

How can placebo effects best be applied in clinical practice? A narrative review

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Abstract: Placebo effects are documented in a number of clinical and experimental studies. It is possible to benefit from placebo effects in clinical practice by using them as effects additive to those of documented and effective treatments. The purpose of this paper is to discuss how doctors and other health workers may benefit from placebo effects within an ethical framework. A narrative review of the literature relating to placebo effects in clinical practice was performed. We searched PubMed and selected textbooks on placebo effects for articles and book chapters relating to placebo effects in clinical practice. By drawing on placebo effects, doctors may access patients' self-healing potentials. In practice, doctors may best benefit from placebo effects by influencing the patient's expectations through communication. An important principle is to give the patient information stating that a particular treatment is effective, as long as this is based on realistic optimism. A patient-centered style involving elements such as developing trust and respect, exploring the patient's values, speaking positively about treatments, and providing reassurance and encouragement might aid in activating placebo effects. The total effect of a documented treatment will partly depend on how well the placebo effects have been activated. Thus, placebo effects can be understood as a form of supplemental treatment.

Keywords: placebo effects, doctor-patient communication, expectations, biopsychosocial model

Introduction

The term "placebo" is often used about non-effective medicines that are typically referred to as "sugar pills" in colloquial English. However, a number of studies have shown that inactive medications have effects if accompanied by positive information about the treatment. Placebo effects may thus be defined as psychological and/or physiological responses that follow the administration of active and non-active substances when coupled with affirmation of the treatment effects. Placebo effects can even be obtained when placebo effects are honestly and clearly described to the patient.^{1,2}

Placebo effects have been studied and observed in relation to a number of conditions, such as pain,³ sleep disorders,⁴ depression,⁵ and Parkinson's disease.⁶ In addition, placebo effects may influence the immune system and the endocrine system.⁷ In a psychotherapeutic setting, placebo effects may also contribute to some of the therapeutic effect.⁸

Placebo effects have been studied thoroughly for several decades, but the phenomenon has been known for hundreds of years. The first placebo-controlled study can be traced back to 1799.⁷ Placebo effects are probably as ancient as our civilization. It may be reasonable to assume that benefits from ancient remedies and herbs in part could

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be related to placebo effects. Beecher was one of the very first doctors to illuminate the phenomenon of placebo when he gave wounded soldiers inert saline injections during the Second World War.⁷ During recent decades, research interest in placebo effects has gained ground due to more advanced research methods, including the controlling of placebo effects in clinical trials.⁷

Despite the fact that placebo effects are well-documented, individual differences can influence placebo effects. Some people respond more strongly than others,⁹ and individual differences should be taken into account. Placebo effects may be most effective in conditions like pain, depression, and motor diseases.^{7,9} As previously mentioned, placebo effects are seen in both experimental and clinical settings. However, controlled studies investigating how placebo effects can be used as additive effects in clinical practice are still scarce.

Placebo effects can be related to biological, psychological, and social factors⁹ and can be understood from a biopsychosocial perspective.¹⁰ While the biomedical model rests mainly on treatment within a physiological and biological framework, the biopsychosocial model incorporates biological, psychological, and social factors.¹¹ An important aspect of the biopsychosocial model is the patient-provider interaction.¹²⁻¹⁴

In a treatment setting it is unethical to deliberately misinform the patient. However, placebo effects can be an important factor in a biopsychosocial context. This paper discusses how to take advantage of placebo effects as additional effects in a clinical setting. We do not focus on placebo effects in clinical trials or “pure” placebo treatment (ie, with pharmacologically inactive substances). Placebo effects may be present even when no medication is prescribed. However, we will concentrate on how to utilize placebo effects as additive effects, ie, when prescribing substances that are pharmacologically active, but where the placebo effects might enhance the effectiveness of the medication.

