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Trial designs and exploration of the placebo response

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Summary The 'placebo response' is a concept derived from the use of dummy (sham) interventions as 'controls' for active interventions within the context of a randomised controlled trial (RCT). Clearly if there is nothing in the sham treatment it can have no effect, so the response must be dictated by other contextual or incidental factors. However, the assumptions and processes that underlie the classical RCT make it difficult to explore these incidental factors, leaving us with the paradox that while the RCT defines placebos, we cannot easily explore placebo responses within RCTs. Furthermore, complexity makes the 'simple' RCT an inadequate approach to assess interventions in chronic diseases. A variety of alternative trial designs (such as stepped wedge designs, pre-randomisation and cluster randomisation) are discussed. Different approaches, including nested qualitative research and realist research approaches, are recommended as ways forward for the investigation of the placebo response.

Introduction

A placebo is a dummy or sham treatment. It contains no ingredient active against the target condition; therefore, it can have no activity — there can be no 'placebo response'.[1] However, when placebos are used in randomised clinical trials (RCTs) they produce an effect that is larger than that observed in no treatment control groups. Hence, current concepts of the 'placebo response' come from trial data in which a dummy treatment has been used as the 'control' for an active treatment, usually a drug.

The importance to drug trialists of using a dummy control tablet to compare with an active intervention is clear: if we are to be certain that a drug is effective, then we need to make sure that it works better than giving 'nothing'. The placebo response is the change that is observed when we give the dummy tablet, and we subtract that from the change seen in the active drug-treatment arm in order to assess the true efficacy of the drug. However, the response to the dummy treatment cannot be a response to the 'nothing' that is in the tablet, it must be a response to 'something'. That something could be the many 'contextual factors' or 'incidental effects' surrounding the administration of an intervention, such as the interaction between patient and prescriber, the wider environment, the rituals, the expectations of each party, the meaning that the colour of the tablet might convey, prior experiences and a host of other factors[2] (Table 1); or it could be a spurious finding, caused by factors relating to the artificial nature of the RCT, or issues such as the natural history of the target condition and 'regression to the mean'.[3]

The evidence-based medicine (EBM) movement relies heavily on data from RCTs and is particularly keen on trials that include a 'control' group, allowing what is seen as a fair and accurate assessment of the 'true' efficacy of the intervention being tested. The 'placebo response' is seen as a distraction at best and a nuisance at worst and is not investigated by people pursuing EBM. That paradigm has served us well for the assessment of drug efficacy in many acute medical conditions, such as myocardial infarction,

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Table 1 Some of the determinants of a placebo response to dummy tablet therapy (from Doherty and Dieppe[2]).

1.	The appearance, colour, number, price and branding of the tablets
2.	The method (ritual) and frequency of delivery
3.	Response expectancy
4.	Provider effects and patient-provider interactions
5.	Behavioural conditioning (previous experience)
6.	The environment and context

where it has helped us understand the value of, for example, 'clot-busters'.[4] Unfortunately, the same model is now being widely used to assess more complex interventions (interventions in which there is more than one component and in which these components may interact), and for chronic disease, where it is less appropriate. Furthermore, if we only pursue a conventional trial-based approach to the exploration of the placebo response, we will find it hard to do anything other than assess the size of the effect, rather than being able to understand it.

It is crucial that we do pursue research that will help us understand the placebo response, as in some conditions it seems to be of more value to the target population than the active drug. The work of Irving Kirsch suggests that the majority of the beneficial effects attributed to antidepressant medication can be put down to the placebo response,[5] and recent work on the treatment of pain in osteoarthritis comes to a similar conclusion — placebos had about twice as much power on pain as any of the commonly used active interventions such as non-steroidal anti-inflammatory drugs.[6]

Therefore, we need to examine issues around trial designs that affect our ability to explore the placebo response further and consider other approaches that might improve our understanding. These are the subjects of this article.

Problems inherent within RCTs

The conventional RCT involves several assumptions and processes that make it difficult to explore the placebo response.

The assumptions include

1. that a clear, single disease diagnosis has been made prior to the use of an intervention and
2. that the characteristic effect of the intervention being tested is quite distinct from any incidental (placebo) effects that might be observed.

Key processes include:

1. obtaining ''fully informed'' consent prior to the use of the intervention
2. assessment of efficacy by measuring one or more biomedical outcomes related to the disease (diagnosis) being targeted
3. the maintenance of trial fidelity and
4. usually, the absence of a 'no treatment' control group.

The requirement of a clear, single 'diagnosis' is a problem for at least two reasons. First, the majority of older people seeking healthcare have more than one health problem.[7] Second, a clear diagnosis is often not possible (as in 'medically unexplained symptoms' for example), but may subsequently become obvious as a result of the response to the intervention.

The 'characteristic' effect of an intervention is the effect that we expect the intervention to have on the target disease, based on our biomedical theories of causation; the 'incidental' effect is mediated by all the other things that are going on when we use an intervention (i.e., the placebo effect). As pointed out by Paterson and Dieppe,[8] the classical RCT assumes that incidental effects are generic and not linked to any therapeutic theory and that characteristic and incidental effects are distinct and additive; but as these authors demonstrate, such assumptions do not apply in the case of many of the interventions that we use for chronic disease. For example, a physiotherapist is modifying the interventions being used in a treatment session in response to feedback being given by the patient (e.g., ''it feels right when you do that exercise, but not when you do this one'') and is relating and responding to the patient throughout the period of the treatment.

''Fully informed'' consent is a problem because it is an intervention in its own right and one that is particularly relevant to the placebo response. Fully informed consent necessitates telling the patient exactly what to expect from the intervention, including all possible benefits and harms. One of the main explanations for the 'placebo response' is that it is mediated by our expectations — we experience a certain change in our bodies in response to the intervention because that is what we expected would happen.[9] If this is an important factor (as I and many others believe it is), then we must treat all trial data with some suspicion, as patients in trials have been 'primed' to expect a certain type of change, and they therefore respond in exactly that way.

The need for simple 'outcome measures' related to the theoretical notion of what the characteristic effect of the intervention to be tested also poses a problem.[10] Both the intervention under investigation and the context (incidental) effects resulting from everything else that is going on within the trial might result in unexpected consequences that we will not detect if we rely on simple biomedical outcome measures relating only to what we expect. We may need to ''expect the unexpected''.

'Trial fidelity' is about making sure that the intervention is kept exactly the same for all participants, under the same circumstances, to ensure that any between group differences can be attributed to the intervention. That may be useful in the context of an RCT but is not what happens in the real world. Health-care professionals adjust their interventions to the needs of the individual patient and use them in a wide variety of different settings and environments. This may be one of the reasons for the gap between EBM-derived 'evidence' and the experiences of doctors and patients and for the lack of generalisability of much trial data. In addition, the extent to which a therapy is individualised (or not) could be a major factor influencing the 'placebo effect'.

In order to investigate the placebo response we need to be able to compare it with a 'no treatment control group',