recommendation on just one unpublished modern study, these well-respected scientists appear to have gone beyond the available evidence. Transcranial direct current stimulation is not a new intervention for depression, with a number of studies published in the 1960s and '70s (Bindman *et al*, 1964; Lippold & Redfearn, 1964; Lolas, 1977). However, the results were not uniformly positive and certainly not persuasive enough for this intervention to have been adopted by clinicians. Although I acknowledge that our knowledge of the brain has improved, Fregni *et al* do not present evidence to show how modern tDCS is superior to that used four decades ago. We need to know a lot more about tDCS before it can be accepted as an effective treatment, and must await the results of many ongoing trials. In the meantime, those with depression in the developing world should be dissuaded from unplugging their car batteries and clamping the leads on to their foreheads.

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Authors' reply: We thank Professor Sachdev for his letter and we certainly agree that further studies on the antidepressant effects of tDCS are needed and that the standards of application of a given therapy in any part of the world should be matched. It is certainly not acceptable that inferior treatments are used in developing countries. However, although antidepressants are often available in developing countries, problems with distribution and management of these medications often preclude regular and effective clinical treatment. For instance, in São Paulo, a relatively rich city in Brazil, shortage of antidepressants is common (Brazilian Ministry of Health website, http://portal.saude.gov.br/saude/). Those with depression are regularly faced with the choice between stopping antidepressant treatment or paying for it with their own money. Poor patients often have to interrupt their treatment, risking worsening or relapse of their depression. The situation is even worse in poorer countries. Furthermore, it is well established that higher prevalence rates of depression are found among poor, illiterate and urban migrants (Almeida-Filho *et al*, 2004). Therefore, those most in need are less able to afford regular antidepressant treatment.

We agree that medications should be the first line of treatment for those with newly diagnosed depression. However, we cannot ignore the fact that many in poor areas are not being treated for depression at all. Therefore, our intention is to simulate the search for new, inexpensive approaches for the treatment of depression. Our suggestion of tDCS is based on several well-conducted studies showing its modulatory effects on brain activity (Nitsche *et al*, 2003), past positive trials of this technique in depression (Lolas, 1977) and our preliminary data showing a significant antidepressant effect (Fregni *et al*, 2005). The main differences between the current tDCS protocols and those used in the 1960s and '70s derive from recent knowledge of stimulation to optimise cortical modulation and therefore clinical effects (Nitsche *et al*, 2003). Furthermore, substantial evidence from studies of transcranial magnetic stimulation and electroconvulsive therapy suggests that electrical stimulation is a powerful treatment for depression (George *et al*, 2002).

Our message is simple: a large number of those with depression are suffering because they cannot afford medicine, therefore new solutions should be offered. Transcranial direct current stimulation might represent such a solution and should be investigated further.

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Drug combinations for rapid tranquillisation

It is important to develop cost-effective and efficient methods of treatment in emergency psychiatry, especially where resources are poor. Alexander *et al* (2004) in their paper comparing two methods of rapid tranquillisation concluded that the injectable haloperidol–promethazine mix is as effective as lorazepam and suggested that in India the former is more cost-effective. We acknowledge the findings of their study but would like to make some observations regarding cost-effectiveness and methodology.

The preferred combination for rapid tranquillisation at the two largest psychiatric centres in India (the National Institute of Mental Health and Neurosciences, Bangalore, and the Central Institute of Psychiatry, Ranchi) (combined monthly out-patient attendance of >9000) is haloperidol with lorazepam rather than haloperidol with promethazine. This is guided by the literature as well as existing practice (McAllister-Williams & Nicol Ferrier, 2002; Hughes & Kleespies, 2003). This combination is about 25% cheaper than the haloperidol–promethazine mix (CIMS, 2004). Since promethazine has both alpha-1 and dopaminergic antagonism its combination with haloperidol is more likely to produce hypotension and neuroleptic malignant syndrome in agitated patients, who are often dehydrated and have electrolyte imbalance. On the other hand lorazepam decreases the required dose of haloperidol. Hence we feel that the

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combination of haloperidol with promethazine for rapid tranquillisation may not be the most cost-effective or the most efficacious even when resources are poor.

