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Implications of the 'placebo effect' for CAM research

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Summary The 'placebo effect' concept is intrinsic to the architecture of the double blind placebo randomised controlled trial (RCT), the oft quoted 'gold standard' method of clinical research whose findings are supposed to inform our understanding of the interventions used in clinical practice. The 'placebo effect' concept is often used in discussions of both clinical practice and clinical research, particularly when discussing why patients report improvements with complementary and alternative medicines (CAMs). Despite its frequent use, 'placebo effect' is a non-sequitur, thus confusion abounds.

In routine healthcare patients are not told that they might receive placebo. However, in clinical trials the opposite is true. Telling people that they might receive a placebo really complicates things. The uncertainty invoked by information that a placebo may be given can impact trial recruitment, the delivery of the intervention, and the reporting of outcomes, as can the 'meaning responses' invoked by other types of information provided to patients in standard RCT designs.

Future CAM research should consider alternative RCT designs that help ensure that participants' experiences are uncontaminated by 'meaning responses' to information that they may receive fake treatments, i.e. placebos.

Introduction

Placebos and 'placebo effects' in clinical practice and clinical research

The concept of the 'placebo effect' is intrinsic to the architecture of the double blind placebo randomised controlled trial, the oft quoted 'gold standard' method of clinical research whose findings are meant to inform our understanding of the interventions used in clinical practice. Although, a non-sequitur, the term 'placebo effect' frequently occurs in discussions about clinical practice and clinical research, particularly when discussing why patients report improvements with complementary and alternative medicines (CAMs).

Unfortunately findings from clinical research designs which utilise placebos are often difficult to translate into clinical practice. One reason for this is that placebos are delivered very differently within these two contexts (i) clinical practice and (ii) clinical research, and these differences have important consequences. When placebos are delivered in everyday healthcare, the patient does not know that they are receiving an inert treatment. However, in the context of clinical research, the patient does know before hand that they might be receiving a placebo. Telling people that they might receive a placebo really complicates things. To illustrate this I describe a personal experience of participating in a placebo randomised controlled trial, the complications that ensued and the questions it left me with.

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A double blind placebo randomised controlled trial

My first experience of placebos in CAM research was over a decade ago when I was one of ten homoeopaths participating in a double blind placebo randomised controlled trial of 'homeopathy' for patients with chronic fatigue syndrome.[1]

We all knew many patients who wanted treatment, yet when the trial began there were problems recruiting enough patients. Then some trial participants decided to quit the trial at the end of the first consultation and have homoeopathic treatment outside the trial in order to avoid the possibility of receiving a placebo. The homoeopaths found it was difficult to establish strong therapeutic relationships in the context of the trial, and at follow up appointments, it was frustrating not knowing if any lack of improvement was because of an incorrect homoeopathic prescription or because the patient was receiving placebo.

Towards the end of this trial, this frustration led some of us to subvert the blinding, by prescribing one particular homoeopathic medicinal product (Carcinosinum 30c) that we thought all patients with chronic fatigue syndrome would have a reaction to. Those patients who did not react we deemed to be in the placebo group. If we 'knew' or suspected that a patient was receiving placebo, we naturally then focussed on helping our patients get better using all our other therapeutic skills: nutritional advice, counselling, etc.

Questions

My experiences in this trial left me with lots of questions. Why didn't patients want to participate? Why was it difficult to establish a good therapeutic relationship with patients in the trial? What aspect of homoeopathy was the trial testing? — the therapeutic system of homoeopathy, treatment by homoeopaths, or homoeopathic medicinal products?.[1] How could this trial inform real world decision making regarding chronic fatigue syndrome and homoeopathic treatment? Should there have been a 'no treatment' group included in the design? Why was a placebo RCT design regarded as 'gold standard' research when the experience for both the patients and the homoeopaths was so different from usual care? Was there a trial design where the experience for patients and homoeopaths was uncontaminated by the trial design? Analysis of the results found that both verum and placebo groups improved, with the verum group doing better than the placebo group, but the difference between the groups was not statistically significant.[2] What did the trial results mean?

Recruitment to trials

A few years after this placebo trial experience, I started to explore the vast literature on clinical trials as part of my PhD research. I discovered the majority of randomised controlled trials (RCTs) had problems recruiting sufficient numbers of patients,[3] with many trials closing prematurely due to slow recruitment. Why were patients keen to obtain healthcare, but reluctant to participate in healthcare RCTs? Was the problem that recruitment to RCTs affected by the information that potential trial participants were provided with?

Key messages in informed consent procedures for clinical trials

Standard informed consent procedure for RCTs provides all potential trial participants with full information prior to participation in the trial regardless of their eventual group allocation. But what meaning do people give to the information provided in standard informed consent procedures? Translating this information into simple language, we see that potential participants are provided with multiple key messages.

Patients are told that 'there may be a treatment available for you. . .' regardless of whether they are allocated to the treatment being trialled. Clinicians recruiting patients to trials have to admit to not knowing which treatment is best. Clinicians also have to communicate that the decision as to which treatment the patient is allocated to (treatment as usual/new treatment/placebo) is a decision made by chance and not by the patient and/or clinician. Moreover, in placebo RCT designs, patients are told that they may receive a placebo (but won't know if they are or not).

'Meaning response' to informed consent procedures for clinical research

Moerman and Jonas[4] argued that 'meaning response' (i.e. the ''meaning,'' to which people, when they are sick, often respond), is a useful way of approaching 'placebo effect' discussions. If we consider clinical research designs using placebos, it is obvious that a meaning response is invoked as soon as potential trial participants are informed that they might receive a placebo. Indeed, meaning responses may be invoked by each and every type of information provided (see Fig. 1). For example, if my clinician tells me that they do not know which treatment is best, I may then decide to find a clinician who does. Or if my clinician tells me that he is going to toss a coin to decide which treatment I will receive I will be very tempted to walk out of the consulting room and find a clinician who will use a better method for deciding my treatment. Or if I am informed that there is the possibility I may receive a placebo when I have a strong (or weak) preference for the trial intervention, it is quite likely that I will seek the trial intervention outside the trial in order to avoid the possibility of receiving placebo.

Increasing uncertainty

The majority of the messages embedded in the standard informed consent procedures for RCTs are dissonant with the messages communicated in routine healthcare, and dissonant to the establishment of a good therapeutic relationship. Many of these messages increase the sense of uncertainty experienced by the patient compared to their experiences in routine healthcare.[5] Patients are particularly concerned about whether they were receiving real (or fake/placebo) acupuncture treatment.[5] Differences in the psychosocial context between RCTs and usual practice can