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Placebo-Controlled Pharmaceutical Research in Schizophrenia: Attitudes of Helsinki Committees in Israel

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Abstract

Background. The issue of medical research among mentally ill individuals is complicated. On the one hand, there is a need for research to improve treatment for mental disorders. On the other hand, there is constant concern about the ability of mentally ill individuals to astutely participate in such research. The aims of this study were to examine the positions of the chairpersons of Helsinki Committees (ethics committees – "ECs") in Israel regarding placebo-controlled trials among hospitalized mentally ill individuals.

Methods. We sent a questionnaire to the chairpersons of ECs in all hospitals that have psychiatric departments in Israel. The questionnaire included questions regarding placebo-controlled pharmaceutical studies of schizophrenia patients.

Results. Fourteen completed questionnaires were returned (64% response rate). Seventy-one percent of responders stated that placebo-controlled drug trials are appropriate with schizophrenia patients. Thirty-six percent noted that their EC had approved at least one placebo-controlled schizophrenia drug trial in the previous three years. Seventy percent of responders stated that, in theory, they would approve placebo-controlled schizophrenia drug trials. Thirty percent of responders stated that they would not approve them.

Introduction

The issue of medical research among mentally ill individuals is complicated. There is a major need for research to improve treatment for mental disorders. Existing therapies do not cure schizophrenia and do not sufficiently treat negative symptoms of the illness or the cognitive impairments associated with the disease. (Committee for Proprietary Medicinal Products, 1998). Many current treatments often cause serious side effects such as weight gain, extrapyramidal symptoms, and metabolic syndrome. The best interests of an individual patient demand the best available treatment currently available. However, the best interests of the mentally ill population as a group demand development of new drugs.

For conditions such as schizophrenia, investigators often design placebo-controlled trials that offer the advantage of potentially generating clear-cut results. Unfortunately, subjects in the placebo arm of such studies (other than adjuvant studies) must forgo medication that may be providing some benefit to them. In 2002, after years of controversy, the World Medical Association "clarified" the Helsinki Declaration to permit placebo-controlled medical research under certain circumstances:

> **Note of clarification on paragraph 29 of the WMA Declaration of Helsinki**
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> The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:
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> - Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or

- Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.

All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.

The last sentence in this clarification reaffirms EC authority to evaluate trials for the scientific necessity of using a placebo control that may not benefit the subjects. The Declaration of Helsinki is available at http://www.wma.net/e/policy/pdf/17c.pdf.

The Use of Placebos in Clinical Trials

Various study designs can be used to evaluate treatment efficacy, such as placebo-controlled trials; active-drug comparison trials, dose-ranging trials, historical control groups, and control groups with no treatment (Temple, 1981). The latter two designs are not considered valid for psychopharmacological studies.

When a placebo arm is included in the study design, the goal is to evaluate the test drug in comparison to other dosages or none at all. A placebo arm establishes a clear benchmark for comparison of treatment arms. Active controls are useful for head-to-head comparisons between drugs, but may lead to negative or inconclusive results before a new drug's best dosage, formulation, administration and target market are established. Drugs for mental illness may have idiosyncratic effects on different patients. Discouraging results early in the clinical research process may deprive patients of new options for treatment that may be more effective or produce fewer side effects. The use of an active control may yield ambiguous results if the active control has not been evaluated vs. placebo.

Nevertheless, investigators should seriously consider options to placebo-controlled trials. Subject recruiting and retention are likely to be more difficult. In a metastudy assessing completion rates in clinical trials evaluating psychotropics for five psychiatric disorders, subjects assigned to the placebo arm had significantly lower completion rates in antipsychotic clinical trials (Khan et al., 2007).

In the United States, to gain Food and Drug Administration (FDA) approval, significant proof of the efficacy of a drug based on controlled trials must be presented (Laughren, 2001). In the United States and Canada (Addington, 1995), approval of the majority of investigative new drug applications is based on the results of placebo-controlled trials. In Europe, EMEA approves drugs based on trials in which the new preparation is compared to placebo and/or treatment with standard medication.

