the randomized clinical...
trial (RCT†) nor informed consent were normative. The two appear to go hand in hand [4].

As a rule, subjects in RCTs are truthfully informed that they will receive either a certain treatment or a placebo — that is, a visibly indistinguishable replica whose effect, if any, derives not from its actual composition but from the expectations it engenders. Because the placebo effect is largely dependent on expectation and subjects who know they have a 50/50 chance of an active treatment can only expect so much, the standard RCT is not an ideal tool for eliciting the power of the placebo, something it was never intended to do in the first place. A considerably stronger therapeutic effect is produced when subjects are told positively that the treatment they are receiving is an active one [5]. However, many studies that follow this practice compromise the informed consent that ought to be in place in any experiment involving human subjects.

While a placebo response of some degree is commonplace in trials using placebo as a control, there cannot be many cases in which placebo produces the same response as drug across a study population. One such rarity is a small study of irritable bowel syndrome (IBS) in which experimenters deliberately led the subjects to believe that two of the inert treatments they received were active. Specifically, in an attempt to determine if verbal suggestions of pain relief contribute to the sensation of relief, the subjects were told, “The agent you have been given is known to significantly reduce pain in some patients,” just after a balloon was inserted into their rectum. Bearing out the importance of verbal cues to the experience of pain, the study found that the placebo treatments reduced pain just as effectively as rectal lidocaine [6].

Given that the study hinged on getting the subjects to mistake placebo for a medication, it comes as a surprise to the reader of the study report that “All patients signed informed consent prior to the start of the study.” How can this be? Were the participants truthfully informed, in something approaching a Cretan paradox, that they were going to be deceived? There is no indication of that. On the contrary, the study report maintains that the labeling of placebo as an active treatment was truthful, in that a placebo jelly had been shown in a previous study to reduce “evoked rectal pain.” Thus, by describing the jelly as “an agent ... known to significantly reduce pain,” the experimenters could fool the subject into expecting an actual treatment while technically satisfying informed consent. Though the principle of informed consent was built into clinical trials so that subjects would know they had an equal chance of receiving placebo or drug, in this case an informed consent document served to excuse the presentation of placebo as drug.

It is because placebo can reduce pain in some cases that the experimenters were able to describe it in a way that makes it sound like an active treatment. This double entendre, worthy of a team of lawyers, was compounded by another troubling circumstance: “the doctor who performed the experiment was the doctor that the patients normally consulted in the clinic and with whom the majority of the patients had a good relationship,” in the words of the study report. A trusted doctor makes a particularly good confederate in an experiment all the more deceptive because it is technically truthful. (As thoughtful commentators have noted with this study, among others, in mind, “Especially problematic is the use of deception in experiments conducted by clinicians who have a prior clinician-patient relationship with the patients enrolled in the study” [7].) Mentioned incidentally in the study report is that the doctor “took time to talk with each patient before the experiment,” although what the doctor said is not reported — a significant gap in a study of the contribution of verbal suggestion to the placebo effect. In this sense, part of the study took place off the record.

Perhaps even more paradoxical than a study that turned on an equivocation but purported to be truthful and employed a standard script except when the doctor performing the experiment “took time to talk
with each patient,” was a European study of a few years before comparing the benefits of active and inactive pacemakers. Finding that inactive devices yielded both subjective and objective benefits, the pacemaker study is one of many that have revealed the surprising scope of the placebo effect, although like related studies of sham surgery it leaves the reflective reader puzzled. For according to the study report, “Study protocol was approved by the local ethics committees of all participating hospitals. All patients gave their written informed consent to participate in the study” [8]. Did cardiac patients knowingly consent to the implantation of a pacemaker that would be switched off for 3 months behind their back, as the protocol required? It is reasonably theorized that subjects in clinical trials who suspect they are receiving placebo enjoy less placebo effect because they are haunted with uncertainty [9]. If I suspected the pacemaker in my chest might actually be off, it would not only haunt me with uncertainty, it would send palpitations right through me. But if informed consent can cut into the placebo effect, there may be ways of framing the language of consent forms that reduce that possibility.

