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Ethics of a placebo-controlled trial in severe mania

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In October 2005, editors of the IJME learnt that the British Journal of Psychiatry had published a report of a placebo-controlled trial of an atypical anti-psychotic drug. The drug was tested on 290 people experiencing an episode of acute mania. The trial was conducted on in-patients of eight health facilities in India.

A letter raising questions about this study has been submitted to the British Journal of Psychiatry. It was also felt that the journal should carry a discussion on this subject. We therefore publish here a comment on the study itself, raising specific questions about the trial. This is followed by a comment on ethical issues in placebo-controlled trials in general. Finally, the corresponding author of the study has been invited to respond.

Editors

Bipolar disorder is a severe mental disorder, called manic-depressive disorder in older classifications of mental disorders, characterised by severe mood swings. During the manic phase, the person typically becomes irritable and agitated, is unable to sleep, experiences a rapid flow of thinking, and may become psychotic. The hallmark feature of the phase is the loss of insight: the person is unaware of their illness and often needs to be brought to medical facilities by concerned relatives. In severe cases, the person may need a period of hospitalisation to bring symptoms under control. Indeed, acute manic episodes are one of the commonest reasons for hospitalisation in psychiatric care.

Khanna et al have recently published a clinical trial evaluating the safety and efficacy of risperidone, an atypical antipsychotic drug, for acute mania, in the British Journal of Psychiatry (1). This article describes a placebo-controlled randomised controlled trial of risperidone for patients with severe manic episodes. The trial was carried out in eight centres in India, and was funded by Johnson & Johnson Research and Development; four of the six authors work for the funding body and are based in the USA and Belgium. In the introduction to their article, they state that "bipolar disorder is a debilitating illness characterised by drastic swings in mood, energy and functional ability". They note that there is abundant evidence of the efficacy of a number of different treatments for acute mania, in particular conventional antipsychotics (such as haloperidol, a cheap drug considered by many as the gold standard for acute mania) and mood stabilisers (such as lithium). In the light of these facts, and the nature of the disorder, this trial raises some important ethical issues.

First, is there an ethical basis for a placebo-controlled trial in severe mania? The authors note in their discussion that the symptoms of their patients were "substantially more severe than those of patients with bipolar disorder participating in trials elsewhere", indicating that these were the most seriously ill patients to be recruited in published trials for acute mania. The ethical principle is that no trial participant must be harmed in any way. This typically translates to ensuring that the control group in a trial must receive what is usual evidence-based care in the circumstances. Haloperidol is cheap, freely available and constitutes usual care even in government facilities in India. Indeed, the majority of patients (>80 per cent) in the placebo group were already receiving psychotropics at the time of enrollment including 41 per cent receiving haloperidol and 42 per cent receiving chlorpromazine (similar to haloperidol); they were "washed out", ie these effective treatments were discontinued as a prerequisite for participation in the trial. Thus, not only was this group of extremely sick individuals denied usual care, but they were actually deliberately stopped from receiving such treatment.

Second, how was signed informed consent obtained (as is mentioned in the paper) from such severely ill manic patients, the majority of whom had florid psychotic symptoms, when insight and capacity to make informed decisions are typically seriously impaired? What was the independent safeguard to ensure the rights of these patients to freely consent to participate in a trial in which they would be taken off the effective treatment they were already receiving and be possibly subjected for three weeks to a placebo? The authors comment that the rate of "completion" of the trial was high in this trial as compared to developed countries

and cite that reasons for this are that patients were more severely ill and that they remained in hospital throughout the trial. This implies that these very sick patients, who were not given (and indeed, who were stopped from continuing) a cheap and effective treatment, were kept in hospital (at least some in the private sector) for longer than they possibly needed to.

Third, was there any financial transaction between the authors and the drug company? In my experience, many private physicians receive payment for participation in clinical trials. Given that the first author is based in a private facility in New Delhi, a declaration of conflict of interest (not mentioned in the publication) should have been made. As it stands, one must assume that the authors received no renumeration at all; if they did, then they would have contravened the mandatory requirement of declaring a conflict of interest.

Fourth, there is no mention anywhere of any institutional review board (IRB) approval for this trial. Given that patients were recruited from eight centres in India, what were the IRBs which gave approval for this trial?

Fifth, what new information does this trial add that justifies the trial in the first place? In the introduction, the authors provide three citations in support for their statement that atypical antipsychotic monotherapy (for example drugs like risperidone, without any other concomitant medication) is effective and well tolerated for acute manic episodes. Furthermore, risperidone was licensed for use in India in the late 1990s and the indications noted for its use in the Monthly Index of Medical Specialities (MIMS) include psychotic syndromes such as those which are seen in acute mania. What does this trial add to the evidence base for patients in India? Surely, a more appropriate question for a low-income setting would have been to compare the atypical drug, which is more expensive, with a conventional drug, which is much cheaper, on clinical, safety and, most importantly perhaps, economic outcomes?

Reference

1. Khanna S, Vieta E, Lyons B, Grossman F, Eerdekens M, Kramer M. Risperidone in the treatment of acute mania. Br J Psychiatry 2005; 187: 229-234.

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