# Using the placebo response in clinical practice

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*Clin Med*
2003;**3**:347–50

**ABSTRACT – This paper reviews the psychological mechanisms that lead to placebo responses and the physiological basis for reduction in symptoms. Some psychological mechanisms (expectancy, conditioning) lead to symptom reduction but are unlikely to reduce underlying pathology. Other mechanisms (therapeutic relationship, empowerment) may additionally reduce later pathology. The nature, size and duration of the placebo response depends on the placebo inducing context. In clinical practice, the placebo response creates an adjunctive response to that of active treatment. It is a useful, but fickle, boon as it is difficult to predict when it will occur.**

**KEY WORDS: empowerment, expectancy, placebo, psychology, therapeutic relationship**

The term placebo response has been defined recently as 'the reduction in a symptom as a result of factors related to a subject's/patient's perception of the therapeutic intervention'.[1] Research on placebos often involves psychological symptoms such as depression or pain, so there is a tendency to treat placebo responses as 'not real' or only psychological. However, placebo responses can create a variety of physiological changes. Not only is placebo pain reduction mediated in part by endorphin release,[2] but placebos create endogenous dopamine release in Parkinson's disease[3] and changes in bronchial muscle tone (peak expiratory flow rate) in asthmatics.[4] Placebo responses are just as real as any other therapeutic response – what distinguishes them is their cause.

When evaluating pharmacological and other treatments, placebo responses are an inconvenience that must be controlled by using randomised controlled trials (RCTs). However, in clinical practice, placebo responses have an impact on patient outcome. It is increasingly recognised that, when properly handled, the placebo effect is a 'boon to busy clinicians and their patients'.[5] The aim of this paper is to examine how this boon can be exploited in clinical practice.

## How large is the placebo response?

One way of evaluating the overall impact of placebo responses is to compare the outcome in the placebo arm of an RCT with that of the treatment or verum arm. Table 1 reproduces the results of a meta-analysis of improvement rates in the placebo and verum (active) arms of several RCTs.[6] The authors conclude that:

- placebo responses vary considerably between different diseases, and
- clinically significant numbers of patients improve without active treatment.

It was also concluded from RCT data that, contrary to common belief, placebo responses can be long term, at least 12 weeks in duration.

One difficulty in evaluating the long-term impact of the placebo response is that some chronic diseases remit spontaneously. The true effect of the impact of placebos requires comparison with the natural history of the disease rather than with a baseline of no change. With this comparison, the extent of placebo response is reduced.[7] A review[1] comparing placebo with natural history in RCTs of analgesia which included a natural history arm suggests a mean effect size of 0.15 (ie a small effect). However, when placebos are compared with natural history in placebo studies in which patients think they are receiving an active agent (in an RCT patients know they may or may not receive an active agent), there is a much greater effect size of 0.95 (ie a large effect). This difference is important because it shows that context has a major effect on the placebo response. That is, the placebo effect in real clinical practice is greater than in blinded clinical trials.

Although meta-analyses of RCTs conclude that placebos responses are remarkably common, it has been suggested that it is not sensible to average

**Table 1. Improvement rates as a function of disorder** (reprinted, with permission, from Ref 6).

| | % Improved | |
|---|---|---|
| **Disorder** | **Verum** | **Placebo** |
| Affective disorder | 65 | 46 |
| Panic disorder | 49 | 23 |
| Personality disorder | 65 | 35 |
| Dementia | 32 | 10 |
| Rheumatoid arthritis | 45 | 23 |
| Pain | 68 | 21 |
| Cancer | 37 | 33 |

placebo responses because they are disease- and context-specific.[8] They appear to be particularly strong where there is a psychological component: for example, a meta-analysis comparing the placebo arm of an RCT with natural history in depression gives an effect size of 0.79.[9] The authors of the meta-analysis suggest that 25 per cent of the effect of an antidepressant is due to natural history and regression to the mean, fifty per cent is due to placebo and 25 per cent due to the active pharmaceutical agent. The large placebo effects in antidepressant treatments have recently been debated as they throw into question the use of antidepressant medication.[10]

The placebo effect is notoriously fickle and not, as sometimes believed, associated with neuroticism.[11] A good example of the unpredictability of the placebo response is found in research on the effects of suggestion in asthma.[4] For some patients, placebo inhalers are about two-thirds as effective in increasing peak expiratory flow as the active agent (salbutamol) but in other patients there is no effect. Moreover, a placebo response can occur on one occasion and not on another with the same patient. It is not easily predicted on an individual basis.