A probing commentary published a few years ago found “misleading statements that informed consent was obtained from the research participants” to be endemic in research on the placebo effect [10]. According to the authors, such statements are often no more than boilerplate language employed to give the appearance of good practice. Along with the tactic of leaving the use of deception to be “inferred by the reader” (who may or may not actually infer it), the conversion of the ethical safeguard of informed consent into a stumbling block for the subject and even the reader points to a troubling syndrome in the placebo literature. The authors of the commentary, whom I will designate M and K, proceed to critique three studies, one of which exhibits a “lack of full transparency” from start to finish, with the finish being the published report of the results. As it happens, K contributed to this study; in reproaching the trickery of placebo research, he does not spare himself. The published report in question cites the consent, albeit not the informed consent, of the subjects, thereby equivocating with the reader just as the consent form, which concealed the deceptive component of the experiment, equivocated with the subjects [11]. In fact, the trickery of placebo experimentation goes beyond straightforward lies to include the use of artful ambiguities (as in this case), half-truths, and deliberate omissions in informational scripts and “verbal suggestions” [12].

A leading investigator of the placebo effect, Fabrizio Benedetti, has suggested that “words and drugs may use the very same mechanism and the very same biochemical pathways.” (Hence, in patients with Parkinsonism, “verbal suggestions of motor improvement activate the same dopamine receptors in the very same brain areas” as anti-Parkinson agents [13].) As words come to resemble therapeutic agents in their own right, it is only to be expected that researchers would exploit subtle verbal effects and use language in carefully ambiguous ways to elicit the responses they are looking for. In due course, I will cite as an example of this practice a study whose authors include M and K themselves and which was actually designed to avoid the ethical shortcomings of placebo research.

Placebo research is so bound up with deception in one guise or another that the very attempt to manage deception ethically can create further problems. In an intricately constructed experiment on the influence of expectation on drug effects, which employed a balanced placebo design — with some subjects receiving a drug presented as placebo, some a placebo presented as drug, and others either drug or placebo presented without deception — the consent form advised subjects that information presented to them in the course of the study “may be inaccurate.” Given that “inaccurate” here really means “deliberately false,” the wording introduces an element of euphemism into the act of disclosure. The same document stated: “The drugs that you might receive are commonly prescribed or over-the-counter, non-experimental drugs, and they are given
in doses that are unlikely to cause you any discomfort.” Were I to read this in the same form that notified me that I might be receiving inaccurate information, I wouldn’t know what to think. Is the information that the drugs are in common use somehow inaccurate itself [14]? Given the sort of binds that deception leads to, it is no wonder that placebo researchers are interested in the possibility of doing away with it altogether. Presenting placebos as placebos eliminates both the ethical problem of deception and the tactical problem of framing consent language that does not give away too much. Moreover, if undisguised placebos were found to yield therapeutic benefits in clinical trials, the results could in principle be translated into the clinic.

**OPEN PLACEBOS**

It may be a measure of interest in open (that is, undisguised) placebos that a “Nonblind Placebo Trial” of 1965 has been cited as precedent-setting in the placebo literature and is still adduced as a kind of proof of principle, despite such ethical deficiencies as the use of actual patients rather than volunteers and such methodological shortcomings as the lack of a control group. Conducted by Park and Covi, the study in question, involving fifteen “neurotics” recently admitted to a psychiatric clinic, took place in 1963 and ran for just 1 week. Upon entering the study, the subjects were told, according to a “carefully enacted” script,

> “Many different kinds of tranquilizers and similar pills have been used for conditions such as yours, and many of them have helped. Many people with your kind of condition have also been helped by what are sometimes called ‘sugar pills,’ and we feel that a so-called sugar pill may help you, too. Do you know what a sugar pill is? A sugar pill is a pill with no medicine in it at all. I think this pill will help you as it has helped so many others. Are you willing to try this pill?” ... The statement that the pills had helped many others was usually repeated again, especially if the patient asked questions concerning the treatment, conveying doubtful attitudes about its possible effectiveness [15].

The shift from the statement that the pill “may help you” to the statement that the pill “will help you as it has helped so many others” anticipates what is now a sort of principle in the placebo literature: that definite expectations of benefit from a placebo treatment are more potent than conditional or uncertain ones. Clearly, the subjects were being prompted to accept “a pill with no medicine in it at all” as some sort of therapeutic agent — a suggestion enhanced by the label on the pill bottle, which bore the name of Johns Hopkins Hospital. And it appears the subjects complied.

