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Editorial

Editorial: Demystifying the Placebo Effect

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Placebo effects are a tantalizing concept that have captured public attention since at least 1955, when Henry Beecher (1) cataloged evidence across 15 large studies (total $n = 1{,}082$ patients) and concluded that 35.5.% (±2.2%) of individuals "respond" to placebo. The results presented by Beecher seem plausible at first read. The goal of placebos in medical research is often described as "to distinguish pharmacological effects from the effects of suggestion . . . and to obtain an unbiased assessment of the result of experiment" (1, p. 1602). Inherent in this goal is a claim that all medical interventions might have some causal effect that operates via psychological mechanisms and that the strength of such an effect is independent of the mode of intervention (2, 3). However, without clearly articulating the nature of this causal effect, we cannot refute or support the existence of this effect.

The counterfactual or potential outcome framework for causal inference (4) states that an exposure has a causal effect on an outcome if the expected value of the outcome had everyone received that exposure or treatment is on average different from the expected value of the outcome had those same individuals received some other exposure or treatment (4). A key element of this framework often missing from the conversation about placebo effects is the requirement to specify the other exposure or treatment of interest. As we shall see, the omission of an explicit nonplacebo comparison group for the placebo group introduces unrealistic assumptions, confusion, and spurious findings into the definition and estimation of the placebo effect and "placebo response."

Although the placebo effect is not often of clinical interest to epidemiologists, understanding what is meant by this concept, and how biases can provide misleading inference, can help shed light on potential sources of bias in other single-group studies that might be more consequential. For example, in recent months, a desire to rapidly identify effective treatments for COVID-19 has resulted in a number of single-arm medication "trials" wherein all individuals are given an exploratory treatment, and "response" to this treatment is assessed based on some outcome measure such as disease biomarker levels at the end of follow-up (5). Similarly, it is not uncommon for researchers who compare the change in levels of some variable over time within a particular exposure group to attribute the results of this comparison to a causal effect of the exposure of interest. However, these outcome-change score studies are subject to many of the sources of bias that I describe here for the placebo effect (6).

In addition, because belief in placebo effects might lead patients to seek out potentially ineffective alternative medicine treatments (7), studies that inappropriately define the placebo effect or that do not sufficiently address sources of bias in estimating this effect could contribute to an erosion of public trust in pharmaceuticals (8). Finally, for many outcomes, such as mortality, placebos likely have no effect, and therefore, when the placebo effect can be validly confirmed to be absent, placebos might be useful as negative control exposures (9).

NOTATION

Let Y denote the outcome at the end of follow-up. This might be a binary or time-to-event variable like mortality, or a continuous variable such as pain level. Let Z represent random assignment. Conventionally, $Z = 1$ denotes the therapeutic treatment arm, and $Z = 0$ denotes the placebo arm. It might also be of interest to denote actual treatment received as X, where $X = 0$ for individuals who receive the placebo regardless of treatment assignment. Finally, let $\mathbf{L}$ represent all other covariates of interest.

Now, we define Y^z as the counterfactual outcome that would have been observed for someone randomized to $Z = z$ under the assumption of consistency. This assumption is valid when we have a clearly defined intervention, such as assignment to placebo. As such, $Y^{z=0}$ is the counterfactual outcome that would have been observed for someone randomized to placebo. $Y^{z=1}$ is commonly used to denote the counterfactual outcome that would have been observed for someone randomized to the therapeutic treatment. Here, we are interested in placebo versus something other than the therapeutic treatment, so we will denote $Y^{z=-1}$ as the

