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Authors' reply: Dr Procopio draws attention to two main points. First, he raises the possibility that under-dosing might be the primary factor associated with the partial response to clozapine observed in our study population prior to the addition of sulpiride to their regimen. We are aware of such possibility, which might account for some of the beneficial effects described. However, we would like to stress our main claim which emphasised the role of the altered serotonin–dopamine receptor occupancy ratio which was achieved by the enhanced D_2 dopaminergic blockade of sulpiride (a selective D_2 antagonist) and could not have been attained (to a similar degree) with higher doses of clozapine (a relatively weak D_2 antagonist). Furthermore, all of our patients have shown an initial response to clozapine, which was later followed by a relatively long and steady non-responsive period. At the same time, some of our patients were unable to tolerate higher doses of clozapine because of troubling side-effects. Moreover, it is of note that clozapine-related seizures appear to be close-related, and high-dose therapy $\geqslant$600 mg/day) is associated with substantially increased risk than are doses of 300–600 mg/day (Devinsky *et al*, 1991). Furthermore, we would like to refer to a similar and substantial clinical improvement which was recently reported with the combination of clozapine and pimozide (Friedman *et al*, 1997) and clozapine–risperidone regimens (Henderson & Goff, 1996) in partial responders to clozapine. Both pimozide and risperidone are relatively potent D_2 blockers and in these cases the mean daily doses of clozapine were 425 and 479 mg, respectively, which are in the same range as in our study (403 mg/day). These studies examined the efficacy of the described combinations in patients who were maintained on clozapine treatment alone for longer periods (8–12 months) before adding either pimozide or risperidone. Hence, it seems that some patients with schizophrenia either partially responsive to clozapine or unable to tolerate higher doses could substantially benefit from enhancing the D_2 dopaminergic blockade.

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Amisulpride in schizophrenia

Sir: We read with interest the editorial by Thomas & Lewis (1998) on atypical antipsychotics, and value their review of these drugs which have significantly affected the management of schizophrenia. However, we were surprised to note the omission of amisulpride in their consideration of atypical antipsychotics, despite its being mentioned in their introduction. After extensive use in France, amisulpride has only recently become available in the UK and has been the focus of several papers in the *Journal* (Boyer *et al*, 1995; Loo *et al*, 1997; Speller *et al*, 1997).

Thomas & Lewis comment that the atypical antipsychotics have not been shown to benefit primary negative symptoms in schizophrenia, and certainly the majority of studies dealing with this issue have been subject to considerable confounding variables (such as simultaneous improvement in positive symptoms and extrapyramidal side-effects; King, 1998)

Amisulpride would appear to be one of the few antipsychotic drugs which has been studied with consideration of these pitfalls (Boyer *et al*, 1995; Loo *et al*, 1997) and the findings support a positive outcome with primary negative symptoms. Speller *et al* (1997) found no such improvement over the course of one year, but given that their sample had a median age of 63 years and duration of illness of 36 years, the lack of response was perhaps not surprising.

We would suggest that the positive results of the amisulpride studies merit further examination, given that negative symptomatology is for many patients the most debilitating aspect of their illness. Or could Euroscepticism be influencing our approach to the drug treatment of schizophrenia?

Boyer, P., Lecrubier, Y., Puech, A. J., et al (1995) Treatment of negative symptoms of schizophrenia with amisulpride. *British Journal of Psychiatry*, **166**, 68–72.

Loo, H., Poirier-Littre, M.-F., Theron, M., et al (1997) Amisulpride versus placebo in the medium-term treatment of the negative symptoms of schizophrenia. *British Journal of Psychiatry*, **170**, 18–22.

King, D. J. (1998) Atypical antipsychotics and the negative symptoms of schizophrenia. *Advances in Psychiatric Treatment*, **4**, 53–61.

Speller, J. C., Barnes, T. R. E., Curson, D. A., et al (1997) One-year, low-dose neuroleptic study of in-patients with chronic schizophrenia characterised by persistent negative symptoms. Amisulpride v. haloperidol. *British Journal of Psychiatry*, **171**, 564–568.

Thomas, C. S. & Lewis, S. (1998) Which atypical antipsychotic? *British Journal of Psychiatry*, **172**, 106–109.

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Systematic does not necessarily mean comprehensive

Sir: The recent review of brain abnormality in schizophrenia (Lawrie & Abukmeil, 1998) is described as systematic. The reviewers identified studies by a "computerised literature search from 1986 to June 1996 with Medline on CD-ROM using the search terms 'MRI' and 'schizophrenia' ". Journals were also hand-searched and reference lists scrutinised. There are important problems with this search. It is not enough simply to state that a CD-ROM system has been searched over a designated period. It should be made explicit exactly which disk issues were searched. Not to do so makes replication of the review impossible and causes the resulting product to stray from being systematic at all.

