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Placebo-controlled studies in depression: necessary, ethical and feasible

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Abstract Placebo-controlled trials are used widely in the development of new pharmacological treatments. They have sometimes been challenged as being unethical, in clinical situations where patients can receive an existing effective and acceptable treatment. It has been argued that studies of potential antidepressants should employ only a comparator-controlled design, whereby new compounds have to be found at least as efficacious as existing treatments. By contrast, others have argued that sole use of comparator-controlled trials is itself unethical, as more patients will be exposed to potentially unhelpful treatments. This article reviews the rationale for conducting placebo-controlled treatment studies in depressed patients, examines the underlying ethical issues, and describes the provisions that should be applied when investigating the efficacy and tolerability of potentially valuable new antidepressant treatments. Placebo-controlled studies of new antidepressants are justified, both scientifically and ethically; restrictions on placebo-controlled investigations will hinder the arrival of more efficacious and better tolerated antidepressants.

Key words antidepressants · placebo-control · comparator-control

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Introduction

The last decade has seen increased interest in drug discovery in medicine and a growing awareness of the need for doctors to practice 'evidence-based' medicine, the cornerstone of which is the randomised controlled trial (Kupfer and Frank 2002). At the same time, there has been much controversy about the use of placebos within randomised controlled trials (Rothman and Michels 1994). This concern was reflected in the fifth revision of the Declaration of Helsinki (World Medical Association 2000), which states „the benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic and therapeutic methods".

This statement seems to severely restrict the option of placebo-controlled pharmacological research (Vastag 2000). Partly in response to criticism that this revision was a somewhat secretive and rushed process, the World Medical Association (WMA) later announced the development of a working group to examine certain provisions, specifically the controversial placebo control guideline (Forster et al. 2001). At present, the WMA recognises that placebo-controlled trials are ethically acceptable, even when other proven treatment is available, in these circumstances: where for compelling and scientifically sound methodological reasons placebo is needed to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; and where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition in which patients

who receive placebo will not be subject to any additional risk of serious or irreversible harm.

The United States Food and Drug Administration requires two or more positive placebo-controlled trials to approve a new therapeutic drug. The European Agency for the Evaluation of Medicinal Products has incorporated a broad interpretation of the revised version of the Declaration of Helsinki (EMEA 2001). It recognises that placebo response rates are highly variable; that placebo-controlled comparisons are needed to permit adequate evaluation of efficacy; and that comparison with placebo helps distinguish manifestations of disease from adverse reactions to medicinal products. It states that use of placebo control may be ethically acceptable, when for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a treatment, or where a method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk or irreversible harm. However, many local ethics committees within Europe are reluctant to approve placebo controls in treatment studies with new antidepressants.

Greater attention on the ethical issues underlying drug development requires the scientific community to summarise the arguments for and against continued use of placebo controls, when designing research and investigating new compounds (Charney 2000). Put simply, one view is that use of placebo is not appropriate when an effective treatment for that condition already exists, and that assessment of the efficacy of new treatments can be accomplished through use of active controls. Another view is that placebo controls are necessary to determine the assay sensitivity of the trial, and are ethical when patients provide fully informed consent and are not harmed by the act of forgoing established treatments (Temple and Ellenberg 2000).

This paper summarises the discussion in a recent consensus meeting held in the Ludwig Maximilian University in Munich in March 2002, in which senior European psychiatrists, clinical psychopharmacologists and ethics committee members debated the relative merits of placebo-controlled and comparator-controlled studies, in the evaluation of potential new antidepressant drugs. The other participants in the meeting are listed at the end of this paper. Although focused on the investigation of potential new therapies for depressed patients, we hope that our conclusions will contribute to the wider discussion about the use of placebo treatment in medical research.

Why are controlled trials necessary?

The response of a patient to a 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 skill and persuasiveness of the doctor; and the setting of treatment. The response to treatment of mental health problems with psychotropic drugs is particularly affected by these variables, whose confounding effects can only be minimised by using double-blind randomised controlled trials (Rhodes et al. 1999).

