manner at any time. The appropriate use of placebos in clinical trials for bipolar disorder has recently been reviewed by Vieta & Carné (2005), who point out that the regulatory agencies (Food and Drug Administration, European Agency for the Evolution of Medical Products) and consumer associations support their use to ensure that ineffective drugs are not authorised for this condition.

Basil *et al* question why data from a site that was withdrawn because of concerns about data quality were included in the safety analyses. It is a conventional procedure in clinical trials to omit efficacy data but not safety data from such sites. They also question the 'legitimacy' of the informed consent obtained from the patients. It is our experience that patients with severe illness are capable of giving their informed consent to participate in a trial. Capacity to consent is not automatically lost because of a symptom score on the Young Mania Rating Scale.

Basil *et al* question the ethics of including a placebo arm in the trial. A placebo group was included because patients with mania generally show a high and variable placebo response, making it difficult to identify their responses to an active medication. Placebo-controlled trials are valuable in that they expose the fewest patients to potentially ineffective treatments. In addition, inclusion of a placebo arm allows a valid evaluation of adverse events attributable to treatment *v.* those independent of treatment. For these reasons, regulatory agencies (Food and Drug Administration, European Agency for the Evaluation of Medicinal Products) and the consumer associations support the use of placebo controls (Vieta & Carné, 2005).

Most (83%) of the placebo patients had been receiving treatment for bipolar disorder for at least 30 days before being hospitalised for the treatment of severe acute mania. This indicated that their current treatments were not adequately treating their symptoms and illness. Thus, as expected, a high response to placebo was shown by these patients. Significant improvements *v.* baseline were seen on each of the efficacy measures in patients receiving placebo or risperidone. For example, improvements in YMRS total scores at week 3 end-point were −10.5 (s.e.=1.3) in patients receiving placebo and −22.7 (s.e.=1.1) in patients receiving risperidone ($P<0.001$ *v.* baseline in both groups). The proportion of placebo patients whose severity of illness (Clinical Global Impression scale) was rated as 'not ill', 'mild', or 'very mild' increased from 1% at baseline to over one-third (37%) at end-point (the increase was from 0% to 72% in the risperidone group).

Declaration of interest

B.L., F.G., M.E. and M.K. are employees of Johnson & Johnson Pharmaceutical Research and Development, which supported the study.

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Editor's reply: We thank our correspondents for pointing out an important issue that we need to address more assiduously in our reviews of papers. We agree fully that the *British Journal of Psychiatry* needs to ensure that a greater policy of openness towards low- and middle-income countries is not accompanied by any lowering of ethical standards.

However, there are clear divisions of opinion here. When the protagonists for each of these make their eloquent arguments, it may seem strange that any should remain rather uncomfortably on a rickety fence when the alternative certainties are so much more inviting. Well, we are still wobbling because we feel it is right to wobble. The two sides of this argument, put crudely, are (a) it is unethical to exploit patients in low-income countries for studies that would never be allowed to proceed in rich countries, and (b) research performed for a global scientific community has to provide general evidence, not specific to one group or country, and so worldwide efficacy studies are necessary.

Drs Murtagh & Murphy, Basil *et al*, and Srinivasan *et al* all allege, directly or indirectly, that the patients in India have been selectively exploited for research purposes and this is fundamentally unethical. Patel (2006) also asks whether there is a personal financial aspect to the trial that has been undeclared. The allegation 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' (Srinavasan *et al*) is a serious charge.

However, the case for the trial is also strong. Although Basil and his colleagues suggest that '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', regulatory bodies such as the Food and Drug Administration insist on at least two placebo-controlled studies that demonstrate superiority of the index drug over placebo in order to get a licence approved. Although one may criticise the Administration for this requirement, it is scientifically unimpeachable and is a general one for drug treatments. A very similar trial has also been carried out in the USA in which risperidone was also compared with placebo treatment (Hirschfeld *et al*, 2004) (and which should have been disclosed with the paper of Khanna *et al*, 2005). The findings suggest that when risperidone is licensed for the treatment of mania it is possible to argue that both these positive trials represent an advance in patient care. A subsidiary argument, a practical one not always well-received in ethical circles, is that participation in a research study can, and should be, a proper and ethical way of providing good patient care, exemplified by the recent comments of Phillips *et al*

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(2005): 'the clinical treatment of young people identified as being at high risk of developing a psychotic disorder, particularly the use of neuroleptics, should be provided only in the context of a research trial, where standards of informed consent and monitoring are highest'.

