ETHICS OF PLACEBO USE IN RANDOMISED STUDIES: PRIMER FOR PHYSIOTHERAPISTS

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ABSTRACT: *Evidence based practice is driving the need to establish effectiveness of interventions employed by health professionals. The need to show effectiveness for interventions employed by physiotherapists has not been greater. This has led to an increase in the body of evidence available on physiotherapeutic methods. The quality of the evidence, however, has made it difficult to draw definitive conclusions on the effect of some of these interventions. There is therefore a call for improved methodologies in physiotherapy effectiveness studies. These needs may prompt even greater use of randomized trials with or without a placebo arm, which are regarded as the best way to show effectiveness. The use of placebo rather than an active comparator has advantages in showing absolute effectiveness of interventions. However, there may be ethical concerns posed by its use in clinical trials. The balance is therefore required between good ethics and sound science. The goal of this article is to provide physiotherapists with a basic knowledge of the ethics of placebo use in randomized studies. This should prepare researchers to better balance ethical needs with scientific imperatives when designing effectiveness studies.*

KEY WORDS: PLACEBO, RANDOMIZED CONTROLLED TRIALS, ETHICS, EFFECTIVENESS STUDIES, PHYSIOTHERAPY.

INTRODUCTION

The use of placebo in research has long been recognized. Randomized, double blind, placebo and/or active controlled trials are the gold standard for establishing effectiveness and safety of interventions (Herbert & Bo, 2005). When the objective is to establish the effectiveness and safety of an investigational intervention, the use of placebo control is often more likely than that of an active control to produce a scientifically reliable result (Council for International Organizations of Medical Sciences (CIOMS), 2002; International Conference on Harmonization (ICH-E10) guideline, 2001). The internal validity of a study could be enhanced too by using a placebo comparator (ICH-E10, 2001). Placebo-controlled trials are therefore the benchmark used by regulatory agencies, like the United States Food and Drug Administration (FDA), in the evaluation of new medical treatments (Freedman et al, 1996).

The use of a placebo is unethical where there is a risk of serious or irreversible harm. However, there is no general agreement on its use in other conditions of less than serious risks to research participants. Placebo use in research has been very controversial, especially so because standard or proven treatment may be withheld from the placebo group (Miller & Brody, 2002). Limiting the use of placebo could be "paternalistic" or too protective. And insisting on fiduciary obligations of healthcare providers may impact on a patient's autonomy. But it could also be argued that a patient might be altruistic at times, making the placebo debate very interesting. The argument for and against the use of placebo has produced views at least on three main fronts (Emanuel & Miller, 2001). The placebo-orthodoxy view believes that methodological considerations should be at the forefront, while the active-controlled orthodoxy holds the rights and welfare of patients superior to gaining scientific knowledge. The moderates are in between these extreme views. However, there is consensus on the need to conduct research that reflects both good ethics and sound science (National Placebo Working Committee (NPWC), 2004).

The debates over placebo revolve around the potential risks and harm that research subjects might suffer if treatments are withheld, and scientific rigor, hence the ability of studies to provide information that is valid. The fiduciary duty of clinicians calls for care that will not compromise patients' welfare in any way. Most of the placebo debates have been around pharmaceutical and surgical placebo trials, and very few have focused on research in rehabilitation in general and physiotherapy in particular. There have been some reviews of placebo and its effect in physiotherapy (Clemence, 2001; Gielen, 1989). Essentially, there is a paucity of literature and active debate on the ethics of placebo use in physiotherapy research.

Physiotherapy research, like most rehabilitation research, has evolved to a stand-alone status, rather than the traditional leaning on medicine for evidence. This status creates the need for an independent body of knowledge that is unique to the profession (Robertson, 1995). In doing so, physiotherapy must embrace a high level of scientific research to show evidence of effectiveness for treatment methods employed, among other things. Recent years have

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seen the upsurge in these types of enquiries which is commendable. However, there are still some gaps in knowledge of clinical effectiveness, which is readily appreciated by reviewing results of systematic reviews and clinical guidelines (Tunis et al, 2003). Findings of these reviews consistently point to inadequacies and the need to improve the quality of studies. The gaps in available evidence undermine efforts to improve the scientific basis of both clinical and policy decisions in healthcare. If evidence of benefit is needed urgently, and placebo use may provide some of the needed answers, then we need to be aware of the moral/ethical reasoning and guidelines underpinning placebo use.