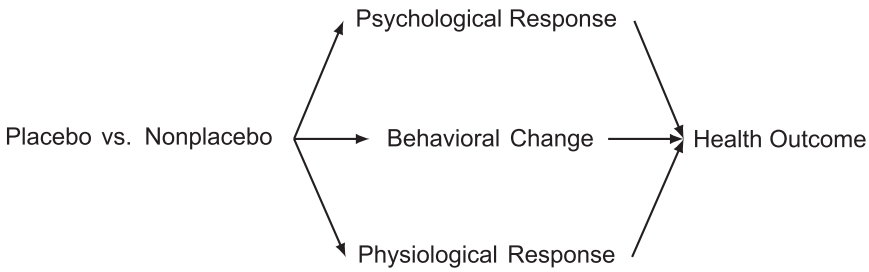

Figure 1. Possible mechanisms through which a placebo might act upon an outcome. The appropriate choice of nonplacebo control will depend on which mechanism is of interest. The nonplacebo control should be hypothesized not to operate via the mechanism of interest.

counterfactual outcome under some other nontherapeutic exposure, including no exposure. Note that although $Y^{z=0}$ and $Y^{z=-1}$ are defined for all individuals, at maximum, only one of these outcomes is ever actually observable for any given individual.

Similarly, we define $Y^{x=0}$ as the outcome that would be observed when someone receives placebo regardless of randomization, $Y^{x=-1}$ when someone receives the nonplacebo control, and joint counterfactuals such as $Y^{(z=0,x=0)}$ when someone is randomized to and receives placebo.

Finally, we define t as an indicator of follow-up time, with $t = 0$ at baseline and $t = \tau$ at the end of follow-up.

A FORMAL DEFINITION OF THE PLACEBO EFFECT

Given that causal effects are defined with respect to a comparison exposure, the "placebo effect" as a single entity does not actually exist—any effect of placebo must include a specification of some nonplacebo control group of interest (i.e., $Z = -1$), even if that group is hypothetical. That is, we cannot talk about the causal effect of placebo; we must talk about the causal effect of placebo versus something else.

Placebos have been hypothesized to have causal effects via suggestion or other psychological mechanisms, via behavioral change, and via heretofore unknown physiological or pharmacological mechanisms (1, 7, 8, 10, 11). The ideal comparison group for a given placebo will depend on the mechanism of interest under study (Figure 1). For example, if the placebo of interest is a sham surgery hypothesized to operate via a psychological mechanism (e.g., reassurance), an appropriate nonplacebo control might be "no surgery." Alternately, we might want to know the placebo effect if everyone received sham surgery compared with everyone being required to wait for some defined time period before surgery. Importantly, even if both effects are nonzero, they might have different magnitudes or different directions.

We now formalize the 2 categories of placebo effects.

First, we can defined an "intention-to-treat placebo effect" as a comparison between the average outcome that would have been observed if everyone in the trial had been randomized to placebo versus if everyone in the trial had been randomized to the nonplacebo control.

Second, we can define the "per-protocol placebo effect" (i.e., the effect of receiving placebo) as a comparison between the average outcome that would have been observed if everyone in the trial had been randomized to placebo and actually received it versus if everyone in the trial had been randomized to some other nonplacebo control and actually received that control treatment. The per-protocol placebo effect most closely matches the concept of "placebo response" (12) in incorporating the idea of receiving placebo, not just being assigned to placebo.

On the absolute scale, using the notation and definitions above, we could write these effects as:

Intention-to-treat effect of placebo versus nonplacebo control: $E[Y^{z=0}] - E[Y^{z=-1}]$.

Per-protocol effect of placebo versus nonplacebo control: $E[Y^{z=0,x=0}] - E[Y^{z=-1,x=-1}]$.

COMMON APPROACHES TO ESTIMATING PLACEBO EFFECTS REQUIRE UNTENABLY STRONG ASSUMPTIONS

Three common approaches to estimating the placebo effect are: 1) the outcome at the end of follow-up in the placebo arm (for example, % reporting symptoms below some threshold) (13); 2) outcome change from baseline to the end of follow-up in the placebo arm (12, 14–16); and 3) comparison of placebo adherers and placebo nonadherers with no or minimal adjustment for confounding (17–20). Under very strong assumptions, these approaches could provide an estimate of a placebo effect (Figure 2). However, in nearly all cases these assumptions will be unreasonable. I briefly explain the required assumptions and why they are inappropriate (Table 1).

