

## CONTROVERSY

# Placebo-controlled trials in psychiatry on trial

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The well-conducted randomised controlled trial (RCT) is widely regarded as providing the most unbiased estimate of the true efficacy of interventions (1, 2, 3). Ethical concerns have been raised by professionals and lay people since the advent of the RCT. These largely involve the issues of whether true equipoise (a state of uncertainty where a person believes it is equally likely that either of two treatment options is better), which forms (or should form) the basis for conducting an RCT, is possible in clinical research (4); the use of placebo controls, especially where effective treatments exist (5, 6, 7); and the problem of how informed, voluntary and competent the consent obtained for such trials really is, especially in vulnerable populations and when research is conducted in settings of routine clinical care (7). More recent concerns pertain to the ethics of conducting clinical trials in the developing world (8). An additional issue is that of the ethics of conducting clinical trials in resource-poor settings that appear to be purely for the regulatory purposes of foreign agencies.

### **Do patients lose out by participation in randomised-controlled trials?**

One of the concerns about RCTs is that by randomisation, patients are exposed to risks they would not face if they had not participated in such trials. Systematic reviews of the evidence indicate that participation in RCTs is not associated with greater risks than receiving the same treatment outside RCTs (9) and that participants given the active intervention as well as controls had better outcomes than those who declined participation, even after adjusting for prognostic confounders (10). This suggests a non-specific "Berksonian" effect of better care accruing from trial participation.

### **Are placebo-controlled trials justified?**

There is general agreement that placebo or untreated controls are not appropriate in trials of therapy for life-threatening conditions if a treatment that prolongs or preserves life is available. The disagreement centres on trials of therapy for non-life-threatening conditions. In general, the empirical evidence supports the conduct of RCTs if true equipoise exists, that is, if both drugs offer equal benefits, or the known potential side-effects of the treatments are unequal. In Article II.3 of the 1996 version of the Declaration

of Helsinki of the World Medical Association (WMA) placebo controls were permitted only in studies where no proven diagnostic or therapeutic method existed (7). Reacting to criticism that this not only limited the use of placebos but ruled out the testing of all new therapies for conditions for which even partially effective "proven" treatments existed, Article II.3 was replaced by the new Article 29 with a clarification in 2001 (7) that clinical trials with a placebo control group would be ethically justified "for compelling and scientifically sound methodological reasons"; or if its use is for "a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm". This then would require a study-specific review of the justifications for placebo use, based on scientific merit and study-specific risk involving careful subject selection and risk-reduction procedures; this has been reported to be applicable to trials of people with schizophrenia (11).

It has been suggested that the need for concurrent placebo control groups in new studies on psychotic patients might be minimised by making comparisons with external placebo; this requires an assumption that the novel medication will perform the same way in a study with only active controls as it would have in a placebo-controlled trial; this assumption is not borne out by the evidence from 32 RCTs involving 7,264 patients randomised to atypical antipsychotics that showed that in atypical antipsychotic medication arms, the degree of improvement was nearly double in active-controlled trials than that seen with the same drugs and dosages in placebo-controlled studies (12).

There is compelling evidence from a systematic review of 75 RCTs that there is a substantial placebo response rate in people with major depression ranging from 12.5 per cent to 51.8 per cent, supporting the view that the inclusion of a placebo group is scientifically important in trials of new antidepressant medications (13). The placebo response rate in acute mania has not been systematically reviewed but in the trial under scrutiny (14) between 35 per cent and 40 per cent of people with acute mania on placebo who were all at least moderately ill at trial commencement were not ill or only mildly ill at the end of the trial (Figure 3, page 232).

This appears to justify the use of placebo in this trial from a scientific point of view, since spontaneous remission is not unusual in acute mania and would not be detected were a placebo not used.

Placebo-controlled trials are not uniformly unethical when known effective therapies are available; rather, their acceptability is determined by whether the patient will be harmed by deferring therapy. If patients are not harmed, such trials could ethically be carried out (15). If the trial were conducted in an inpatient setting with careful evaluation of all participants for worsening, non-response in a reasonable period of time, or adverse effects, and the protocol permitted withdrawal of any participant at the discretion of the investigator, then harm could be minimised. All participants in the trial in question (14) were permitted lorazepam for various indications, in addition to the study drug, and 99 per cent of participants received it, including those allocated to placebo; benzodiazepines are of some benefit in the symptomatic treatment of people with acute mania. The report also provides some details of trial completion rates and reasons for discontinuation in Table 2 on page 231 that reflect the fact that drop-out rates are higher in the placebo control arms of RCTs of conventional and atypical antipsychotics (16).

Would drop-outs and non-response alter the overall prognosis of those on placebo? Placebo treatment of manic and psychotic patients involves several potential risks. Among them are the distress and disruption produced by the continuation of manic or psychotic symptoms, the progression of the illness with the potential for poorer recovery from an episode and the risk of suicide. Indications from other sources suggest that rates of suicide and attempted suicide did not differ significantly between the placebo-treated and the drug-treated groups from among 10,118 participating patients in placebo-controlled antipsychotic drug trials (17) nor in 11 placebo-controlled studies of the treatment and prevention of acute manic episodes and bipolar disorder that included 1,511 patients of whom 1,005 were on placebo (18). However, in the absence of systematic information about the other potential and not insubstantial risks apart from suicide, this remains an area of current uncertainty that requires systematic study and follow-up.

