The placebo effect in neurological disorders

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Recent evidence suggests that the placebo effect is mediated by the dopaminergic reward mechanisms in the human brain and that it is related to the expectation of clinical benefit. On the basis of this theory, we propose some criteria for the proper investigation of the placebo effect, and review the evidence for a placebo effect in Parkinson’s disease, depression, pain, and other neurological disorders. We also discuss the evidence for the use of placebos in long-term substitution programmes for the treatment of drug addiction.

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Any treatment (physical, pharmacological, or psychological) for a medical condition can potentially have a dual effect for the patient: that related to the treatment itself (eg, the intrinsic pharmacological property of an active drug) and that inherent in the perception that the treatment is being received.1,2 The latter is known as the placebo effect.3 Double-blind randomised placebo-controlled trials were originally designed to control for such an effect. Since distinction between the effects of an active psychological treatment and the placebo effect may be difficult,4 in this review we focus on placebo responses associated with physical and pharmacological treatments.

We start off by reviewing the history and definitions of “placebo” and “placebo effect”, then attempt to describe the ideal methods to investigate the placebo effect, before discussing the placebo effect as it relates to neurological disorders. We use the term neurology here in its broadest sense; that is, including medical conditions, such as depression, once believed to be in the field of psychiatry.

Placebos and the placebo effect

Historical background

“Placebo” is Latin for “I shall please”. Traditionally, the word placebo has had negative connotations, which have often been reflected in the medical literature. In 1811 (Hooper’s Medical Dictionary), placebo was defined as “an epithet given to any medicine adapted more to please than to benefit the patient”.5 More recent definitions tend to avoid pejorative terms.6

Most medicines, potions, and remedies used in ancient times would today be labelled as placebos.4 One can assume that if any of these treatments had benefits, they must have been related to the placebo effect. This assumption has led some to speculate that the placebo effect could have evolved by natural selection.7 Accordingly, placebo responders would have a higher chance of survival. However, many studies have been done and none has shown a consistent placebo-reactor profile.8,9 Cultural factors should also be taken into account in assessment of the placebo effect. For example, the magnitude of the placebo effect in ulcer disease may vary from one country to another.10

Definitions

It is important to distinguish between placebo and placebo effect.1 Essentially, any sort of treatment can act as a placebo, but what determines whether there is a placebo effect is the response of the patient to the intervention. The magnitude of the response to the placebo varies according to its supposed potency.11 For example, placebo surgery seems to be more effective than a placebo pill.12,13

Definitions of the placebo effect are abundant in the literature. Perhaps one of the most commonly used is that provided by Wolf who defined the placebo effect as: “any effect attributable to a pill, potion, or procedure, but not to its pharmacodynamic or specific properties”.4 One problem with most definitions is their implication that the placebo effect is non-specific. Kirsch, however, pointed out that, whereas the ingredients of a placebo preparation may be totally non-specific, the effects of placebos can be very specific.14 The specificity of the placebo effect depends on the information given to the patient (ie, the expectation). For example, placebos can have opposite effects on heart rate or on blood pressure depending on whether they are given as tranquillisers or as stimulants.15 Thus, precise definition of “placebo effect” is difficult.

Other treatment effects

There are some effects associated with treatment—such as the effect of informed-consent procedures, the effect of medical and nursing care (the “Hawthorne” and “halo” effects), and the patient-doctor relationship—that can contribute to the perception of clinical benefit.16 Whether these effects can be legitimately considered as part of the placebo effect is a matter of debate. There are, however, other factors leading to the spurious perception of benefit from the treatment received that need to be identified and differentiated from the placebo effect.
The power of placebos to alleviate a great variety of medical conditions has long been recognised but has recently been challenged. We describe here what we consider to be the requisites for investigating the placebo effect under ideal conditions, and which medical conditions or populations of patients might not be suitable for such investigations. On the basis of recent evidence, we also emphasise the link between the expectation of benefit and the placebo effect. Characteristics of different study designs are summarised in the table.

**Optimum populations of patients**

The power of placebos can be conceptualised as the mind’s healing power. The patient’s “belief” that he or she may be receiving a beneficial treatment is the factor thought to determine the placebo effect. The simple act of taking a pill, or of having a sham operation, can be regarded not only as a trigger of the placebo response.