In addition to the specific assumptions discussed below, these all further require the assumption of no, or noninformative, loss to follow-up, and well-defined causal questions, including clear specification of what is meant by both "placebo" and "nonplacebo control."

Intention-to-treat placebo effect estimation using outcome at end of follow-up

Estimating an intention-to-treat placebo effect using the outcome at the end of follow-up requires the strongest assumptions. Because a causal effect is by definition the contrast between 2 counterfactual outcomes, this method implicitly assumes that the counterfactual outcome under the (unspecified) nonplacebo control would have been exactly zero.

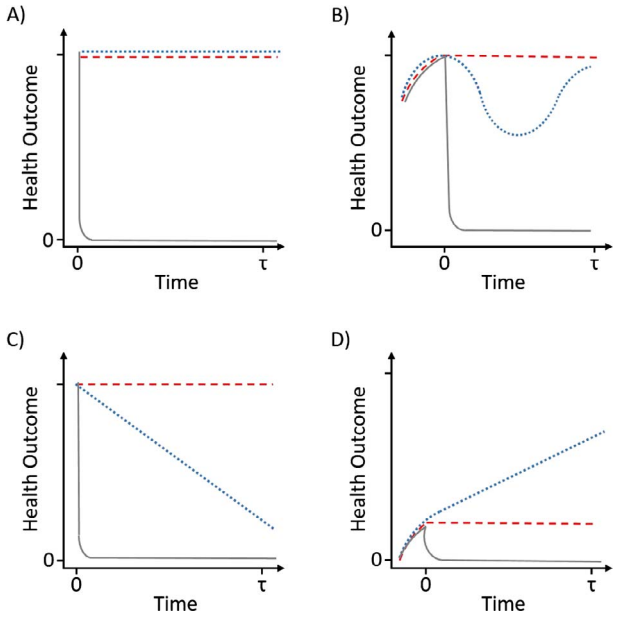

Figure 2. Four hypothetical trajectories for a health outcome among individuals assigned to placebo over time. A) The outcome does not change over time for placebo-arm participants. B) The outcome is cyclic over time for placebo-arm participants. C) The outcome decreases over time for placebo-arm participants. D) The outcome increases over time for placebo-arm participants. In all, the blue dotted line represents the observed outcome trajectory for individuals in the placebo arm; the solid gray line represents the counterfactual outcome trajectory for the placebo arm, had they not been given placebo, that is assumed when the analysis uses the average outcome at the end of follow-up in the placebo arm as an estimator of the placebo effect; and the red dashed line represents the counterfactual outcome trajectory for the placebo arm, had they not been given placebo, that is assumed when the analysis uses the average difference between end of follow-up and baseline in the placebo arm as the estimator.

To see why, remember that our goal is to estimate a comparison such as $E[Y^{z=0}] - E[Y^{z=-1}]$. Under the consistency assumption, the observed outcome among individuals assigned to placebo is equal to the counterfactual outcome they would have had, had they been assigned to placebo, and randomization ensures that the exchangeability assumption is met—that is, the counterfactual outcome under placebo observed among those assigned to placebo is equal on average to the counterfactual outcome that would have been observed if everyone had been assigned to placebo (i.e., $E[Y|Z = 0] = E[Y^{z=0}]$). Therefore, in order for our estimator, $E[Y|Z = 0]$, to return a valid estimate of our causal effect of interest,$E[Y^{z=0}] - E[Y^{z=-1}]$, we must assume that the counterfactual outcome if everyone had received the nonplacebo control is exactly zero (i.e., $E[Y^{z=-1}] = 0$). Table 1 gives a proof for this intuition.

Note, this is true regardless of what zero represents. For example, for a beneficial outcome 0 might reflect complete symptom resolution, whereas for a harmful outcome it might represent 0% survival.