In clinical practice, where patients are expecting to receive an active agent, placebo responses, natural history of the disease and clinical efficacy of treatments together form a complex mix. When a patient reports improvement from an active agent, the improvement may be due to a combination of placebo, active agent and spontaneous remission acting together, and it is difficult to know the relative contribution of each factor. The physician tends to evaluate the effectiveness of a therapy on the basis of experience, and is naturally inclined to attribute improvement only to the active treatment. However, a treatment may be effective but not as efficacious as believed as it includes a placebo-mediated contribution. The large placebo effect in the treatment of depression may be an exception, but placebo effects themselves are not.

Before the advent of modern medicine, skilled clinicians used their 'bedside manner' to relieve patient suffering. This approach is, in part, a way of creating patient perceptions that relieve symptoms: that is, a placebo. Placebos are not as effective as the modern medicine chest – which is the purpose of RCTs.[9] Nevertheless, the old-fashioned tool of the bedside manner remains useful today either when medicines are ineffective or where placebo responses potentiate the effect of an active treatment. The potentiating or adjunctive effect of the placebo response is particularly important in clinical practice, because the effectiveness of an active treatment can be enhanced if contextual factors contribute to a strong placebo response.

## Psychological mechanisms associated with the placebo response

Four psychological mechanisms are associated with the placebo response:

1 Expectancy.
2 Conditioning.
3 Therapeutic relationship.
4 Empowerment.

When used in its narrower sense, the term placebo refers only to expectancy and conditioning, which is the sense in which placebo research is normally conducted. In its broader sense, 'placebo' covers all four processes. This is more useful in clinical practice because it covers any way in which the bedside manner has a therapeutic effect and patients' perception of the therapeutic intervention has a symptom reducing effect.

### *Expectancy*

Patient expectancies arise from:

- culture (ie information passed on by family and friends)
- information given by the physician (eg 'you will soon start feeling better), and
- physical agents (eg pills, inhalers, medical treatments which the patient believes are effective).

Patients sometimes expect negative health outcomes, referred to as the nocebo effect.[12] An extreme case of this is voodoo death, but it also occurs in, for example, contagious hysteria, where a group of people (statistically more common in teenage females) develop mysterious symptoms such as fainting and nausea.

Physicians should manage patients' expectancy and consider treatment choices by first exploring patients' prior expectations. Those with a negative perception of a particular treatment are less likely to benefit compared with those who have positive expectancies. The physician can also create patient expectancies, particularly where they are previously not well established, by aiming to create an impression of confidence in the treatment provided. In situations where a physician may be unsure what is causing the patient's problems, saying 'I don't know what is the matter with you' or 'there is nothing I can do for you', while honest, is unlikely to create an expectancy of improvement.

The physician needs to appear to the patient to be an expert in order to develop confidence in the treatment prescribed – an impression achieved by careful explanation, not by the use of technical jargon. People who describe the advantages and disadvantages of a particular course of action are perceived as more trustworthy than those who give only one side of the argument.[13,14] At the same time, patients like to feel that their doctor is also genuinely concerned about them, as concern guarantees optimum treatment. The term 'concerned optimism' sums up an approach likely to maximise placebo response through expectancy.

### *Conditioning*

The phenomenon of conditioning was discovered a century ago by Pavlov who showed that dogs could be conditioned to salivate to a bell. If a patient experiences symptom relief from the active properties of a particular tablet, symptom relief will, over time, be conditioned to the tablet. Thus, if a placebo tablet is substituted for the real tablet, symptom reduction will occur. Conditioning and expectancy combine so that, for example, placebo pain relief is most effective when the patient expects

pain relief and has also been conditioned to the pain relieving effect of a particular therapy.[1]

Conditioning shows that the presentation of a treatment to the patient is important. It can explain why patients who are happy with one particular type of treatment sometimes find an identical, but differently packaged, pharmacological agent less effective. The conditioned response to the original type of packaging is lost with the new packaging. The practical significance of conditioning is that patients who settle with one type of presentation of treatment can sometimes find it difficult to shift to another – this needs to be considered when changing patients to a generic drug.

