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The placebo effect

The placebo effect is a fascinating phenomenon in clinical practice. Studies have shown that there is a significant placebo effect in a wide range of medical conditions including psychiatric disorders. This article looks at the background of the placebo effect, defines the common terms used, describes the various hypotheses that have been put forward to explain this seemingly inexplicable phenomenon and also covers the issue of using placebos in research trials, highlighting the important ethical dilemmas involved. Throughout, specific emphasis is given to psychiatry.

Background

The term placebo is derived from the Latin verb 'placare', 'to please'. The American anaesthetist Henry K. Beecher (1955) coined the term 'placebo effect'. He reported that, on average, about a third of patients with a range of conditions improved when they were given placebos. This subsequently led to the development of placebo-controlled trials, whereby a new drug is said to have significant benefit only if it shows superiority over placebo. The placebo effect has also been a source of recent interesting debate in psychiatry with some claiming that a considerable proportion of benefit from antidepressant medication derives from the placebo effect (Kirsch & Sapirstein, 1998), whereas others (Leutcher *et al*, 2002) have stressed that response to placebo and to antidepressants involves distinct biological mechanisms.

Definitions

In general, a placebo is an inert substance that has no inherent pharmacological activity. It looks, smells and tastes like the active drug with which it is compared. An 'active placebo' is one that has its own inherent effects but none for the condition that it is being given for (e.g. use of atropine as the control drug in trials of tricyclic antidepressants). A placebo need not always be pharmacological. It could be procedural, for example, sham electroconvulsive therapy (ECT), where the patient is anaesthetised but not given ECT. Surgical placebo is a procedure where the patient is anaesthetised and superficial procedures (e.g. skin incision, burr hole) are performed without the actual surgery.

Placebo equivalents are also employed in complementary medicine. For example, sham acupuncture consists of needles placed at non-acupuncture points. A recent study (Linde *et al*, 2005) showed that real acupuncture was no more effective than sham acupuncture in reducing migraine headaches, although both interventions produced benefits compared with a waiting list control.

Why does the placebo effect occur?

Natural remission theory

This states that the improvement that occurs with the administration of placebo is coincidental and would have occurred even without it. This theory explains the beneficial effects of placebo in short-lived conditions like common cold, headache, etc, but does not satisfactorily explain why even patients with chronic conditions such as hypertension or schizophrenia show improvement with placebo.

An allied hypothesis is the 'regression to the mean' theory. Regression to the mean is a statistical concept; according to this, if an initial test result is extreme and if the test is repeated, statistically there is a greater likelihood for the second result to be closer to the mean than for it to be more extreme than the first result. Usually only patients who are significantly unwell (e.g. depression score above a certain cut-off point) are eligible to enter a trial. Hence, at follow-up they are more likely to show an improvement (depression score being closer to the mean than the first score) than a deterioration, owing to regression to the mean (McDonald *et al*, 1983).

Classical (Pavlovian) conditioning

In the original experiment of Pavlov, the dog salivated at the sound of the bell even without any food, as it had previously been conditioned to expect food by pairing the bell with food. Food is the unconditioned stimulus, salivation owing to food is the unconditioned response;

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the bell is the conditioned stimulus and salivation owing to the bell is the conditioned response.

In a similar manner, patients who have had past experience of getting better with active medication may be conditioned to anticipate improvement by any subsequent prescription, including placebo. Using the classical conditioning analogy, the active medication is the unconditioned stimulus, improvement owing to active medication is the unconditioned response, the placebo is the conditioned stimulus, and improvement owing to placebo is the conditioned response.

Other psychological factors

Patient expectations are important in determining the placebo effect. Treatments that are perceived as being more powerful tend to have a stronger placebo effect than those that are perceived to be less so. Thus, placebo injections have more effect than oral placebos, capsules are perceived as being stronger than tablets, bright-coloured placebos are more effective than light-coloured ones larger placebos have more effect than smaller ones, and two placebos have more effect than one. Also, the status of the treating professional is directly related to the placebo effect. The same compound has been found to be more powerful if it is branded than when it is unbranded (Branthwaite & Cooper, 1981).

In a novel study, Benedetti *et al* (2003) examined the impact of the patient's awareness that they are having a certain treatment administered/withdrawn on the outcome. They studied three treatments in three groups of patients – intravenous morphine for post-thoracotomy pain, intravenous diazepam for post-thoracotomy anxiety and stimulation of the subthalamic nucleus for idiopathic Parkinson's disease. In each group, some patients were informed of the fact that they were receiving the treatment (e.g. by a doctor administering the injection) but others were not aware as they received an infusion from an automatic pre-programmed machine. In all the groups, the efficacy of the respective interventions was greater when the patient was aware of the procedure than when they were not. Similarly, being aware that a treatment was being withdrawn worsened the symptoms much more than when the treatment was withdrawn without the patient's knowledge. From a psychiatric point of view, neither the hidden administration nor hidden withdrawal of diazepam had any significant positive or negative effect respectively but the open administration of diazepam improved anxiety symptoms and open withdrawal worsened them.

