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ANALYSIS

Informed consent and clinical trials: where is the placebo effect?

Lack of knowledge about placebos affects participants' understanding of trials and breaches the ethical obligations of researchers, argue **C R Blease**, **F L Bishop**, and **T J Kaptchuk**

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Informed consent requires researchers to provide participants with information about research that is accurate, complete, and understandable.[1] Researchers also have an ethical obligation to ensure participants understand the investigational nature of the study. In clinical trials we argue that adequate information must include understandable descriptions of the function of placebos[2] and their effects (box 1). This is essential to ensure trial participants are fully informed about the potential benefits and risks of the study. The ethical imperative to ensure that participants understand placebos is made stronger by continued debate about use of placebos and active controls.[4]

Nevertheless, evidence suggests that investigators often fall short of their ethical obligations. In the 1980s the term "therapeutic misconception" was coined to refer to the widespread failure of participants to understand fundamental aspects of clinical trials, including research design, purpose, and the function of placebos and randomisation.[5] In 2009 a systematic review of studies of informed consent processes concluded that therapeutic misconception is common among research participants, with adequate understanding of the goals and methods of trials being found in only half of the reviewed studies.[6]

Misunderstandings about the purpose of trials are still widespread.[7] More recent studies show that willingness to participate in clinical trials is correlated with misconceptions about primary purpose.[8 9] We argue that misconception is, in part, perpetuated by the failure of investigators to provide adequate information about the role of placebos in clinical trials and possible placebo effects.

Placebo responses

Placebo controls in randomised trials function as methodological safeguards for systematic bias, normal fluctuations, regression to the mean, and, importantly, the effects of the therapeutic encounter. Although our knowledge about placebo responses is still far from complete, we know that for many conditions, especially those with subjective symptoms, patients receiving placebos have similar health benefits to participants taking effective drugs. Temple and Ellenberg note that for many common classes of drugs, multiple trials of approved medicines have shown no difference in effect between drug and placebo treatment (box 2),[4] although superiority to placebo has been shown in at least two randomised trials.

Some of the observed response in placebo groups is undoubtedly the result of spontaneous improvement, but increasingly research shows that the therapeutic encounter itself can reduce symptoms through empathic witnessing, emotional support, medical rituals, symbols, and paraphernalia (eg, placebo pills).[3] Additionally, studies show that participants treated with placebo often report many of the adverse effects associated with the investigational intervention (nocebo effects), probably because of expectations or misattribution of already existing symptoms.[10]

Substantial basic science research has already shown the involvement of certain neurotransmitters (eg, endorphins, dopamine, cholecystokinin, and cannabinoids) in placebo effects (or nocebo effects), and that these effects engage specific, relevant, and quantifiable regions of the brain.[3]

It is helpful to differentiate placebo responses from the placebo effect. Placebo responses refer to changes in patients' symptoms after administration of placebos (including spontaneous remission); placebo effect refers to changes attributable to outcomes related to psychobiological mechanisms associated with the therapeutic encounter.[11] In controlled trials placebo responses can be expected whenever the disease commonly has spontaneous improvement and placebo effects from clinical engagement are mostly likely when participants' self appraisals are involved. Placebo treatment is likely to relieve pain[12] but will not shrink tumours.[13] But subjective symptoms of oncological diseases and their treatment such as nausea, fatigue, or hot flushes can be reduced by placebos.[13 14]

This substantial body of knowledge has not been reflected in informed consent procedures. One reason for this may be lack

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Box 1: What are placebos?[3]

According to typical patient information leaflets used in clinical trials: "A placebo is a dummy treatment which looks like a genuine medicine but contains no active ingredient."

Placebos are designed to look—and ideally taste, smell, and feel—like the drug that is being tested so that participants do not know which they are receiving. Placebos are often made out of substances such as cellulose, flour, or lactose.

Can placebo treatment have any positive benefits?

There is evidence that placebos have measurable effects on many symptoms, including pain, depression, fatigue, and other perceptions of bodily dysfunction. When patients receive attention from medical professionals about their symptoms, and then receive a treatment (even if that treatment is a placebo), the brain's natural pharmacy is activated releasing neurotransmitters and engaging areas of the brain that help to relieve symptoms. Evidence suggests that placebo effects mainly involve relief of symptoms but are unlikely to affect underlying disease

Box 2: Common drug classes for which effects of drug and placebo are often indistinguishable in randomised trials[4]

- Analgesics
- Anxiolytics
- Antidepressants
- Antihypertensives
- Hypnotics
- Antianginal agents
- Angiotensin converting enzyme inhibitors for heart failure
- Postinfarction β blockers
- Antihistamines
- Motility modifying drugs for reflux disease
- Non-steroidal asthma prophylaxis

of training of biomedical researchers on the science of placebo effects.[6]

Existing standards for research

Research participants are typically provided with extensive information on the possible benefits and negative effects of the investigational intervention. However, information about placebos is often incomplete and inaccurate, contributing to therapeutic misconception.