Four types of double-blind controlled trial can be conducted (Prien 1988). In the first, differing dosages of an investigational compound are compared: such an approach is used infrequently in large clinical studies as all patients are exposed to potentially ineffective or hazardous treatments. The second type compares the investigational compound with an existing treatment of proven effectiveness (a 'comparator-controlled' or 'active-controlled' trial). The third type 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. The fourth, favoured by many researchers and some regulatory bodies, includes both placebo and an active control, for comparison with the investigational drug.

It could be argued that there are many proven treatments for depression, and as such it is no longer necessary to conduct placebo-controlled trials. However, the findings of a recent review of 75 placebo-controlled trials of antidepressant treatment, published between 1981–2000, lend support to the continued use of placebo in future treatment studies (Walsh et al. 2002). First, the response to placebo varied considerably (from around 10 % to more than 50 %), and approximately 30 % of patients showed a substantial clinical improvement with placebo. Second, 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 active 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 (Walsh et al. 2002). As the placebo response is highly variable, often substantial, and increasing, randomised controlled trials that rely on comparison with 'standard' antidepressants may well generate unreliable results.

Design of comparator-controlled studies

There are two types of comparator-controlled studies, with differing aims. The first type is designed to investigate whether the new compound is superior to an existing proven compound (a 'superiority trial'). Although such studies have clear value in establishing whether a new treatment would be helpful in clinical practice, they need to be very large and take a long time to conduct, and as such form only a minority of all comparator-controlled studies. A well-designed study that shows superiority provides strong evidence of the effectiveness of the new treatment, within the limitations of statistical significance; no further information external to the trial

is needed to support the conclusion of efficacy (Temple and Ellenberg 2000).

The second type of comparator-controlled study is designed to investigate whether the new compound has equivalent efficacy to existing treatments (a 'non-inferiority' or 'equivalence' trial). These are probably of less value to clinicians, unless other benefits for the new treatment are revealed during the course of the study, such as improved tolerability. Before the study starts, the non-inferiority margin (delta) should be set: this is the degree of non-inferiority that the trial will attempt to exclude. If the confidence interval for the difference between treatments excludes a degree of inferiority as large or larger than the margin the test treatment can be declared non-inferior. However, a study which finds that two treatments are of equivalent efficacy could mean that both treatments were indeed efficacious; but it could also indicate that neither treatment was efficacious (Temple and Ellenberg 2000).

What are the merits of comparator-controlled studies?

The proponents of comparator-controlled studies argue that they have many advantages over the placebo-controlled approach. First the study is designed to answer a relevant clinical question („is this new drug better than an existing treatment?"): the study can provide useful information about the relative efficacy and tolerability of new and standard treatments. Second, in theory at least, doctors do not expose any study participant to potentially inactive treatments, with reduced doctor and patient concerns about taking part in the study. Another presumed advantage is that because patient recruitment is made somewhat easier, studies can be larger in size and conducted more quickly. Furthermore, there is some evidence that fewer patients will withdraw during the course of the study due to a perceived lack of efficacy. Finally it is argued that use of comparator-controlled designs may facilitate approval of the study by local ethics committees.

What are the problems with comparator-controlled studies?

Most of the disadvantages of comparator-controlled studies relate to the problem of establishing 'assay sensitivity', i. e. the ability of a study to distinguish an effective from a less effective treatment. If a study lacks adequate assay sensitivity, it may fail to show superiority of one treatment in a superiority trial, and can lead to a false conclusion of equivalence in a non-inferiority trial.

For a non-inferiority trial to be recognised as having sufficient assay sensitivity, it must be clear that there is good historical evidence that the chosen comparator drug has been found consistently superior to placebo. In addition, the methodology of the study should be similar to those earlier studies that revealed the efficacy of the comparator treatment. The validity of the non-inferiority design depends on the investigators having been able to regularly demonstrate the superiority of active drug over placebo. This is a troublesome stipulation on both counts, as many placebo-controlled treatment studies have not been able to demonstrate that the 'active' drug is more efficacious than placebo (Khan et al. 2002), and even in positive placebo-controlled trials, some study centres are unable to distinguish active drug from placebo (Niklson et al. 1997).

