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ORIGINAL PAPER

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Placebo-controlled trials in major depression are necessary and ethically justifiable

How to improve the communication between researchers and ethical committees

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Abstract Despite numerous placebo-controlled clinical trials with antidepressants were conducted in humans and a large amount of data was already published in the last two decades, the members of the 4th European Expert Forum on Ethical Evaluation of Placebo-Controlled Studies in Depression were agreed that placebo-controlled trials with antidepressants also in the future are essential. Placebo-controlled studies measure the effect size in a reliable way and establish sensitivity and internal validity. They are scientifically sound and interpretable in terms of efficacy and are, therefore, clinically more relevant than non-placebo-controlled clinical trials. The "Note of Clarification" of the Declaration of Helsinki opens up where such trials are acceptable.

This statement of the members of the 4th European Expert Forum is directed to academia, members of Ethic Committees, regulators, and industry to facilitate their decisions towards clinical studies with antidepressants. "Checklists" for the contents of patients information are given as well as for the investigator.

Placebo-controlled clinical trials are scientifically necessary, ethical and feasible. The administration of the placebo is in itself a non-specific treatment and experts agree that there appears to be no increased suicidal risk in the placebo-group of carefully selected and monitored study patients.

Key words clinical studies · antidepressants · placebo-control

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Introduction

In clinical trials using novel drugs under clinical development, patient safety is paramount. However, aims of a clinical trial, apart from gathering safety data, can be manifold and include an exploration of whether the new drug (e.g. an antidepressant) is superior to standard treatment or has at least equal efficacy with possibly fewer adverse reactions. The eventual aim being to establish a benefit-risk profile for the medication and its use in a specific condition.

In performing such clinical trials it has to be kept in mind that the response of a patient to drug treatment is affected not only by the pharmacological properties of the compound, but also by a number of other variables, such as the features of the illness, the personality of the patient, the doctor-patient relationship, and the setting of the treatment. The patient's response to treatment of mental health problems with psychotropic drugs is particularly affected by these variables, the confounding effects of which can only be minimised by using double blind randomised controlled trials [3].

The investigational compound may be compared with an existing treatment of proven efficacy (a 'comparator-controlled' or 'active-controlled' trial), but in many cases this does not allow to make a final decision about the quality of the therapy. The most important and predictive type of a clinical trial involves a comparison between the investigational drug and placebo (a 'placebo-controlled' trial), and is preferred when there is

no proven effective treatment for the condition being treated. Another type of a clinical trial, favoured by many researchers and some regulatory bodies, includes both placebo and active-control arms, for comparison with the investigational drug. This limits the chances of false positive or false negative study results; in other words it allows maximum assay sensitivity.

It could be assumed that it is no longer necessary to conduct placebo-controlled trials in depression, because of the large amount of data already published. However, the findings of a recent review of 75 placebo-controlled trials of antidepressant treatment published between 1981 and 2000 lend support to the continued use of placebo in future treatment studies [5]. Firstly, the response to placebo varied considerably (from around 10 % to more than 50 %) and approximately 30 % of patients showed substantial clinical improvement on placebo. Secondly, the proportion of patients who responded to placebo has increased by around 7 % per decade, and a similar increase has also been seen among those receiving control medication. This temporal change probably results more from the method of patient recruitment and the inclusion of subjects with milder and briefer depressions, than it does from changes in the diagnostic criteria for depression [5]. As the placebo response is highly variable, randomised controlled trials that rely on comparison with "standard" antidepressants may well generate unreliable results with limited assay sensitivity.

Placebo-controlled trials in depression are feasible, ethical and necessary

Ethics Committees (EC) often do not have members who are specialists in psychiatry. Hence it is understandable that unfounded concerns can occur. For example, there may be concerns of higher rates of suicidal activity in patients with major depression who are allocated to the placebo arm in placebo-controlled depression trials.

These types of concerns were discussed at the 3rd European Expert Forum on placebo-controlled studies in depression in 2003 by ethics committee members, senior European psychiatrists and clinical psychopharmacologists. The following recommendations were put forward for EC members to consider when assessing a protocol for a clinical trial in depression:

- Is there a public versus personal interest?
- Should severely ill (non-suicidal) patients be included in the clinical trial to enhance outcome signals and to avoid skewing the patient population to the less severely ill patients only?
- Should outpatients be included in order to generalise the patient population and limit to those who are not resistant to treatment?
- Careful recruitment by the responsible physician should be guaranteed.

Furthermore an accompanying 'non-scientific letter' should be appended to the protocol explaining to the lay EC members the ethical basis of the trial. It should specifically include:

- A detailed explanation of the nature of the disorder (e.g. depression) under study.
- An explanation of placebo-response and its therapeutic value.
- An explanation of the measurements used and their clinical significance.
- A risk-benefit analysis of the drug under investigation, the use of placebo and any controls.