Intention-to-treat placebo effect estimation using change since baseline

Estimating an intention-to-treat placebo effect by comparing change in the outcome from baseline to the end of follow-up among individuals assigned to placebo is often called "placebo response" (18). Under this approach, the intention-to-treat effect of assignment to placebo versus a nonplacebo control, $E[Y_{t=\tau}{}^{z=0}] - E[Y_{t=\tau}{}^{z=-1}]$, is estimated using the observed difference in outcome measurements at baseline versus at the end of follow-up among the placebo-arm participants: $E[Y_t|Z = 0, t = \tau] - E[Y_t|Z = 0, t = 0]$.

Consistency and randomization ensure that the observed outcome at the end of follow-up among individuals assigned to placebo is a valid estimate of the counterfactual outcome at the end of follow-up if all individuals had been assigned to placebo (i.e., $E[Y_t|Z = 0, t = \tau] = E[Y_{t=\tau}{}^{z=0}]$). Now, we no longer assume the outcome in the nonplacebo control group at the end of follow-up is exactly zero. Instead, we make the slightly less strong, but still potentially unreasonable, assumption that the average observed outcome in the placebo group at the start of follow-up would be exactly equal to the average counterfactual outcome in the nonplacebo control group at the end of follow-up (i.e., $E[Y_t|Z = 0, t = 0] = E[Y_{t=\tau}{}^{z=-1}]$). That is, we assume that if the individuals assigned to the placebo arm had not been assigned to the placebo arm but instead to some other control group, their outcome values would have on average remained unchanged over the entire follow-up duration.

For some conditions, this might be a reasonable assumption. For example, if the outcome is performance on some skill-based test, values might be expected to be on average unchanged when no intervention is delivered. However, when the outcome is disease progression or symptom severity, it is often common for the outcome to worsen, improve, or fluctuate naturally over time in the absence of any medical intervention (Figure 2). Such natural changes will likely violate the assumption required for using change among placebo-arm participants as an estimator of the placebo effect. This is also a problem for analyzing change trajectories when exposures other than the placebo are of interest (6, 21)

Furthermore, in many randomized trials, the value of the outcome measurement at baseline is used as part of the trial eligibility criteria—that is, only individuals who meet some cutoff for severity will be allowed to enroll in the trial. In these cases, natural fluctuations in disease symptoms will necessarily mean that enrolled individuals are more likely to be chosen if they are at or near their peak symptom value, and any second measurement time point will be expected to show a change in outcome through the simple process of regression to the mean (22, 23).

Per-protocol placebo effect estimation assuming no confounding exists

Finally, a third common approach is to compare the outcome at the end of follow-up among individuals in the placebo arm who adhere to their assigned placebo protocol

Table 1. Potential Estimators for the Placebo Effect and Their Assumptions[a]