The problem of poor assay sensitivity was highlighted over a decade ago when the results of all six double-blind studies comparing imipramine, nomifensine and placebo were examined (Leber 1989). No single study was able to find a significant difference in efficacy between imipramine and nomifensine on the Hamilton depression rating scale, but there were substantial differences from baseline to end-point with both treatments. Unfortunately this was also the case with placebo: only one study (the smallest) was able to show an advantage for 'active' drug over placebo. Nomifensine became available for clinical use but was withdrawn later, when the association with haemolytic anaemia had become established.

Another disadvantage is that comparator-controlled studies tend to minimise any differences between treatments. Doctors and patients tend to accept that both treatments are efficacious, and also tend to attribute any adverse events to the study medication. Furthermore, most of the methodological flaws in a trial (for example, the inclusion of inappropriate patients, or the use of outcome measures that are insufficiently sensitive to change) act to obscure the real differences between treatment groups. In comparator-controlled studies, borderline cases tend to be categorised as treatment responders, thereby inflating the apparent efficacy of both study treatments. In addition, there are more patient dropouts due to adverse effects, with an ensuing greater difficulty in detecting safety outcomes.

Further disadvantages of comparator-controlled studies stem from the fact that the 'active' comparator drug may not necessarily be 'standard' treatment, and may be ineffective or harmful. As mentioned above, equivalence does not prove efficacy. Furthermore, no direct assessment of the effect size is possible without the use of a placebo control. Finally, an important practical issue is that to reveal real differences between two 'active' treatments requires large sample sizes, which means that the study takes longer to complete, and costs more to conduct. This in turn can delay the arrival of effective new treatments for clinical use. Some of the advantages and disadvantages of comparator-controlled studies are shown in Table 1.

Table 1 Comparator-controlled studies

Advantages	Disadvantages
Provide data on relative efficacy and tolerability	Lack of assay sensitivity may lead to an erroneous conclusion regarding efficacy
In theory, patients are not exposed to potentially inactive treatments	Equivalence of treatments does not prove efficacy
Patient recruitment may be easier	Active comparator may not represent standard treatment
Fewer patient withdrawals due to lack of efficacy	More drop-outs due to adverse events
May facilitate approval by local ethics committees	Differences between treatments tend to be minimised
	Sample size must be large to detect differences reliably
	Study costs may be higher

What are the arguments for placebo-controlled trials?

Advocates for placebo-controlled treatment studies argue that it is ethical to perform such studies even when there are existing interventions with proven efficacy, because of the methodological limitations in comparator-controlled studies. Many studies of antidepressant drugs have failed to distinguish 'active' compounds from placebo, usually because of differences in clinical populations, centre effects and high rates of improvement in both treatment arms. Without a placebo group to ensure validity, a finding that there was no difference between the test and comparator compound could be misleading.

The use of a placebo control means that treatment studies can be conducted in smaller groups, than is the case with comparator-controlled trials. When two 'active' compounds are compared, the additional advantage achievable with the investigational drug is usually relatively small; so many more patients are required to demonstrate the superiority of one treatment over another. This carries the risk of exposing a considerably larger number of patients to a potentially ineffective or hazardous treatment, than would occur through a comparison with placebo. By including a placebo arm, both the effect size (the difference between the response to active treatment and the response to placebo) and the 'number needed to treat' (i. e. 1/[active response rate minus placebo response rate]) for the investigational drug can be estimated. The clinical relevance of the study findings is therefore more certain (Fritze and Möller 2001).

By continued use of placebo-controlled studies, investigations of potential new antidepressant treatments will be conducted more rapidly. If regulatory authorities were to require that new compounds had to ensure superiority in efficacy over existing treatments, compounds that are only as efficacious but significantly better tolerated may not be developed. Furthermore, the economic risks of conducting large studies may lead pharmaceutical companies to shy away from developing antidepressants with novel mechanisms of action (Fritze and Möller 2001).

What are the problems with placebo-controlled trials?

Despite the theoretical arguments for continuing with placebo-controlled trials, it could be argued that exposing depressed patients to placebo might expose them to an increased risk of potential adverse outcomes. These might include a delay in the onset of recovery, a reduced rate of response to treatment, and a reduced duration of treatment. Other hazards might include a greater risk of attempted or completed suicide, and a greater risk of other untoward consequences of persistent depression, such as loss of employment and breakdown of interpersonal relationships.

