CROSSROADS: WHERE MEDICINE AND THE HUMANITIES MEET

Are Placebo-Controlled Studies Ethical in Psychiatric Research?

Eric Cadesky*†, Hons. B.Sc.

Although the general use of placebos dates back to the 16th century (1), they represent a relatively new method of testing drugs (2). With the current pressure on psychiatrists to treat patients quickly and inexpensively, drug companies are competing to gain licensure for their new products. In order for a drug to be approved, however, both the United States Food and Drug Administration and the Canadian Health Products and Food Branch require research with placebo controls (3,4). However, ethical aspects of such practice have been criticized in the academic and non-academic literature (e.g. 5-7). Thus, the question demands attention: Are placebo-controlled studies justifiable in psychiatric research?

In this paper, I will argue that the use of placebos in psychiatric research can be ethical and that placebo arms provide valuable information for both researchers and patients. First, I will define the basic principles that underlie the ethical assessment of placebo trials. The second part of this review will examine and evaluate both the ethical and scientific criticisms laid against placebo-controlled trials. This will be followed by a discussion of the ethical and scientific merits of placebo arms. In the final section, I will offer practical guidelines on how to properly and ethically use placebo arms in psychiatric research.

DEFINITION OF ETHICAL PRINCIPLES

The use of placebo controls touches on four main ethical principles (for review see reference 8). Armed with these four principles, we can examine the ethical criticisms that have been laid against the use of placebo controls in research, as well as the ethical merits of this practice.

The first principle is that of autonomy. This principle holds that individuals should be allowed to make independent choices, for themselves, that are in accordance with their own values and principles. This idea is manifest in the use of informed consent: Only those who act autonomously can make decisions on medical interventions pertaining to their health.

The second principle is beneficence. It posits that we should perform acts that benefit others. The definition of 'benefit' can be made by a patient in conjunction with health care professionals.

Paternalism, the third principle, is a special type of beneficence. It states that decisions regarding treatment should be made by those with professional knowledge; that is, decisions should be made for patients by physicians because they possess medical knowledge. Although paternalism was once the basis of medical decision making, its prevalence has declined in recent years because it can lead to the exclusion of a patient's values: the exercise of medical paternalism can conflict with a patient's ability to act autonomously. Further, enforcing one's values on another may lead to exploitation.

Nonmaleficence is the principle that forbids the intentional infliction of harm. It is often referenced with respect to the medical axiom "First, do no harm." The Hippocratic oath contains references to both beneficence and nonmaleficence: "I will use treatment to help the sick according to my ability and judgment, but I will never use it to injure or wrong them" (8). Similar to beneficence, the definition of 'harm' is subjective and can vary among individuals.

* To whom correspondence should be addressed: 3655 Promenade Sir William Osler, Montreal, QC, H3G 1Y6. E-mail: ericcadesky@hotmail.com.

† Faculty of Medicine, McGill University.

ARGUMENTS AGAINST PLACEBO RESEARCH

Ethical arguments against placebo-controlled studies

The act of placing patients in a placebo group has been equated with the negligent withholding of treatment (5). This could be construed as a violation of beneficence. In some cases, however, the standard treatment may not be otherwise available to the subject (4); an example of this is cognitive behavioural therapy (CBT). In fact, without involvement in the study, CBT could be 'withheld' due to inaccessibility or cost; thus, participation in the study affords each subject a chance to receive the treatment.

