

ECNP Consensus Meeting, September 26, 1996, Amsterdam  
**Alternatives to placebo-controlled trials in psychiatry<sup>1</sup>**

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**Abstract**

Patients receiving placebo do not merely receive an inert substance but also receive support, concern, and reassurance that assists the therapeutic alliance and encourages the positive attitude that forms the basis of cognitive treatment. Response to non-specific factors is seen in all fields of medicine but is particularly potent in psychiatry. The placebo response is variable across settings and across time and is unpredictable. Historical data cannot therefore provide an adequate control for treatment effects in studies of new drugs. The scientific position is clear that a comparison against placebo is required for the unequivocal demonstration of the efficacy of a treatment.

Evidence from at least two positive well designed and conducted placebo-controlled studies is generally accepted as appropriate to establish the efficacy of a drug.

Attention to diagnosis, severity of illness, and to possible comorbid conditions is needed in the design and conduct of placebo-controlled studies in order to optimise the chance of obtaining valid data.

The use of all data obtained, including dropouts due to lack of efficacy, should be maximised. The use of placebo may not be possible in some conditions that represent medical emergencies or may be difficult to justify in serious disorders where an effective treatment has already been established. Alternative designs to placebo-controlled studies can be considered.

Consistent superior efficacy compared with a well accepted, effective treatment, given in an easily defended dose, is considered to be good evidence of efficacy provided that the studies are well designed and well conducted. Evidence of superior efficacy to an established effective comparator treatment may be regarded as evidence of efficacy.

The demonstration of a dose–response relationship where one dose is found to be significantly better than another, can be taken as evidence for efficacy, particularly where there is already placebo-controlled evidence of the efficacy of the identified dose.

Where a new treatment is found, under controlled conditions, to be equivalent to an existing well accepted comparator treatment, given at a clearly effective dose, this may be taken as evidence of efficacy, but only if the comparator is consistently superior to placebo and if equivalence has been defined beforehand. The claims for efficacy based on results from equivalence studies are less easily sustained than the evidence from placebo-controlled studies or studies demonstrating superior efficacy, due to the fact that those studies have no internal validation. © 1999 Elsevier Science B.V./ECNP. All rights reserved.

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**1. Introduction**

In September 1996 the European College of Neuro-psychopharmacology held a workshop to consider the need for placebo-controlled trials in psychiatry and possible alternative approaches to establishing the clinical efficacy of pharmacological compounds. The meeting addressed the usefulness of placebo-controlled trials in determining the extent of a therapeutic effect, in correcting for the natural course of the disorder, and in reducing bias due to

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Participants: M. Ackenheil, O. Benkert, M. Bourin, M. Briley, R. Buller, A. Cameron, H. D'Haenen, A. Gerebtzoff, S. Kasper, Y. Lecrubier H.-J. Möller, A. Puech, A. Sitzen, H. Thiel Beck, J. Tiller, J.M. Van Ree, B.J. Van Zwieten-Boot, C. Vekens, L. Von Knorring, A. Wood.

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expectations of investigator and patient. Alternatives to placebo-controlled trials and the ethical and methodological issues were discussed. This statement summarises the discussions and the conclusions.

## 2. Background

The use of placebo-controlled studies in the efficacy testing of potential new pharmacological treatments continues to be the subject of discussion and even controversy. There has been some polarisation of opinion on the issue of whether the inclusion of a placebo control group in studies can be justified if it means that an established effective treatment will be withheld from some patients. As a result placebo-controlled studies that are deemed to be an ethical and honest evaluation of treatment by the investigators might have difficulty gaining acceptance with those holding a censorious view on the use of placebo.

It is apparent from some of the recent discussion of placebo-controlled trials that the nature of placebo is not fully understood. Because placebo is used as a control for an active treatment it is sometimes assumed to be ineffective. In fact the placebo is not merely treatment with an inert substance. Patients who receive a placebo are provided with support and concern; they are reassured by the perception that the complaint or disorder is understood and is being taken seriously. The treatment setting is important and serves to encourage the positive attitude on the part of the patient that forms the basis of cognitive behaviour therapy. The placebo response embraces a variety of these non-specific factors and, depending on the how receptive the patient is to reassurance, will combine in many cases to produce improvement. This is true in all fields of medicine but the effects can be particularly potent in psychiatry. In addition placebo controls for the natural course of the disease which may vary over trials. The response to placebo may be time-limited as there is evidence that depressed patients who respond to placebo have a high subsequent relapse rate (Montgomery et al., 1993; Anton et al., 1994).