Estimand	Estimator	Assumptions	Proof
Intention-to-treat placebo effect			
$E[Y^{z=0}] - E[Y^{z=-1}]$	Outcome at the end of follow-up in the placebo arm: $E[Y\|Z=0]$	1. Assume partial exchangeability[b], due to random assignment of placebo. 2. Assume partial consistency[b] due to clear definition of placebo. 3. Assume $E[Y^{z=-1}]=0$.	$E[Y^{z=0}] - E[Y^{z=-1}]$ $= E[Y^{z=0}\|Z=0] - E[Y^{z=-1}]$ $= E[Y\|Z=0] - E[Y^{z=-1}]$ $= E[Y\|Z=0] - 0$ $= E[Y\|Z=0]$
$E[Y_\tau^{z=0}] - E[Y_\tau^{z=-1}]$	Change since baseline in the placebo arm: $E[Y_\tau\|Z=0,t=\tau] - E[Y_\tau\|Z=0,t=0]$	1. Assume exchangeability[c] by end of follow-up. 2. Assume consistency[c]. 3. Assume $E[Y_\tau\|Z=-1,t=\tau]=E[Y_\tau\|Z=-1,t=0]$ (i.e., no outcome change in the absence of placebo) and $E[Y_t\|Z=-1,t=0]=E[Y_t\|Z=0,t=0]$ (i.e., equivalent baseline values).	$E[Y_\tau^{z=0}] - E[Y_\tau^{z=-1}]$ $= E[Y_\tau^{z=0}\|Z=0,t=\tau] - E[Y_\tau^{z=-1}\|Z=-1,t=\tau]$ $= E[Y_\tau\|Z=0,t=\tau] - E[Y_\tau\|Z=-1,t=\tau]$ $= E[Y_\tau\|Z=0,t=\tau] - E[Y_\tau\|Z=0,t=0]$
Either of the above	Explicit nonplacebo control group: $E[Y\|Z=0] - E[Y\|Z=-1]$	1. Assume exchangeability[c]. 2. Assume consistency[c].	$E[Y^{z=0}] - E[Y^{z=-1}]$ $= E[Y^{z=0}\|Z=0] - E[Y^{z=-1}\|Z=-1]$ $= E[Y\|Z=0] - E[Y\|Z=-1]$
Either of the above	Comparison of placebo arm with individuals not enrolled in the trial with control for known and measured confounding: $\sum_{\mathbf{L}} E[Y\|Z=0,\mathbf{L}]f[\mathbf{L}] - \sum_{\mathbf{L}} E[Y\|X=-1,\mathbf{L}]f[\mathbf{L}]$	1. Assume conditional exchangeability[d] by end of follow-up, given a set of confounders $\mathbf{L}$. 2. Evaluate at the counterfactual. 3. Assume $X=-1$ is equivalent to $Z=-1$. 4. Assume consistency of $Z=0$ for $z=0$ and of $X=-1$ for $z=-1$.	$E[Y^{z=0}] - E[Y^{z=-1}] = \sum_l E[Y^{z=0}\|Z,\mathbf{L}]f[\mathbf{L}] - \sum_l E[Y^{z=-1}\|Z,\mathbf{L}]f[\mathbf{L}]$ $= \sum_l E[Y^{z=0}\|Z=0,\mathbf{L}]f[\mathbf{L}] - \sum_l E[Y^{z=-1}\|Z=-1,\mathbf{L}]f[\mathbf{L}]$ $= \sum_l E[Y^{z=0}\|Z=0,\mathbf{L}]f[\mathbf{L}] - \sum_l E[Y^{z=-1}\|X=-1,\mathbf{L}]f[\mathbf{L}]$ $= \sum_l E[Y\|Z=0,\mathbf{L}]f[\mathbf{L}] - \sum_l E[Y\|X=-1,\mathbf{L}]f[\mathbf{L}]$
Either of the above	Comparison of placebo adherers and nonadherers with no confounding control: $E[Y\|Z=0,X=0] - E[Y\|Z=0,X=-1]$	1. Assume joint exchangeability[e] for Z and X. 2. Assume consistency for Z and X, such that the observed outcome under $(Z=0,X=-1)$ is equivalent to the counterfactual outcome under $(z=-1,x=-1)$.	$E[Y^{z=0,x=0}] - E[Y^{z=-1,x=-1}]$ $= E[Y^{z=0,x=0}\|Z=0,X=0] - E[Y^{z=-1,x=-1}\|Z=-1,X=-1]$ $= E[Y^{z=0,x=0}\|Z=0,X=0] - E[Y^{z=-1,x=-1}\|Z=0,X=-1]$ $= E[Y\|Z=0,X=0] - E[Y\|Z=0,X=-1]$