The Helsinki Declaration of the World Health Organization (9) has been used as ammunition against placebo-controlled studies. Some interpret the Declaration as a statement that individuals should never be placed in a situation where they may receive inferior treatment (5). This argument touches on the principle of paternalism: the idea that researchers know best and will make ethical judgments for all subjects. However, this is in conflict with the principle of autonomy, which holds that educated individuals should have the option of participating in a study if they are willing to take the risk of receiving placebo. They may want to contribute to a study that may eventually help or prevent harm to themselves and others, or they may want to risk placement in a placebo group for the chance to receive superior treatment. Either way, the principle of autonomy states that this choice belongs to the informed subject. Paternalism also ignores the fact that some patients do not want the standard treatment. They may be more amenable to placebo because of many factors such as an increased sensitivity to side effects, a desire to become pregnant, or coexisting medical condition (2). Moreover, patients should have the right to refuse medication that they do not see as beneficial, even if medical practitioners disagree. Analogously, Jehovah's witnesses can refuse blood transfusions on account of their religious beliefs; as upheld in the Canadian legal system, autonomous beliefs override the implementation of an action that others would deem beneficial (10). Another problem with interpreting the Declaration to suit an anti-placebo stance is that there is no clear definition of 'best' in the assurance to individuals of the 'best proven diagnostic and therapeutic method' (9). Likewise, there is no consensus of how to define the 'effectiveness' of a treatment and little agreement on who should have the authority to interpret this definition.

The issue of defining the meaning of the Helsinki Declaration raises the ethical concern that capricious definitions of 'effective' and 'proven' can lead to the licensure of useless or harmful drugs. Aside from a violation of the principle of nonmaleficence, the legalization of such drugs will also have negative consequences that are less readily apparent. Resources and time will be wasted while evaluating the drug's long term effects and compliance to the drug even though it may not be better than placebo (11). This point does not elucidate a weakness in placebo-controlled studies, but rather one of drug-regulating bodies and the vagueness of their statutes.

Consent – which is integral to the exercise of autonomy – has also been a fiercely debated issue (5). Elliott and Weijer (7) question whether subjects who consent to studies involving placebo arms are capable of giving truly informed consent for the following reasons: they may not be competent or well-enough informed, they may feel pressure to consent, or they may be acting out of desperation. Additionally, the issue of trust is also important because subjects may consent to a clinician's research as a 'thank you' for past treatment. Also, patients may not distinguish between research and clinical treatment and may assume that the clinician still has their best individual interest in mind. For these reasons, treating clinicians should exclude from their research any patients with whom they have a personal or significant professional history.

Scientific arguments against placebo-controlled studies

One of the main scientific criticisms of placebo-controlled studies is that they do not use proper blinding procedures (6). Many subjects spend time guessing which condition they are in; further, because they must be told beforehand of the potential side effects, subjects can often guess what treatment they have been given (12). Ney et al. state: "To have a truly blind procedure, the active placebo must have identical physiological effects to those of the medication being studied" (12). This criterion seems unfair because it demands strict physiological matching between new therapies and placebos, but not between new therapies and standard ones. It is reasonable to assume that new treatments would often not induce physiological sensations that are identical to the ones that the standard treatment does; therefore, the 'differential effect' argument is not specific to placebos, but to drug trials in general.

The question of utility has been raised by those who feel that placebo-controlled studies are only useful for proving that a treatment is no better than placebo (6). Interpreting the acceptance of the null hypothesis in this way, however, is contrary to statistical practice and is not parsimonious. Aside from the actual equivalence of two treatments, many reasons may exist for a null finding such as poor design, improper execution of

methodology, or too few subjects. Therefore, negative results are more likely to be uninterpretable than positive ones.

Another concern of placebo use is that many placebo-controlled trials are not published (5). However, if there is a dearth of published studies for drug approval, how can one know that placebos are unsafe? Indeed, the available literature does not unanimously support this claim. As an example, in one study of depression (n = 3000), no difference in suicide rate was found between a group given a placebo and a group given fluoxetine (13). Placebo-controlled trials should not be used if there is a high risk of negative impact to participants.

Past placebo research has been criticized because of inconsistent administration methods (6). Colour, shape, dosage, and dose schedule of placebos have all varied in past experiments. I agree that such administrative variables should be kept constant in order to compare past studies. A placebo should be delivered in the same way as the comparative treatment. Although the administrative variability of past experiments does call into question their results, this variability is in no way proof that a properly designed placebo experiment is unethical. Individual differences exist in response to placebo treatments (6); however, this problem is not specific to placebos because there is variability in individual responses to all drugs.