### *Therapeutic relationship*

There is considerable evidence that a patient's interpersonal relationships are an important predictor of health. One review[15] concludes that social support (in particular, the emotional support component) affects a range of physiological parameters in the cardiovascular, endocrine and immune systems. This is partly because social support acts as buffer against stress but it also appears to have direct physiological effects associated with reduction of long-term disease status (eg reduced cardiovascular reactivity and cortisol, improved immune function).

The physician is part of the patient's interpersonal relationships; this is important, at least for the patient. It is not surprising, therefore, if the quality of the relationship between physician and patients affects health outcome. Practitioners who adopt a warm, friendly manner, providing emotional and cognitive support, provide better outcome than those who adopt more formal consultations.[16] In particular, patient centredness appears to be an important aspect of satisfaction and outcome.[17] A well-conducted interview with a patient often leaves that patient feeling much better, even though no prescription has been given.

### *Empowerment*

The medical term 'empowerment' is based on an earlier psychological theory, 'learned helplessness'.[18] This theory shows that when animals or humans are placed in conditions of lack of control (ie when actions do not affect outcomes) a variety of negative changes occur:

- psychological changes (eg depression, motivational and cognitive deficits),[18] and
- physiological changes associated with long-term stress (eg raised cortisol and immune suppression).[19]

Being 'unempowered' is an unhealthy state. It is easy for medical treatment to become an unempowering experience. When patients are cared for in hospital following, say, elective surgery, cognitive function declines as time passes due to the unempowering effect of having all their needs cared for in a controlled hospital environment.[20] By contrast, empowerment can be increased in long-term residential homes by encouraging the residents to make choices about their own lives.[21]

## Key Points

**The placebo response is a boon, but a fickle boon, in clinical practice**

**Placebos can reduce reported symptoms and create physiological changes, but placebos are particularly effective with non-specific health complaints**

**The size of the placebo response varies between patients, it can be of a long duration but both size and duration are difficult to predict in advance**

**Neurotic people are no more likely to be good placebo responders than non-neurotic people**

**The placebo response can be enhanced by good communication skills exhibiting concerned optimism about the patient**

Disease itself is often disempowering. The physician can help remedy this by giving patients information and actively involving them in the decision making process through a process of concordance. Indeed, if patients are likely to come to a 'sensible' decision on the basis of information provided, it is better to give them that choice rather than make it for them, as the act of choosing is empowering.

## Conclusions

The placebo response can result through four different psychological processes, in each of which the physician is able to create physiological changes and symptom reduction from psychologically mediated effects. However, different psychological processes are associated with different physiological mechanisms. For expectancy, the physiological changes appear to be those associated with reduced symptom perception (eg increased endorphins and dopamine or reduced bronchial muscle tone) rather than changes that reduce pathology over the long term. For example, placebo inhalers have been shown to increase peak flow in asthma, but not to reduce the underlying inflammation. This does not mean that expectancies cannot produce a reduction in pathology, but that the existing mechanisms associated with expectancy suggest otherwise.

By contrast, for social support and empowerment the physiological changes are likely to have long-term therapeutic benefits. Immune enhancement can have a variety of effects, for example reduction in cancer incidence. The size of the placebo effect and how long it lasts therefore depend on the psychological process or processes exploited by the physician. The physician may create expectancies of healing that reduce symptoms but not the underlying pathology, or create perceptions that reduce pathology in addition to symptomatology.

It is interesting to observe that evaluations of placebos though RCTs[1,7] assume the more restricted definition of the placebo process, that it is an expectancy or conditioning mediated effect. However, an RCT adds more than expectancy of improvement;

there is also the increased human contact, particularly in relation to outcome assessment. It is the personal experience of the author that patients often form good relationships with assessment delivering research assistants, and that the latter become genuinely concerned about the patients.

The message of this paper is simple: the way to maximise the placebo response is good quality communication and psychological management. If there is anything extra to conventional accounts of good communication, it is the need to provide the patient with a perception of 'concerned optimism' in the treatments provided. Good communication and psychological management should be applied to all patients irrespective both of their treatment and of their temperament. Sometimes it will lead to a reduction in symptoms and/or reduction in underlying pathology, sometimes it will not. The placebo is a useful but fickle boon in clinical practice.

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