Table continues

Table 1. Continued

Estimand	Estimator	Assumptions	Proof
Per-protocol placebo effect $E[Y^{z=0,x=0}] - E[Y^{z=-1,x=-1}]$	Comparison of placebo adherers and nonadherers with no confounding control: $E[Y\|Z=0,X=0] - E[Y\|Z=0,X=-1]$	1. Assume joint exchangeability[e] for Z and X. 2. Assume consistency for Z and X, such that the observed outcome under $(Z=0,X=-1)$ is equivalent to the counterfactual outcome under $(z=-1,x=-1)$.	$E[Y^{z=0,x=0}] - E[Y^{z=-1,x=-1}]$ $= E[Y^{z=0,x=0}\|Z=0,X=0] - E[Y^{z=-1,x=-1}\|Z=-1,X=-1]$ $= E[Y^{z=0,x=0}\|Z=0,X=0] - E[Y^{z=-1,x=-1}\|Z=0,X=-1]$ $= E[Y\|Z=0,X=0] - E[Y\|Z=0,X=-1]$
	Comparison of placebo adherers and placebo nonadherers confounding is known and measured: $\sum_{\mathbf{L}} E[Y\|Z=0,X=0,,\mathbf{L}]f[\mathbf{L}\|Z=0] - \sum_{\mathbf{L}} E[Y\|Z=0,X=-1,\mathbf{L}]f[\mathbf{L}\|Z=0]$	1. Assume joint conditional exchangeability[f] for Z and A, and evaluate at the counterfactual. 2. Assume conditional independence of the counterfactual from Z, given X and L (i.e., exclusion restriction: Random assignment only affects outcome via the intervention received). 3. Assume consistency for Z and X, such that the observed outcome under $(Z=0,X=-1)$ is equivalent to the counterfactual outcome under $(z=-1,x=-1)$	$E[Y^{z=0,x=0}] - E[Y^{z=-1,x=-1}]$ $= \sum_l E[Y^{z=0,x=0}\|X=0,\mathbf{L},Z=0]f[\mathbf{L}\|Z=0] - \sum_l E[Y^{z=-1,x=-1}\|X=-1,\mathbf{L},Z=-1]f[\mathbf{L}\|Z=-1]$ $= \sum_l E[Y^{z=0,x=0}\|X=0,\mathbf{L},Z=0]f[\mathbf{L}\|Z=0] - \sum_l E[Y^{z=-1,x=-1}\|X=-1,\mathbf{L},Z=0]f[\mathbf{L}\|Z=0]$ $= \sum_l E[Y\|X=0,\mathbf{L},Z=0]f[\boldsymbol{L}\|Z=0] - \sum_l E[Y\|X=-1,\boldsymbol{L},Z=0]f[\mathbf{L}\|Z=0]$

[a] Variable definitions: Y denotes the outcome at the end of follow-up. Z represents random assignment, with $Z=0$ for the placebo arm and $Z=-1$ for the nonplacebo comparator arm. A denotes actual treatment received, where $X=0$ for individuals who receive the placebo regardless of treatment assignment. $\mathbf{L}$ represents all other covariates of interest. Superscripts indicate counterfactuals.

[b] Partial exchangeability means that the counterfactual outcome under a given treatment assignment, Y^z, is independent of the actual treatment assignment received, for individuals within the placebo arm $(Z=0)$. Similarly, partial consistency means that the counterfactual outcome under a given treatment assignment, Y^z, is equal to the observed outcome for individuals actually assigned to the placebo arm $Z=0$.

[c] Exchangeability means that the counterfactual outcome under a given treatment assignment Y^z, is independent of the actual treatment assignment for all values of $Z=z$. Similarly, consistency means that the counterfactual outcome under a given treatment assignment, Y^z, is equal to the observed outcome for individuals actually assigned to the placebo arm $Z=0$.

[d] Conditional exchangeability means that the counterfactual outcome under a given treatment assignment Y^z, is independent of the actual treatment assignment, conditional on some set of measured covariates, $\mathbf{L}$, for all values of $Z=z$.

[e] Joint exchangeability means that the counterfactual outcome under a given combination of treatment assignment and adherence level, $Y^{z,x}$, is jointly independent of the actual assignment and adherence levels, Z and X for all $Z=z$ and $X=x$.