ECs are chartered to protect the safety and welfare of research subjects. If they find that a study creates risks greater than justifiable for the potential benefits to the subjects, they may not rightfully approve the study. Although an EC may conclude that a study may greatly benefit patients in general, their charter extends only to the safety and welfare of the subjects in the study. The above Declaration of Helsinki clarification thus does not permit ECs to compromise the safety and welfare of study subjects for the greater good of the general population. They must evaluate the scientific necessity of a placebo arm only within the context of the study subjects. They may not put a single subject at significant risk for the greater good. The U.S. created the first ECs specifically in reaction to clinical trials that injured study subjects for the greater good.

Schizophrenia is an especially serious mental illness. Given the great need for new treatments, we examined the positions of EC chairpersons in our home country of Israel about placebo-controlled trials among hospitalized mentally ill individuals.

Methods

We sent a questionnaire to the EC chairpersons of the 22 hospitals (including ten psychiatric hospitals and twelve general hospitals) in Israel that have psychiatric departments.

The questionnaire included questions about placebo-controlled pharmaceutical studies involving schizophrenia patients, for example:

- In your opinion, is it appropriate to perform placebo-controlled drug studies among the mentally ill?
- Has such a study been approved recently by your Helsinki Committee?
- Is the informed consent process for participation in the study closely supervised?

The questionnaire was sent with a pre-addressed return envelope that enabled anonymity of the respondents.

Results

Fourteen completed questionnaires were returned (64% response rate).

Most of the responders (71%) stated that placebo-controlled drug trials are appropriate with schizophrenia patients. However, only five responders (36%) stated that their EC had approved one or more placebo-controlled schizophrenia drug trials in the previous three years, of which one trial was terminated early by the EC.

Sixty-two percent of respondents stated that special legislation is not necessary for clinical trials in the mentally ill population.

Discussion

In Israel, the Ministry of Health must approve pharmacological studies involving investigational new drugs after approval by an EC.

Physicians sometimes find it difficult to participate in placebo-controlled studies and, clinically, prefer trials using active controls. However, most physicians are aware that placebo-controlled studies are sometimes unavoidable. A new medication may be effective, but not more effective than an existing drug; thus there is no demand that the new drug be more efficacious than an existing drug, but rather that it should have benefits, such as less side effects, and/or reduction of negative symptoms or improved cognition. On the other hand, if a new drug reaches the market based on successful placebo-controlled research, the same physicians that opposed the placebo-controlled trials of that drug are now apt to take advantage of its availability. Thus, there is a conflict between an across-the-board ethical objection to placebo-controlled trials and the ethical obligation to use the resulting drugs for the benefit of patients. If the results of these trials are acceptable for use, how can the trial itself not be acceptable? Does the fact that the trial was not performed in my hospital enable me to benefit from the results? Such ethical dilemmas need resolution or at least guidelines.

The 30% minority of EC chairpersons who disapproved of placebo-controlled schizophrenia studies may not have been put to the test with a scientifically valid study that was practical to implement. In addition, it seems that the difficulties in placebo-controlled schizophrenia trials account for the fact that only five institutions (36%) reported having performed this type of clinical trial in the prior three years.

However, despite the difficulties associated with initiating placebo-controlled schizophrenia studies, in our survey we found that once an EC approves such a study, termination by the

EC is extremely rare: Survey respondents reported early termination of only one study. Thus, high standards in the EC review process seem to yield studies that can be completed.

Our survey revealed that, in principle, most IRBs in Israel would approve placebo-controlled schizophrenia trials, although there is a need to extend legal and ethical knowledge about research among the mentally ill to both investigators and EC members.

Although a draft of a law regarding medical research in Israel has been submitted, to date there are only guidelines (http://www.health.gov.il/Download/pages/GuidelinesforClinicalTrials.doc). Notably, a majority of EC chairpersons (62%) do not believe that there is a need for special legislation for research among the mentally ill.

Raising awareness and discussion of the issues will promote deeper understanding and greater ability to cope with specific cases. Extension of existing knowledge in the fields of health, legislation and ethics, and requiring formal training for investigators and members of IRBs will help the medical research community cope with the medico-legal and ethical dilemmas associated with pharmaceutical research involving the mentally ill.

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Declaration of Helsinki (Document 17.C) is an official policy document of the World Medical Association, the global representative body for physicians. It was first adopted in 1964 (Helsinki, Finland) and revised in 1975 (Tokyo, Japan), 1983 (Venice, Italy), 1989 (Hong Kong), 1996 (Somerset-West, South Africa) and 2000 (Edinburgh, Scotland). Note of clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002.

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