Of these, the most debated is the risk of suicidal behaviour. However, an examination of suicide risk in placebo-controlled trials performed by the United States Food and Drug Administration has yielded encouraging results. In this review, a total of 45 studies involving 7 antidepressants were examined. Among the 19639 participating patients, 34 committed suicide (a rate of 0.8 % per year), and 130 attempted suicide (2.9 % per year). The rates of suicide and attempted suicide did not differ among the groups. The annual rates of suicide and attempted suicide were 0.4 % and 2.7 % with placebo, 0.7 % and 3.4 % with comparator antidepressants, and 0.8 % and 2.8 % with investigational antidepressants, respectively (Khan et al. 2000).

Similar findings were seen in an analysis of all double-blind placebo-controlled treatment studies submitted to the Netherlands Medicines Evaluation Board during the period from 1983 to 1997 (Storosum et al. 2001). In 77 short-term studies, involving a total of 12,246 patients, the incidence of attempted suicide was 0.4 %, and the incidence of completed suicide 0.1 %, in both the placebo and active compound groups. In eight long-

term studies with 1949 patients, the risk of attempted suicide was 0.7 % in both placebo and active compound groups, and the risk of completed suicide was 0 % in the placebo group, and 0.2 % in the active group. There were no significant differences in the incidence of suicidal behaviour between the treatment groups. As patients who are considered to be at 'suicide risk' are excluded from participation from treatment studies, the fear of an increased risk of attempted suicide in the placebo group should not be an argument against the performance of short-term or long-term placebo-controlled studies (Storosum et al. 2001).

But of course there may be other drawbacks, in exposing depressed patients to placebo. In the FDA analysis of antidepressant treatment (Khan et al. 2000), the response to treatment was also examined; the change in severity of depressive symptoms, as measured by the Hamilton depression rating scale (HAM-D) (Hamilton 1960) was evaluated, comparing mean baseline scores to mean endpoint scores, using the last-observation-carried forward technique. The reduction in HAM-D score was greater, as the study duration increased, regardless of the treatment condition. In these treatment studies, the degree of symptom reduction was 40.7 % with investigational antidepressants (n = 4510) and 41.7 % with active comparators (n = 1416) compared to 30.9 % (n = 2805) with placebo. These findings indicate that the reduction in depression severity is greater with antidepressants than with placebo, although patients who are allocated to placebo can experience a substantial reduction in symptoms.

A further potential hazard to receiving placebo is that treatment might be stopped earlier, even in placebo responders. This issue has also been examined in the FDA analysis. The patient study completion rates favoured the investigational antidepressants, but not by a large margin: in the 42 studies that reported patient completion rates, 18 favoured investigational drugs, 11 favoured active comparators, and 15 favoured placebo (Khan et al. 2000). Clearly, this should be examined in other databases, together with attempts to investigate other patient outcomes such as return to employment: these outcome measures are being incorporated into randomised controlled trials more frequently, as part of the pharmacoeconomic evaluation of new antidepressants. Some of the strengths and weaknesses of placebo-controlled studies are shown in Table 2.

What provisions should be applied for patient protection in placebo-controlled trials?

Given that there are strong scientific arguments for continuing with placebo-controlled studies with antidepressants, it is essential that patients who may be exposed to placebo are provided with sufficient protection to ensure their participation does not put them at undue or increased risk of a poor outcome.

The requirements for the ethical performance of placebo-controlled studies have been reviewed previously (Paykel 1990). Patients should only participate in such studies having given fully informed consent, being aware of the method of random allocation, the double-blind conditions, and the use of placebo. There should be detailed provisions for the careful monitoring of the participating patients, such as regular and frequent assessments, and the ready availability of research staff between appointments. Patients should have a right to withdraw from the study at any point, without this prejudicing their further medical care. The study sample should be selected appropriately, typically involving depressed outpatients with illness of moderate severity; patients at high risk of suicidal behaviour (such as those seen after a recent suicide attempt) should be excluded from participation. The placebo period should be limited to the minimum necessary period, whilst still ensuring the study has sufficient scientific validity.