Methods

A narrative review of the literature relating to the placebo effect in clinical practice was performed. We used the PubMed database and searched for articles in the field of placebo and clinical practice. The following search combinations were used: “placebo effect” and “clinical implications” (generated 15 hits) and “placebo effect” and “clinical practice” (generated 166 hits). We also searched selected textbooks on the placebo effect for book chapters relating to the placebo effect in clinical practice. In addition, we reviewed the reference lists of the included articles to find

relevant articles missed in the database search. The search resulted in more than 180 relevant articles and book chapters, from which we selected the papers discussed below. As this was a narrative review, we were unable to include and discuss all the relevant literature, and have had to select the literature that we deemed most relevant to our focus.

Discussion Expectations

An expectation is an imagination of a specific outcome and is a central mechanism by which placebo effects may occur.^{9,15,16} There is a connection between the degree of expectations and the strength of the placebo effects.^{15,17} Expectations may be influenced by verbal information, the appearance of a medication, previous experiences, and interaction between the patient and doctor.⁹ The strength of placebo effects depends on whether the treatment information is positive, negative, or neutral. The total effect of a pharmacological treatment is thus composed of biologically active ingredients and biopsychosocial contextual factors (eg, placebo effects). For example, Krell et al found that the effect of one antidepressant was strengthened if the patient had positive expectations of the drug.¹⁸ Up to 90% of their patients with an expectation of improvement experienced relief of their depressive symptoms when they thought that the medication would be “very effective”. By comparison, only 33% experienced improvement if they thought the medication was “somewhat effective”. A later study found comparable effects.¹⁹

Further, Benedetti et al demonstrated the significance of expectations in pain relief.²⁰ Patients with postoperative pain were administered an intravenous painkiller. Patients who were informed that they had received a painkiller experienced greater relief than those who lacked this knowledge.

If a treatment is accompanied by information stating that it is in all probability effective, this will positively influence the outcome of treatment.²¹ Enthusiastic information provides more pain relief than more neutral information, even if the actual treatment remains the same.^{22,23} Information about a biologically active medication may reverse or neutralize the pharmacological effect. The patient’s expectations can in some cases be of greater significance with regard to the outcome than the administered pharmacological substances.^{24,25}

Placebo effects as psychophysiological responses

Placebo effects may be considered to be physiological effects and not only as results of a social desirability bias.²⁶ This is documented in a large number of studies drawing on methods

of investigation such as electroencephalography, heart rate variability, or functional magnetic resonance imaging.⁹ For instance, Wager et al³ used functional magnetic resonance imaging to show that activity in the pain-sensitive areas of the brain was reduced after administration of placebos.

Further, it has been assumed that placebo effects are either caused or strengthened by a reduction in levels of fear and anxiety.^{27–29} It has been noted that an antidepressant prescribed for depression causes a similar activation pattern in the brain as treatments with placebo.³⁰ Depressive patients who fail to respond to placebo treatments or antidepressants show no change in their brain activation pattern.³¹ These findings indicate that emotional factors can be related to placebo effects.²⁷

Clinical implications of placebo effects

Placebo effects may work to strengthen the effect of a particular therapy regardless of how well documented the therapy is,^{21,32,33} and several studies have shown that many clinicians draw on placebo effects in clinical practice.^{34–36} Two studies, from the USA and Israel, found that approximately half of doctors used placebo medication in clinical practice.^{35–37} It should be noted that findings from such studies are based solely on questionnaires/interviews, where a reporting bias may contribute. The results cannot therefore be generalized to all doctors.

Benefiting from potential placebo effects is important in order to achieve an optimal result. Understanding the mechanisms behind placebo effects is therefore important for health care professionals. It is important to emphasize that exploiting the additional effects of a placebo mechanism is not the same as providing a full and pure placebo treatment. The placebo effect should not be a substitute for other more effective treatments.^{33,38}

Biopsychosocial contextual factors (eg, factors related to the health care setting, to clinician-related factors, and to cultural factors) are important for treatment outcomes.¹⁰ Placebo effects are one such contextual factor⁹ and cannot be separated from the whole context. Consequently, it is difficult to estimate the size or importance of placebo effects in a particular clinical setting. Put in different words, when a clinician activates placebo effects as additional effects, the clinician is making use of biopsychosocial contextual factors in such a way that this benefits the patient.

