

# Harmful placebos

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Harmful placebos. Credit: [Shutterstock](#)

How could a sugar pill placebo cause harm? A new review of data from 250,726 trial participants has found that 1 in 20 people who took placebos in trials dropped out because of serious adverse events (side effects). Almost half of the participants reported less serious adverse events. The adverse events ranged from abdominal pain and anorexia to burning, chest pain, fatigue, and even death.

The study found that the apparently strange phenomena of sugar pills producing [harm](#) can be explained by misattribution and negative

expectations.

## Misattribution

Someone in a trial might have a symptom like a stomach ache for any number of reasons that are not related to the trial. Because they are in a trial, they think the trial intervention caused the ache. This gets reported as an adverse event when it would have happened anyway.

## Negative expectations

The way patients are warned about adverse events can sometimes cause an adverse event. Effects of negative expectations are called 'nocebo' ('negative placebo') effects. "Our study provided preliminary data indicating that some trial participants experience nocebo effects," reports lead author Jeremy Howick. Other studies provide more definitive evidence that the way patients are warned about adverse events can affect whether they report them. For example, a study found that patients in a randomised trial of aspirin or sulfinpyrazone for treating unstable angina who were warned about gastrointestinal adverse events were six times more likely to withdraw from the study due to reported gastrointestinal adverse events. A more recent study published last year in *The Lancet* found that patients were more likely to report adverse events when they knew they were taking statins, compared to when they didn't. This is probably because the belief that statins cause adverse events like muscle pain can actually produce the muscle pain.

Finding ways to reduce adverse events among patients in [placebo](#) groups is important for improving trial quality (since fewer participants will drop out), and improving trial ethics (by avoiding harm). The question is: how?

"Misattribution can be hard to avoid," says Jeremy Howick, 'because it's

hard for someone to know whether a symptom like a stomachache would have occurred anyways or whether it was because of the trial. However, I believe we can reduce the harm caused by negative expectations."

For example, telling patients that a new treatment is safe for 90% of patients contains the same information as saying it causes adverse events like headaches in 10% of patients. But the second way may be more likely to actually cause the [adverse events](#) than the first.

Unfortunately, guidance for informing trial participants about trial intervention harms, in a way that is ethical, understandable, and does not produce nocebo effects, is currently under-researched. A recent study suggested that information provided to trial participants often fails to tell them what they wish to know, and that it is presented in a way that is difficult to understand. Ongoing research at the Universities of Oxford and Cardiff is looking at ways to inform patients in [trials](#) about the best way to provide balanced information about the benefits and harms of participating in trials. Their preliminary research suggests that patients are provided more information about trial harms than trial benefits.

Says co-author Professor Kerry Hood (Director of Cardiff Centre for Trials Research): "We believe it is possible to balance the information about trial benefits and harms in a way that is fact-based and that does not cause unnecessary harm. This can be achieved by ensuring that the benefits, as well as the harms, are explained in a way [patients](#) understand."

The full paper, "Rapid Overview of Systematic Reviews of Nocebo Effects Reported by Patients Taking Placebos in Clinical Trials," is published in *Trials*.

**More information:** Jeremy Howick et al. Rapid overview of systematic reviews of nocebo effects reported by patients taking

placebos in clinical trials, *Trials* (2018). DOI: [10.1186/s13063-018-3042-4](https://doi.org/10.1186/s13063-018-3042-4)

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