Role of endogenous opioids

In a systematic review, ter Riet *et al* (1998) concluded that endogenous opioids (e.g. endorphins) play a significant role in mediating placebo-induced analgesia. Previous studies had shown that placebo-induced analgesia is partially reversed by administering the opioid antagonist naloxone (Grevert *et al*, 1983). There is also growing interest in the role of neurotransmitters, particularly dopamine, in placebo effects on mood and behaviour.

Pattern of placebo improvement

Among psychiatric disorders, the placebo effect has been most extensively studied in depression. 'Pattern analyses' have shown that the improvement as a result of placebo in depression tends to be abrupt, occurs early in treatment and is less likely to persist (Quitkin *et al*, 1991), whereas improvement in response to antidepressants tends to be gradual, occurs later and is more likely to persist. Even among patients apparently responding to the active drug, if the pattern of improvement is consistent with a placebo response (i.e. abrupt and early), the improvement tends to be short-lived.

Stewart *et al* (1998) investigated whether they could predict relapse of depression from the initial pattern of response. Patients who had responded to treatment with fluoxetine for 12–14 weeks were then randomly allocated to continuation/maintenance treatment for 50 weeks with either placebo or fluoxetine. Those patients who had shown a placebo pattern of improvement during the initial fluoxetine phase relapsed in a similar manner whether they continued on fluoxetine or were switched to placebo, but patients who had shown a true drug pattern of improvement relapsed more if they were switched to placebo in the maintenance phase. This study adds strength to the hypothesis that, even among drug responders, only a certain proportion will benefit from maintenance treatment.

Hrobjartsson & Gotzsche (2001) conducted a major systematic review of placebo-controlled trials involving 40 clinical conditions, including hypertension, asthma, pain, depression, schizophrenia, anxiety and epilepsy. They concluded that placebos tended to have no significant effects on binary outcomes, and possibly had small beneficial effects on continuous subjective outcomes and in the treatment of pain.

Use of placebos in clinical trials

It is generally accepted that a double-blind randomised controlled trial (RCT) is the best research method to study the efficacy of clinical interventions.

However, the use of placebos for conditions for which effective treatments are already available raises an important ethical question. Should a new treatment be compared with an established treatment or should it only have to demonstrate superiority over placebo in order to be accepted as another effective treatment? Rothman & Michels (1994) have criticised the use of placebo-controlled trials to test new drugs for conditions with potentially irreversible consequences, such as onchocerciasis and rheumatoid arthritis, when established treatments for these conditions already exist.

Death by suicide is associated with major psychiatric disorders such as depression, and the use of placebo-controlled trials to test the efficacy of new drugs is fraught with ethical issues.

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Another important question involves the masking of the double-blind trials. Margraf *et al* (1991) reported that a majority of patients in a double-blind study of alprazolam *v.* imipramine *v.* placebo could correctly guess whether they were on an active drug or placebo. In addition, the 'masked' assessors were even able to distinguish between the two active drugs.

Informed consent entails the patients being made aware that they will be receiving either an active drug or placebo. Therefore, it may not require more than just monitoring one's side-effects closely to accurately determine whether one is on active medication or placebo.

In addition to ethical issues, RCTs with a placebo control group have other limitations. RCTs only demonstrate statistical significance. If the sample size is very large, even if the difference in clinical outcome between the two groups is small and clinically insignificant, it may be detected as being significant by the statistical test.

In any RCT, the placebo is made by the manufacturer of the active drug. Hence, placebos used in one study will be different in form (size, shape, tablet/capsule, etc.) from those used in another study, depending on the form of the active drug. This may account for the wide variation in placebo response observed for the same condition.

Side-effects of placebos

When a placebo produces prominent side-effects it is known as a 'nocebo'. The term 'nocebo effect' encompasses the negative consequences resulting from the administration of a placebo. In placebo-controlled studies of psychotropic drugs, the placebos tend to cause a similar range of side-effects as the active drugs but usually with a much lower incidence rate. Non-specific side-effects, such as headache and nausea, tend to be more common than more specific ones such as acute dystonia or QT prolongation. 'Placebo sag' refers to the attenuation of the placebo effect with repeated use (Peck & Coleman, 1991). There are historical reports of placebo dependence (Vinar, 1969).

The nocebo effect clearly illustrates the role of patient expectations in perceived side-effects. Usually patients included in trials of psychotropic medication have already received previous treatment with active medication in the past, as most major psychiatric disorders tend to follow a chronic course. Hence, even if they are given placebo this time, they may anticipate side-effects similar to those that they experienced when they were receiving treatment with the active drug. Also, patients may be influenced by the list of side-effects experienced by their friends or relatives who have received such treatment in the past, and by the list of potential side-effects described by the researchers before obtaining informed consent.

Just as doubts have been cast on the beneficial effects of the placebo, so have questions been raised about the nocebo effect. Even healthy people who are not taking any medication have been shown to have a high prevalence of a range of symptoms which are similar to the side-effects investigated during RCTs. Thus, side-effects reported by patients on placebo may be a reflection of pre-existing or spontaneously occurring symptoms rather than being placebo-induced. Similarly, RCTs may be overestimating the side-effects (especially the non-specific ones) of active drugs.