In a content analysis of informed consent material within 45 large randomised trials in the UK, patients were given much less information about placebos than the target treatment.[15] Most described placebos as "inert," or "inactive" ("dummy" or "fake" medication); eight (18%) of the information leaflets asserted that placebo treatments were "undesirable or ineffective" and that receiving a placebo was a "disadvantage of participating in the trial."

The test treatments were prioritised and couched in positive terms as being "potentially beneficial," with 39 (87%) leaflets indicating that participants might experience some adverse effects if allocated to the intervention arm. Only one leaflet informed participants that those allocated to the placebo group might also experience benefits but did not offer any explanation for this. None mentioned that patients sometimes perceive or misattribute common adverse events while receiving placebo treatment.

These shortcomings are not restricted to UK trials. A recent Finnish study of 52 randomised trials found that only 35% of disclosure protocols provided a rationale for the use of placebos in trials.[16] Of these statements, only 12 (23%) described why placebo use was necessary in the research, and only six (12%) discussed possible adverse effects of placebos.

Problems with current information

It might be countered that there are reasonable justifications for failing to inform patients about placebo effects. One argument is that such disclosures risk undermining the methodological integrity of clinical trials. Telling participants about placebo effects could influence their expectations and thus augment or diminish placebo or drug responses, biasing the outcome of the trial. However, the evidence that disclosure (or non-disclosure) influences placebo responses is unclear or contradictory.[17 18] Furthermore, even if placebo or drug responses were altered, the Declaration of Helsinki makes it clear that informed consent concerns take precedence over methodology.[1]

Informing patients that even if they receive placebos they might still experience health benefits (and adverse events) is likely to resolve therapeutic misconceptions about the purpose of the trial and correct the false belief (perpetuated by current research approaches) that placebos have no effects. Such knowledge would help participants to make informed choices and sense of their experiences.[19]

Failure to fully inform participants about placebo effects has been shown to cause distress. For example, in a qualitative study of debriefing of patients with irritable bowel syndrome after a randomised trial, some patients in the placebo group were deeply agitated. One patient strongly protested that the person debriefing was mistaken because she felt she had benefited from the treatment.[20] Even during the trial patients were worried that improvement is not real, with many remarking, "maybe I made up the whole thing."[21]

Such incidents could be avoided by informing patients about placebo effects before the trial using accurate and accessible evidence based information.[22] Accurate information is likely to improve patients' understanding of their experiences during trials and may mitigate the reluctance among researchers to tell participants their treatment assignment after the trial has finished.[23]

In addition, participants should be told what is in the placebo pills. Such pills are seldom completely inert. In clinical trials they are usually microcrystalline cellulose or lactose pills, which can potentially cause harm (and influence trial outcomes). For example, a study of megestrol acetate for anorexia associated with cancer used a lactose placebo, but subsequent studies have found that lactose intolerance is common among patients with cancer and may be aggravated by chemotherapy and radiation therapy.[24] The placebo in this trial may therefore have induced adverse effects among participants and exaggerated the benefits of the active drug.

Improving disclosure

Improving standards of disclosure about placebo effects in clinical trials could help reduce therapeutic misconceptions among participants. One approach is to develop generic information leaflets that describe placebos and explain placebo effects in accessible terms,[22] elaborating on the information in box 1. Online materials and resources might supplement such leaflets. An alternative approach would be to work with patients to develop template phrases about placebos and their effects that investigators could insert into existing patient information materials and research ethics committees could recommend. Working with patients is essential to ensure that information is accessible, engaging, and communicates effectively with participants in clinical trials.[25]

Disclosures about placebo responses should be carefully formulated to be as illness and symptom specific as possible. For example, for treatments of conditions that are known to elicit placebo responses (eg, benign prostatic hyperplasia,[26] perimenopausal hot flushes[27]), patients should be told that previous studies suggest that they may experience symptom improvement. If no placebo effects are expected—for example, in trials that add a second medication to standard of care for treating cancer tumours—participants might be told that placebos are unlikely to affect the tumour and are designed to help scientists to assess outcomes objectively. Patients should also be advised about side effects of the medication and that these could occur because of the medication or the worry about a new medication ("nocebo effect").[10]

Improved scientific literacy about placebos and placebo effects, and the importance of communicating these to research participants, is an ethical imperative. Clearer understanding will benefit both participants and scientific progress.

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Summary points

- Studies show persistent, routine failures of informed consent processes in clinical trials resulting in confusion about the primary goal of research
- Informed consent should include information about the role of placebos and their effects
- In some trials it may be necessary to convey information about the content of placebo pills
- Disclosure information should also be tailored according to the illness and symptoms being investigated, since some conditions are more placebo responsive than others