REVIEW ARTICLE

Placebo: Misunderstandings and Prejudices

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SUMMARY

Background: The role of placebos is often misunderstood, leading both to overvaluation and to inappropriate disdain. The effect of a placebo that contains no pharmacologically active substance is often confused with the effect of administration by a physician. The aim of this article is to review the current data on placebos, evaluate these data critically, and provide a well-founded and understandable explanation of the effects that placebos do and do not possess.

Methods: Selective literature review.

Results: Recent studies employing modern imaging techniques have provided objective correlates of the effect of placebo administration for certain indications. A recent paper even suggested a genetic basis for it. Two main mechanisms underlie the effect of placebo administration: conditioned reflexes, which are subconscious, and the patient's expectations, which are conscious. Further factors include the physician's personality and the setting in which the treatment takes place.

Conclusions: The mechanisms of action of placebo administration, with which positive therapeutic effects can be achieved with little effort, should be consciously exploited by physicians when giving their patients pharmacologically active medications as well.

Key words: drug safety, drug research, treatment study, complementary medicine, medical prescriptions

Why an article about placebos? The term “placebo” is familiar to both physicians and laypersons and is often used as a synonym for lack of effectiveness, as in “only a placebo effect.” The effect of preparations used in alternative or complementary medicine is also often equated with that of placebos and are thus disparaged (1). As ineffective substances, placebos are an essential element of clinical drug trials. By definition, their role is to allow a control group to be treated without therapeutic effect. Time and again, however, an effect *is* ascribed to placebos. The title of a recent study (2) even suggests a genetic basis for the placebo effect, giving rise to media debate under the headline “Placebo Gene.” Does such a genetically determined sensitivity really exist, or is this, as so often with placebos, yet another misconception? The present article aims, on the basis of a selective literature review, to assemble the latest data about placebos, interrogate them critically, and on the basis of the result build up a comprehensible and well-founded picture of both their effects and their lack of effects (3–6, e1).

Definition of placebo and nocebo

The word “placebo” has its origin in the Latin “placere” and means literally “I shall please.” According to the classical definition, a placebo is a “sham drug” without any pharmacologically active substance, which is externally indistinguishable from the true drug (“verum”). The placebo itself cannot therefore trigger any effect. If there is any effect, it can only be the giving of the placebo, i.e., its being administered by the doctor to the patient, that is doing it. When the term “placebo effect” is used in this article, what is meant is this effect of the administration of a placebo.

Apart from the pure placebos, which contain only starch or other inert fillers, so-called active placebos also exist. These are genuine medicines that are either given at an ineffective dosage or, because of their spectrum of effect, have no effect on the disease under investigation. When the drug being tested is one that has characteristic side effects that the patient will notice, one may in special cases consider using an active placebo with similar side effects in the control group. Although it would be impossible to carry out a double-blind study for many drugs without adopting this procedure, it does involve ethical difficulties (7, 8).

Patients who take placebos report not just desired effects, but also undesired effects (9). The phenomenon that preparations devoid of active substances can have ill-making effects has, by analogy to placebo effect, been ascribed to the “nocebo effect” (“nocebo”: “I shall

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BOX

Apparent and real components of the placebo effect

The effect of a placebo can be mimicked by the natural course of the underlying disease and by the statistical phenomenon of regression to the mean. A genuine placebo effect is mainly mediated by unconscious conditioning and conscious expectations. Other factors also come into play, such as the mode of administration and the context in which it takes place; the patient-physician relationship is important here.

Simulated effect of placebo administration

- Natural course of the disease
- Regression to the mean

True effect of placebo administration

- Unconscious conditioning
- Conscious expectations
- Mode of administration
- Context of administration
- Doctor-patient relationship

harm”) (10). A negative, pessimistic basic attitude on the part of the patients, bad experiences with previous drug treatments, negative information that the patient receives from the doctor, pharmacist, or the press can all evoke side effects—as can reading the package insert with its long list of warnings (11).