The assessment of the efficacy of a new treatment for a psychiatric illness has to include some means of accounting for these non-specific treatment effects.

## 3. The need for placebo

The most important reason for using a placebo in a randomised controlled efficacy study is to act as an internal validation. The observed response to a pharmacological agent has to be judged in the context of the expected or observed response to placebo. The comparison with placebo makes it possible to ascribe a difference observed between groups to the activity of the investigational drug, assuming that the randomisation process has ensured that

all other factors that might affect response are equally distributed between the groups. The positive results of a placebo-controlled study provide the best scientific evidence of efficacy.

A direct, randomised head to head group comparison between drug and placebo is particularly necessary if the therapeutic effect of a treatment is small or variable and the response to placebo is high or differs in different settings. In most psychiatric indications both conditions apply; placebo response rates vary widely according to the treatment setting and response to drugs is unpredictable. Placebo-controlled studies provide the most unequivocal evidence of efficacy.

One placebo-controlled study can provide evidence of efficacy depending on the robustness of the results, though most experts would prefer to make a judgement on the basis of two studies and it is generally accepted that evidence is needed from two positive placebo-controlled studies to establish the efficacy of a drug. However, the evidence from one positive placebo-controlled study has been accepted by regulatory authorities as sufficient for the approval of some treatments in conditions where further studies would be too difficult to undertake or could not be ethically justified. To require more than two placebo-controlled studies showing strong efficacy would be ethically questionable because some individuals would be exposed unnecessarily to placebo after efficacy had already been established.

## 4. Placebo response rates

In depression studies the response to placebo in general is reported to be high in primary care, and lower in psychiatric hospital settings; it is highest in mild depression and lowest in severe depression with moderate severity occupying the middle ground but there is a high variability between studies. In obsessive compulsive disorder, a low placebo response was seen in the early studies which used rigorous patient selection criteria and investigated patients with long prior duration of illness. A higher placebo response rate is seen in more recent studies. On the other hand drug response was higher in the earlier studies and lower drug response rates are reported in recent studies possibly due to the inclusion of therapy resistant patients. In general, the placebo response is reported to be lower and more stable in single centre studies and higher and more variable in multicentre studies, probably reflecting the contribution of different confounding factors in different centres.

A recent review of studies carried out to test the efficacy of new antipsychotic drugs is a clear demonstration of the variability of response in schizophrenia (Storosum et al., 1998), a disorder where there is a general perception that response to placebo is low. These studies would have endeavoured to include appropriately diagnosed patients in

whom response to treatment would be expected. The patients included were mainly suffering an acute episode on a chronic disorder, though not acute in the sense of emergency. Very few first episode or drug naïve patients were included.

An analysis using the last observation carried forward showed the highest effect size for the reference drug was between 25 and 30%, but in some studies it was much lower. Using responders instead of mean change as a measure showed even greater variability with a range of 50–60% for the reference drug, but a range from 20 to 50% for placebo. In the reference controlled studies the number of responders on haloperidol was lower than responders on placebo in placebo-controlled trials.

From this analysis, it is apparent that the hitherto widely held view that the placebo response in schizophrenia is low and stable is incorrect. The placebo response in some studies or settings is the same as response to an active drug in others.

These results underline the potential of reliance on historical controls to mislead and stress the need for prospective randomised placebo-controlled studies.

Because of this array of difficulties it is important, (a) to refine the design of placebo-controlled studies to optimise the chance of obtaining valid information, and (b) to maximise the information obtained.

## 5. Patient selection

The diagnostic criteria currently used in efficacy studies do not appear to be sufficiently precise to accurately define the individual patient who will have a low response to placebo and good response to drug. Over the years, additional entry criteria, independent of diagnosis, have been added to the protocols for efficacy studies to help define a population in whom a more predictable drug placebo difference can be detected.

