

Placebo: history and impact on clinical trials outcome  
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Superstitions and lack of experimental science dominated the first several thousand years of human history. Experimental science in the second millennium was associated with a better understanding of natural causes of diseases and therefore invented effective remedies to some but it heavily suffered from subjectivity and misinterpretations until the introduction of double blind placebo controlled clinical trials in the mid of the last century which have become the most valid method of proving efficacy of new agents. However, these trials have become so restricted by inclusion and exclusion criteria and regulations that their results are barely generalizable. Furthermore, increased placebo effect especially over the last 30 years has been responsible for failure to reproduce results of old trials and for failure of trials to achieve statistical significance despite the use of legitimate investigational agents. Furthermore, the content of placebo is not regulated and may affect the outcome. Placebo effect is produced by many factors including natural history of the illness, change in the participants life style, regression to the mean, improved practitioners performance, expectations and conditioning. The share of these factors is not the same and depends on the studied outcome and type of the trial. Studies on pain such as diabetic neuropathy and migraine and on Parkinson disease are associated with the highest placebo effect (20-40%) and expectation of benefit seems to play a major role. Studying the neurobiology of placebo provided a better understanding of its mechanism and validated its pathways, genetics, and cultural variations. Methods were introduced to reduce the placebo effect including changing studies designs and outcome measures, and excluding subjects with high placebo response (with certain baseline characteristics). So far, none of these methods could change the trials size of effect. On the other hand, the placebo effect can be augmented to achieve a better clinical benefit in the health care arena by introducing excitement in its form, shape, color and method of administration.