ARGUMENTS IN SUPPORT OF PLACEBO RESEARCH

Ethical arguments in support of placebo-controlled studies

Some theorists assume that the purpose of research is to find a treatment that is more effective than the current standard (5,6). Rather than focusing on and debating how to define such a gold standard, we should aim to expand the list of efficacious drugs and broaden access to treatment. Consistent with the principle of autonomy, expanding the list of efficacious drugs would allow patients to weigh the relative benefits and harms of each treatment and make an informed decision on which is best for them. The stance that only a few drugs should be available because they are the best treatment may appear to be consistent with the principle of beneficence. However, some patients may define a standard treatment as 'harmful' if there is a high probability of unpleasant side effects. Some of these side effects may be irreversible, such as tardive dyskinesia resulting from the use of phenothiazines to treat schizophrenia (14,15). By denying patients a wider range of treatment options, the autonomy of the patient is violated. For this reason, patients should know their options and have the power to make decisions about treatment (if they are capable).

Scientific arguments in support of placebo-controlled studies

Although the study of ethics informs us of what we should do with placebo trials, science gives us the impetus for why we would want to use them. In general, it is difficult to determine drug efficacy on its own because of the unpredictable courses of many psychiatric disorders and the changing nosology of psychiatry (2).

Placebo arms can distinguish side effects of a medication from the effects of a disorder (14). Addington et al. (14) state that placebos are best used when placebo response rates are high, variable or close to the response rates of 'effective' therapies; when standard therapies carry a high risk of negative side effects; or when a standard therapy is only effective against certain symptoms of a disorder. Placebo trials allow us to control for factors that could obscure and confound the demonstration of drug effects such as time, attention from others, a change of setting, pampering, hope, and legitimization of the sick role. Placebo trials can be used to calibrate the skills of the research group by focusing on the sensitivity of the instruments used and the accuracy and reliability of the raters (14); this is important because no statistical analysis can correct the poor design of a study. Moreover, there is no accepted statistical method that can prove the equivalence of two or more treatments. If equivalency is one's null hypothesis, then nothing can be concluded from a failure to reject this null hypothesis. This failure may have been due to true equivalence or poor design, lack of thoroughness and lack of statistical power (14).

Placebo arms allow scientists to judge the conclusions of other studies. For example, one study may find a drug to be no more effective than placebo and conclude that such a drug is not effective. However, if the placebo response rate was high, then the subjects chosen may not have required any medication and would not have been expected to respond differently to a drug condition.

The use of placebo trials with children and adolescents can also be both ethical and scientifically instrumental. Placebos allow time for observation between initial evaluations and the start of a medical treatment. This is particularly important because children and adolescents have high response rates to placebo (11). More specifically, placebos are an important issue in child and adolescent depression. This condition has a high incidence of 'spontaneous' symptom remission which can be verified through placebo trial. As well, placebo-controlled studies are needed to scientifically examine the prescription of antidepressants to children. Currently, although the

efficacy of antidepressants for depression in adults is known, there is no scientific evidence that antidepressants are more useful for children than placebo (16). Still, antidepressants are widely prescribed despite reported negative and sometimes fatal repercussions for children (16). Clinicians prescribe them, see an improvement in symptoms, and conclude that the improvement was due to the prescribed medication. Such phenomenological conclusions are unscientific because improvements may have occurred without treatment (16).

Placebos can also be important for diagnosing patients in psychiatric research. Patients can be grouped according to whether their condition is primarily somatoform or biomedical. Individuals who suffer from seizures can be easily separated into epileptic and nonepileptic groups based on their reaction to a placebo injection: if seizures are induced by a saline solution, the patient suffers from psychiatric seizures (17). To avoid deception, subjects must first be told that they may receive active or placebo injections. Placebos can also be used for studying the diagnosis of malingering because reaction to a placebo could be supporting evidence of a suspected factitious disorder (17).

