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Placebo: new insights into an old enigma

Edzard Ernst

Complementary Medicine, Peninsula Medical School, Universities of Exeter and Plymouth, 25 Victoria Park Road, Exeter, EX2 4NT, UK

Our understanding of the placebo effect has deepened through intensive research activity during recent years. It seems important to make a clear distinction between the placebo effect in clinical trials and the placebo effect in clinical practice. In the first scenario, our effects are directed towards minimising its influence on the results whereas, in the second scenario, we might consider maximising it for the benefit of the patient. It also seems important to differentiate between the 'true' and the 'perceived' placebo effect. The 'perceived' placebo effect equals the 'true' placebo effect plus a multitude of other factors. This article reviews new research on the mechanisms of placebo effects, discusses the role of placebos in clinical trials and explores the place of placebo in clinical practice. It concludes that a better understanding of this area will probably benefit basic research, clinical research and patient care.

Placebo effects are important to most healthcare professionals. For the clinical researcher, placebo effects constitute the background noise in a clinical trial that needs to be eliminated from the results so that they become interpretable. For the clinician, they are relevant as they can contribute to the total therapeutic response to (non-placebo) interventions.

Placebo effects are associated with much uncertainty and often a degree of irritation. The late Patrick Wall pointed out that 'this subject provokes a shudder of discomfort like a cold hand in the dark' [1]. The terms 'placebo' and 'placebo effect' are used in confusingly different ways. To some, the placebo effect can signal the capacity of the body to heal itself [2–4], whereas for others, it is merely an artefact in clinical trials.

In recent years, many researchers have realized that much could be gained by a better understanding of placebo effects and, therefore, have taken a keen interest in this area. Consequently, our knowledge has moved forward considerably. Several monographs have become available (e.g. see Refs [5,6]), and a multitude of original research has expanded our knowledge. Therefore, it is timely to review this subject. This article is an attempt to do just that and to highlight some of the recent insights into this fascinating subject.

Corresponding author: Ernst, E. (Edzard.Ernst@pms.ac.uk)

Defining the terms 'placebo' and 'placebo effect'

Defining the terms 'placebo' and 'placebo effect' is far from easy, and numerous definitions have been proposed [7–14] (Box 1). Not all of them are fully satisfactory or cover the two above-mentioned roles placebos can have in clinical trials (i.e. an artefact that requires elimination) and in clinical practice (i.e. a therapeutically valuable response which, in the interest of patients, should be maximised). Grünbaum [15] differentiated between intentional and inadvertent placebos. In the first category, the therapist does and in the second he/she does not believe the treatment is remedial for the condition in question. Moerman and Jonas stated that 'placebos do not cause placebo effects. Placebos are inert and do not cause anything.' [16] These authors therefore advocate substituting the term placebo response with the word 'meaning response', that is, 'the physiologic or psychological effects of meaning in the origins or treatment of illness' [16].

It has even been argued that placebo cannot be logically defined at all [17]; therefore, no generally accepted definition exists [12]. Clear thinking about placebo is also not helped by the numerous misconceptions that exist in this area (Table 1). They are as old as the interest in placebo, and range from the notion that placebo effects contribute a fixed percentage to the total therapeutic response to the myth that placebo effects are always of short duration. Even though shown repeatedly to be wrong, these mis-

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BOX 1

A selection of definitions for placebo and placebo effect

Placebo

- An inert treatment, given as if it was a real treatment [7].
- A sham treatment without biological activity, used in pharmacology to control for the activity of a drug [8].
- An inert substance or procedure that alters a physiological or psychological response [9].
- An intervention designed to simulate medical therapy, which at the time of use is believed not to be a specific therapy for the condition for which it is offered [10].
- Any therapeutic procedure that has an effect on a patient, symptom, syndrome or disease, but which is objectively without specific activity for the condition being treated [11].

Placebo effect

- A change after a placebo intervention [12] (termed a 'perceived' placebo effect [13]).
- An effect caused by placebo administration [12] (termed a 'true' placebo effect [13]).
- An effect of patient–provider interaction [12].
- Any effect attributable to a pill, potion or procedure, but not to its pharmacologic or specific properties [14].

conceptions have assumed a life of their own and continue to confuse us. Essentially, they are brought about by oversimplifications of complex matters. The abundance of terminology related to placebo (Table 2) is an additional complicating factor. Many of these terms overlap and continue to be used imprecisely. In the following discussion, I will use 'placebo' to describe an inert treatment, given as if it was a real treatment [7], and I will differentiate between the 'perceived' placebo effect [13], that is, the change after a placebo intervention, and the 'true' placebo effect [13], the effect caused by placebo administration [12].

