to usual psychiatric treatment for bipolar disorders. *International Journal of Neuropsychiatry*, in press.

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Trial of risperidone in India – concerns

The study by Khanna *et al* (2005) on the effectiveness of risperidone in acute mania raises many questions.

Why was the study done? The authors do not indicate that existing treatments have limitations that led them to test risperidone as an alternative.

Why was a placebo used when an effective treatment exists? This is particularly worrisome because, as the authors state, acute mania can be life-threatening and carries an increased risk of suicide.

Patients undergoing psychiatric treatment are a vulnerable group. How did patients give informed consent during an episode of acute mania?

Where were the trial sites? Who were the participants and what quality of care did they receive? What were the adverse events? How were seven participants from the placebo group lost to follow-up?

Regarding the 'wash-out' period before the trial, is it medically and morally justified to withhold treatment from patients during an episode of illness in intensive care?

Four authors state that they are drug company employees. Do the other authors have any competing interest to declare?

In what sense was the trial conducted according to the Declaration of Helsinki? Why do the authors mention the Declaration as revised in 1989, rather than a more recent revision?

We suggest that this trial could not have been conducted in a high-income country but may have been conducted in India because regulatory requirements could be fulfilled there. The use of a placebo when an effective treatment exists – and other elements of the study as mentioned above – goes against the Helsinki guidelines and those of the Indian Council of Medical Research (2000). Finally, publication of such studies in a leading journal such as the *British Journal of Psychiatry* gives credibility to unethical medical research and practice and is a matter of serious concern.

Declaration of interest

The authors are editors of the *Indian Journal of Medical Ethics* and have previously written or spoken against certain drug company practices, including sponsored research.

Indian Council of Medical Research (2000) *Ethical Guidelines for Biomedical Research on Human Subjects*. http://icmr.nic.in/ethical.pdf

Khanna, S., Vieta, E., Lyons, B., *et al* (2005) Risperidone in the treatment of acute mania: double-blind, placebo-controlled study. *British Journal of Psychiatry*, **187**, 229–234.

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Although it is encouraging to see the *Journal* take an active role in redressing 'editorial racism' as discussed in a previous editorial (Tyrer, 2005), there is a need to ensure that promotion of positive discrimination does not exacerbate the problem.

We feel that a recently published randomised double-blind placebo-controlled trial of risperidone performed in India illustrates the dangers inherent in such a policy (Khanna *et al*, 2005). The report had a number of serious shortcomings, which included omission of crucial details of the process of randomisation, interrater reliability and the measures taken to ensure masking. However, the most worrying aspect of the trial was the use of a placebo in the control group and the apparent absence of any ethical approval to proceed with this study. What was the justification for denying severely unwell and vulnerable patients access to appropriate treatment? Why was there no discussion about the ethical dilemmas associated with this study?

We support the *Journal* policy of combating editorial racism by promoting positive discrimination in the instructions to referees. However, the *Journal* must not relinquish its responsibilities as the official journal of the Royal College of Psychiatrists by failing to act as final arbiter for the quality (including the ethics) of the *Journal*'s content.

Khanna, S., Vieta, E., Lyons, B., *et al* (2005) Risperidone in the treatment of acute mania: double-blind, placebo-controlled study. *British Journal of Psychiatry*, **187**, 229–234.

Tyrer, P. (2005) Combating editorial racism in psychiatric publications. *British Journal of Psychiatry*, **186**, 1–3.

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With a sample size of 290 patients the report by Khanna *et al* (2005) buttresses the data about efficacy of atypical antipsychotics in the treatment of acute mania, but the article also raised the following concerns.

One of the sites had to be withdrawn from the study after enrolling three participants because of concerns about data quality. However, the data from these individuals were still included in the safety analyses. We are of the opinion that if there were concerns about the data from one particular site, then that site should have been excluded from any further analyses.

We also have concerns about the legitimacy and validity of the informed consent obtained from 145 patients with acute mania and a mean Young Mania Rating Scale score of 37.5 to be enrolled in the placebo arm of a clinical trial. Article 4 of the World Medical Association Declaration of Helsinki (World Medical Association, 1989) states that biomedical research involving human participants cannot legitimately be carried out unless the

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importance of the objective is in proportion to the inherent risk to the participant. Delayed treatment of acute mania is associated with considerable acute and long-term morbidity from both illness and its secondary consequences (Post, 2000). Randomising a patient with acute mania to the placebo arm of a 3-week trial leads to considerable delay in treatment.

In this trial 145 patients with acute mania were assigned to the placebo arm. We consider it unethical and inhumane to treat 145 patients with acute mania with placebo. All future trials concerning the efficacy of a medication for acute mania should use an arm with one of the proven medications as a comparator and not include a placebo arm.