Thus, the patient should meet three requirements if the researcher is to have the best chance of detecting a placebo effect: consciousness must be intact; mental faculties must be preserved; and some sort of pathological dysfunction, of moderate intensity, should be present (ie, the individual has to be ill). Patients who are comatose, who have severe mental problems, or whose medical condition is mild, are unlikely to be good candidates for investigation of the placebo effect. This does not necessarily mean that the placebo effect might not be present in such situations; rather, that our ability to detect it may be substantially reduced.

Whether children are a suitable population for investigation of the placebo effect is also debatable. Because the placebo effect, in our view, depends on expectation, and that is in turn dependent on many factors, including experience, children may not manifest the effect to the same degree as adults.

**The importance of study design**

Although the ideas developed here are applicable to crossover studies, in the next section we concentrate on the parallel-group design to avoid additional problems of interpretation associated with carry-over and period effects.

### Investigation of the placebo effect

The power of placebos to alleviate a great variety of medical conditions has long been recognised but has recently been challenged. We describe here what we consider to be the requisites for investigating the placebo effect under ideal conditions, and which medical conditions or populations of patients might not be suitable for such investigations. On the basis of recent evidence, we also emphasise the link between the expectation of benefit and the placebo effect. Characteristics of different study designs are summarised in the table.

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which the active treatment differs from the placebo, whereas comparison of the first two groups estimates the degree to which the untreated. Some investigators have proposed that patients are randomly assigned to three groups: one receiving the active treatment (in most studies a new treatment); one receiving the placebo; and one that is untreated. One group may receive a pill or some other sort of placebo treatment, but the pill is devoid of any real placebo power.

Another approach is the three-group study,22 in which patients are randomly assigned to three groups: one receiving the active treatment (in most studies a new treatment); one receiving the placebo; and one that is untreated. Some investigators have proposed that comparison of the first two groups estimates the degree to which the active treatment differs from the placebo, whereas comparison of the second and third groups estimates the placebo effect.23,24 However, even in this study design, the patients’ expectation of benefit may be too low, because a fully informed patient may realise that there is only a one in three chance of getting some benefit. After randomisation, the degree of expectation may decrease in those patients included in the untreated group. Arguably, this change should make detection of the placebo effect easier. However, patients with such low a priori expectation of benefit might be expected not to fluctuate much in their clinical status after being allocated to the untreated group. In addition, patients who volunteer for studies with low probability of benefit may have particularly low expectations, and may therefore not be representative of the population as a whole.

Unsurprisingly, many studies with these designs (table) have failed to demonstrate a placebo effect.25 This observation is interesting in itself, however, because it shows that the simple act of being exposed to a placebo is not enough to provide benefit to the patient. Several letters have been published in response to the claim by Hrobjartsson and Gotzsche that placebos are powerless (see N Engl J Med 2001; 345: 1276–78).

Many of the correspondents independently expressed arguments similar to ours about the relation between expectation of benefit and detection of the placebo effect.

RCTs in which several active drugs (or different effective doses of an active drug) are compared with a placebo are likely to evoke a much higher expectation of benefit (and consequently a greater placebo effect) than those in which only a single dose of one active drug is used. In such RCTs with many treatment options, each with different groups of patients, the inclusion of an untreated group could potentially inflate the placebo effect if, after randomisation, the untreated group experienced a negative effect (ie, decline below baseline; table).

**Psychological characteristics of the patient**

The psychological characteristics of the patients included in the study can be another source of confounding. As explained earlier, patients with no expectation of benefit are not likely to manifest a placebo effect. Another factor to consider is the patient’s knowledge—about his or her disease, the efficacy of the available active drugs, and the potential for placebos to affect the particular disease.

The patient’s knowledge of whether he or she may be receiving a placebo during the study might be relevant to the placebo response. For example, the placebo effect may be greater in patients who have not been informed that they might receive a placebo during the study.20 Thus, from a technical point of view, the best way to detect a placebo effect may be deliberately not to inform the patients that they may be receiving an inactive treatment; this approach would in most circumstances be unethical.

