

Philosophy *of* Medicine

Letter

The Adverse Event Paradox

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The placebo effect has a sibling, known as the nocebo effect, which is the expectation by study participants that they will experience negative, treatment-related effects (adverse events). In a similar fashion to the placebo effect, nocebo effects have been studied and shown to impact the control arm of trials (Colloca and Miller 2011). Prior to the start of clinical trials, prospective participants are required to express their consent to the study protocol and, depending on the kind of trial (for example, Phase I, II, III, IV, and so on), any negative effects of the treatment may be well known. It is part of the consent process to inform prospective study participants of potential negative effects that have been linked with the treatment in previous trials—without this knowledge the consent obtained could not be rightfully called “informed.” For participants, this means that should they consent and enter the trial, they know what negative effects are likely; their expectations for improvement are then bound up, to some real psychological extent, with their experience of adverse events (Kirsch 2010). Adverse events are paradigmatic of active treatments—in some sense medications do not have side effects; they only have positive and negative effects based on what the individual taking the medication hopes to achieve. And if one hopes to achieve improvement with respect to some ailment, one may also expect to experience adverse events, the very same adverse events communicated prior to the onset of the study.

The adverse event paradox (AEP) arises because the same logic behind comparing placebo to treatment with respect to improvement ought to be applied to the comparison of adverse events. Participants may improve as a result of their expectations of a positive outcome—the placebo effect—and should all participants receive active medication, researchers would be unable to identify whether improvement was the result of the drug or the placebo effect. For this reason, a placebo arm is used and the true drug effect is calculated by comparing improvement on the placebo to improvement on the drug to discover the effect size of the treatment and/or a statistically or clinically significant difference in improvement. Participants in the control group tend to experience adverse events and, in some cases, the adverse events experienced are common across both groups (see, for example, Wang et al. 2020). This is most likely because all participants have been briefed on the potential adverse events and so they all expected them. When the adverse events experienced by both groups are similar and present at similar rates, the AEP is at



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play because researchers need to judge the comparison between adverse events across groups in the same way they compare improvement across groups—this is the fundamental reason for using a placebo control arm in the first place.

For illustrative purposes, consider the following trial: the control arm experienced an incidence of adverse events of 35 percent and the experimental arm experienced such events at 37 percent. Thus, the drug effect must have *only* contributed 2 percent to the experience of adverse events. If this difference is not statistically significant, it is the result of chance; or if there is no absolute difference (for example, adverse events are 35 percent for both groups), no difference can be said to have been observed. The same would be true in trials where participants in the placebo arm experience more adverse events than those taking the active medication. Thus, in its simplest form the paradox is as follows:

- i. Placebos are used in randomized controlled trials (RCTs) to judge the true effects of drugs by contrasting improvement on the drug with improvement on the placebo and concluding the difference to be the true drug effect.
- ii. Drug safety is computed by comparing adverse events for those on the drug with adverse events for those on the placebo.
- iii. The comparison of adverse events ought to occur in the same manner as the comparison of improvement, which means that if there is no difference (statistically, clinically, and so on), the drug ought to be claimed to produce no adverse effects.

What is paradoxical is that (iii) certainly cannot reflect the reality of drug effects because it would mean that a great many medications produce no negative effects beyond those brought about by nocebo. This is seen in the RCT literature: treatment and control arms experience similar incidences of adverse events. For example, Yeming Wang and colleagues' trial on remdesivir (2020) found similar incidences of adverse events in both treatment and control arms, whereas John H. Beigel and colleagues' trial on remdesivir (2020) found more grade 3 or 4 and more serious adverse events in the placebo group. Similarly, in their study of nirmatrelvir plus ritonavir, Jennifer Hammond and colleagues (2022) found the placebo arm actually saw more overall adverse events, more serious adverse events, and more discontinuation as a result of adverse events. Remdesivir and nirmatrelvir plus ritonavir are antivirals for Covid-19 and this may be biasing but this is also observed in studies on naltrexone, an opioid antagonist. In their review of adverse events of placebo trials on naltrexone, Monica Bolton and colleagues concluded that their "systematic review and meta-analysis found no evidence of a difference in risk of SAEs [serious adverse events] for oral naltrexone compared to placebo" (2019, 11). The literature shows that RCTs do exhibit results that are indicative of the AEP: the placebo arms all experienced similar incidences of adverse events compared to the treatment arms. Such experiences can be explained by the nocebo effect, which renders the adverse events a product of one's psychology and not the active ingredients in the medication.

The AEP lies in the logic of using a placebo arm and in the fact that RCTs do report similar incidences of adverse events on placebo and active medication. Researchers cannot simply dismiss adverse events experienced by the control arm, nor can they refuse to compare adverse events in the same way as they compare improvements. The paradox is that researchers appear unable to claim that active medication produces adverse events because this would either undermine the logic of placebo RCTs or dismiss the nocebo effect. What is open to researchers is to show how active medication produces adverse events beyond the nocebo effect and/or to show error and bias in coding, collection, or analysis of

adverse events, which unnecessarily inflates adverse events in placebo arms or underestimates adverse events in treatment arms.

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