

When is a placebo effect not an effect?

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ABSTRACT – It is often stated, paradoxically, that a treatment is not effective when trials have shown a placebo effect. This should be rephrased ‘that the tested treatment is not more effective than the placebo’ if we are not to confuse ourselves and the public in the current debate on complementary and alternative medicine.

KEY WORDS: acupuncture, alternative medicine, pain, placebo

The otherwise excellent review of reviews on the effect of acupuncture published in the August 2006 issue of *Clinical Medicine* contains a conflict in terms that needs to be resolved.¹ On page one Derry *et al* state that the reviews ‘provide no robust evidence that acupuncture works’. On the same page, however, an editorial insert remarks on ‘the important and beneficial effect of the placebo response’ implying that acupuncture does work, as a placebo. The first statement only becomes true if reworded to ‘the reviews provide no robust evidence that acupuncture works better than placebo’. The literature on randomised controlled trials (RCT) provides a sound evidence base that placebo effect is real and measurable.² If we do not communicate with ourselves more precisely we cannot expect journalists, the legal profession and the public, to understand our position in the contentious area of alternative medicine. It would be safer to call it complementary medicine since we, the medical profession, wittingly or unwittingly, have always used placebos together with our more tangible use of prescriptions and the knife.³

This common ambiguity in medical parlance has troubled me since studying placebo response with an experimental psychologist in 1983.⁴ Placebo effect was a more potent therapeutic weapon than expected. This should not have been a surprise as the power of suggestion in influencing behaviour is well known in its guises as hypnotism, medical advice and in the multibillion pound advertising industry.

Suggesting that recovery is going to occur is basic to all rehabilitation. Physiotherapists have always used encouragement with various therapeutic modalities many of which, including transcutaneous electrical nerve stimulation (TENS)⁵ and acupuncture,¹ may not have been proved to be more effective than placebo. Witchdoctors and faith healers were doing this before Aesculapius invoked the aid of a

snake. Many traditional herbal remedies, such as the poppy, willow bark, cinchona, foxglove and colchicine, have survived the RCT inquisition, though now chemically refined and standardised in Western medicine with clearly defined undesired side effects. The conclusion was that it was customary, quite rational, and indeed ethical, to use placebo (suggestion) in rehabilitation and in routine medical practice. This implies a wider definition of placebo which has often been limited to the deliberate misinformation that the patient is having an active substance believed by the prescriber to be inactive. There are many aspects to placebo, which literally means ‘I shall be acceptable or pleasing’. As suggestions do not always please, the term ‘nocebo’ was coined for the opposite effect. The patient’s response may be a ‘pleasing effect’ or an ‘adverse effect’ (nocebo effect). Those who respond favourably are termed placebo responders and those who do not, ‘non-responders’, or putatively ‘nocebo responders’.

The placebo response depends on the subject’s beliefs which determine their expectations and response. Their beliefs will depend on the placebo message delivered by the therapist who will usually be enthusiastic and convey an optimistic message by word and body language reinforced by mechanical, electrical stimuli and ‘the laying on of hands’ as in massage and, in Western and Chinese medicine, simply taking the pulse. The response will also be conditioned by previous beliefs and by peers who offer advice embellished by phrases such as ‘I swear by it’.

Relevant research

A study of TENS was performed as it was similar to acupuncture but easier to apply. An initial formal RCT study on hand pain in rheumatoid arthritis (RA) compared the standard dose with no TENS stimulation. The light diode on the TENS stimulator was left on for both tests. Neither patients nor assessors knew whether the current was turned on or off but the test cases could feel the current. As this could not be blinded the study was repeated with the electrical signal flashing across a visual display unit (VDU) screen whether the TENS current reached the patient or not.⁶ A standard neutral verbal statement was made. A similar gain was then obtained in resting pain and pain on gripping for both test and control groups. Two scores of joint tenderness

showed a parallel reduction but the starting level was lower in the high frequency TENS group. None showed a change in measures of grip power and grip work. It was concluded that the VDU screen provided a powerful visual placebo suggestion which obscured the effect of the electrical stimulus. Lewis *et al*⁷ obtained similar results in osteoarthritis. This could be explained as a distraction effect.⁸ A Cochrane review⁵ has not shown TENS to be more effective than placebo.