[f] Joint conditional exchangeability means that the counterfactual outcome under a given combination of treatment assignment and adherence level, $Y^{z,x}$, is jointly independent of the actual assignment and adherence levels, Z and X for all $Z=z$ and $X=x$, conditional on some set of measured covariates, $\mathbf{L}$.

with the outcome among individuals in the placebo arm who do not adhere to their assigned placebo protocol. Under some assumptions, this can provide an estimate of the per-protocol effect of placebo versus nonplacebo control. In fact, this approach is not in itself an unreasonable method in that the placebo nonadherers might, in many cases, provide a reasonable estimate of the outcome expected from a control group that had received all study care except the specific placebo medication (i.e., a nonplacebo control group).

However, most implementations of this approach in the literature have made the strong assumption that adherence or nonadherence to placebo is either entirely random, or is predicted only by baseline (prerandomization) covariates regardless of the duration of treatment (17, 20, 24, 25). This is an extremely strong assumption of no confounders (common causes) of the adherence-outcome relationship, and when violated it can lead to extremely large estimates of the placebo effect even where none exist (9, 20, 26–28).

AN IMPROVED FRAMEWORK FOR ESTIMATING PLACEBO EFFECTS

The approaches described above have been widely used to estimate placebo effects, with little recognition or discussion of the required assumptions to endow these estimates with a causal interpretation (12, 14–16). For example, a recent meta-analysis of placebo-arm "response rates" for ulcerative colitis found 64 studies that reported rates of symptom response in the placebo arm and concluded that placebo response rate was highest among those trials with the most stringent symptom inclusion criteria (29). Furthermore, a search of the National Center for Biotechnology Information's PubMed for "placebo effect" returns over 6,000 articles, but less than 50 of these also mention "causal" or "causal inference."

The required causal assumptions for estimating a placebo effect using the methods described above are strong and likely unrealistic for almost all randomized trials. However, this does not mean that placebo effects cannot be validly estimated. Instead, researchers interested in the causal effects of placebo versus nonplacebo controls should use methods that rely on weaker, potentially more reasonable, assumptions, beginning with a clear identification of the causal question of interest, hypothesized mechanism of placebo effect, and selection of appropriate nonplacebo control group.

Intention-to-treat placebo effect estimation using an explicit nonplacebo control group

When the intention-to-treat placebo effect is of interest, the approach that makes the fewest assumptions, and is therefore the most likely to provide a valid effect estimate, is to design a trial in which individuals can be randomized to both placebo control and nonplacebo control arms (3). Such a trial could also include an active treatment arm but need not, as with a recent randomized trial of placebo versus study visits only for assessing potential psychological benefits of placebo in irritable bowel disease symptom relief (10). This intention-to-treat placebo effect might still need to be adjusted for loss to follow-up, but it can otherwise be validly obtained via a simple comparison of the outcome at the end of follow-up in the 2 control arms (30). In fact, this is the only approach guaranteed to validly estimate the intention-to-treat effect of placebo versus an explicit nonplacebo control.

Intention-to-treat placebo effect estimation assuming confounders are known and measured

Alternatively, the intention-to-treat placebo effect could, in some cases, be estimated by comparing the outcome among individuals randomly assigned to the placebo arm and individuals who were eligible to participate in the randomized trial but who declined to participate or were not contacted for enrollment. This comparison no longer has the guarantee of validity, because individuals who enrolled in the trial might be systematically different from individuals who did not enroll in the trial. However, with careful adjustment for all variables that both predict trial enrollment and are prognostic for the outcome, an estimate of the intention-to-treat placebo effect could be obtained.

This estimate makes the somewhat stronger assumption that all confounders for trial participation and the outcome are known, measured, and appropriately accounted for in the analysis (for example, via standardization). While there might be scenarios under which this assumption is not plausible, it is much less strong that the previously discussed common assumptions that the nonplacebo control outcome is on average exactly zero or equal to the baseline value in the placebo arm.

