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The placebo effect revisited: Lessons learned to date

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KEYWORD

Placebo effects

Summary This article summarizes six lessons that can be learned from over a half century of scientific research on the placebo effect. These lessons are that the placebo response is not the placebo effect, it is meaningless to ask what the magnitude of the placebo effect is, it is easy to be fooled by regression artifacts, expectancy and conditioning are not conflicting processes that can be pitted against each other, some of our questions can be answered by history, and the outcomes of active treatments can be enhanced by attention to placebo components.
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Lesson 1: the placebo response is not the placebo effect

The terms ‘placebo response’ and ‘placebo effect’ are sometimes used interchangeably, but they are not, in fact, the same thing. A treatment response is the change that one observes following the administration of the treatment (*post hoc*). A treatment effect is the change produced by the treatment (*propter hoc*). It is a fundamental rule of logic that *post hoc* does not imply *propter hoc*. Placebo controls are used in randomized clinical trials to prevent this logical error. The drug effect is not the drug response; rather, it is the difference between the drug response and the placebo response. By the same token, the placebo effect is the difference between the placebo response and the changes that would be observed even without the administration of a placebo. To assess the placebo effect, one has to subtract changes due to the natural history of the disorder and regression toward the mean.

As an example of how different placebo effects can be from placebo responses, consider one-month remission rates

of the common cold. The placebo response will be close to 100%. The placebo effect will be nil.

Lesson 2: there is no unitary placebo effect

Various researchers have attempted to assess the magnitude of placebo responses and effects.^{1,2} The underlying assumption of these discussions is that there is a single placebo effect, the magnitude of which can be determined. In fact, there are multiple placebo effects, and their magnitudes depend on a variety of factors. They depend, for example, on the condition being treated. Substantial placebo effects have been found in the treatment of depression and irritable bowel syndrome,^{3,4} but not for infertility, bacterial infections, the common cold, hyperglycemia, cervical dilatation, or marital discord, all of which were included in meta-analytic assessments of the placebo effect.⁵

Placebos responses also vary as a function of the nature of the placebo. In the treatment of Parkinson’s disease, for example, the response to placebo pills is very small, whereas the response to placebo surgery is large.⁶ “How large is the placebo effect?” is a question that cannot be answered meaningfully. It is akin to asking how powerful medical treatment is, without specifying the condition being treated or the treatment being used.

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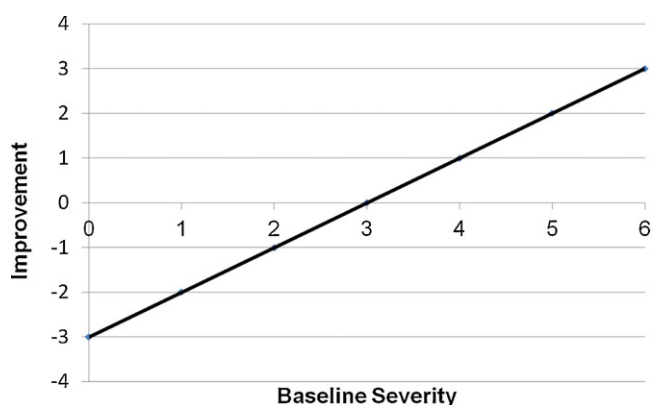


Figure 1 Improvement as a function of baseline severity, based on the distribution of baseline and post-treatment scores displayed in Fig. 2.

Lesson 3: don't be fooled by regression artifacts

The claim is sometimes made that the response to some treatment is related to the severity of the condition being treated. Fig. 1 displays a hypothetical relationship between baseline severity and improvement following treatment. The relationship is substantial; the correlation is a whopping .71.

Fig. 2 shows the distribution of baseline and post-treatment scores from which Fig. 1 was obtained. Notice that there is no relation between the baseline and post-treatment scores, and both distributions are reasonably close to normal curves. The correlation of .71 is simply what one might expect by chance when difference scores between two random variables are correlated with the score on one of them. That is the statistical artifact known as regression toward the mean.