History

The first documented placebo test goes back to investigations by the natural scientist and later president of the USA Benjamin Franklin (e2). In his day, there was a popular healing method, propagated by the German doctor Franz Anton Mesmer and called after him “mesmerism.” Under the direction of a committee assembled by the king of France, Franklin succeeded in overturning the opinion that the body contained a fluid that could be influenced from outside and could be guided by “mesmerization,” by showing that the success of the treatment depended exclusively on the belief that the mesmerist was present. The therapeutic efficacy of drugs has been investigated by means of placebo-controlled, double-blind, randomized clinical studies since the middle of the 20th century.

Effectiveness of placebos

The estimation of the effect of placebos was for decades strongly colored by the influential publication by Beecher with the suggestive title, “The powerful placebo” (12). These words were title, summary, and quotation in one. In this 1955 publication, Beecher analyzed several studies that used placebos, most of them his own, and drew some very decided conclusions from

them. These included that placebos have a reproducible effect in about one-third of patients; that the stronger the symptoms of a disease, the stronger the effect of the placebo; and that the placebo effect usually lasts for quite a long time.

None of these three statements has stood up to careful analysis in later studies. First, the placebo effect shows a remarkable variability between 7% and 49% of the treated patients; second, the placebo effect is not correlated with the severity of symptoms; and, third, the duration of the placebo effect varies within a wide range from minutes to years (6, 13).

Beecher, too, broached in his studies the question of a “placebo personality” that would allow response to a placebo to be predicted. Evidence for this is hard to find, however, such that the existence of a placebo personality and hence predictability of the response to a placebo have also been described as a myth (14). The discussion on this subject, however, was recently much enriched by a publication mentioned at the beginning of this review, in which Furmark et al. proved the existence of a genetic disposition to respond to placebo (2). They showed that a polymorphism of two genes that play an important role in serotonin metabolism determines the effect of a placebo treatment for social phobia. In this study, the tryptophan-hydroxylase-2 polymorphism allowed a statistically significant prediction of the placebo effect with an accuracy of 70.8%. Since serotonin has been shown to play a role in certain areas of the brain (e.g., the amygdala) in the pathogenesis of this illness and in its treatment with serotonin reuptake inhibitors, it seems plausible that this carrier substance should also play a role in the placebo response. To generalize from that, as has been seen in many instances in the media, and speak of a “placebo gene” is misleading and exaggerated, since this genetic sensitivity relates to only one set of symptoms and one specific mechanism of effect.

The placebo effect varies in strength for different indications. Two retrospective analyses of a total of 156 clinical studies showed that, in comparison to non-treatment, the placebo treatment had a significant and effective influence on subjective endpoints but very little on objective continuous endpoints (15, 16). However, one study of hypertensive patients showed that systolic and diastolic blood pressure values were reduced by a placebo, and this was the case both for blood pressure measurements taken by a physician in a hospital and for automatic ambulatory blood pressure measurements (e3).

Placebos have no effect on either subjective or objective binary (yes/no) endpoints, e.g., relapse after nicotine withdrawal (15, 16). On the other hand, they can be highly effective on subjective continuous endpoints, such as pain. Just telling a patient that they have been given a strong painkiller can have a noticeable analgesic effect. British rheumatologists analyzed 198 placebo-controlled studies of patients with arthritis and showed that a placebo not only reduced pain but also improved function and reduced joint stiffness (17).

Mechanisms of effect of placebos

According to the current predominant and well-proven theories, the main mechanisms of the placebo effect are conditioned reflexes and patients' expectations (6). That is, both conscious and subconscious phenomena are at work (*Box*).

Conditioned reflexes

The definition of the conditioned reflex goes back to the historical studies by Pavlov (e4). Pavlov observed in an experimental setup with dogs that the sight of food stimulated their gastric secretions. If the food was presented at the same time as an acoustic signal, after a brief habituation the acoustic signal alone was enough to trigger the gastric secretions. Now, most patients have had the experience in life of taking medicine and finding that it improves their symptoms. If, therefore, when they have new symptoms, they are offered medicine, they subconsciously assume that it will help again. The consequence of this attitude is that even a placebo can be effective. However, if the patient notices that the new medication is helping less than the earlier one, this positive attitude reduces, and thus so does the effect of the next placebo administration. In other words, the patient becomes deconditioned (e5).