The issue of whether to involve depressed inpatients in placebo-controlled studies is controversial. Some believe that inpatient status protects against suicide, others note that receiving in-patient care offers no protection against suicidal behaviour (Schene et al. 1993). Although many placebo-controlled studies would only be undertaken in depressed outpatients, in some studies hospitalised inpatients might also be considered for inclusion, provided they are not severely ill, and are able to withdraw at any time. Finally, there should be explicit criteria for the withdrawal of patients in the event of non-response to treatment, and the protocol should include provisions for patients who withdraw early, or who remain symptomatic at the end of the study. Some of the strategies used to minimise risk to patients whilst conducting placebo-controlled studies are shown in Table 3.

Table 2 Placebo-controlled studies

Advantages	Disadvantages
Requires smaller sample size	Possible increased risk to patients from use of placebo
Study costs may be reduced	
Validates investigational treatment, providing data on effect size, and 'number needed to treat'	
Clinical relevance of findings is clearer	

Table 3 Strategies to minimise risk to patients in placebo-controlled studies

- Provision of fully informed consent to treatment
- Careful selection of patients
- Careful monitoring of patients
- Ready availability of research staff
- Patient is able to withdraw from study at any point
- Minimise duration of placebo treatment whilst ensuring scientific validity
- Provision of clear criteria for withdrawal of patients from study

Is there a third way?

For clinical research to be ethical, it must fulfil several requirements. The most important are that the research project is scientifically valid and it must minimise the risks to which the research participants are exposed (Emanuel et al. 2000). Clinicians, researchers and regulatory bodies should recognise that placebo-controlled and comparator-controlled studies have distinct objectives, and each type of study has a role in the evaluation of potentially groundbreaking treatments. Placebo-controlled studies are needed to establish the efficacy of a new antidepressant, and to help with the design of further studies in which the new compound can be compared to 'reference' antidepressants (Emanuel and Miller 2001).

There are many advantages in employing a three-arm study design. This approach allows an assessment of the assay sensitivity of the trial, and permits measurement of the effect size of the new drug. It can also compare the relative efficacy of treatment to that with a proven antidepressant, and allows a comparison of the tolerability profiles of two drugs, by examining the placebo-adjusted incidence of any treatment-emergent adverse events. Incorporation of a comparator antidepressant can make it harder to identify the investigational drug by patients and doctors, thereby helping preserve the double-blind nature of the treatment study. Furthermore, many regulatory bodies favour this study design (Committee for Proprietary Medicinal Products 2002). However, three-arm studies will need to involve a larger number of patients than that needed in the more simple placebo-controlled design, and for this reason such studies take longer to complete.

Conclusions

If the investigational antidepressants of the future were to be tested only against 'standard' treatment, rather than against placebo, about half of the treatment studies would yield invalid results (Khan et al. 2002). As such, some effective antidepressants would be rejected incorrectly as being inactive, thereby reducing the range of treatment options for a condition that is often hard to treat. Perhaps more worryingly, some ineffective treatments would be accepted falsely as being effective when they were not, and would become available for clinical use, thereby putting patients at risk of continued depression and its untoward consequences.

Based on extensive consultation and recent publications (Lavori 2000; Rush 2000) the United States National Depressive and Manic-Depressive Association has produced a consensus statement on the use of placebo in clinical trials in patients with mood disorders. It concludes that placebo-control has a clear role in treatment studies in affective disorders, and that any findings of equivalence between a new drug and standard treatment are not evidence of efficacy, unless the new drug is also significantly more effective than placebo (Charney et al. 2002; Kupfer and Frank 2002).

The consensus of the European Expert Forum is that both placebo-controlled studies and comparator-controlled studies are necessary, when investigating potential new antidepressant treatments. Placebo-controlled studies are required by regulatory bodies, before a new treatment can be licensed, but this requirement is being hindered by the actions of ethics committees, who may be unaware of the flaws inherent in comparator-controlled investigations. We acknowledge that there are emotional and rational arguments when considering ethical issues. We believe that placebo-controlled studies continue to be ethical, providing they are scientifically valid, and designed to ensure that all the participating patients are supported and protected – before, during and after the study. They remain feasible in practice, providing the study investigators are supported by a research environment that recognises that the existing antidepressant drugs are not ideal, and that more research is needed to develop better treatments for the debilitating and burdensome illness that is depression.

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