Mechanisms of the placebo effect

The two main theories to explain the placebo effect are unconscious conditioning and conscious expectation [8,18]. They are, of course, not mutually exclusive but interact with each other; conditioning can shape expectations, which, in turn, can mediate the placebo response [9]. The conditioning theory posits that the placebo effect is a Pavlovian response: essentially, patients learn to experience improvement after medical treatments because, in the past, they benefited from consulting a doctor. Such conditioning has been shown in a range of situations; even the effects of exogenously applied insulin can be conditioned [19]. The expectancy theory states that the expectations of the patient (and of the therapist) are raised through the ritual of administering a medical treatment. These expectations, in turn, bring about symptomatic improvements that we call placebo effects [20]. Placebo responses are enhanced markedly through (verbal) instructions informing the patients that the treatment (s)he is about to receive is, in fact, a powerful drug; this is particularly well documented in studies of placebo analgesia [21]. Patient motivation interacts with expectation and, therefore, probably has a modifying effect on the placebo response [22]. These findings might go some way to explain why placebo effects are so notoriously difficult to quantify in clinical trials [23–25], whereas in clinical practice they often seem rather obvious.

In recent years, the neurobiological mechanisms involved in the placebo response have been researched intensely [26]. Dopamine and endorphins, both endogenous opioids, are now understood to be important mediators of the placebo effect [8,27,28]. In addition, mechanisms that are unrelated to endogenous opioids also seem to exist [29]. Brain imaging techniques have shown that placebos can mimic the effects of the active drugs and activate the same areas in the brain [8,30,31]. This is true for placebo dopamine administered to Parkinson's disease patients [32], for placebo analgesics given to patients suffering from pain [33–36], for placebo antidepressants taken by depressive patients [37,38] and for placebo caffeine given to healthy volunteers [39]. In the case of endorphin-mediated placebo analgesia, individual variations can be explained by the affective elements of the pain experience, the affective state of the patient during pain and by sustained pain sensitivity [40].

Placebos in clinical trials

Clinical trials are prospective experiments for assessing the results of medical interventions. Like any scientific experiment, they require a positive or negative control. The most suitable negative control is usually placebo. In a typical placebo-controlled trial, one group of patients receives the experimental treatment while another, otherwise comparable, group receives a placebo. For patients, the two should be indistinguishable, which is a precondition for effectively blinding patients.

Conceptional clarity is essential for understanding the factors that contribute to a therapeutic response [13]. The perception of a therapeutic effect can be owing to a range of separate phenomena

TABLE 1

Some common misconceptions about placebo and placebo effect

Misconception	Truth
The change of symptoms seen in the placebo group of a clinical trial are owing to the placebo effect	There can be numerous contributors to this 'perceived' placebo effect (see the main text and Figure 1)
The placebo effect is ~1/3 of the total therapeutic effect	It can vary from 0–100%
About 1/3 of the population respond to placebo	There is considerable context-dependant variation
Placebo-responders (people who reproducibly respond) are distinct from non-responders	There are no such characteristics
Only 'imagined' complaints respond to placebo	Improvements after placebo have been demonstrated for most symptoms
Placebo effects are invariably short-lived	Long-term effects have been documented

TABLE 2

Related terminology

Term	Explanation
Doctor–patient relationship Therapeutic relationship Therapeutic intent Context effect Iatrotherapeutic effect Iatroplacebogenic effect	Effects caused by the patient–provider interaction
Non-specific effects	(i) Effects of all factors except the specific effect of an intervention (ii) Effects that are not unique to a given intervention
Incidental effect	Therapeutic effects that are not characteristic effects
Characteristic effect	Effects that, according to current theory, are responsible for the therapeutic effect
Hawthorne effect	Effects caused by the fact that study participants are under observation

[21]. They include the specific effects of the treatment and the 'perceived' placebo effect, which, in turn, is composed of the 'true' placebo effect and several other factors depicted in Figure 1. [13] To be certain about the contribution of each factor to the total therapeutic effect, it is necessary to rely on comparisons of treatment groups that differ only in terms of exposure to that particular factor.