Alexander *et al* used the Clinical Global Impression Scale to rate aggression and violence. We feel that use of more aggression-specific measures, such as the Overt Aggression Scale (Coccaro *et al*, 1991), which assesses different aspects of aggression and its severity, would have generated more specific results.

Alexander *et al* also showed that the combination injection produces sedation quicker than intramuscular lorazepam. However, this finding should be viewed with caution because the lorazepam group included more patients with mania, more patients with substance misuse or already on benzodiazepines (who could have developed tolerance to benzodiazepines) and more patients with marked or severe illness (which would necessitate a higher dose of medication to control aggression and violence). Together these factors might have contributed significantly to the results.

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Authors' reply: We thank Drs Ranjan and Chandra for their considered response to our article. Although we acknowledge variations in prescribing practice, we know of at least two other centres nearby (the Institute of Mental Health and the Government Hospital, Chennai) that use the haloperidol–promethazine combination for rapid tranquillisation; the monthly combined out-patient attendance of the three centres is also greater than 9000.

Our wider survey of drug formularies, including the source of Ranjan and Chandra, and local pharmacies reveals that the price of injectable haloperidol (5 mg/ampoule) ranges between Rs 4.00 and Rs 5.50; that of promethazine (50 mg/ampoule) between Rs 3.00 and Rs 7.00; and that of lorazepam (4 mg/ampoule) between Rs 7.00 and Rs 15.00. We therefore reiterate our contention that the haloperidol–promethazine mix is cheaper than (even reduced doses of) haloperidol and lorazepam.

We agree that the Overt Aggression Scale would have generated more specific results. However, the outcomes for this pragmatic trial were not chosen to generate specific results; they were chosen by the doctors and nurses of the emergency rooms to be of clinical utility. From the reaction we have already had to this study these outcomes do seem acceptable and welcome to others.

We acknowledge that there were nine more people with mania, six more misusing substances and five more already on benzodiazepines in the lorazepam arm than in the comparison arm. There is no indication, however, that the integrity of the randomisation procedure was compromised, as such chance imbalances could occur in the absence of stratification. It is unlikely that these imbalances account for the findings, as the difference in the numbers of people 'clinically improved' between the two interventions at 15, 30, 60 and 120 min were 31, 25, 20 and 14, respectively, and in numbers 'asleep' 40, 47, 35 and 14.

Although recommended by important review articles and guidelines, we have found only four randomised studies in which a total of 80 people received the combination of haloperidol and lorazepam (Arana *et al*, 1986; Battaglia *et al*, 1997; Bieniek *et al*, 1998; Subramaney *et al*, 1998). None of these studies reports useful data on time to tranquillisation/sleeping; most report scale-derived data that are difficult to interpret clinically. For such limited data to direct practice at the two largest psychiatric centres in India, as well as many other places, would seem imprudent. The effects of haloperidol plus promethazine, we would still suggest, are better proven than other prevalent approaches. Recent influential guidelines in the UK have noted this and the sister study (TREC Collaborative Group, 2003) to be the only large trials of high methodological quality in this area (National Collaborating Centre for Nursing and Supportive Care *et al*, 2004).

Certainly the study and others like it need to be repeated so that the evidence upon which we treat people at this vulnerable time is robust. Practice on lesser evidence is surely unethical.

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Limitations of rapid tranquillisation trial

In their excellent paper Alexander *et al* (2004) systematically conducted a comparison trial of intramuscular lorazepam and haloperidol–promethazine in violent or agitated patients. The authors utilised a prospective follow-up design and used proper diagnostic assessment measures, thus taking care of most of the

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