No standard for the placebo?

October 18 2010

Much of medicine is based on what is considered the strongest possible evidence: The placebo-controlled trial. A paper published in the October 19 issue of *Annals of Internal Medicine* – entitled "What's In Placebos: Who Knows?" calls into question this foundation upon which much of medicine rests, by showing that there is no standard behind the standard – no standard for the placebo.

The thinking behind relying on placebo-controlled trials is this: to be sure a treatment itself is effective, one needs to compare people whose only difference is whether or not they are taking the drug. Both groups should equally think they are on the drug – to protect against effects of factors like expectation. So study participants are allocated "randomly" to the drug or a "placebo" – a pill that might be mistaken for the active drug but is inert.

But, according to the paper's author, Beatrice Golomb, MD, PhD, associate professor of medicine at the University of California, San Diego School of Medicine, this standard has a fundamental problem, "there isn't anything actually known to be physiologically inert. On top of that, there are no regulations about what goes into placebos, and what is in them is often determined by the makers of the drug being studied, who have a vested interest in the outcome. And there has been no expectation that placebos' composition be disclosed. At least then readers of the study might make up their own mind about whether the ingredients in the placebo might affect the interpretation of the study."

Golomb pointed out these limitations to the placebo in a pair of letters to

the journal Nature 15 years ago.

"A positive or negative effect of the placebo can lead to the misleading appearance of a negative or positive effect of the drug," she said. "And an effect in the same direction as the drug can lead a true effect of the drug to be lost. These concerns aren't just theoretical. Where the composition has been disclosed, the ingredients of the placebo have in some instances had a likely impact on the result of the study – in either direction (obscuring a real effect, or creating a spurious one). In the cases we know about, this is not because of any willful manipulation, but because it can in fact be difficult to come up with a placebo that does not have some kind of problem."

Since 15 years have elapsed, the situation might have improved. Therefore, Golomb and her colleagues analyzed just how often randomized trials published in the past two years in each of the top four general medical journals actually disclosed the makeup of placebos.

The answer is not reassuring, according to the researchers, who found that the placebo ingredients for pills were disclosed in fewer than 10 percent of cases. (The nature of the "control" was significantly more likely to be stated for other types of treatments – like injections, acupuncture, or surgery – where people are more likely to question what "placebo" actually means.)

"How often study results are affected by what's in the placebo is hard to say – because, as this study showed, most of the time we have no idea what the placebo is," Golomb concluded.

Provided by University of California -- San Diego