Every researcher knows about regression toward the mean, but that does not always keep them from being taken in by it. I learned this lesson the hard way, after having reported a .90 correlation between the placebo response and drug response in a meta-analysis of antidepressants.³ The magnitude of this correlation was too high to be true, and indeed, it was at least partially due to regression toward the mean. What I had neglected to take into account was

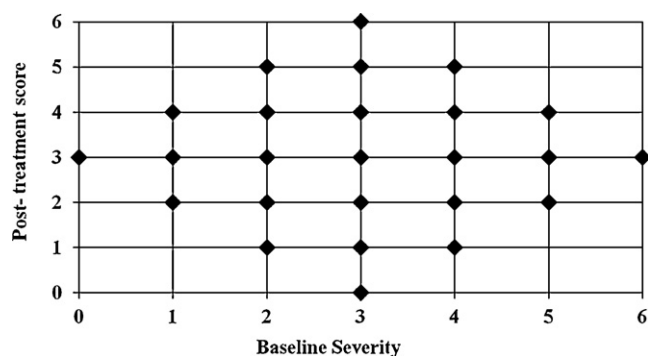


Figure 2 Distribution of baseline and post-treatment scores that generate the relationship between improvement and baseline severity displayed in Fig. 1.

the fact that drug and placebo baseline scores were correlated, because different studies and different minimum entry criteria that applied to both the drug arm and the placebo arm of the trial. The high correlation between drug and placebo improvement was due to the facts that (1) the drug and placebo baseline scores were correlated with each other, and (2) baseline scores are correlated with improvement scores, because of regression toward the mean.

Lesson 4: expectancy and conditioning are not conflicting processes

Conditioning and expectancy are sometimes pitted against each other as opposing processes. In fact, they are not. Contemporary theories of conditioning stress that classical conditioning, even in animals, is a process in which information about the environment is learned, so that behavior can be adjusted accordingly.^{7,8} In other words, conditioning is the process by which expectancies are learned.

With respect to placebo effects, the mediation of conditioning effects by cognition has been shown in studies using surreptitious lowering of the intensity of a pain stimulus as a conditioning procedure.⁹⁻¹¹ In these studies, acute pain is induced experimentally to two locations on participants' arms, one where a placebo has been applied and the other where no placebo has been applied. During the conditioning phase, the intensity of the pain stimulus is reduced only at the location where the placebo had been applied. This procedure greatly increases the placebo effect during the subsequent test phase, during which the intensity is the same at both locations. However, this effect depends on keeping the information about the lowering of stimulus intensity hidden from the participants. When they are told the intensity is being lowered, the conditioning does not work.⁹⁻¹¹

Lesson 5: learn from history

Although direct experience (e.g., conditioning) is the most powerful way of inducing and altering expectancies, they can also be affected by verbal communication, observation of others (a.k.a., modeling or vicarious conditioning), and other sources of information. These too can play an important role in producing placebo effects. In fact, placebo effects cannot be just conditioned responses. As Shapiro and Shapiro noted, "until recently, the history of medical treatment is essentially the history of the placebo effect."¹² These treatments included bloodletting, lizard's blood, crocodile dung, pig's teeth, putrid meat, fly specs, frog's sperm, powdered stone, human sweat, worms, spiders, furs, and feathers. The question is, what were the unconditional stimuli (i.e., active treatments) with which these were associated, allowing them to become conditional stimuli (i.e., placebos)?

Lesson 6: enhance the placebo component of treatment

Placebo effects do not require placebos. That is because even active medical treatments have placebo components.

This is a corollary of lesson 1, in which I distinguished between responses and effects. The response to an effective medical treatment is made up of various components. These may include a treatment effect (the treatment response minus the placebo response), a placebo effect (the difference between the placebo response and no treatment at all), the natural history of the disorder, and regression toward the mean. There are circumstances in which placebo and drug effects are not additive,¹³ but these appear to be the exception rather than the rule.¹⁴ Because placebo and drug effects are usually additive, enhancing the placebo component of treatment can enhance the treatment response.