### **How informed, voluntary and competent is consent obtained in randomised controlled trials?**

Firstly, should randomised controlled trials be done in people with acute mania or psychosis? The answer is yes, since the efficacy for interventions in acutely ill people with mania or psychosis cannot be answered by studying another population. The concerns pertain to the validity of informed consent in vulnerable populations. Many participants of undisputed

capacity to consent are still unable to differentiate between treatments that increase research validity such as using placebos to mask treatments and those that are therapeutic, and this 'therapeutic misconception' is all the more likely when research trials are conducted in treatment centres and by their usual treatment teams. While mania or psychosis does not automatically render a person incompetent to consent, it does raise issues of the validity of the consent obtained and the need for systematic attempts to assess this. One way to ensure this in trials done on vulnerable subjects is to appoint independent qualified professionals to assess the potential subject's capacity to participate in research involving more than minimal risk (19). If, on the other hand, patients with potentially compromised capacity, such as the ones reported in the trial (14), were to be included, then proxy consent from a responsible relative could additionally be obtained, to ensure that those most likely to know the patient's wishes and safeguard the patient's interests are involved in decision-making.

Systematic evaluation has shown that participants in randomised trials recall information poorly, are not often aware that placebos form one arm of treatment, demonstrate inadequate comprehension of the process of chance in treatment allocation, understand and use only a proportion of what is presented in consent forms, do not really understand the issue of equipoise, and participate not for altruistic reasons but because they expect some improvement by participation (10, 20, 21). While creative interventions to improve understanding may improve patients' capacities to consent (22), this requires researchers to be cognisant of the need for ensuring that the consent obtained is valid. This is more likely to be achieved if obtaining informed consent is considered a "process" that requires a continual dialogue between physician and patients with mutual monitoring throughout, rather than an "event" symbolised by the signing of the consent form (23). The pressure of competitive recruitment in industry-sponsored multi-centre trials, the substantial emoluments that trial recruitment confers, and the stringent data monitoring associated with many such trials, makes obtaining valid informed consent, the component of the trial that is supervised and evaluated the least, the most likely to be compromised.

Research into informed consent from India is scant; in a postal survey of 3,622 physicians in India, several constraints in obtaining informed consent were noted, chief among which was illiteracy of patients, and variations in the amount of information thought necessary to be divulged (24). This then leaves local research ethics committees with a considerable role to play in ensuring the ethical conduct of randomised controlled trials, particularly when placebos and vulnerable subjects are involved. It is uncertain, however, whether local research ethics committees comprise people with uniformly

adequate knowledge of the scientific and ethical issues involved in research on human subjects or whether each member is aware of the CONSORT guidelines (24) or the WMA Declaration of Helsinki (7); appointment to such committees is rarely based on competence in these areas. It is also uncertain whether data from systematic reviews are insisted upon before a trial is approved, whether data monitoring is overseen, prospective stopping rules are adhered to and deviations from protocol noted routinely. Audits, whether internal or external, of research ethics committees also appear to be non-existent. Just as it is required to assess the adequacy of blinding in the CONSORT guidelines, it ought to be an additional requirement that procedures to ensure the validity of informed consent also be reported. The role of regulatory bodies such as the Indian Council of Medical Research in reviewing the conduct of such trials and the functioning of local research ethics committees also needs review.

### Research in resource-poor settings conducted primarily for overseas regulatory approval

The epidemic of industry-sponsored trials in the country, many with placebo controls, for psychiatric disorders where effective treatments exist, raises the additional question of whether it is ethically correct for clinician-researchers, with limited resources of manpower and time, to participate in these trials that are clearly being conducted solely for regulatory bodies overseas, when there are many unanswered questions of clinical relevance to health care in the region. Additional concerns pertain to the lack of power the individual researcher has in ensuring that trial results, whether positive or negative, are fully reported; by recruiting between 5- 20 patients to these trials, the researcher is in effect waiving publication rights, because one cannot independently publish site-specific results with such small numbers. Prospective registration of clinical trials (25) and mandating that industry-sponsored trials (as well as non-industry-sponsored trials) publish all results may reduce these reporting biases as well as the other well-known problem of "salami" or multiple publications from a single trial; but this does not mitigate the need to evaluate reasons for participating in such trials. While financial and other incentives are often a strong inducement for participation, the lack of any new science should raise questions about participation. Some potential researchers might be encouraged to realise that non-industry-sponsored pragmatic trials addressing questions of relevance to mental health care in India, with clinically relevant outcomes, robust clinical design and relatively low costs, are possible to conduct during routine clinical care (26).

Such concerns highlight the lack of satisfactory regulation in many parts of the world to ensure patients' interests are adequately protected while scientific knowledge accumulates. This commentary also highlights the genuine uncertainty regarding some of the controversies that surround the

science and ethics of RCTs and the need for more systematic and culture-specific quantitative and qualitative research to inform the design of future trials, especially among vulnerable populations in resource-poor countries.

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