Interestingly, some human conditions or diseases seem to be more 'placebo-prone' than others. Patients with pain or depression have been noted to respond particularly well to placebo. The recent study by Clegg *et al.* [41] provides an interesting example. It suggested that orally administered glucosamine and chondroitin (supplements frequently promoted for alleviating the pain of osteoarthritis) are no better than placebo in the symptomatic treatment of osteoarthritis, and demonstrated an unusually large and long-lasting 'perceived placebo effect'. Sixty percent of the patients receiving placebo noted at least a 20% decrease in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score from baseline to week 24 [41]. The example demonstrates how powerful the 'perceived' placebo effect can be. It also suggests that the widespread assumption that such effects are invariably short-lived (Table 1) is not necessarily correct.

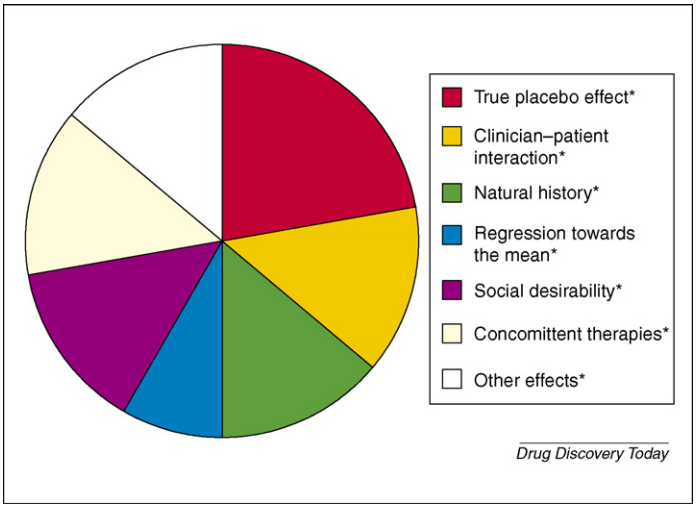

FIGURE 1

Factors which can contribute to 'perceived' placebo effects in clinical trials. *The effect sizes can vary depending on the exact circumstances of the experiment and are arbitrarily chosen in this graph. The factors can overlap; for instance, clinician–patient interaction and social desirability could be seen as part of the 'true' placebo effect as they can depend on the belief the patients attributes to them.

So, placebo controls help to create interpretable results in clinical trials but there are also arguments against their use. Placebo controls can involve withholding effective treatment, which might seriously harm trial participants [42]. In such circumstances, placebo controls might be deemed unethical. By contrast, the lack of placebo controls can render the results of a clinical trial uninterpretable; such research would be seriously flawed and, by definition, unethical [43]. One obvious solution to this problem is to design trials such that both the experimental and the control group receive all essential treatments; the tested therapy and the placebo would then be given in addition to all necessary treatments, and no patients would remain untreated. However, this solution does not apply if it is the essential treatment that is being tested or if such combined treatments are not an option.

To interpret any effect seen in the placebo group of a clinical trial as being entirely owing to placebo is an undue (but prevalent) simplification [13,44]. Mere temporal relationships between treatment and outcome are clearly insufficient for establishing causality. The factors which can contribute to this 'perceived' placebo effect [13] (Feinstein suggested the term 'post-placebo response' [45]) are numerous: natural history of disease, regression towards the mean, social desirability (the tendency of patients to state that symptoms have improved even if they have not) and concomitant treatments that patients did not mention (Figure 1). Therefore, the 'perceived' placebo effect is composed of the 'true' placebo effect plus a multitude of other, possibly overlapping, factors [13,46].