Of the 14 who completed the short study, all but one reported improvement, with the group as a whole showing a 41 percent decrease in symptoms. The possibility that some simply reported to the experimenters what the latter were looking for — now a recognized risk of open-placebo experimentation — was not considered. It is also notable that, in a converse of the doubts known to haunt those randomized to placebo in a conventional trial, six of the 14 believed the sugar pills did contain medication, according to the study report. For whatever reason, six subjects presumed that the psychiatrists who ran the study were lying to them. (In experiments with a balanced placebo design, as above, one group is in fact told it will receive placebo but gets drug instead.) Though wrong about the contents of the pills, the suspicious subjects were onto something.

While the shortcomings of the Park and Covi trial, including but by no means limited to the lack of a control group, were detailed in 2008 by David Jopling [16], no one to my knowledge has commented on the trick that this supposed exercise in openness turned upon. As we know, the script “enacted” for the patients stated twice over —
for some, three times — that many other pa-
tients have been helped by sugar pills. But
those other patients were helped precisely
because they were deceived into believing
the pills an active medication. In 1963, doc-
tors still used placebos at their own discre-
tion, and even in randomized clinical trials,
which were not yet the norm of medical re-
search, informed consent was not necessary.
In the Health Insurance Plan of New York
(HIP) trial, also launched in 1963 and con-
sidered the first RCT of cancer screening,
the control group did not even know it was
part of a trial [17].

Inasmuch as the “Nonblind Placebo
Trial” was the first of its kind, the “many
others” referred to in its script could not in
fact have received placebos disclosed as
placebos. On the contrary, they received
placebos masked as actual medications,
pre-
sumably expected the benefits of such med-
ications, and, in accordance with the
dynamics of the placebo effect, these expec-
tations shaped their experience to one degree
or another. Note, too, that if we remove the
references to “many others” from the script,
what we are left with is a bare sugar pill with
no claim on anyone’s credence at all. In this
way, the script smuggles the fruits of decep-
tion into a study purporting to do away with
deception. It is therefore as much of an
equivocation as the sort of consent language
faulted by M and K for its deliberate ambi-
guity. (Indeed, Jopling takes the sugar-pill
script as an informed consent document.)

“Are you willing to try this pill?” the script
asked.

The principle that we tend to expect the
benefits that “many others” appear to derive
from a medical treatment is a potent one
with a place of importance in the history of
placebo research [18]. In the first investiga-
tion of the placebo effect in England, John
Haygarth and his colleagues tested the effi-
cacy of certain dubious brass devices said to
be able to draw pains out of the body (“trac-
tors”) by treating a handful of patients at the
Bath General Hospital with identical-look-
ing articles fashioned of wood. By and large,
the subjects responded to the sham instru-
ment exactly as if it were “real,” thereby
demonstrating that the tractor itself was a
sham. But Haygarth knew it was not enough
to simply wave the article over the subjects
of his experiment. In order to really recom-
mand the treatment to them, he, like Park
and Covi, made sure to refer to the many
others who had been helped by tractors.
Writes Haygarth:

If any person would repeat
these experiments, it should be
done with due solemnity. During
the process, the wonderful cures
which this remedy is said to have
performed ought to be particularly
related. Without these indispensa-
ble aids, other trials will not prove
as successful as those which are re-
ported above. The whole effect un-
doubtedly depends upon the
impression which can be made
upon the patient’s Imagination
[19].

The “due solemnity” of this deceptive ex-
periment bears comparison with Park and
Covi’s “carefully enacted” script, just as the
“wonderful cures” attributed to tractors
presage the “many others” helped by sugar
pills. An experiment in transparency em-
ployed potent conventions of deception.

Moreover, since Park and Covi, the in-
vocation of the many others who have ben-
efited from placebos — albeit not open
placebos — has continued in nonblind
placebo trials. In a recent study involving
children diagnosed with Attention Deficit
Hyperactivity Disorder (ADHD), subjects as
young as 6 were told supposedly openly
about the placebo. (Can a 6-year-old com-
prehend something as paradoxical as an inert
pill that is not really inert?) The script used
with children from 10 to 12, which is almost
identical to that used for younger children,
reads in part:

This little capsule is a placebo.
Placebos have been used a lot in
treating people. It is called ‘Dose
Extender.’ As you can see, it is dif-
ferent from Adderall. Dose Exten-
der is something new. It has no
drug in it. I can promise you that it
won’t hurt you at all. It has no real
side effects. But it may help you to
help yourself. It may work well
with your Adderall, kind of like a
booster to the dose of Adderall.
That’s why it’s called a Dose Ex-
tender. I won’t be surprised when I
hear from you and your parents and
your teachers that you’re able to
control your ADHD better [20].

