

## Abstract

**Background:** Placebos are commonly employed in clinical trials as inactive treatments to which experimental treatments are compared against in order to control for psychological “noise.” Randomized double-blind placebo control studies are considered the “gold standard” in epidemiologic research because they can provide the strongest possible evidence of causation if designed correctly. One phenomenon that poses a threat to the integrity of this evidence is the placebo response (PR), or popularly referred to as the “placebo effect.” Expectancy is considered a central PR mechanism and boasts the most empirical support among all proposed mechanisms. Expectancy is not limited to treatment efficacy. Experimental variables also affect expectancy and subsequent PR. Unlike standard clinical care, there is no guarantee that subjects in a randomized placebo control trial will receive experimental treatment. This uncertainty affects expectancy and subsequent PR. The randomization ratio (RR) represents the distribution of subjects across conditions and thus the probability of receiving either experimental or placebo treatment. It can be considered a numerical representation of uncertainty. The RR of 1:1 (50-50 chance of being randomized to experimental or placebo condition; maximum uncertainty) has long been considered the norm, but an increasing number of trials have begun employing unbalanced RR, mainly to conserve resources (e.g., multi-armed trials). RR can have a significant impact on the outcome of the trial. It influences subjects’ perception of the trial, decision to participate, and both rate and strength of the drug response (DR) and PR. Studies generally agree that larger allocation to experimental treatment (and smaller allocation to placebo) result in increased DR and PR. However, there are many limitations in the available evidence that make reaching this conclusion tentative. **Objectives:** The purpose of the current study was to determine the extent to which RR moderates the PR (within the U.S. general population). **Methods:** The experiment included eight groups with varying randomized ratios and employed a performance-based measure that was successfully enhanced by a placebo treatment. **Results:** A monotonic trend was observed between the randomization ratio and the magnitude of the placebo response, such that greater placebo responses were observed in groups with greater likelihoods of receiving active treatment. **Conclusion:** The results of this study provides support for the theory that the randomization ratio employed can affect the placebo response.