

POSITION PAPER

The Use of Placebos in Psychiatry: A Response to the Draft Document Prepared by the Tri-Council Working Group

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INTRODUCTION

In March 1996 the Tri-Council Working Group (set up by the Medical Research Council of Canada, the Natural Sciences and Engineering Research Council of Canada, and the Social Sciences and Humanities Research Council of Canada) released a draft of the document, "Code of Conduct for Research Involving Humans." The Councils are seeking written comments on the draft Code from researchers, from research ethics boards, and from organizations and institutions that are concerned with ethics in research. This document was submitted by the Canadian College of Neuropsychopharmacology.

Article 18.5 of the draft document, "Code of Conduct for Research Involving Humans" (1996) prepared by the Tri-Council Working Group states:

A new intervention must be weighed against the best current intervention. The use of placebos in clinical trials is ethically unacceptable where clearly effective interventions are available.

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1. Summary

While placebos must be used with caution, preventing the use of placebos in all situations where there is currently 1 or more drugs available will increase the number of patients exposed to experimental drugs in the early stages of development. Thus it will increase the number of patients exposed to some drugs that are ineffective and/or unsafe. Whether a new drug needs to be tested against placebo or an existing drug should be considered carefully on a case by case basis. Thus Article 18.5 should be amended in the final version of the "Code of Conduct for Research Involving Humans."

2. Introduction

Recently the use of placebo has been debated hotly. Of particular concern is the use of placebo in psychiatric patients, given their possibly fragile mental state and diminished cognitive function. The use of placebos in psychiatry has been strongly supported by some because of the small margin between the efficacy of placebo and most psychotropic drugs. While few would disagree with the use of placebo in situations where there is no accepted treatment, the testing of the 2nd and subsequent generations of

psychotropic drugs is a contentious issue. This issue is the focus of the discussion that follows.

3. The placebo effect

Placebo effects are complex. As Ernst and Resch (1995) have pointed out, the response seen in the placebo arm of a clinical trial is often wrongly equated with the placebo effect. The extent of the true placebo effect depends on, among other factors, the attitudes of the physician and patient, the suggestibility of the patient, and the type of treatment. The perceived placebo effect (the response seen in the placebo arm of a clinical trial) includes the natural course of the disease, the tendency of most biological variables to regress towards the mean, and unidentified parallel interventions (resulting, for example, from the fact that a patient will receive extra attention during a clinical trial and may also become sensitized to the problem once enrolled and take actions that influence the clinical outcome) (Ernst and Resch 1995).

The magnitude of the true and perceived placebo effects can be significant in some disorders. Brown (1994) has even proposed that "the initial treatment of a sizable proportion of depressed patients should be 4 to 6 weeks of placebo." While most clinicians would probably not agree with this statement (Dago and Quitkin 1995), the magnitude of the perceived placebo effect is a factor that needs to be considered in the design of a clinical trial.

4. Placebo-controlled trials

The discussion in this section focuses on placebo-controlled trials of antidepressant drugs because the difference in response rates to antidepressants and placebo is relatively small. A review of 79 placebo-controlled trials of tricyclic antidepressants, which included 5 159 patients, concluded that 63% of the patients on a tricyclic antidepressant improved moderately or more than that, compared with 35% on placebo, a difference of 28% (Davis and others 1993). Thus only about one-quarter of the patients seemed to benefit from receiving the active drug in trials of short duration.

The placebo-controlled trial is often regarded as the gold standard, but it is far from that. One of the major problems with placebo-controlled trials is the frequent lack of integrity of the double-blind design. Often the treating physician or the patient is able to discern whether the treatment is in fact an active drug or placebo (Fisher and Greenberg 1993). Designs with an experimental drug, a standard drug, and placebo are probably closer to being blind than studies comparing only the experimental drug and placebo (Greenberg and others 1992). For antidepressants, the margin between placebo and active drugs has been found to be smaller in these 3 group

trials than in simple comparisons of active drug to placebo (Greenberg and others 1992). One possible mechanism of unblinding is the detection of the greater incidence of side effects in those receiving active drugs relative to the incidence in those receiving placebo. This has led to the use of active placebos that produce side effects but no therapeutic effect. A review of antidepressant outcome studies using active placebo controls has suggested that the superiority of antidepressants to placebos is greatly reduced under these conditions (Thomson 1982).

5. Trials comparing an experimental drug to an established drug

An alternative to the placebo-controlled study is a comparison of the experimental drug to an established drug. This type of study has its own problems, the most important of which is that, if no differences are noted between the 2 treatments, it does not necessarily imply that the 2 are equivalent or that the experimental drug is better than placebo (Laska and others 1994). Lack of adequate statistical power may be the reason for failing to detect a difference between 2 drugs. When a placebo is included in a study, it serves as a means of calibrating the skills of the research group and the appropriateness of the design (Klerman 1986). Leber (1991) gives a number of examples of trials of antidepressants in which the experimental drug was as effective as a standard drug (imipramine or desipramine). This might lead to the conclusion that the experimental drug was effective. These trials, however, also included a placebo group, and neither the experimental drug nor the standard drug was found to be better than placebo.

Studies that fail to demonstrate that a medication is better than placebo when the medication is usually accepted as being active are likely to have some deficiency (although such a result will occur occasionally by chance). It is possible to argue that standards of the conduct of clinical trials have improved and that no modern, large multicenter trial would fail to detect a difference between an established drug and placebo. There are limits, however, to our knowledge of psychiatry and to the conduct of trials. For example, there are suggestions that subtle shifts have occurred in patient populations, as a result of changes in environmental and psychosocial factors, and in patient management. Certainly, the diagnostic criteria for depression have been evolving. Thus relying on historical data demonstrating that a particular drug is better than placebo will always add a degree of uncertainty to a trial not including a placebo.