It may be difficult for all physiotherapy researchers to be able to sieve through the enormous placebo literature. International ethics guidelines give provisions to allow the use of placebo in research enquires if needed to answer scientific questions validly (CIOMS, 2002; NPWC, 2004). Despite these provisions, there is still uncertainty as to what constitutes an effective or proven therapy, unavailability of which is a condition for placebo use to proceed. It is worthy to note that most guidelines on placebo use focus mainly on pharmaceutical trials. While other types of placebo trials will be accommodated by these guidelines, the responsibility to justify the use of placebo may be on the individual researcher because the ethics review committee must be satisfied that placebo is a reasonable option (CIOMS, 2002) It is therefore essential for physiotherapists to be aware of the discussion around placebo to be better prepared to justify its use in their study designs.

ETHICS OF PLACEBO RESEARCH.

The condition of clinical equipoise (see definition below), as the fundamental ethical consideration for conducting randomized placebo trials, is acknowledged by the research community (NPWC, 2004). Clinical equipoise is but one of the ethical justifications and its other forms are discussed below.

Historically, ethical concerns revolve around the fiduciary duty of the healthcare giver, and the fact that fiduciary (caregiver) should do the best for the beneficiary (Declaration of Helsinki, 1964). It is therefore common sense to see that the process of randomization that may put a patient in a group that receives placebo (or some substandard) treatment is against this common belief. A state of equipoise has been proffered as a necessity before a patient could be randomized legitimately without sacrificing or opting out of the fiduciary position. *Equipoise is the situation of honest ambivalence, uncertainty or indifference.* There are three different forms that have been discussed.

- **Clinician's equipoise:** Fried (1974) suggests that justification for randomization necessitates that a clinician be genuinely uncertain as to the relative merits of the treatment alternatives (as cited by Miller & Weijer, 2003). The moral justification therefore is that there must be ambivalence in the mind of the clinician regarding what might be the best treatment. This view has been challenged on at least two grounds (Veatch, 2002): Firstly, it is very difficult to achieve total indifference given two options, and secondly, the clinician's view may be biased due to limited knowledge of the available evidence of the case in question, or due to some moral values or belief. In these instances, the clinician equipoise and randomization is no longer justified. Though, Miller and Weijer (2003) reported that Fried (1974) did not indicate in his writings the extent of evidence needed for this equipoise to be disturbed, his proposition has always been interpreted to mean absolute uncertainty by the clinician.
- **Clinical equipoise (or clinician community equipoise):** Seeing the problem that may be associated with clinician's equipoise, Freedman (1987) argued that this equipoise as interpreted from Fried's (1974) writings may be too fragile and difficult a standard to meet for a trial to even commence (Miller and Weijer, 2003). Freedman (1987) therefore proposed another ethical justification for randomization based on the indifference or genuine uncertainty of the whole clinical community on which of the available treatments is preferred. Freedman's (1987) work caused a shift in clinical trial ethics, because it was seen as being more objective (Veatch, 2002). Once there is disagreement over the relative merits of therapeutic alternatives by the relevant expert clinical community, a state of clinical equipoise is said to exist. This makes it easy then for a researcher to ethically ask a patient to submit to randomization, despite having a personal preference for one treatment option. Based on the same premise, researchers are justified to allow trials to continue till the end, even when the incoming results clearly show that one treatment may be better, in as much as the available evidence is not enough to sway the judgement of the clinical community. This of course does not mean that a clearly beneficial option should be withheld if the evidence has shown its superiority over other options. Most trials have provision for early termination if the study has achieved the goals set out at the commencement. Trials justified in this way must be designed such that there is a reasonable expectation that if successfully completed, clinical equipoise will be disturbed (Miller & Weijer, 2003).