In depression studies, for example, the duration of the episode required for entry has been lengthened from 2 to 4 weeks or longer. Minimum severity criteria such as a HAMD score of 18 or a MADRS score of 22 are used in order to exclude mild illness. Confounding comorbidity has been shown to influence the drug or placebo response and the criteria for entry to the study often exclude concomitant alcohol or drug abuse, comorbid epilepsy or brain disease, or coexisting personality disorder which might complicate response. Diagnostic practice has been scrutinised and training sessions for both diagnosis and rating of severity are often provided.

The inclusion of a placebo control group in a study may have a covert influence on patient selection as investigators may tend to enter patients with milder illness. Patients with more serious or resistant illness may be included in reference controlled studies where the investigator feels more confident that all individuals will receive active

treatment. These hidden biases may affect response rates and dropout rates and need to be investigated.

## 6. Information from dropouts

The rate of early withdrawals from studies varies with the type of study. In the review of schizophrenia studies, for example, the rate of dropouts in the placebo-controlled studies was 50–80% and was clearly higher than in reference-controlled studies (Storosum et al., 1998). The inclusion of placebo raises the level of patient and investigator concern and understandably increases the readiness to withdraw patients having an equivocal response from the study. Much of the high dropout rate recorded in studies is due to lack of efficacy, undefined, in both the placebo and active drug groups.

The rate of dropouts due to inefficacy would provide one measure of efficacy and is a practical endpoint for judging the therapeutic usefulness of a treatment. It is particularly important to use the data from dropouts due to lack of efficacy if a study has a high drop out rate. The clinical relevance of a mean difference measured on a severity rating scale can be assessed in a responder analysis. However the responder analysis is biased towards survivors in a trial and is probably a source of bias where there is a differential dropout rate due to adverse events. Information on withdrawals due to lack of efficacy provides useful additional data which may be captured in a last observation carried forward analysis.

Analysis of dropouts due to lack of efficacy could be refined to include separate analysis according to baseline severity of the patients. A further measure of therapeutic usefulness that has been used is that provided by a survival analysis comparing the time to withdrawal due to lack of efficacy.

## 7. Does the need for placebo vary with the disorder?

The most rigorous scientific position is that a comparison against placebo is required for the unequivocal demonstration of the efficacy of a treatment. The difficulty encountered in conducting placebo-controlled studies varies to some extent in different disorders and treatment settings. Ethical objections to placebo-controlled studies may be raised in disorders where the risk associated with the use of placebo is perceived to be high and alternate effective treatments have been established. Examples that have been quoted are severe depression, severe schizophrenia with behavioural disturbances, or uncontrollable severe mania. These are often considered medical emergencies and where there is risk to life a placebo-controlled study is difficult to undertake. In these circumstances, alternatives to placebo-controlled studies have to be given serious

consideration even if the results might provide a scientifically less convincing basis for establishing efficacy.

On the other hand, there are other serious conditions, for example, recurrent brief depression, for which no treatment to date has been shown to be effective in placebo-controlled studies. In such cases placebo-controlled studies are both needed and justified despite the risks associated with the disorder.

Some modifications to the population studied have become accepted because of the ethical constraints of placebo treatment. In major depression, for example, special attention is paid to very severe or suicidal patients, who are sometimes excluded from studies, or are included in restricted numbers and investigated in closely controlled therapeutic environments. In these studies, permitted withdrawals because of deterioration or signals of deterioration can usefully serve as evidence of lack of efficacy. The duration of the studies obviously needs to be as short as possible to reduce the period of risk, and the numbers required in the study should be just large enough to establish efficacy.

## 8. Alternatives to placebo-controlled studies

### 8.1. Superior efficacy

There are grounds for accepting that a new treatment is effective if it can be shown to be superior to an existing comparator treatment whose established efficacy has been accepted. Regulatory authorities have approved some treatments in psychiatry on this basis. For example, the approval of clozapine as an antipsychotic drug, was based on a demonstration of superior efficacy compared with conventional antipsychotics in prospectively identified resistant schizophrenia (Kane et al., 1988).