**Allocation concealment**

Apart from randomisation (ie, patients’ random allocation to the active drug or placebo group), another requisite crucial to any RCT is the double-blind strategy (ie, neither patients nor examiners should know patients’ allocations).15 To preserve the masking of the study, the a priori probability of drug-induced side-effects has to be similarly distributed among the groups. When this condition is not met (eg, chemotherapy produces characteristic side-effects), the results can be compromised. In this case, both the investigator and the patient can see through the “masking”, which results in measurement and reporting biases.26 For example, patients who believe they are not receiving the active drug may actually decline below baseline (negative placebo effect). In addition, the patient’s knowledge of the treatment he or she is receiving will surely alter his or her expectations.15

**Pain, depression, and Parkinson’s disease**

The literature on the placebo effect is mostly based on standard two-group RCTs, in which changes in the placebo group with respect to baseline are entirely attributed to the placebo effect. As previously discussed, such changes are, however, likely to be confounded by other factors (eg, regression to the mean). Nevertheless, three neurological disorders in which a prominent placebo effect has been repeatedly reported are pain,27 depression,28 and Parkinson’s disease.29–31 These three disorders are sometimes associated.29 Interestingly, all three are associated with dysfunction of neurotransmitters and neuropeptides in the CNS,32 and may therefore be ideal candidates for exploring the mechanisms underlying the placebo effect.

**Placebo effect and pain**

The placebo effect in pain associated with a great variety of medical disorders is powerful and consistent.1,14,21,22,33 We concur with Turner and colleagues33, who concluded that physicians should use this effect to their (and their patients’) advantage. Many neurological conditions are associated with pain, and the placebo effect is applicable to all of them. For example, de Craen and colleagues’ meta-analysis showed a placebo effect in 26–32% of patients with migraine.11 The route of placebo administration influenced the placebo effect, probably as a consequence of the expected treatment potency. In addition to the clinical relevance of placebos in pain disorders, experimental observations on placebo analgesia provided the first evidence for a biochemical mechanism underlying the placebo effect.11 This original observation, that placebo analgesia can be blocked by
naloxone, suggested that placebos can induce the release of endogenous opioids. This theory has gained further support from the recent observation that placebo analgesia is associated with patterns of cerebral-blood-flow activation (particularly in the rostral anterior cingulate cortex) similar to those seen after injection of an active opioid. Similar changes are seen in association with hypnosis-induced analgesia.

Placebo effect and depression
Depression is also susceptible to benefit from placebo interventions. Although Hrobjartsson and Gotzsche failed to detect a placebo effect in depression in their meta-analysis, they regarded depression as a binary variable, which must have reduced the power of the study. Moreover, they limited their analysis to studies that included an untreated group (ie, study designs that underestimate the placebo effect; table). In trials of antidepressants, some 35% of patients receiving placebo show improvement. Some authors suggest that the overall effect is even higher. For example, Kirsch and Sapirstein concluded from their meta-analysis of 19 trials of antidepressants that about 75% of the effectiveness of these drugs derives from the placebo effect. Because such a strong placebo effect may result in a negative interaction, detection of the effect of an active treatment may be very difficult in studies of depression, leading to spurious rejection of benefit.

There is evidence that depressed patients who respond to placebo antidepressants show a specific pattern of prefrontal activation as detected by quantitative electroencephalography. This pattern is distinct from that seen in patients who respond to active medication, and also different from the activation observed in patients who do not respond to either placebo or active drug.

Placebo effect and Parkinson’s disease
We have already pointed out that there is extensive clinical evidence for a prominent placebo effect in Parkinson’s disease. This effect is biochemically mediated by the activation of the damaged system (ie, the nigrostriatal dopaminergic pathway), which leads to the release of dopamine in the striatum (figure 1). The biochemical placebo effect in Parkinson’s disease is as powerful as the effect of an active drug (apomorphine), and also similar in magnitude to the effect of amphetamine in healthy people and patients with schizophrenia. The dopaminergic projection to the nucleus accumbens, a region especially involved in reward-related mechanisms, is also susceptible to the placebo effect in Parkinson’s (unpublished observation). This observation suggests that activation of the dopamine system may also mediate the placebo effect in other medical conditions is unknown. For example, although placebo-induced pain relief could be due to the release of endogenous opioid substances, Zubieta and colleagues reported that sustained pain induces release of endogenous opioids in several cortical and subcortical areas that are also known to receive dopaminergic projections. This finding suggests that dopamine release may also be involved in the placebo effect encountered in several pain disorders (figure 2), and may, in fact, be a common process in many medical disorders susceptible to the placebo effect.

There may additionally be a negative interaction between the effect of the active drug and the placebo effect in Parkinson’s disease—as the placebo effect increases, the...
effect of the active drug decreases. This evidence strengthens the idea that the effects of placebos and active drugs may not summate in a simple fashion. Nevertheless, because the interaction is negative, conclusions reached from an RCT in which the positive effect of an active antiparkinsonian drug is found to be statistically significant are still valid.