In addition it should be emphasised to the EC members that due to the high variability of response in depression trials, a marketed substance may not be consistently shown to be efficacious in the setting of a clinical trial but this is not an indication that most depressive patients have not been treated correctly until entering the trial. The failure rates of depression trials are high for a variety of multifactorial reasons. Often, the efficacy signal can be better detected if inter-rater reliability is optimised and rescue or drop-out criteria which are too open are avoided.

Accordance with the Declaration of Helsinki

The 'Note of Clarification' to article 29 is an official part of the 'Declaration of Helsinki' and reconciles the 'Declaration' with the potential to perform placebo-controlled clinical trials in depressed patients. According to the first sentence of the 'Note', compelling scientific arguments exist for performing placebo-controlled clinical trials with antidepressants and well-designed studies are supposed not to carry increased risk factors.

According to several studies, no difference in rates of suicide and attempted suicide was found in placebo-controlled studies compared to active control compounds [2]. These showed annual suicide rates in 45 antidepressant studies of investigational drug 0.8 %, active comparator 0.7 %; placebo 0.4 %. Storosum et al. showed suicide rates in 77 short-term antidepressant studies of active comparator 0.1 %; placebo 0.1 % and suicide rates in 8 long-term studies of active comparator 0.2 %; placebo 0 % [3].

Table 1 contains proposed the EC "checklist" for placebo-controlled antidepressant clinical trials with respect to the contents of the informed consent form [1], while Table 2 contains the proposed Investigator "checklist" for placebo-controlled antidepressant clinical trials [1].

Comparison to a placebo is valuable in distinguishing disease manifestations from adverse reactions of the medicinal product. Three-armed trials including both a placebo and an active control should be recommended in certain situations. Generally a study duration of 6 weeks should be sufficient.

The main advantages of placebo-controlled studies

Table 1 Checklist for placebo-controlled clinical trials with antidepressants

Explanation of the aims of the study to the patient
What are the expected effects of the investigational compound/comparator?
Disclosure of probability receiving placebo
Randomisation
Duration of study
Care of patient during the study/course
Description of planned investigations and visits
Responsibilities of the patient
Responsibility of the investigator (e. g. to follow the protocol)
Advantages for the patient
Potential disadvantages and adverse events
Alternative treatment options
Ethical assessment of the study
Data management/confidentiality data
Guarantee of further treatment after premature discontinuation
Further treatment after the end of study
Insurance
Information/access to the investigator

Table 2 Checklist for placebo-controlled clinical trials with antidepressants – patients' welfare – checklist for the investigator

High risk patients (i.e. those judged to be at increased risk of suicide) to be excluded
Careful monitoring of emergent risks at regular visits (e. g. efficacy, tolerability, suicidality, psychotic reactiones, increased anxiety)
Is the study duration adequately long to show a drug effect?
Sufficient number of assessments by an experienced rater required
Quality and experience of the institution
What are the study exit criteria (e. g. worsening of depression, increase of suicidality, laboratory values, adverse events)?

in depression are that smaller sample sizes are required, study costs may be reduced and new drugs search the patients in need earlier. Furthermore in a placebo-controlled study, data on effect size and number needed to treat are validated making the clinical relevance of the findings clearer.

Conclusion

Placebo-controlled clinical trials in depression are scientifically necessary, ethical and feasible. The administration of the placebo is itself a non-specific treatment and experts agree [5] that there appears to be no increased suicidal risk in the placebo group of carefully selected and monitored study patients.

Placebo-controlled studies measure the effect size in a reliable way and establish sensitivity and internal validity. They are scientifically sound and interpretable in terms of efficacy and are, therefore, clinically more relevant than non-placebo-controlled studies. Furthermore they expose fewer patients to ineffective or potentially harmful drugs. Safety issues can be detected more easily and they allow faster arrival of new treatments the prescriber and the patient.

Only placebo-controlled studies can give unambiguous evidence of efficacy and if future antidepressants were only tested against standard treatment, half of the studies would yield invalid (false positive or false negative) results.

Only with placebo-controlled studies can we be sure to establish efficacy and tolerability of a new antidepressant medication. Without placebo-control, the psychopharmacological progress will be slowed down. The "Note of Clarification" to the Declaration of Helsinki opens up circumstances where such trials are acceptable, and the fears surrounding placebo-controlled clinical trials with antidepressants seem to be due to a wide-spread information deficit to EC members in this special field.

This paper should aid in discussions with academia, members of ECs, regulators and industry to overcome this information deficit.

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