Veatch (2002) opined that clinical equipoise might not be enough justification for randomization. Miller and Weijer (2003) agreed with the above position and argued that clinical and clinician's equipoise address complementary moral concerns. Some of the problems that have plagued the clinical community equipoise include: dispute over whether the justification should be on the basis of indifference in the scientific or clinical community and likely clinician's guilt if he/she has a personal preference for a treatment even if the clinical community is indifferent (Veatch, 2002).

The problem of justifying uncertainty based on the clinical or scientific community is particularly evident in physiotherapy, for example in ultrasound research. Ultrasound is widely used among clinicians in physiotherapy and its frequency of use may not be declining (Lindsay et al, 1995). The high frequency of use could be interpreted to be a sign of anecdotal evidence of clinical effectiveness. However, the evidence from the research community is that there

may be little evidence so far for the use of ultrasound (van der Windt et al, 1999, Robertson and Baker, 2001). An exception to this was the study by Ebenbicherler et al. (1999) pointing to the benefit of ultrasound. It therefore becomes difficult to decide which of these views should determine the presence or absence of uncertainty.

- **Patient (subject) equipoise:** Veatch (2002) proposed that since both clinician and clinical community indifferences may not be an adequate justification for randomization, subject indifference may be a necessity then for justifying randomization. His stand was in line with the principle of autonomy. He argued that if "it is the individual subject who is randomized and who runs the risk of ending up in an arm of the trial with placebo", then the basis for choosing to participate should be their inability to form a clear preference for any of the available treatment options. This approach is more pertinent because clinician and clinical community consensus are not definitive neither are the benefit/harm estimates. Criticism of this approach is related to possible research participant altruism. It can be argued that the three approaches above could be complimentary to each other, thereby strengthening the reasoning on ethical justification for randomization.

ETHICAL GUIDELINES

Historically, international ethics guidelines probably started with the Nuremberg code (1949), which emphasized some balance between the risk of research and the benefit it sets to achieve. Other notable research guidelines are the Declaration of Helsinki (World Medical Association, WMA), the CIOMS and the ICH-E10 guidelines. Most national ethics bodies subscribe to the value statements in the above guidelines.

The Declaration of Helsinki (1964, and its revisions) is a fundamental document in the field of ethics and has influenced the formulation of international, regional and national legislation and codes of conduct (CIOMS, 2002). Placebo use in research was embodied in the Declaration of Helsinki. Article 29 of the declaration read as follows: "The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists." Clarification of Article 29 while reaffirming the previous position, adds that the use of placebo controls may be permissible even if "proven therapy" is available in certain situations when no additional risks of serious or irreversible harm is anticipated. The CIOMS guideline (2002) also provides that placebo may be ethically acceptable if there is no "Established Effective Treatment" (EET). Withholding the EET would expose subjects, at most, to temporary discomfort or when the use of EET will not yield reliable results, and placebo would not add any risk of serious harm. The ICH-E10 guideline is similar to the CIOMS. Similar to all of the guidelines is the fact that effective therapy must be absent to consider a placebo.

RESEARCH GUIDELINES IN SOUTH AFRICA

The prominent research ethics guidelines in South Africa are those of the Medical Research Council (MRC), (1993, revised 2004), the Department of Health (DOH) research guidelines and the Guidelines for the Good Practice in the Conduct of Clinical Trials (2000).