Whether the same applies to other disorders remains unknown. If confirmed, such a negative interaction between the placebo effect and the effect of the active drug may lead to the paradoxical situation in which a researcher might want to minimise the placebo effect in a particular patient involved in an RCT, but maximise the placebo effect when the same patient is seen in the usual clinical setting. Whereas the aim in the first case would be to obtain “clean” estimates of the effect of a new drug, the aim in the second situation would be to maximise the clinical benefit, and perhaps lower the risk of potential side-effects.

The evidence for a strong biochemical placebo effect in Parkinson’s disease reinforces the view that RCTs are necessary not only when testing new drugs, but also when evaluating the potential efficacy of surgical interventions. Indeed, there is some indication that physical placebos may be even more powerful than oral placebos. In a recent study of surgery for Parkinson’s disease, the degree of improvement at 18 months was the same after a sham operation and after stereotaxic intrastriatal implantation of fetal porcine ventral mesencephalic tissue. Another study on the efficacy of dopaminergic-cell implants in Parkinson’s disease, however, has not shown as prominent a placebo effect as feasible. Naturally, ethical issues and consideration of the disease, however, has not shown as prominent a placebo effect on the efficacy of dopaminergic-cell implants in Parkinson’s disease is a disorder in which the response to treatment can be assessed directly by the examiner. This direct measurability might allow a better evaluation of the placebo effect. For example, a prominent placebo effect has been reported in all domains of parkinsonian disability (although there was a trend for a greater effect on bradykinesia and rigidity than on tremor and gait/balance). We emphasise, however, that clinical scales of motor function are also subjective measurements. Indeed, patients may sometimes be less prone to experience (and report) clinical changes than clinicians to observe them.

Although we propose that dopamine may be a common biochemical substrate for the placebo effect, this idea does not exclude the possibility that other neurotransmitters or neuromodulators have a role, perhaps varying from one disorder to another. The critical role of endogenous opioids in placebo analgesia is one such example.

The placebo effect in other neurological disorders

Interestingly, several other neurological disorders thought to be associated with dysfunction of dopaminergic neurotransmission in either the nigrostriatal or the mesocorticolumbic dopamine pathway (or both) may be susceptible to the placebo effect. These disorders include dystonia, tremors, tics/Tourette’s syndrome, tardive akathisia, tardive dyskinesia, restless legs syndrome, obsessive-compulsive behaviour and panic disorder. Definite conclusions about the mechanism of the placebo effect are hard to reach from these studies, however, because many of the disorders are heterogeneous in nature (eg, dystonia) and in most of the conditions there is uncertainty about whether the underlying pathophysiology is due to an increased or decreased dopaminergic state or even a combination of the two (eg, decreased activity in one dopaminergic pathway and increased activity in another). In addition, some of these results are based on single observations or studies with insufficient statistical power.

Placebos to treat drug addiction

Placebos might also have a role in substitution strategies for the treatment of drug addiction, a disorder that seems to be related to dopamine-related reward mechanisms. In fact, there is emerging evidence to suggest that a variety of behavioural disorders may be related to what has been called the “reward deficiency syndrome”. Individuals with this syndrome search for “unnatural rewards” to compensate their intrinsic reward deficit. In other words, individuals with the reward deficiency syndrome would be at risk for abuse of drugs such as alcohol, nicotine, cocaine, amphetamine, and heroin; would tend to show obsessive-compulsive behaviours, that might lead to abnormal gambling, eating, and sex; and would be prone to practise high-risk behaviours. For example, a substantial proportion (15%) of drug abusers also show obsessive-compulsive behaviour or have a history of attention-deficit/hyperactivity disorder (12–32%). Tourette’s syndrome