The question then becomes, how can we enhance the placebo component of a medical treatment? One answer is to spend more time with patient and take more care forming a therapeutic alliance. General practitioners may be pressed for time. In the United Kingdom, where I have been living for some years, they have about 10 min to devote a patient during a typical visit. They just do not have the time to foster a solid therapeutic relationship. This constriction may have a cost in terms of treatment outcome.

Data from a study conducted by members of the Program in Placebo Studies (PiPS) show the benefit of the taking the time to engender an enhanced therapeutic encounter.⁴ We randomized patients suffering from irritable bowel syndrome to either a wait list control condition, placebo treatment with a standard medical interview conducted by a neutral clinician, or the same placebo treatment with an enhanced interview, in which the clinician took the time to listen and express empathy toward the patient and confidence in the treatment. The standard placebo treatment was more effective than doing nothing at all, but the enhanced placebo was significantly more effective.

Learning this last lesson and putting it into practice may require the investment of resources to make it possible, but it is an investment that has the potential to pay off in better patient outcomes, and by fostering better outcomes, it may, in the long run, even be cost-effective.

Conflict of interest

None declared.

References

1. Beecher HK. The powerful placebo. *Journal of the American Medical Association* 1955;159(December (17)):1602–6.
2. Hróbjartsson A, Gøtzsche PC. Is the placebo powerless? Update of a systematic review with 52 new randomized trials comparing placebo with no treatment. *Journal of Internal Medicine* 2004;256:91–100.
3. Kirsch I, Sapirstein G. Listening to Prozac but hearing placebo: a meta-analysis of antidepressant medication. *Prevention and Treatment* 1998;1(Article 0002a) <http://psycnet.apa.org/journals/pre/1/2/2a/> [accessed 26.06.98].
4. Kaptchuk TJ, Kelley JM, Conboy LA, Davis RB, Kerr CE, Jacobson EE, et al. Components of the placebo effect: a randomized controlled trial in irritable bowel syndrome. *British Medical Journal* 2008;336:998–1003.
5. Hróbjartsson A, Gøtzsche PC. An analysis of clinical trials comparing placebo with no treatment. *New England Journal of Medicine* 2001;344:1594–602.
6. Goetz CG, Wu J, McDermott MP, Adler CH, Fahn S, Freed CR, et al. Placebo response in Parkinson's disease: comparisons among 11 trials covering medical and surgical interventions. *Movement Disorders* 2008;5:690–9.
7. Rescorla RA. Pavlovian conditioning: it's not what you think it is. *American Psychologist* 1988;43:151–60.
8. Kirsch I, Lynn SJ, Vigorito M, Miller RR. The role of cognition in classical and operant conditioning. *Journal of Clinical Psychology* 2004;60(April (4)):369–92.
9. Montgomery GH, Kirsch I. Classical conditioning and the placebo effect. *Pain* 1997;72(August (1–2)):107–13.
10. Watson A, El-Deredy W, Bentley DE, Vogt BA, Jones AKP. Categories of placebo response in the absence of site-specific expectation of analgesia. *Pain* 2006;126:115–22.
11. Watson A, El-Deredy W, Vogt BA, Jones AKP. Placebo analgesia is not due to compliance or habituation: EEG and behavioural evidence. *NeuroReport* 2007;18(8):771–5.
12. Shapiro AK, Shapiro E. The placebo: is it much ado about nothing? In: Harrington A, editor. *The placebo effect: an interdisciplinary exploration*. Cambridge, MA: Harvard University Press; 1997. p. 12–36.
13. Kirsch I, Rosadino MJ. Do double-blind studies with informed consent yield externally valid results – an empirical-test. *Psychopharmacology* 1993;110(March (4)):437–42.
14. Benedetti F, Maggi G, Lopiano L, Lanotte M, Rainero I, Vighetti S, et al. Open versus hidden medical treatments: the patient's knowledge about a therapy affects the therapy outcome. *Prevention & Treatment* 2003;6 <http://journals.apa.org/prevention/volume6/pre0060001a.html> [accessed June 23].