This method also requires assumptions about positivity or overlap. That is, individuals selected as members of the control group must have been eligible to be trial participants. Individuals who were rejected from the trial due to failure to meet inclusion requirements or because they met 1 or more exclusion criteria should therefore not be included in the comparison group. In addition, if all individuals with a specific set of covariates had refused invitations to participate in the trial, despite having been eligible, then there will also not be positivity, and individuals with these same characteristics should also be excluded from the control group.

Per-protocol placebo effect estimation assuming confounders are known and measured

Finally the per-protocol placebo effect could be estimated from a trial in which individuals are randomized to both placebo and nonplacebo controls, and adherence to each is collected. The per-protocol placebo effect could also be estimated by comparing placebo-arm adherers and placebo-arm nonadherers whenever the nonplacebo control of interest is similar to the experience of placebo-arm nonadherers (for worked examples see Murray and Hernán (26, 27)). Both of these approaches require the assumption that all confounders for adherence and the outcome are known, measured, and appropriately adjusted for in the analysis.

For trials where intervention and control care is delivered only once (so-called point interventions), prerandomization or baseline confounders will be sufficient, and any analytical

method that accounts for these confounders can provide an unbiased estimate of the per-protocol placebo effect. However, in many trials, interventions and controls are delivered at multiple time points (sustained interventions). In these cases, confounding should be assessed throughout follow-up. Whenever any confounders are suspected to also be caused by prior adherence to placebo, adjustment must be made using g-methods, which can account for adherence-confounder feedback (30, 31).

CONCLUSION

The terms "placebo effect" and "placebo response" are generally used to imply that, through some psychological or biological process or some change in other health or risk behaviors, individuals who take a placebo treatment experience improvement in health outcomes relative to what would have been expected if they had not taken placebo (2, 3, 11, 13, 23). This implies that a per-protocol placebo effect is of most interest. However, there are several key methodological biases which prohibit the interpretability of many placebo effect estimates.

First and foremost, the placebo effect cannot be defined without reference to a clear nonplacebo control. The placebo effect of a sugar pill versus no study contact might be different from the placebo effect of the same sugar pill versus regular study visits. The appropriate control group will depend on the mechanism of interest for the specific health condition, placebo, population, and outcome of interest.

Second, many reported placebo effects rely on extremely strong assumptions about the expected value of the outcome among the study individuals if they had received a hypothetical nonplacebo control, rather than collecting data on a control group of individuals who do receive a nonplacebo control. When these assumptions are incorrect, we might falsely conclude there is no placebo effect even though a placebo effect does exist, or the existence of a placebo effect when there is truly no placebo effect. Furthermore, in the absence of an explicit nonplacebo control group, regression to the mean is an extremely likely source of spurious conclusions about the size and direction of the placebo effect (23).

Finally, even when explicit control groups are used to estimate what would have happened to placebo-arm participants if they had not received placebo, control for confounding both at baseline and postrandomization might be needed (30). It is not uncommon for researchers to assume no confounding at all or to assume only baseline confounding despite lengthy follow-up and sustained placebo treatment. Table 1 summarizes the required assumptions for the methods discussed in this paper to provide valid estimates of causal effects.

The concepts presented in this paper apply to causal inference in applications other than the placebo effect. Whenever the goal is to estimate a causal effect, clear causal estimands and questions with explicit comparison groups must be specified. Assumptions about the relationships between available observed data and the desired counterfactual contrast must be made, and analyses of change in outcomes, single-group outcomes, or outcomes adjusted only for confounders at a single time point are likely to be biased whenever the strong assumptions described in this work are violated.

Placebo effects are in many ways an oxymoron, and yet many people believe that they exist, at least for self-reported or subjective health outcomes. However, without more rigorous definition and investigation of these effects, the existence of placebo effects cannot be scientifically supported or refuted. Investigators interested in the possible psychological, behavioral, or physiological effects of placebos should clarify the reference group of interest, use an appropriate study design to reduce the reliance on unreasonable assumptions, and estimate both intention-to-treat and per-protocol placebo effects with appropriate control for confounding and loss to follow-up, following the same guidelines as the investigation of any other causal effect of a medical intervention.

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