Expectations

In contrast to the subconscious sequence of events involved in the conditioned reflex, the patient also has a conscious expectation when taking medicine. The doctor's prescription, the pharmacist's instructions, the comments of friends and relatives, and any knowledge that the patient him- or herself may have lead to the conscious assumption that improvement should follow. The remarkable thing is how robust this attitude of expectation can be. In one study (e6) that used placebos, the patients were even told openly that they were receiving a tablet without any active substance. The only additional comment that was allowed was that "it had helped many people." Despite the objective information about the absence of any active ingredient, this positive remark ensured that the placebo administration was effective in 13 out of 14 patients and reduced their subjective symptoms by 41%. The influence of expectations on therapeutic effects becomes especially clear when drugs or placebos are studied in an "open-hidden paradigm", i.e., with and without the patients' being aware of their administration (5).

Additional factors

Various factors can modulate a placebo effect. It has been shown, for example, that the color, size, and shape of orally administered drugs can have an effect (6). Red, yellow, and orange lead to an expectation that the drug will stimulate, while blue and green produce an expectation of a calming effect (18).

Price also has an influence: expensive drugs work better than cheap ones (19). This phenomenon can be demonstrated beyond the placebo example, in other consumer situations. In one recently published study,

Overall effect of a drug

The overall effect of a drug stems not only from its specific pharmacological effects but also from general effects such as are observed with placebo administration. For this reason it is possible, by purposefully employing components that trigger a placebo effect, to increase the efficacy of genuine drugs. In this way, conventional pharmacotherapy can be improved for very little extra effort.

proband was offered several wines that were described only by their price. In a blind tasting, the same wine did much better when it was described as more expensive (20).

Other factors in placebo administration relate to the doctor's influence on the patient's attitude to his or her disease. These can be referred to collectively as the "context effect" (21). This includes both objective medical information from the doctor and his or her personal charisma and the atmosphere within which the treatment takes place. A study of 262 patients with irritable bowel syndrome showed the following (22): the first group (I) was only examined, the second (II) received sham acupuncture, and the third (III) sham acupuncture combined with an empathetic, confidential interview. In group II symptoms improved significantly compared to group I, and in group III the improvement was even greater than in group II, with again a significant difference between groups II and III. On the other hand, no correlation has so far been clearly established between an attitude of positive expectation on the part of the doctor and healing effect, so the proposal of the term "curabo effect" ("curabo": I shall heal) appears to be premature (23).

Simulated placebo effects

The effect of a placebo can be mimicked by statistical effects. The main ones are the natural course of the disease and regression to the mean.

Natural course of a disease

Most diseases have a more or less defined natural course characterized by a succession of alternating improvements and deteriorations in the symptoms. Fortunately, in the majority of cases these alternating disease events have a positive trend, i.e., they tend towards healing. If a patient with this kind of tendency to get well is given a placebo, it can appear that the

improvement is due to the placebo (6). The problem is now to define a suitable control, since normally, for a treatment with an active substance, it is the placebo itself that serves as the control. An analysis of the problem quickly shows that it is difficult if not impossible to test the placebo effect itself. Leaving out the placebo in the comparison group would make double-blind studies impossible, and would evoke negative feelings in the patients because it would be obvious that they were not receiving any treatment.

Regression to the mean

The phenomenon of regression to the mean, observed in many biological processes, is the following: that in a group defined on the basis of particular qualities, these qualities are less pronounced on testing at a later date (24). If, for example, a drug trial recruits patients with particularly severe headaches, it is to be predicted that at a follow-up examination after a few weeks the headaches will on average have become weaker. The probability that very severe headaches will regress over time simply is greater than the probability that they will increase. Another biological example is the fact that children's height correlates with that of their parents, but it is not identical. That is, children of tall parents are taller than the children of short parents, but they are not as tall as their own parents (e7). Regression to the mean can thus result in the assumption of a placebo effect where in fact none exists.

Effect of nocebos

Much less research has been done into the nocebo effect. The reason given for this is that it is ethically unjustifiable to provoke disease in healthy people using the nocebo effect. The nocebo effect, like the placebo effect, is often based on a conscious attitude of expectation. Both the mental anticipation of a future event and the strength of the expectation influence the extent of the response to a nocebo (9). A patient who fears that particular external influences make one ill may develop symptoms. A common term for this phenomenon is "self-fulfilling prophecy." Nonspecific side effects that may be explained by the nocebo phenomenon are often vague, mild complaints such as nausea, tiredness, insomnia, and stomach ache, or else symptoms of the underlying disease itself (e.g., pain).