The original MRC guidelines (1993) referred to the use of placebo in research; however, this part was omitted in recent revisions (MRC, 2004). The reason was to avoid duplicating the DOH guideline, which focuses specifically on the issue of good practice in conducting clinical trials (Labuschagne, 2005). The MRC (1993) guidelines based ethical justification for placebo use on the condition of uncertainty of the effects of treatment being considered. Although, the MRC acknowledged problems with placebo or dummy treatment, it agreed that placebo use was preferable to the continued use of treatment of unproven effectiveness or safety. The guidelines reiterated that whenever there is limited evidence, treatment could be withheld for the purpose of research, if no long-term harm could reasonably be foreseen and valid consent is obtained. It was further advised that there be availability of beneficial treatment after trial, early termination if warranted and early withdrawal of patients in cases of adverse reactions/complications.

The Guideline for Good Practice in the Conduct of Clinical Trials (2000) was intended to provide clear standards for the conduct of trials within the context and realities relevant to South Africa. The guidelines reflect regulatory and legislative requirements, and as such lend themselves to widespread use within the academic and clinical research communities. Like most guidelines of its kind, they focus on the "management and regulation of drug trials on human participants", and as such they do not address clinical trials in complimentary medicines or non-pharmacological interventions. Even so, the guidelines' basic principles may guide research in other areas of medical practice in the absence of alternatives. These guidelines state that justification should be provided if placebo will be used in research. This responsibility is certainly on the researcher willing to use placebo. The Department of Health (DOH) Research Ethics Guidelines (2004) on the other hand see the use of placebo in a clinical trial ethically unacceptable where the use of a therapy or intervention is available, which has been demonstrated to be effective for a particular condition.

Analysis of the international and national ethics guidelines shows that important to the discussion at this point is a clear definition of what constitute a proven or effective therapy. All the guidelines evaluated did not give any definition of effective therapy. The lack of clearly defined interpretation of effective or proven therapy as used in research ethics guidelines has implications. This is particularly true for professions that are just trying to establish some form of evidence base, because some research may be restricted except with acceptance of sound methodology that includes placebo use in certain instances. It is probably then safe to say that the interpretation of the guidelines will differ widely from one ethics review committee to the other using the same guidelines, depending on the research type, the professional area of study, and also the available levels of evidence. Unfortunately this interpre-

tation dilemma can be observed on how ethics committees decide on the same study using the same guidelines (Young & Annable, 2002). Having identified as challenging the problem of consistency with placebo policy guidelines interpretation, a working definition for effective therapy was suggested recently in Canada by the National Placebo Working Committee (NPWC, 2004). The NPWC definition is an important step in clarifying when placebo use may be warranted. This will go a long way to making the review of placebo studies less restrictive and consistent, especially for professions with fewer EET.

It also needs to be emphasized that most debates (and guidelines) about placebo revolve around its use in drug trials, where subjects could face serious risks. But what about treatments of minor conditions as alluded to in the Declaration of Helsinki? Obviously not all guidelines have enough specifics to take care of other placebo use in situations where risks may be minimal. Since most guidelines are drawn to address issues in drug trials, it is especially challenging for researchers in rehabilitation, who have to prove that placebo use is needed for their research questions. This information will therefore serve such researchers who need to prove that placebo use is justified for their study.

CONCLUSION

Physiotherapy, like many healthcare professions is moving rapidly to establish evidence of effectiveness for the treatments employed in day-to-day practice. Most treatments currently employed may be in the category of standard therapy rather than EET. There are still some gaps in the knowledge of clinical effectiveness, which is readily appreciated by reviewing results of systematic reviews and clinical guidelines. More research is needed to provide conclusive evidence of benefit, which may require the use of placebo. The ethics of placebo use is tied to that of randomization, and is justified in certain situations of uncertainty. International and national ethics guidelines allow for placebo use if ethically justified. Regional and national guidelines on clinical trials are written specifically for pharmacological trials. Although, these guidelines are applicable to non-pharmacological placebo trials, the onus is usually placed on the researcher to prove beyond doubt why a placebo is justified in their study design. While rigorous ethical analysis will still continue to be an important part of the study approval process, an adoption of a universally agreeable definition of EET will go a long way in providing the basis for certain effectiveness studies. Physiotherapists with the information provided in this article might be able to argue better for placebo use in their research.

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