The problems of traditional positive control clinical trials have led to the introduction and recent increasing popularity of active control equivalence studies (ACES). ACES are

trials in which the investigators wish to demonstrate that a new experimental treatment is equivalent to a standard treatment (Herson 1990; Makuch and Johnson 1990; Makuch and others 1990). In an ACES, the null and alternative hypotheses can be reversed relative to the conventional controlled trial, so that an increase in variance will decrease the probability that the 2 treatments will be found to be equivalent. Thus there is increased motivation to carry out the study rigorously to obtain the result that is usually desired. Significantly more patients per group are required for ACES, however, than are needed for placebo-controlled trials. For example, Pocock (1983) cites a trial comparing an experimental drug to amitriptyline:

Suppose amitriptyline is expected to produce a favourable response in about 70% of patients. In a randomized trial one could specify that a new antidepressant will only be considered acceptable if it can be demonstrated with 95% confidence that it is at worst 10% inferior to amitriptyline. Suppose one accepts a 20% risk that even if the drug is really effective one will fail to show it as acceptable in this sense. Then 332 patients are needed on each treatment.

This is a number almost an order of magnitude higher than that needed to show a difference between amitriptyline (or a drug of similar efficacy) and placebo.

While ACES are preferable to traditional positive control clinical trials in terms of the effect of increased variance, they still have other problems in common with more traditional designs. Of the many problems listed by Herson (1990), probably the most important is that a trial conducted with an inappropriate population or with measures that are less than optimal or with other design deficiencies (except those that will increase variance) is likely to result in the 2 drugs appearing equivalent, even if they are not equivalent. Thus the interpretation of ACES depends not only on historical information about the efficacy of the standard drug, but also on the adequate planning and execution of the study.

6. The use of medication with no therapeutic effect in clinical trials

The use of placebo in clinical trials is problematic if an active medication exists because the patients are being deprived of a potentially therapeutic medication. In the case of antidepressant drugs, the margin between the active medication and placebo is small. In addition, in any acceptable clinical trial employing placebo, the design should incorporate factors that are beneficial to the patient. For example, the patients in a trial should be seen more frequently than most depressed patients are seen. The psychotherapeutic benefit inherent in this more frequent exchange is obviously an advantage the patient receives for participating in the trial. While such benefits may in some small way mitigate

concerns about the use of placebo, however, they certainly do not eliminate them.

Participation in a placebo-controlled trial is the most obvious situation in which a patient will get an inactive medication, but it is certainly not the only one. While statistics on this matter are not available (although drug companies, the Health Protection Branch [HPB] and the Food and Drug Administration [FDA] must have this information), some new drugs are found to have no therapeutic effect. The lack of good animal models of psychiatric disorders will always limit what can be achieved in preclinical studies. Thus, even with the best preclinical evidence available, some drugs are found to be ineffective in clinical trials. Furthermore, there are many examples of drugs that pass toxicological testing, but have unacceptable side effects or toxic effects in clinical testing. The view of Lasagna, reinforced by Rickels (1986), that "too often the placebo-treated patients turn out to be the lucky ones in a drug trial, deprived only of a toxic and ineffective chemical," is an extreme one, but it raises an important issue.

Placebo and failed experimental drugs are not the only compounds given to patients that lack therapeutic efficacy. Trials designed to find the lowest therapeutic dose of a drug necessarily try to incorporate a dose that will have diminished efficacy. In the case of antidepressants, where the margin between active dose and placebo is small, a dose found to be significantly less effective must necessarily have an effect that is for all practical purposes indistinguishable from placebo. In the case of drugs with greater toxicity, such as neuroleptics, the need to find the lowest therapeutic dose is of great importance. It is difficult to see how this could be achieved without exposing some patients to placebo doses.

7. Conclusion

Antidepressants have demonstrated efficacy in the treatment of depression. Newer antidepressants have some advantages over older drugs, but no newer drug has been shown unequivocally to be superior to the original antidepressant imipramine in terms of therapeutic efficacy. In the testing of new antidepressants, possible designs that could have been used are placebo-controlled trials and ACES. In a situation where a new drug is clinically effective, the use of ACES will result in no patients being given an ineffective medication. When a new medication is found not to be effective, however, or when a subtherapeutic dose is given, the number of patients exposed to an inactive medication is considerably greater in ACES than in a placebo-controlled trial. In addition, many more patients are exposed to a potentially toxic compound.

While the use of placebo is clearly problematic, preventing any placebo-controlled trials when there is a proven

treatment is not necessarily the best way of diminishing the number of patients exposed to inactive treatments.

8. Recommendations

These arguments suggest that Article 18.5 in the draft of the document, "Code of Conduct for Research Involving Humans" prepared by the Tri-Council Working Group should be revised.

Trials of new medications should be considered individually, and Research Ethics Boards should weigh various factors when considering the type of trial that will be least detrimental to the patients participating. The factors that should be taken into account when considering whether a new drug should be compared with a standard drug or with placebo include (but should not be limited to) the following: the similarity of the drug in terms of chemical composition and mechanism of action to established drugs, the possible side effects of the experimental drug that may lead to unblinding in a placebo-controlled trial, the stage of investigation of the experimental drug and whether the evidence for its efficacy is derived from preclinical or preliminary clinical data, the margin of efficacy between established drugs and placebo, the potential toxicity of the drug, and the possible harm to a patient of not responding while participating in a trial.

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