Both obsessive-compulsive and attention-deficit/hyperactivity disorders are encountered in many patients with Tourette’s syndrome. As indicated, the placebo effect may be prominent in Tourette’s syndrome, a disorder in which dopaminergic dysfunction is widely assumed to have an important role, although whether there is a primary hyperdopaminergic or hypodopaminergic state (or some combination of the two) is unclear. Thus, several observations suggest that Tourette’s syndrome may be the result of an overactive plasma-membrane dopamine-transporter system, resulting in excessive removal of dopamine from the synaptic cleft. In particular, patients with this syndrome have: low concentrations of the dopamine metabolite homovanillic acid (HVA) in their CSF; increased density of dopamine D1 receptors, which may be a compensatory mechanism for synaptic dopamine deficiency; and increased density of dopamine-transporter sites. In addition, these patients benefit from treatment with direct dopamine agonists. Indirect dopamine agonists (eg, methylphenidate) are the treatment of first choice for patients with Tourette’s syndrome and attention-deficit/hyperactivity disorder. In these patients, tics may actually improve on methylphenidate, although tic worsening has also been reported.
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Search strategy and selection criteria
Data for this review were identified by searches of PubMed with the keyword “placebo effect” in combination with the appropriate term for each neurological disorder. Articles and book chapters were also identified through searches of the extensive files of the authors; some references were provided by anonymous reviewers. Abstracts from meetings were included only when they were considered particularly relevant to the topic. Only papers published in English were reviewed.

However, all these findings are also compatible with a hyperdopaminergic state in Tourette’s syndrome. Indeed, this may be the prevailing view among neurologists. For example, the primary defect could be upregulation of dopamine D2 receptors, which could lead to decreased dopamine release and upregulation of dopamine transporter sites as compensatory mechanisms. The combined action of these effects could explain the low concentrations of HVA in CSF in patients with Tourette’s syndrome. The response to direct dopamine agonists in this context could be explained by their action on presynaptic dopamine receptors, which would decrease dopamine release even further.

Immune-mediated disorders
Immune-mediated neurological disorders such as multiple sclerosis can also display a placebo effect, the potency of which varies among studies.76,77 Ader72 observed placebo-induced changes in blood-cell counts in eight of ten patients with multiple sclerosis included in a protocol of cyclophosphamide therapy. Animal models of placebo-induced immunosuppression77 support the notion that the immune system can be modulated by brain processes, which could have implications for the role of placebos in other disorders associated with altered immunological functioning.74 Neurotransmitters, dopamine in particular,75 have been implicated in neuroimmunomodulation. The nigrostriatal and mesolimbic dopamine pathways, as well as other central pathways (eg, tuberoinfundibular) and peripheral dopamine systems may influence the immune responses. Indeed, direct dopamine agonists seem to have a beneficial effect in several autoimmune diseases, including rheumatoid arthritis and systemic lupus erythematosus.76

Other disorders
The recent meta-analysis by Hrobjartsson and Gotzsche18 found no evidence for a placebo effect in several disorders associated with a risk of vascular events, as well as dementia, epilepsy, schizophrenia, and other disorders such as anxiety and insomnia. Apart from the considerations mentioned earlier about the optimum criteria for investigating the placebo effect, an additional problem is that the authors grouped together under the same category disorders with different causes, prognoses, and treatments. For example, epilepsy is a heterogeneous syndrome. There is preclinical evidence that dopamine neurotransmission may have a crucial role in controlling some types of seizures.77,78 This observation opens the possibility of obtaining beneficial effects from placebo-induced dopamine release, although release of other neuroactive substances, such as endogenous benzodiazepines, might contribute to the placebo effect in this situation.

Conclusions
Converging lines of evidence indicate that the placebo effect can be very powerful in neurological disorders such as pain, depression, and Parkinson’s disease. We have shown that the biochemical substrate of the placebo effect in Parkinson’s disease is the release of dopamine in the striatum.23 The placebo effect in other medical disorders may also be mediated, at least in part, by dopamine release.

On the basis of previous studies and our own results, we propose that the neural circuits involved in reward-related mechanisms, and in particular the dopaminergic system, have a critical role in the placebo effect. This idea suggests that placebos could also be used in long-term substitution strategies for the treatment of drug addiction.17 Although the potential for placebo addiction exists,17 a reduction in the use of illicit drugs would represent a major achievement in terms of health and social safety.

Finally, the expectation theory of the placebo effect has major implications for the future design of powerful placebo studies. Studies aimed at investigating the power of placebos should ensure that certain conditions are met in order to optimise the expression of the placebo effect. We hope that the points addressed here will assist in the design of better studies in the future. The placebo effect can no longer be thought of as a nuisance that we have to combat and annihilate. Instead, we should learn to maximise the placebo effect inherent in any active drug that we give to a patient, and apply this knowledge to our clinical practice.

Authors’ contributions
All authors contributed equally to the manuscript.

Conflict of interest
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References
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Review


16 Ernst E, Resch KL. Concept of true and perceived placebo effects. BMJ 1995; 311: 551–53.