With the nocebo effect, too, conditioned reflexes play a role. In a person with psychosomatic stomach ache, the hormone cholecystokinin provokes a pain reaction in the brain. This conditioning, elicited by a fear-triggered messenger substance, evokes the side effects expected on taking the medicine (25).

Treatment with placebos

Placebo effects probably make up a part, if not all, of the effectiveness of alternative and complementary medicine (1) (*Figure*). However, since the knowing administration of a placebo for therapeutic purposes means bringing about a false state of affairs that is kept hidden from the patient, it needs to be investigated, as a

matter of principle but also as a matter of law, whether purposive administration of placebo does not constitute a deception that must be ethically justified in each individual case (e8–e10).

Summary

In orthodox medicine, the placebo effect is an important instrument in the physician's armamentarium. This form of placebo effect ought to be freed from its negative associations, because it very often does help the patient. In addition, conscious use of "the doctor as a drug" only takes a very small amount of extra time, which would be more than justified by the increased benefit. If physicians prescribing pharmacologically effective substances were to offer as much care and attention as are given during many complementary medical treatments, the effectiveness of drugs could be increased, the dose reduced, and the therapeutic spectrum broadened. It would be regrettable if orthodox medicine were to fail to avail itself of this therapeutic benefit and the possibility it offers of great effects for little effort.

Conflict of interest statement

The authors declare that no conflict of interest exists according to the guidelines of the International Committee of Medical Journal Editors.

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REFERENCES

- Shang A, Huwiler-Müntener K, Nartey L, et al.: Are the clinical effects of homeopathy placebo effects? Comparative study of placebo-controlled trials of homeopathy and allopathy. *Lancet* 2005; 366: 726–32.
- Furmark T, Appel L, Henningson S, et al.: A link between serotonin-related gene polymorphisms, amygdala activity, and placebo-induced relief from social anxiety. *J Neurosci* 2008; 28: 13066–74.
- McQuay HJ, Moore RA: Placebo. *Postgrad Med J* 2005; 81: 155–60.
- Schönbachler G: Placebo. *Schweiz Med Forum* 2007; 7: 205–10.
- Enck P, Benedetti F, Schedlowski M: New insights into the placebo and nocebo responses. *Neuron* 2008; 59: 195–206.
- Oeltjenbruns J, Schäfer M: Klinische Bedeutung des Placeboeffektes. *Anaesthesist* 2008; 57:447–63.
- Quitkin FM: Placebos, drug effects, and study design: a clinician's guide. *Am J Psychiatry* 1999; 156: 829–36.
- Edward SJL, Stevens AJ, Braunholtz DA, Lilford RJ, Swift T: The ethics of placebo-controlled trials: a comparison of inert and active placebo controls. *World J Surg* 2005; 29: 610–14.
- Barsky AJ, Saintford R, Rogers MP, Borus JF: Nonspecific medication side effects and the nocebo phenomenon. *JAMA* 2002; 287: 622–627.
- Kennedy WP: The nocebo reaction. *Med World* 1961; 95: 203–205.
- Benedetti F, Lanotte M, Lopiano L, Colloca L: When words are painful: unravelling the mechanisms of the nocebo effect. *Neuroscience* 2007; 147: 260–71.
- Beecher HK: The powerful placebo. *JAMA* 1955; 159: 1602–6.
- Kienle GS, Kiene H: The powerful placebo effect: fact or fiction? *J Clin Epidemiol* 1997; 50: 1308–11.
- Geers AL, Helfer SG, Kosbab K, Weiland PE, Landry SJ: Reconsidering the role of personality in placebo effects: dispositional optimism, situational expectations, and the placebo response. *J Psychosomat Res* 2005; 58: 121–7.