However, the nocebo effect is not purely psychological. It has been shown that nocebo hyperalgesia (i.e. an increase in pain as a result of placebo) is mediated by cholecystokinin and is abolished by the cholecystokinin antagonist proglumide (Benedetti *et al*, 1997). In a systematic review of double-blind RCTs comparing fluoxetine and placebo, Casper *et al* (2001) found similar rates of placebo response in men and women but slightly more nocebo effects in women.

Conclusions

Despite half a century having passed since its inclusion in modern medicine, the placebo effect is still poorly understood. Beecher's (1955) original study, which showed an overall average placebo response of 35%, has been strongly criticised for major methodological shortcomings (Kienle & Kiene, 1997).

All discussion regarding placebos is based on the assumption that they are inert. But are they really so? Placebos are generally referred to as 'sugar pills'; sugar is not chemically inert. Similarly, the tablet coating or the capsule covering are not inert. Hence, the possibility that the 'inert' chemical in the placebo may be relevant to the condition being studied should not be dismissed.

Whatever the reasons for the placebo effect, the most important message for clinicians is that just because someone responds to a placebo does not mean that the initial ailment for which they sought help was false.

Declaration of interest

None.

References

BEECHER, H. K. (1955) The powerful placebo. *JAMA*, **159**, 1602–1606.

BENEDETTI, F., AMANZIO, M., CASADIO, C., *et al* (1997) Blockade of nocebo hyperalgesia by the cholecystokinin antagonist proglumide. *Pain*, **71**, 135–140.

BENEDETTI, F., MAGGI, G., LOPIANO, L., *et al* (2003) Open versus hidden medical treatments: the patients' knowledge about a therapy affects the therapy outcome. *Prevention & Treatment*, **6**. http://content.apa.org/journals/pre/6/1/1

BRANTHWAITE, A. & COOPER, P. (1981) Analgesic effects of branding in treatment of headaches. *BMJ*, **282**, 1576–1578.

CASPER, R. C., TOLLEFSON, G. D. & NILSSON, M. E. (2001) No gender differences in placebo responses of patients with major depressive disorder. *Biological Psychiatry*, **15**, 158–160.

GREVERT, P., ALBERT, L. H. & GOLDSTEIN, A. (1983) Partial antagonism of placebo analgesia by naloxone. *Pain*, **16**, 129–143.

HROBJARTSSON, A. & GOTZSCHE, P. C. (2001) Is the placebo powerless? An analysis of clinical trials comparing placebo with no treatment. *New England Journal of Medicine*, **344**, 1594–1602.

KIENLE, G. S. & KIENE, H. (1997) The powerful placebo effect: fact or fiction? *Journal of Clinical Epidemiology*, **50**, 1311–1318.

KIRSCH, I. & SAPIRSTEIN, G. (1998) Listening to Prozac but hearing

https://doi.org/10.1192/pb.30.5.185 Published online by Cambridge University Press

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placebo: a meta-analysis of antidepressant medication. *Prevention & Treatment*, **1**, http://content.apa.org/journals/pre/1/1/2

LEUCHTER, A. F., COOK, I. A., WITTE, E. A., *et al* (2002) Changes in brain function of depressed subjects during treatment with placebo. *American Journal of Psychiatry*, **159**, 122–129.

LINDE, K., STRENG, A., JURGENS, S., *et al* (2005) Acupuncture for patients with migraine. *JAMA*, **293**, 2118–2125.

MARGRAF, J., EHLERS, A., ROTH, W. T., *et al* (1991) How 'blind' are double-blind studies? *Journal of Consulting and Clinical Psychology*, **59**, 184–187.

McDONALD, C. J., MAZZUCA, S. A. & McCABE, G. P., Jr (1983) How much of the placebo 'effect' is really statistical regression? *Statistical Medicine*, **2**, 417–427.

PECK, C. & COLEMAN, G. (1991) Implications of placebo theory for clinical research and practice in pain management. *Theoretical Medicine*, **12**, 247–270.

QUITKIN, F. M., RABKIN, J. G., STEWART, J. W., *et al* (1991) Heterogeneity of clinical response during placebo treatment. *American Journal of Psychiatry*, **148**, 193–196.

ROTHMAN, K. J. & MICHELS, K. B. (1994) The continuing unethical use of placebo controls. *New England Journal of Medicine*, **331**, 394–398.

STEWART, J. W., QUITKIN, F. M., McGRATH, P. J. (1998) Use of pattern analysis to predict differential relapse of remitted patients with major depression during 1 year of treatment with fluoxetine or placebo. *Archives of General Psychiatry*, **55**, 334–343.

Ter RIET, G., De CRAEN, A. J., De BOER, A., *et al* (1998) Is placebo analgesia mediated by endogenous opioids? A systematic review. *Pain*, **76**, 273–275.

VINAR, O. (1969) Dependence on a placebo: a case report. *British Journal of Psychiatry*, **115**, 1189–1190.

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