Post, R. M. (2000) Mood disorders: treatment of bipolar disorders. In *Comprehensive Textbook of Psychiatry* (eds B. J. Sadock & V. A. Sadock), pp. 1385–1430. Philadelphia, PA: Lippincott Williams & Wilkins.

Khanna, S., Vieta, E., Lyons, B., *et al* (2005) Risperidone in the treatment of acute mania: double-blind, placebo-controlled study. *British Journal of Psychiatry*, **187**, 229–234.

World Medical Association (1989) *World Medical Association Declaration of Helsinki: Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects*. http://www.fda.gov/oc/health/helsinki89.html

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Authors' reply: Dr Srinivasan *et al* are in error when they state that this trial (Khanna *et al*, 2005) could not have been conducted in a high-income country. Johnson & Johnson conducted this trial in India at the same time as two trials in other countries (including the USA) as part of a global effort to obtain registration for risperidone monotherapy in bipolar mania. (Hirschfeld *et al*, 2004; Smulevich *et al*, 2005). Quality investigators and sites were chosen and approval from research ethics boards and participant consent were obtained at each site.

We categorically reject the implication that a clinical trial in India is medically inferior or ethically suspect. The investigators and sites in India were comparable in scientific quality and adherence to ethical guidelines to their peers globally. Any suggestion to the contrary is unwarranted, and fosters prejudice by creating a distorted perception of Indian clinical scientists and centres of research.

Below are our responses to the other questions raised by Dr Srinivasan *et al*:

> Why was a placebo used?

Placebo-controlled trials expose the lowest number of patients to a potentially ineffective (new) treatment, while also providing valid data on adverse events attributable to the treatment.

> How did patients give their informed consent during an episode of acute mania?

In this study, patients or a family member provided informed consent as required in the protocol. Patients with psychiatric illness, including mania, can give informed consent: capacity to consent or withhold consent is not automatically lost because of illness.

> Where were the trial sites? Who were the participants? What were the adverse events? How were seven patients from the placebo group lost to follow-up?

The study was conducted at eight sites in India, as reported in the *Journal* article (page 229); participants were those experiencing an acute exacerbation of symptoms of mania and are described in Table 1 (page 231); adverse events are reported on pages 232–233; as in all clinical trials, a few participants could not be contacted at follow-up. In this study, 3% of participants were lost to follow-up, which is in line with previous studies of mania (Sachs *et al*, 2002; Yatham *et al*, 2003).

> Was the wash-out period medically and morally justified?

Stable patients who were responsive to their current medication were not enrolled in this trial. Patients who were enrolled were symptomatic despite their current medication (suggesting that they were not responsive to the treatment) or because they had spontaneously discontinued medication. In order to successfully assess the trial medication, it was necessary that they discontinue their current suboptimally effective medication. This is scientifically and ethically justifiable.

> Do the authors who are not drug company employees have any competing interest to declare?

The two authors who were not Johnson & Johnson employees had no conflict of interest related to this study.

> Was the trial conducted according to the Declaration of Helsinki? Why did the authors cite the 1989 revision of the Declaration and not a more recent revision?

The trial was conducted in accordance with the principles originating in the Declaration of Helsinki. Reference to the 1989 version of the document was made since this was a commonly cited version at the time the study preparations were underway (1999–2000).

Drs Murtagh and Murphy refer to 'serious shortcomings' in our report. These are said to include omitting crucial details of the process of randomisation, interrater reliability and masking. In addition, 'the most worrying aspect of the trial was the use of a placebo in the control group and apparent absence of any ethical approval to proceed with this study'.

There were no such 'shortcomings' in the trial itself but not all methods were detailed in our report. On page 229, we wrote, 'Randomisation was stratified by the presence or absence of psychotic features at baseline, manic or mixed episode, and by treatment centre. After randomisation and the initiation of treatment (baseline), patients remained in hospital for at least 7 days'. On page 230, we wrote, 'Investigators were trained in the use of each of these instruments and certification was required for those administering the YMRS'. Furthermore, page 229 states, 'Signed informed consent was obtained for all participants and the study was conducted according to the *Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects*, in the 1989 version of the Declaration of Helsinki'. The study had the approval of national and local research ethics boards. These are standard descriptions of such procedures and are similar to those provided in many published reports of clinical trials.

A placebo control was necessary to establish the effects of medication because people with mania manifest response to placebo which is of variable magnitude. The true efficacy of risperidone in this trial was incontrovertibly established over and above the effects observed with placebo.

Similarly, the safety of risperidone can only be appropriately assessed in the context of adverse events in the placebo arm. Furthermore, patients could be withdrawn from the study and treated in an open-label

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