Just as the Park and Covi script promoted
placebo from something that may help to
something that will help, so in this case the
script seems designed to encourage a self-
fulfilling prophecy, whereby a Dose Ex-
tender that “may help” becomes an actual
therapeutic agent by the power of expecta-
tion. The claim that “Placebos have been
used a lot in treating people” similarly echoes the leading or misleading language
of the Park and Covi script, though it also
brings to mind a line used in the experiment
on the power of verbal suggestion that I
began with: “The agent you have just been
given is known to significantly reduce pain
in some [IBS] patients.” In another reminder
of just how tangled deception and trans-
parency have become, the authors of the IBS
study contend that because placebos have
been known to reduce pain, verbal sugges-
tions for pain relief in general “need not be
deceptive and thereby ethically problem-
atic.” Of course the placebos they refer to
are not open placebos.

Can a placebo openly disclosed as such
reduce pain — say, the pain associated with
IBS? Recently, this possibility was put to the
test by a team including both M and K. In a
widely cited experiment, a group of 37 IBS
patients, of whom 31 completed the study,
were treated with pills labeled as placebo
and described as being “something like
sugar pills” of proven therapeutic power.
After 3 weeks, 59 percent of patients treated
with the placebo reported adequate relief as
compared to 35 percent of the control group,
a finding qualified by a number of limita-
tions laid out by the authors. For present
purposes, though, the important point is that
subjects recruited into this study of “place-
obos without deception” seem to have been
told several times “that placebo pills ... have
been shown in rigorous clinical testing to
produce significant mind-body self-healing
processes” [21]. Therefore, while the study
does represent the first RCT to compare a
group given open placebo to a no-treatment
group, in another respect it continues past
practice, using a variant of the sales pitch
that has been employed in open or semi-
open or indeed deceptive placebo experi-
ments since Park and Covi established it half
a century ago.

The impressive rhetoric of “rigorous
clinical testing” in the study’s script makes
placebo sound like a medication in its own
right, or at least like something of attested
efficacy that “will help you as it has helped
so many others,” in the language of Park and
Covi. What of the benefits attributed to the
placebo treatment? While placebo produces
reports of improvement in countless clinical
trials (as when placebo branded as aspirin
outperformed its generic counterpart [22]),
the claim that such improvement represents
the work of “significant mind-body self-
healing processes” is arguably both tenden-
tious and inflated. Despite the inspirational
rhetoric of “healing,” the only sense in
which the study subjects treated with open
placebo were healed is that many of them
felt better. Their IBS itself did not heal in the
way ulcers, for example, do — with or with-
out treatment. According to the Oxford Eng-
lish Dictionary, the first meaning of “to
heal” is “to make whole or sound in bodily
condition; to free from disease or ailment,
restore to health or soundness; to cure.”
Placebo treatments of IBS do none of this.

Given that the evidence suggests that place-
obos do not in fact stimulate the body’s ca-
pacity for repair, as some champions of the
placebo effect maintain, but act on symp-
toms only [23], given that the IBS exper-
iment accordingly measured improvement of
symptoms and that we hear nothing further
of “self-healing” after the study subjects are
primed to expect it — given all this, we may
question just how transparent the presenta-
tion of the placebo actually was in this officially transparent experiment.

A defender of “placebos without deception” might ask what harm there can be in a slight exaggeration that does, in fact, make for a reduction of distress. However, the same defense might be made of some of the studies faulted by M and K for their use of misleading statements and tactical concealments.

THE CARE EFFECT

The Park and Covi experiment had 14 completers; the “placebos without deception” study had 31 completers in the treatment group. The IBS study involving rectal distension, along with deliberately ambiguous “verbal suggestions” deemed truthful by the authors, had 13 subjects. In addition to the ADHD study already mentioned, which enrolled 70 children, a related study reported in 2007 enrolled 26 [24]. Compared to placebo responders in conventional clinical trials, these 154 persons represent a modest grand total, surely. Beecher’s paper of 1955 took as its database 15 trials with a total of 1,082 patients. Open placebos do not seem to be much of a practical possibility.