As those performing trials will usually be optimists hoping for a positive response their verbal and body language will usually convey a positive placebo message. Pessimists, who may exude a nocebo message, will rarely be motivated to do clinical trials. With this in mind a high dose vitamin E for hand pain in RA⁹ was tested and a neutral suggestion of outcome was made. All trial staff were restricted to the same statement:

It has been claimed that this vitamin helps in rheumatoid arthritis. Though we do not expect it to work we feel obliged to test this claim. As it is a vitamin we do not anticipate any side effects.

Preparation was as for a standard RCT but all subjects received the vitamin E, which doubled as a placebo. None of the subjects reported any benefit, none complained of side effects and none accepted an offer to continue the vitamin after the study was completed. This was considered to be a neutral response to a neutral suggestion.

We concluded that placebo, or nocebo suggestion, can be conveyed by verbal, visual, electrical, and body language signals and, by analogy, through any of our senses. Price² has discussed the effects of the attitude of and statements made by the study team in RCTs. Should the statements made to the subjects in all RCT studies be standardised and reported?

Allan¹⁰ refers to studies of placebo effect in Crohn's disease and the effects of the number of study visits, the duration and severity of disease and of spontaneous remission (the reversion to the mean effect). Rubin *et al*¹¹ describe another version of the nocebo effect. Subjects developing headache when using mobile phones were compared with those who did not in an RCT in which there was a mobile phone signal, a non-pulsing carrier signal and no signal at all. There were no between group differences in headache and other symptoms and the subjects could not tell which category they were in. The sham exposure triggered severe symptoms in some subjects. This was regarded as a nocebo effect.

Dictionary definitions

There is a vast literature advocating unproven remedies. Some dictionaries have absorbed the common medical parlance, which is questioned here. *Collins English dictionary* defines placebo as:

*an inactive substance or other form of therapy administered to a patient usually to compare its effects with those of a real drug or treatment but sometimes for the psychological benefit through his believing he is receiving treatment.*¹²

Placebo effect is defined as, 'A positive therapeutic effect claimed by a patient believed by him to be an active drug'. *Mosby's*

medical, nursing and allied health dictionary describes placebo as 'an inactive substance' and then paradoxically defines placebo effect as 'a physical or emotional change'.¹³ Few heavy specialist medical textbooks even index the word placebo. One neurology text includes a detailed chapter on placebo analgesia.²

How should this be dealt with in the clinic?

Stating that a patient's favoured 'cure' does not work is misleading, as anything can have a beneficial placebo effect. If a full history and examination is done there should be no risk of missing treatable organic disease. The neutral statement, 'If it helps you, it helps you' averts a counter productive and possibly harmful argument as the patient 'knows that it works'. It may be tempting to say that the only good it does is to the profits of the vendor but this leads to the same criticism as there is a placebo, or nocebo, component in any offered treatment or advice. It can usually be possible to explain that the recommended treatment has been shown to be more effective than the alternative favoured by the patient and that unproven remedies enhance the effect of a treatment shown to be more effective. Asking what alternative drugs are being taken can be important as some herbal remedies have quite dangerous side effects and some may interact with the effects of prescribed drugs. As suggested by Allan¹⁰ we should listen carefully with tolerance, sympathy and good humour. This takes longer than the usual consultation time so the doctor must be more tolerant than the patient.

Conclusion

Placebo can be delivered through any of our senses. As the effect depends on beliefs possible modes of delivery are infinite so testing them all is impossible. All therapeutic endeavour results in a combination of a non-specific effect (placebo and/or nocebo effect) and any effect dependent on the specific property of the recommended treatment. So, if doctors are to communicate effectively with themselves and their patients it must be stated that the tested treatment has or has not been shown to have an effect greater than the placebo used. Otherwise, an illogical prejudice is being displayed against placebo effect, which is subconsciously being used all the time. This obfuscates constructive discussion on the alternative and complementary medicine controversy.

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