To differentiate between the 'true' placebo effect [13] and other relevant factors, it is necessary to be able to conduct a comparison with a group of patients who have not received the placebo but are exposed to all the other factors depicted in Figure 1. Such studies provide important information about the 'true' placebo effect; however, they are not necessarily relevant for testing the efficacy of new treatments. Recent meta-analyses of such 'three-armed' studies [i.e. trials that include (i) an experimental, (ii) a placebo and (iii) a no-treatment group] have shaken up 'conventional wisdom about the placebo effect' [21]. Some investigators found that the placebo effect is either extremely small or absent [23–25]. Other evaluations using similar methodology (i.e. pooling the

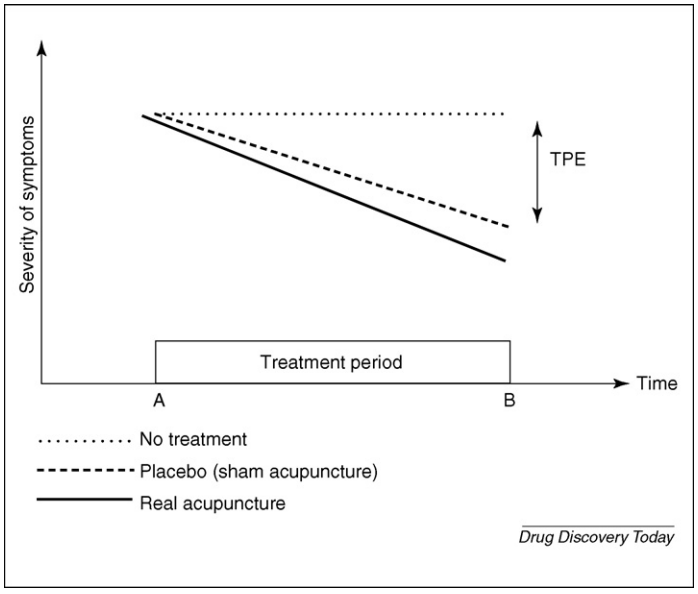

FIGURE 2

The results of the recent acupuncture trials. Eight large acupuncture trials, each with three groups, generated similar results. These trials (total sample size ~5000) related to four different conditions (chronic lower back pain, migraine, tension headache and knee osteoarthritis). Regular acupuncture was given for 8–12 weeks, and before-treatment and after-treatment measurements were taken. At the end of the treatment period, there were only small and inconsistent differences in clinical outcomes between real and sham acupuncture, but large and consistent differences between sham acupuncture and no acupuncture. Abbreviation: TPE, 'true' placebo effect.

results of such 'three-armed studies') have confirmed the existence of the placebo effect but suggested its size to be highly variable [13,47]. There is, of course, plenty of circumstantial and experimental evidence for the existence of a placebo effect [29,48,49]. Miller and Rosenstein argued that the recent analyses [23–25] generated false-negative results (i.e. findings demonstrating the absence of placebo effects whereas, in fact, they do exist) and that 'evidence from placebo analgesia experiments strongly support the reality of the placebo effect' [21].

Perhaps the most convincing evidence for the existence of placebo effects comes from clinical trials of acupuncture. Recently eight large randomized clinical trials (total sample size ~5,000) of acupuncture have emerged that all follow a similar design. They include (i) real- and (ii) sham-acupuncture (placebo) groups in addition to (iii) a group not treated with acupuncture at all [50]. These trials related to different conditions for example, back pain, osteoarthritis and migraine. Their results were remarkably similar (Figure 2). There was only a small and often not statistically significant difference between the outcomes in the experimental and the placebo groups; however, there was invariably a large and significant difference between the placebo and the 'no treatment' groups. Collectively, these findings demonstrate a substantial placebo effect. Therefore, I conclude that placebo effects can be elusive but that they do exist.

Placebos in clinical practice

Knowingly giving placebos to suffering patients is today regarded by most experts as deceit. Therefore, it might not be ethical to administer placebos other than in clinical trials. Sometimes, however, things are not that simple. What if there is no effective treatment for the condition in question, yet the patient longs to receive some intervention? I believe that, in such cases, administering a placebo (e.g. a safe treatment with no proven specific effects for that condition) can be a kind act. Many clinicians seem to agree: the use of placebos in clinical practice continues to be prevalent [51,52], despite the possibility that this could be viewed as being dishonest.

