

## EDITORIAL

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“Randomization remains critical for ensuring against systematic differences in treated and untreated groups (beyond the treatment itself). However, for many outcomes, these findings suggest presence of a placebo in the untreated group may not matter all that much.”

## Are placebos inert or powerful? *Vice versa*

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It is commonly presumed that ‘placebos’ used in clinical trials are both inert and powerful. It is supposed that they are inert, in that their constituents are blithely accepted to have no physiological impact (a supposition embedded in the word/concept ‘placebo’). It is supposed they are powerful, in that it is thought they can, through effects of expectation, engender large effects spanning virtually all outcomes. After all, placebo users evidently improve, spanning a multitude of conditions under treatment [1,2]. Are placebos indeed psychologically active, but physiologically impotent? Or maybe (subversive proposition) *vice versa*?

### Are placebos inert?

There are no substances that are known to be physiologically inert [3]. Even placebo substances that are not absorbed (do not enter the blood when taken orally) cannot be presumed actionless, as sometimes supposed. Thus, nonabsorbed fibers, such as psyllium or cellulose congeners, can benefit constipation and diarrhea [101] (i.e., they are not functionally invisible) and may thwart absorption of other substances – reducing cholesterol for instance [4–6]. Nonabsorbed fats/oils, such as mineral oil or olestra, impede assimilation of fat soluble vitamins [7,8]. Nonabsorbed oral substances still interface with the gut, and may alter gut flora; the gut microbiome (‘the second genome’ [9]) is increasingly understood to have far-reaching implications to nutrient assimilation, biotoxin production and health. Some nonabsorbed substances are even given for the purpose of altering gut flora and thereby symptoms, such as nonabsorbed antifungal nystatin powder.

### ■ Placebo content restrictions

There are no regulations governing the constituents of placebos, and it is not entirely clear whether there should be. Since nothing can be supposed inert, the lesser of the available evils (based on current knowledge at the time) may differ based on the study, the setting, the subjects and the outcomes. However, current knowledge changes, and what looks best now, may be found to be worse later. The important thing is, the placebo should be divulged. Then as knowledge about the stipulated constituents evolves, so may interpretation of the study.

### ■ The content of placebos is largely unknown

An analysis we conducted of randomized, placebo-controlled trials published over a 2-year period, in the top four ISI impact factor general medical journals, found that fewer than 10% of placebo-controlled trials involving pills disclosed the composition of the placebo [10]. A broad range of constituents were represented among those that did.

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■ **Determining the composition of a placebo**

For industry trials, a person from the company with a stake in the outcome will presumably determine the composition of the placebo. There is no evidence, as far as I am currently aware, that manipulation of the placebo contents has been used willfully to alter outcomes of studies. However, due to a lack of disclosure of placebo composition, we are not in a position to know.

Where conflicts of interest are at play, any of a range of stratagems, affecting virtually all elements of study development and dissemination, have been gamed, to advantage an appearance of benefit for the company's product [102] – extending to the data [11] and interpretation [12]. Whether or not gaming of placebo composition has previously occurred, it would be prudent to set an expectation of disclosure.

Moreover, the risk is not exclusive to industry studies, nor does it stem solely from avarice (or, otherwise viewed, business acumen). In the current publishing climate, studies with favorable results may be favored for publication. Therefore, expedient placebo choices might be made, independent of industry conflicts, in order to advantage publication prospects.

Even supposing everyone cared only about the best science, there remain cases in which no identified candidate placebos are *prima facie* neutral.

■ **Evidence of placebos influencing outcomes**

There is evidence that the composition of placebos, when known, has influenced the outcome of trials [3,10]. Lactose placebos have been used in populations with high rates of lactose intolerance – where these plausibly served as the source of ‘unexpected’ benefits of the active drug to gastrointestinal symptoms [13]. Olive oil and corn oil have been used as placebos in studies of lipid-lowering drugs – presumably contributing to the lack of benefit of the active drug to cardiac events – in the setting of ‘unexpectedly low’ event rates in the control group [3, 14]. A nonabsorbed fiber, utilized as the ‘placebo’ in a study of irritable bowel disorder, may have had actual benefit to diarrhea and constipation (as the fiber psyllium is known to do), perhaps contributing to what were interpreted as placebo benefits ‘without deception’ [2,4,15].

■ **Possible solutions: what can be done?**

Disclosure

Disclosure is not a complete solution, but it should be a minimum expectation. With this standard must come new understanding. Just as there is no perfect study design that obviates all possibility of bias and confounding, often, there is no perfect placebo. The pros and cons of placebo choice will simply be integral to the limitations – deliberated, where relevant, just as the various sources of bias and confounding, measurement

error and generalizability are currently. To make it possible for anyone to disclose, everyone should be asked to do so: else those who do will be at a competitive disadvantage in securing funding and publishing.

We are hopeful that there are steps underway toward requirement of a placebo disclosure, as previously suggested in our article in the *Annals of Internal Medicine* [10].

Using no treatment

A principal reason for a placebo arm, instead of a no-treatment arm, is to maintain the blind. The question is: does blinding matter? It can matter in a number of ways, but a major reason is to ensure effects of expectation are equalized across treatment groups. This is important if expectation of benefit leads to benefit. Such effects are believed to be common and large. Are they?

Are placebos psychologically powerful?

Mostly, what are interpreted as placebo effects are distributional effects. To study a treatment, patients are selected at one end of a distribution, for example blood pressure, cholesterol and depression. These commodities vary with time. When one looks at the distribution later, the distribution may look the same, but the positions of individuals within the distribution have shifted. Some who were above the inclusion threshold (who were thus included and followed for change) have dropped below that threshold – regressing to the mean, on average, and ‘improving’. Others who were below the selection threshold are now above, replacing those who have dropped down, but because they were below the threshold, these patients had been cut out of the investigation, and one does not see this offsetting rise. The rise is particularly noteworthy for those at the low end of the distribution. Thus, there is the appearance of improvement, often large, for many outcomes, when people are reassessed later. If people are in an uncontrolled study of the drug, it is often presumed the drug has a large benefit. If people are in the placebo group of a study, because they are on a placebo, the large improvement on follow-up is often attributed to a placebo effect.

“Mostly, what are interpreted as placebo effects are distributional effects.”

■ **Study benefits are expected**

In my own analyses of hundreds of variables in observational studies and randomized trials, for variable after variable, a major predictor of the change score, across legion outcomes, on placebo (or on drug), is the baseline score – indeed, it is commonly the strongest predictor. The farther from the mean a group of subjects

were chosen to be, the larger the average change typically is toward the mean. There are exceptions: for example, for inexorably progressive conditions or variables, such as age, this will not be true.

#### Comparison of placebo to no-treatment arms

Investigators from the Nordic Cochrane Center collated results from studies that included both a placebo arm and a no-treatment arm. For most outcomes, compared with no treatment, the placebos had no effect [16,17]. Modest apparent benefits of placebo were observed with pain and, perhaps, anxiety. This work of Hróbjartsson and Gøtzsche casts doubt on just how common meaningful placebo effects are.

Randomization remains critical for ensuring against systematic differences in treated and untreated groups (beyond the treatment itself). However, for many outcomes, these findings suggest presence of a placebo in the untreated group may not matter all that much. A no-treatment arm may work in some settings, given randomization and provided 'dropouts' and other

behaviors occurring after randomization (e.g., outside use of treatments) are not rendered too differential. OK, that's a big proviso (and not, in fact, the only one).

Nonetheless, more frequent inclusion of a no-treatment arm in clinical trials, in tandem with a 'placebo' arm, may ultimately contribute further information on both methods.

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