KEY MESSAGES

- A placebo does not itself have an effect: its administration has the effect.
- The effect of placebo administration is variable; the placebo effect is seen more often for some indications and symptoms, e.g., pain, than it is for others, e.g., a relapse after nicotine withdrawal.
- No such thing as a "placebo personality" or a generally effective "placebo gene" appears to exist.
- The main mechanisms of effect of placebo administration are conditioned reflexes and the patient's expectations.
- The placebo effect, as an important component of orthodox medicine, ought to be consciously employed in treatment with effective medical drugs.

15. Hrobjartsson A, Gotzsche PC: Is the placebo powerless? *N Engl J Med* 2001; 344: 1594–602.
16. Hrobjartsson A, Gotzsche PC: Is the placebo powerless? Uptodate of a systematic review with 52 new randomized trials comparing placebo with no treatment. *J Intern Med* 2004; 256: 91–100.
17. Zhang W, Robertson J, Jones AC, Dieppe PA, Doherty M: The placebo effect and its determinants in osteoarthritis—meta-analysis of randomised controlled trials. *Ann Rheum Dis* 2008; 67: 1716–23.

18. De Craen AJM, Roos PJ, de Vries AL, Kleijnen J: Effect of colour of drugs: systematic review of perceived effect of drugs and of their effectiveness. *BMJ* 1996; 313: 1624–6.
19. Waber RL, Shiv B, Carmon Z, Ariely D: Commercial features of placebo and therapeutic efficacy. *JAMA* 2008; 299: 1016–7.
20. Plassmann H, O'Doherty JO, Shiv B, Rangel A: Marketing actions can modulate neural representations of experienced pleasantness. *PNAS* 2008; 105: 1050–4.
21. Di Blasi Z, Harkness E, Ernst E, Georgiou A, Kleijnen J: Influence of context effects on health outcomes: a systematic review. *Lancet* 2001; 357: 757–62.
22. Kaptchuk TJ, Kelley JM, Conboy LA, et al.: Components of placebo effect: randomised controlled trial in patients with irritable bowel syndrome. *BMJ* 2008; 336: 999–1003.
23. Graz B, Wietlisbach V, Porchet F, Vader JP: Prognosis or „curabo effect?": physician prediction and patient outcome of surgery for low back pain and sciatica. *Spine* 2005; 30: 1448–52.
24. Zwingmann C, Wirtz M: Regression zur Mitte. *Rehabilitation* 2005; 44: 244–51.
25. Benedetti F, Amanzi M, Vighetti S, Asteggiano G: The biochemical and neuroendocrine bases of the hyperalgesic placebo effect. *J Neurosci* 2006; 26: 12014–22.

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E-REFERENCES

- e1. Koshi EB, Short CA: Placebo theory and its implications for research and clinical practice: a review of the recent literature. *Pain Practice* 2007; 7: 4–20.
- e2. Herr HW: Franklin, Lavoisier, and Mesmer: origin of the controlled clinical trial. *Urologic Oncology* 2005; 23: 346–51.
- e3. Asmar R, Safar M, Queneau P: Evaluation of the placebo effect and reproducibility of blood pressure measurement in hypertension. *AJH* 2001; 14: 546–52.
- e4. Stockhorst U: Classical conditioning of endocrine effects. *Curr Opin Psychiatry* 2005; 18: 181–7.
- e5. Fedele L, Marchini M, Acaia B, Garagiola U, Tiengo M: Dynamics and significance of placebo response in primary dysmenorrhea. *Pain* 1989; 36: 43–7.
- e6. Park LC, Covi U: Nonblind placebo trial. *Arch Gen Psychiatry* 1965; 12: 336–45.
- e7. Bland JM, Altman DG: Regression towards the mean. *BMJ* 1994; 308: 1499.
- e8. Lichtenberg P, Heresco-Levy U, Nitzan U: The ethics of placebo in clinical practice. *J Med Ethics* 2004; 30: 551–4.
- e9. Tilburt JC, Emanuel EJ, Kaptchuk TJ, Curlin FA, Miller FG: Prescribing “placebo treatments”: results of national survey of US internists and rheumatologists. *BMJ* 2008; 337: a1938.
- e10. Zernikow B, Hechler T: Pain therapy in children and adolescents [Schmerztherapie bei Kindern und Jugendlichen]. *Dtsch Arztebl Int* 2008; 105(28–29): 511–22.