Ways to elicit placebo effects

There are ways to induce the additional effects of the placebo mechanism (Table 1). Barrett et al³⁹ suggest a list of eight specific and practical principles that doctors can use to elicit placebo effects. These include: speaking

Table 1 Summary of central principles for using placebo as an additive effect in clinical practice

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- Describe basic mechanisms behind the treatment
 - Give information stating that the particular treatment is effective, provided that this information is realistic
 - Aim for an emotionally warm/empathetic style
 - Try to reduce the amount of stress for the patient
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positively about treatments, providing encouragement, developing trust, providing reassurance, supporting relationships, respecting uniqueness, exploring values, and “creating ceremony”. The aim of using these principles is to create positive expectations, reduce anxiety/stress, and enhance the feeling of being cared for.³⁹ These principles are fundamental and can be related to a biopsychosocial and patient-centered perspective.

It is important to communicate positive expectations regarding the outcome of the treatment and the patient’s ability to cope with the disease and its treatment.⁴⁰ The doctor can do this, for instance, by providing information stating that a particular treatment is effective^{41–43} or by describing basic mechanisms behind the treatment.^{21,44,45} As an example, Benedetti and Amanzio⁴⁶ recommend that negative suggestions should be substituted with positive hints. For instance “here is your pain medicine” can be changed to “Here’s some medicine to help you get better”. Patients should have a clear understanding of the treatment and the desired outcome.⁴⁴ A central principle is thus to communicate realistic optimism and hope. Positive patient experiences with treatment may also lead to more long-lasting placebo effects due to a psychological conditioning effect.^{41,47}

A trusting relationship between the doctor and the patient is central. Building confidence between patients and doctors is an important way of inducing placebo effects.⁴⁰ Kaptchuk et al demonstrated this when they administered placebo without deception in patients with irritable bowel syndrome.⁴⁸ They obtained placebo effects based on the relationship between patients and health workers. Further, they found that switching from a technical style to a more emotionally warm/empathetic style increased the placebo effects from 42% to 82%. Employing a patient-centered approach involving a cooperative and empathetic interactional style may help reduce patients’ anxiety and stress and thereby elicit additional positive placebo responses.^{28,29,40,46,49,50}

Ethical considerations

Clinicians need to consider some ethical issues relating to placebo effects. According to Pittrof and Rubenstein, the

ethical use of placebo effects should always benefit the patient and involve disclosure. Thus, clinicians should always give precise information about the treatment and possible side effects.³³ Further, Pittrof and Rubenstein argue that it is unethical to ignore placebo effects because this phenomenon is so well documented.³³ Placebo effects, when considered as supplements to pharmacologically active substances, should aim to increase patients' well-being.³⁸ It is unethical to deliberately misinform patients. Taking advantage of placebo effects as additive effects in clinical practice should not be confounded with deception. Deception is not ethical and can harm the relationship between clinicians and their patients. The ethical use of placebo effects in a clinical setting should rely on realistic expectations and be based on best practice. The use of placebo in clinical settings might still be seen as controversial by some. However, provided that placebo effects are used as additional effects to best practice medicine, and provided there is no deception of the patient, we believe that placebo effects generally are unproblematic from an ethical perspective.

Summary

Placebo effects have been demonstrated in a number of experimental trials and clinical studies. These effects cause physiological responses, such as reduced activity in the pain-sensitive areas of the brain. It is possible to ethically apply the placebo effect as a supplement to active or verified treatments. Giving information stating that a particular treatment is effective is ethical, provided that such information is realistic. The central principle is to build realistic hope and influence expectations. This may activate the effects of placebo and thereby improve the results of the treatment. This is a way to access the patient's own healing potential as much as possible.

Acknowledgment

We would like to thank our colleagues and patients, who inspired us to write this article.

Author contributions

MB, CB, and RW contributed to the design, drafting, and revising of the article. All authors read and approved the final version.

Disclosure

The authors report no competing interests in this work.

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