Nevertheless, there remain worries about trials in poorer countries. Ethical committees often do not have the same level of independence as they do elsewhere, financial inducements may lead to covert or overt pressures, and there is even sometimes a nationalistic element (e.g. if country X can recruit 100 patients, we must not recruit fewer than 200). This somewhat macho mentality may be behind comments such as that by Khanna *et al* (2005) that the symptoms of mania in the patients seen were 'substantially more severe than those of patients with bipolar disorder participating in trials elsewhere', implying that only countries that can be successful in persuading these 'difficult' patients to take part should be chosen.

We note that the Indian Council of Medical Research has now decided to audit clinical trials systematically to ensure that national recommendations are followed (Mudur, 2005) and the outcome of this will be followed closely. For our part, we have made changes to our refereeing procedure, and have been asking assessors to examine more closely the ethical aspects of papers that are submitted. We shall also be using our new group of international editors (in the case of India this will be Dr Vikram Patel) to advise on ethics both generally and with regard to specific papers, attempting as much as possible to take account of the need for 'autonomy, beneficence, non-maleficence and justice . . . and care ethics' summarised by Bloch & Green's (2006) recent paper.

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Antiparkinsonian prescription and extrapyramidal symptoms

Park *et al* (2005) cite the results of clinical trials as evidence supporting their hypothesis that the use of antiparkinsonian drugs in schizophrenia is an indication of extrapyramidal symptoms (EPS). This may be true for clinical trials (most of which include young adults with no comorbidity) but may not hold true for their observational study, in which other factors such as prescribing habits and comorbidity may affect the reason for prescription of antiparkinsonian drugs. As the mean age of their sample was 48.6 years, which falls within the range in which Parkinson's disease often develops, some patients could have been receiving antiparkinsonian drugs for the illness *per se*. Although this is mentioned as a limitation of the study, it has an adverse impact on the central hypothesis. Since decrements and increments in antiparkinsonian medication followed expectations from changes in antipsychotics (Tran *et al*, 1997), the results could well reflect the prescribing pattern of the general practitioners (GPs) rather than be true evidence for the presence of EPS.

One of the main limitations of the study is the lack of data regarding the reason for switching antipsychotics. As it is mandatory to submit data of all major illnesses (presumably including Parkinson's disease), any indication for prescribing or altering medication and any adverse drug reaction to the General Practice Research Database (GPRD; Walley & Mantgani, 1997), the data could have been provided and would have helped in the interpretation of the results. Furthermore, during the period studied more than 400 GPs provided data to GPRD but data from only 266 were analysed. It is not clear why the data from some GPs were excluded.

Park *et al* (2005) classified their study population as those switched from typical to atypical antipsychotics (TA group) and those switched from typical to different typical antipsychotics (TT group). However, when we add up the total figures provided (3% and 99% were receiving atypicals and typicals respectively in 1992, which changed to 47% and 70% in 2000), it appears that some patients were receiving a combination of both classes of antipsychotics. This could have influenced the trend for prescribing antiparkinsonian drugs.

Park, S., Ross-Degnan, D., Adams, A. S., *et al* (2005) Effect of switching antipsychotics on antiparkinsonian medication use in schizophrenia: population-based study. *British Journal of Psychiatry*, **187**, 137–142.

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Authors' reply: We agree with the comments of Grover & Kulhara on the lack of information about the specific reasons for the prescription of antiparkinsonian drugs in our observational study. We have stated that such prescribing might have been influenced by factors other than the occurrence of EPS. However, previous naturalistic studies have shown that the use of antiparkinsonian medication was highly correlated with clinical indices of EPS when patients were prescribed antipsychotics (Barak *et al*, 2002; Bobes *et al*, 2003; Montes *et al*, 2003). In addition, the sudden change in the incidence of antiparkinsonian drug use following introduction of atypical antipsychotics in the entire population (not just among patients who switched type of antipsychotic therapy) makes it unlikely that physician prescribing habits were a strong alternative explanation for our findings.

Since we observed the same patients over time in the analysis of drug switching, changes in antiparkinsonian drug prescribing following the switch could be explained by the differential effects of antipsychotics on EPS.

Nevertheless, antiparkinsonian drug prescribing is only a marker of EPS and

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