Arguably, some treatments which are being prescribed today are not effective and, therefore, work exclusively through a placebo effect. Think, for instance, of homeopathic medicines, Bach flower remedies, or spiritual healing [53]. Therefore, is the clinical practice of homeopathy (as an example of a treatment from this category) unethical deceit? Homeopaths are convinced that their remedies are effective. Does this conviction legitimize the use of homeopathy? Do not all healthcare professionals have an ethical duty to abide by strong scientific evidence? If that is the case, is prescribing homeopathic medicines unethical? By contrast, if homeopathy produces 'true' placebo effects that are of clinical relevance, why should it not be accepted as a legitimate, evidence-based treatment? [54].

The available information on placebo effects might also justify a further consideration. Can the placebo part of the total therapeutic response to an effective treatment be maximised? In other words, should we take steps to administer an active drug in such a way that the placebo response is optimal? Currently our knowledge might be too incomplete to do this effectively, but intuitively one feels that this might be achieved through a range of strategies [55]:

- Sustained therapeutic partnership
- Listening to patients and giving them sufficient time
- Offering satisfactory explanations for the health problems at hand
- Showing sympathy and empathy, care and concern
- Enhancing the sense of control of patients

Outlook

The renewed interest in placebo has generated a host of intriguing and highly diverse findings that are of interest in the context of this article [56–66] (Table 3). At this stage, these results are, by nature, preliminary – too preliminary to discuss them in detail. They suggest a range of modifiers of the placebo effect, for example, the clinician [56], the frequency of administration [57], the nature of the condition [58,64,66], the origin of the patient [59], the age of the patient [60] and the route of administration [61–63]. Some of these studies are too small or suffer from other limitations; therefore, the results require independent confirmation. Nevertheless, they are intriguing, potentially important and deserve to be studied further.

Concluding remarks

Considerable progress has been made in understanding placebo effects. Conceptual clarity is important for avoiding the confusion that has hindered our understanding in the past. The mechanisms of the placebo response are currently being clarified and the complex phenomena involved in placebo effects are becoming less enigmatic. We will, therefore, be able to evaluate their true significance more objectively. Such new insights could be of value to basic and clinical research and to patient management. Basic research will profit from a detailed comprehension of the under-

TABLE 3

Selected findings from recent research into placebo effects

Main result	Comment	Refs
The size of the placebo effect might depend on the clinician who is treating the patient	In this study, a female doctor was associated with higher placebo response rates than two of her male colleagues	[56]
The size of the placebo effect seems to depend on the frequency of administration	Review of 79 randomized trials on duodenal ulcer treatments	[57]
Placebo responses seem lower than average in patients treated for cancer, nervous diseases and substance abuse	Result is based on an analysis of 141 clinical trials	[58]
Placebo effects might be larger in European studies compared with American studies	Analysis of 416 randomized, placebo-controlled trials	[59]
Adverse effects of placebo might be lower in European studies compared with North-American studies	Result is based on an analysis of 31 and 98 clinical trials with migraine sufferers	[60,61]
Placebo effects seem to be enhanced in studies with children and adolescents	Result is based on an analysis of 31 clinical trials with migraine sufferers	[60]
Subcutaneous injections of placebo seem to generate stronger placebo effects than oral administration	Results based on an analysis of 98 clinical trials with migraine sufferers	[61]
Sham treatments or devices might generate greater placebo effects than oral placebos	Study of 270 pain patients treated with (sham) acupuncture or (placebo) amitriptyline. A systematic review generated similar results.	[62,63]
Placebo effects might be more potent in clinical pain compared with experimental pain	Small trial with 16 patients suffering from lower back pain	[64]
Consistent symptom pattern and low body weight might be associated with less powerful placebo effect	Trial with 220 patients suffering from functional dyspepsia	[65]
Subjective symptoms show larger placebo effects than objective signs	Studies of treatments of lower urinary tract problems	[66]
Adherence to placebo might be associated with positive health outcomes, even lower mortality	Adherence might be a marker for generally healthy behaviour	[67]
Pessimism might be associated with stronger nocebo effects	Experiment with 54 healthy volunteers	[68]
'Perceived' placebo effects in clinical trials have increased in size during recent years	Based on a meta-analysis of studies of major depression (1981–2000) Analysis of 416 studies published between 1986 and 1996	[69] [59]

lying mechanisms. Clinical researchers might be able to design more-effective clinical trials. Patients could benefit from clinicians maximising the potential of placebo effects associated with effective therapies. The thing to remember here is that no placebos are needed to generate a placebo response in patients; this can also be achieved by active treatments.

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