The chosen comparator compound in studies designed to determine superior efficacy must be an accepted effective treatment and the dose selected for the study must be the dose that has been shown to be effective. The range of drugs from which the choice of comparator can be made tends to be quite restricted because of doubts about the optimum therapeutic dose or about the efficacy of particular drugs.

To enable a firm conclusion, superiority results should be robust and consistent over various trials. Studies that demonstrate superior efficacy and whose design and conduct are deemed acceptable should be accepted for establishing efficacy.

### 8.2. Dose–response relationship

The demonstration of a dose–response relationship with one dose shown to have a significant advantage over another provides evidence that clinical improvement can be attributed to pharmacological action. However, in the

absence of a placebo treatment arm caution is needed in interpreting the results from a dose–response investigation. It would, for example, be possible to demonstrate a difference in effect between doses and for neither dose to be better than placebo. Or the demonstrated ‘ineffective’ dose might be worse than placebo. It is not possible to allay these concerns without a placebo-controlled study and for this reason dose–response relationships tend to occupy a role that is supportive of efficacy rather than being cited as primary evidence of efficacy. However, if there is at least one positive placebo-controlled study demonstrating that the indicated dose is effective the separate demonstration of a positive dose–response relationship should be enough to establish efficacy.

Few examples of dose–response relationships have been reported in the psychiatric literature and it can be surmised that this type of evidence will not be obtained easily.

### 8.3. Equivalence studies

Equivalence studies, which seek to demonstrate similar efficacy with no significant difference between treatments, have been used to establish efficacy but they suffer from important inherent methodological problems due to lack of internal validity. The main difficulty relates to the underlying placebo response rate in the population and the particular sample under study. If the expected placebo response is high the demonstration of equivalence is not necessarily convincing. Without a control group for the underlying placebo response in the particular study, it is not possible to be sure if the equivalence results are pharmacological or placebo driven. A further obstacle to equivalence studies is their size, since very large patient samples are needed for valid comparisons between active drugs.

Nevertheless, these studies have a limited place for establishing efficacy. They may be considered when placebo cannot be justified on ethical grounds, or because of risk to the patients. Equivalence designs may be considered appropriate for the more severe forms of mania, schizophrenia, or in at risk populations such as the elderly.

For evidence from an equivalence study to be convincing an effective comparator with established efficacy (demonstrated consistently in placebo-controlled trials) is required and the selected dose easily defended. In equivalence studies the definition of equivalence and the lower limit of difference to be accepted need to be predetermined and should be based on, for example, clinical judgement and the known difference between comparator and placebo.

By and large, equivalence studies tend to be used in those areas where existing treatments are considered adequate, where placebo responses are more predictable, and where it would be difficult to justify the use of placebo.

## 9. Conclusions

(i) The primacy of placebo-controlled studies for the demonstration of efficacy is supported. Results from well-conducted, randomised placebo-controlled studies should form the basis of the evidence of efficacy wherever possible. The evidence generated from a placebo-controlled study to support the efficacy of a treatment is considered to be more credible and more open to generalisation to the wider population than other studies, despite being conducted in a limited population.

(ii) The demonstration of superior efficacy compared with a well accepted, effective treatment, given in an easily defended dose, is considered to be good evidence of efficacy provided that the studies are well designed and well conducted. Consistent evidence of superior efficacy to an established effective comparator treatment, shown in two studies may be regarded as equivalent to evidence of efficacy from two placebo-controlled studies.

(iii) The demonstration of a dose–response relationship where one dose is found to be better than another, can be taken as supportive evidence for efficacy, particularly where placebo-controlled evidence obtains that the dose has been identified as effective.

(iv) Where a new treatment is found, under controlled conditions, to be equivalent to an existing well accepted

comparator treatment, given at a clearly effective dose, this may be taken as evidence of efficacy. The claims for efficacy based on results from equivalence studies are less easily sustained than the evidence from placebo-controlled studies or studies demonstrating superior efficacy. This is particularly the case in disorders or settings where the underlying placebo response rate is high and/or variable. Equivalence studies are best reserved for those disorders where a placebo-controlled study is considered dangerous or ethically questionable.

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