Placebo and Placebo Effect

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What are placebo effects and what are their relevance? Mention of placebo may still evoke images of charlatanism in practice or of nuisance in research. This short article seeks to resolve some confusion in this pervasive phenomenon in medicine. Recent neurobiological insights into mechanisms are not discussed.

Responses to therapy have been attributed to three main processes:

- **Natural history** (including regression to the mean), which recognises the self-limiting nature of some illnesses or random variations in illness expression. Measurement error may also contribute to such observations.
- **Specific effects** attributable to the characteristic content of the intervention, such as a drug or a procedure.
- **The so-called “nonspecific” effects** of treatment, those that may be associated with the sociocultural context in which a treatment is delivered. These are referred to as placebo effects but this concept requires further explication.

**Placebos, placebo responses and placebo effects**

A *placebo* is a substance or procedure that has no inherent power to produce an effect that is sought or expected. Placebos are used as a “control” intervention in experimental trial situations; however it is considered unethical to administer a known placebo in a clinical therapeutic situation (unless informed consent has been obtained). In the experimental case, placebos appear to have their own “pharmacology”, with dose–response, time–effect and side–effect profiles not unlike those of nonplacebos and indeed often related to the comparison nonplacebo.

A *placebo response* is, literally, a response to the administration of a known placebo. That known placebos can exert therapeutic effect is itself a remarkable phenomenon, balanced by the observation that in certain circumstances known nonplacebo treatments may fail to exert their characteristic effect. The result of administration of a placebo may be detrimental or negative – termed a “nocebo” response.

A *placebo effect* is a genuine psychological or physiological effect which is attributable to receiving a substance or undergoing a procedure but which is not due to the inherent powers of the substance or procedure. Because such effects are attributable to the sociocultural context in which a treatment is delivered, to avoid confusion it may be preferable to use the term “contextual effects” rather than “placebo/nocebo effects”. Such effects have been studied mainly with respect to pain but are involved in other clinical conditions.
Two important principles follow:

- A placebo – named here contextual – effect does not require the administration of a placebo.
- A nonplacebo treatment will exert both a characteristic effect and a contextual effect.

Theories of placebo mechanism

Most experimental work deals with the placebo response, to allow inference of specific effect of an intervention. The greater is the difference between the verum (true) response and the placebo response, the more powerful is the intervention, so the investigators seek to minimise the latter. This contrasts markedly to clinical practice, where an attempt is made to maximise the contextual (placebo) effect. Studies of placebo response in experimental situations have been used as models for understanding contextual effects in the clinical sphere.

The main current theories include classical conditioning, a predominantly non-cognitive process of learning through association, and expectancy, which allows access to conscious processes. The apparent tension between these two appears to have been resolved, in humans, by the learning-by-association proposed by the conditioned placebo model being mediated by expectancy.

In brief, the conditioning model links an unconditioned stimulus (US) such as an effective drug that evokes an unconditioned response (UR) with features of the treatment setting, including persons, places or things, such that those neutral features themselves alone may then elicit a component of the UR. Thus those neutral stimuli become conditioning stimuli (CS) and elicit a conditioned response (CR). This reinforces the point made earlier that a nonplacebo treatment will exert both a characteristic effect (UR) and a contextual effect (CR).

This model posits that environmental settings (therapists, uniforms, syringes, pills, rituals) which have been associated with ameliorative effects may thereby become conditioned stimuli for the alleviation of symptoms. Similarly the association of neutral stimuli with aversive stimuli (such as a painful procedure or a tense interview) could condition negative or nocebo effects. This provides one basis for understanding variability in responses between and within subjects: individual learning differences arising out of having experienced particular forms of treatment in particular contexts. Through response generalisation, positive and negative CRs may potentiate or attenuate responses to subsequent treatments. It follows that to maintain a strong contextual effect (CR), the treatment environment must be associated regularly with effective treatment. The use of powerful non-placebos will enhance the contextual component of effect; the use of weak nonplacebos or of placebos will attenuate the nonplacebo (UR) component of effect. This is particularly relevant in chronic conditions, where negative contextual effects from ineffective therapy may generalise, attenuating responses to a subsequent potent nonplacebo, be that a treatment or a treatment provider.
Implications of placebo theory for the clinician

- For practice

The model predicts that every interaction with health professionals plays a role in determining the contextual component of a person’s current and future response to treatment. Expectations or faith or hope are largely learned through experience with the medical system: the challenge is how these effects can be harnessed.

Choice of size, colour, or route of administration of nonplacebo treatments may manipulate response, as may pairing with specific suggestions. Expectancies related to the credibility of the therapist, of the therapeutic setting, and of the specific treatment itself, including the credibility of the ritual of administration may be enhancing factors. However, enhancing positive contextual effects does not extend to the use of known placebos.

The other side of this coin is to limit negative contextual (nocebo) effects. The theory predicts that the experience of unsuccessful treatments may contribute to extinction of the contextual component which in turn may attenuate the effectiveness of even powerful nonplacebos. This consideration implies that therapists should be aware of the effects of using treatments that have questionable efficacy. Furthermore the failure of placebo treatments which are believed by the patient to be nonplacebo treatments may lead to anxiety out of concern that the underlying condition is worse than appreciated. It follows that the use of known placebos for “diagnostic” purposes is fundamentally flawed.

- For training

Expectancies related to the nature of the patient–therapist interaction may be the most important in this area. Factors include aspects of behaviour such as friendliness, consideration of patients’ concerns, provision of time, clear explanations of diagnosis, prognosis and treatment, enthusiasm for treatment, and the choice of words, gestures, or other nonverbal forms of communication. It has been argued that interactional skills should be accorded as much priority in training as the attaining of medical knowledge (formalised as “engage, empathise, educate, enlist and end”).

- For research

Placebo theory informs the potential for manipulating both the contextual effect of nonplacebo treatments and the response to known placebos. In pharmacotherapeutic studies, the comparison of parallel groups under double-blind conditions often fails to control for expectancy. To counter this, designs have been suggested to include expectancy controls. For example, half the subjects are told that they will receive the drug and the other half that they will not. Within each of these two groups, half actually receive the drug and the other half does not. The complicated interaction between expectancy and efficacy may also apply to within-subject designs. It has been shown that there is an order effect: placebos administered after effective nonplacebos were rated as more effective than when administered before them. Modifications of design need to control for such order effects and for the expectancy of the administrators of the trial as well as those of the subjects. The extension of these principles to procedures, to invasive techniques including surgery and indeed to psychotherapy poses particular difficulty.
Further reading


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i Stewart-Williams & Podd, 2004; p. 326
ii Ibid