TYING IT ALL TOGETHER: THE ETHICAL AND SCIENTIFICALLY SOUND PLACEBO-CONTROLLED STUDY

Consistent with the principle of autonomy, patients and their families should be educated before making any decisions about participating in a study (18). Subjects should be included only if they agree to participate; consent forms should be blunt and straightforward, listing all foreseeable effects of participation. Consent should be preceded by informing the individual about their disorder, all of the available treatments, and the risks and benefits associated with each choice. In some cases, a patient's psychiatric condition may prevent him or her from making competent decisions. In these cases, researchers must be cautious, should err on the side of excluding the patient, and, if possible, should speak with the patient's family in order to avoid violating the patient's rights.

Placebos should never be administered to subjects without first telling them that they may be receiving it (1); negligence in the form of prescribing placebo against one's will or knowledge is unethical because it violates the patient's right to make an informed decision about participation in the study. Since many psychiatric disorders are associated with a perceived loss of control, patients should be given more control by choosing whether they will take the risk of receiving a known treatment, one that is potentially better or worse, or nothing.

Practically, placebos may be used if cost and availability restrict access to a standard treatment. In this case, involvement in a placebo-controlled study would constitute a benefit because the patient would have a 50% chance of receiving a rare or expensive treatment that may not otherwise be available to them.

To prevent a conflict of interest and confusion on the part of the subject, researchers should not be those involved in a subject's clinical treatment. Clinical work and research have different aims, as evident by their differentiation under the law (5).

Patients must also be made aware that research is not designed for their own personal benefit during the study. Although personality type, cognitive style and education level have not been conclusively found to predict response to placebo conditions, subjects should still be randomly assigned to groups (2). As with all good clinical research, patients' progress should be closely monitored for significant health disturbances. When properly conducted on a sample that would not be expected to suffer extensively without the standard treatment, the placement of these subjects in a placebo group has little to no chance of permanently damaging them (2).

Less obvious is the ethical use of active placebos, such as atropine in studies on depression. Although it may seem reasonable to assume that inactive placebos inflate the superiority of drugs to placebo, this finding is not conclusive because past studies on the issue have suffered from poor experimental design (2). Until the issue is settled, I suggest that active placebos only be given to subjects who enter into a study knowing that they will almost certainly experience side effects of some kind.

If possible, three-arm trials are the best design. This design involves comparing a new treatment, a standard treatment and a placebo group. 'Active' controls attempt to replicate the side effects of standard treatments for the purposes of blinding. By examining the standard treatment, new treatment and placebo, the three-arm study allows one to simultaneously test the efficacy of a new treatment as well as its benefits relative to the standard treatment. While it is true that some subjects will be deprived access to a standard therapy, placebo arms are needed to judge whether a change in symptoms is associated with a treatment (11). Even if new treatments and standard ones are found to be equally effective, it is important to determine their efficacy above and beyond placebo (2). For example, several treatments in depression research have appeared effective when compared to the standard treatment, but have been found inefficacious when compared to a placebo arm (14).

LIMITATIONS

Although there is much ethical and scientific merit to the use of placebos, this practice is not without its limits. For instance, debate exists as to whether placebos should be given to those with severe disorders because they may be more likely to experience negative outcomes. I think that placebo trials can never be ethically administered if a high probability for harm exists, as is the case for severe disorders in which individuals deprived of medication may harm themselves or others. Another limitation is that short-term placebo-controlled trials may not elucidate long-term effects. However, this is a problem with all comparison tests, including testing new therapies against standard ones. Finally, the exercise of one's autonomy through informed consent may be a difficult or impossible task because some psychiatric disorders, such as depression and schizophrenia, affect decision-making (18).

CONCLUSION

Although many criticisms have been raised against the use of placebo controls, many of these concerns are faulty, general to most research, rooted in paternalism or do not provide better methods of testing drug efficacy. Placebo controls can provide important information about treatments and help broaden the range of choices that individuals have in making autonomous decisions about treatment. Therefore, because of their scientific merit and consistency with the principles of autonomy and beneficence, placebo-controlled studies are indeed ethical and necessary in psychiatric research.

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Eric Cadesky received his Honours Bachelor of Science in Psychology from the University of Toronto in 2000. He has recently completed his first year as a medical student at McGill University. His interests include patient-physician relations, humane medicine and Toronto Raptors basketball.