But this is not to deny that research into the placebo effect (as distinguished from trials where placebos serve as controls) has yielded rich results. Among its intriguing findings is that a drug administered in full view of the patient is markedly more effective than the same drug administered covertly; the first engages expectations — as well as the evocative power of ritual, perhaps — while the second does not. (By the same token, saline solution presented to a patient as a drug may trigger an effect but will be less potent than the drug itself openly administered; in the latter case, the placebo effect is supplemented, if you will, by the drug’s specific activity.) In contrast to studies that turn upon deceptions and semi-deceptions, findings like these point to the benefits of transparency. If a drug seen to be administered by a doctor or nurse has a greater effect than the same quantity of drug administered secretly, perhaps care in and of itself has a therapeutic effect.

A care effect may have been silently imported into the IBS study involving rectal balloons when the patients’ own doctor conferred with them before the pain procedure and, in fact, went on to perform it. By contrast, a care effect is explicitly built into the study of “placebos without deception.” A secondary finding of the study, one which has not attracted much attention or comment, is that 35 percent of the subjects who received nothing but supportive care reported adequate relief of IBS, as compared with 59 percent of those who received the active treatment — in this case, a placebo pill. That those in the treatment group received the same care raises the possibility that much or even most of the relief they reported was attributable not to the pill per se (despite its seeming centrality) but the context of sympathetic care in which it was given and received. Moreover, fully 76 percent of those in the care-only group were well enough satisfied with the result that they did not regret being denied the placebo pill as a result of randomization. Evidently, it is possible to deliver care itself in a way that produces a potent placebo effect — in the process, solving the issue of deception by rendering it completely moot. On the other hand, a placebo prescribed to get the patient out the door — as in Denmark, where the most common reported reason for using placebo is to give the appearance of doing something when “the doctor feels there is no time for a detailed explanation or lengthy discussion” — can short-circuit care itself [25].

The Park and Covi study of open placebos contains case notes, many of which suggest the importance of the context of care in which the giving of placebo was embedded. Patient A “wanted to stay with the same doctor,” as did Patient C. Patient T, though convinced that his pill contained no active ingredient, “had a strong positive reaction to the therapist;” patient U, though likewise convinced, “was very satisfied with the idea of staying with the same doctor and pills.” Patient H reported, “Every time I took a pill I thought of my doctor;” and Patient S said, “For people, each time they take a pill it’s a symbol ... of
someone caring about you.” Perhaps the lesson of the experiment is not that inert pills lend themselves to ethical use but that care itself is such a potent influence that it can endow an inert pill with a semblance of activity.

The theory that care per se contributes importantly to the placebo effect was tested in a study of IBS conducted 2 years prior to the “placebos without deception” trial. Unlike the latter, in which the treatment and no-treatment groups received the same supportive care, in this instance one group received placebo treatment (sham acupuncture) with only minimal care, while the other received the same treatment augmented with care described as “warm and empathetic.” (In sharp contrast to the practice of using placebo to get rid of the patient, the care protocol in this case called for an initial visit of 45 minutes with a practitioner.) The proportions of patients reporting “moderate or substantial improvement on the global improvement scale” at 3 weeks were 20 percent for the placebo-treatment-only group and 37 percent for the group that enjoyed empathetic care in addition to the placebo treatment [26].

We may note that this study of separate components of the placebo effect deceived subjects into thinking they received acupuncture (the device used did not actually pierce the skin) and concealed its own purpose. The “informed consent” given by the subjects turns out to have been considerably less than informed:

All participants gave written informed consent, but the consent disclosure omitted certain descriptors of the trial to protect the study’s scientific validity. Thus, participants were told that the trial was a placebo controlled study of acupuncture for irritable bowel syndrome and were completely unaware of the study’s primary aim to examine placebo effects.

The study thus falls into the pattern of using the very act of disclosure as a mechanism of deception. However, other aspects of the study point in fruitful directions. Taking its lead from this one, a study could disaggregate placebo and care, such that one group received an open placebo in the context of minimal care and another group attentive care but no placebo. Other studies could tease out the elements of attentive care itself so that clinicians might know which practices best promote good outcomes. Given that “benefits of standard medical treatments have two components, the specific effects of the treatment itself and the perception that the therapy is being given” [27], how best to foster the perception of care? In view of our keen responsiveness to words in a medical setting, how might a doctor or nurse explain a treatment? And how much listening should they ideally do? Open placebos may or may not have much application in clinical medicine, but good practices of care certainly do — by definition. Misleading consent language and suggestive double-entendres jeopardize the ethical framework of medicine, while good practices of care strengthen it. Research into the placebo effect would do well to turn to the investigation of such practices.

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