The search was systematic but not comprehensive. We replicated Lawrie & Abukmeil's electronic search on the January 1998 SilverPlatter edition of Medline, requesting that citations be retrieved only from between 1986 and June 1996; 187

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citations were identified. By expanding the search with one thesaurus term so it read: ((MRI or explode 'MAGNETIC-RESONANCE-IMAGING/all subheadings') and schizophrenia) 233 additional records were identified. Many of these would have been of considerable interest to the reviewers. We did not test the added value of other thesaurus terms such as 'NUCLEAR-MAGNETIC-RESONANCE/all subheadings'. By making the schizophrenia part of the search more sophisticated, using a published phrase for identifying Medline schizophrenia studies (Adams *et al*, 1998), 182 more records were identified. This subset has a high false positive rate but there are, quite clearly, citations of direct interest for a comprehensive MRI meta-analysis. When a similar exercise was undertaken on EMBASE an additional 1716 unique records were identified. Again, the false positive rate was high but there were studies of relevance to Lawrie & Abukmeil's review. We did not investigate other rich sources of data such as PsychLit and Biological Abstracts. It is unlikely that the hand-searching of journals and references would have picked up most of the studies.

In such reviews being comprehensive is desirable. Studies that are readily accessible by simple searches on Medline may well have systematically different results to those that are more difficult to find (Egger *et al*, 1997).

Adams, C. E., Duggan, L., Wahlbeck, K., *et al* (eds) (1998) *Schizophrenia Module of the Cochrane Database of Systematic Reviews* (updated 4 December 1997). Available in The Cochrane Library (CD-ROM), Issue 1. Oxford: Update Software.

Egger, M., Zellweger-Zahner, T., Schneider, M., *et al* (1997) Language bias in randomised controlled trials published in English and German. *Lancet*, **350**, 326–329.

Lawrie, S. M. & Abukmeil, S. S. (1998) Brain abnormality in schizophrenia. A systematic and quantitative review of volumetric magnetic resonance imaging studies. *British Journal of Psychiatry*, **172**, 110–120.

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What counts as clinical research?

Sir: Morlino *et al* (1997) report findings on the extent of basic research papers published that they regard as "at variance with the conclusions of Pincus *et al* (1993)". The difference might be related to how 'basic research' is defined. In our study, 'basic biological research' included animal studies and other research reports not involving clinical populations. Many of the papers Morlino *et al* included as "basic research topics such as neurochemistry, neuroanatomy and brain imaging" are likely to have involved clinical populations and probably would have been included in our category of 'clinical psychobiology'.

It is important to be clear in the use of such terms as 'clinical' and 'basic' research. The National Institute of Health's high-level committee to review issues and problems in clinical research spent a great deal of time and effort to develop a standard definition of clinical research (National Institutes of Health Director's Panel on Clinical Research, 1997). Their definition (which engendered some controversy) includes, in addition to epidemiological, behavioural and health services research studies, "patient oriented research" that is not only conducted with human subjects but also with "material of human origin . . . in which it is necessary to know the identity of the patients". Thus, 'basic' research would be limited to animal research and *in vitro* studies utilising human tissues that do not require dealing directly with patients. With these fairly broad criteria they found, overall, that 27% of National Institute of Health grants met the clinical research definition.

Morlino, M., Lisanti, F., Gogliettino, A., *et al* (1997) Publication trends of papers on schizophrenia. A 15-year analysis of three general psychiatric journals. *British Journal of Psychiatry*, **171**, 452–456.

National Institutes of Health Director's Panel on Clinical Research (1997) *Report to the Advisory Committee to the National Institutes of Health Director.* Bethesda, MD: NIH.

Pincus, H. A., Henderson, B., Blackwood, D., *et al* (1993) Trends in research in two general psychiatric journals in 1969–1990: research on research. *American Journal of Psychiatry*, **150**, 135–142.

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Rapid intravenous detoxification in heroin addiction

Sir: Despite its short follow-up period, the study by Seoane *et al* (1997) gives us two crucial pieces of information on the vexed question of accelerated detoxification from opioids. First, the degree of sedation in randomised groups yielded no difference in abstinence rates a month after the procedure. Second, the occurrence of serious side-effects was just under 5% in both the lightly and heavily sedated groups. These reactions included respiratory depression, bradycardia, pneumonia and fever of unknown origin.

Seoane *et al*'s assertion that the incidence of side-effects is lower than with 'conventional' detoxification is only supported by reference to another 'rapid' detoxification series with a complication rate of 5.8%. Traditional detoxification is believed to have a complication rate close to zero.

The prior use of methadone was not revealed. Despite being based on work done prior to 1994, there is no follow-up of data beyond four weeks. This is surprising considering the novelty and controversial nature of the treatment. A study of accelerated opioid detoxification under anaesthetic showed that 43% of patients who could be contacted had ceased their prescribed naltrexone and returned to daily heroin use at 18 months' follow-up (Rabinowitz *et al*, 1997).

Seoane, A., Carrasco, G., Cabré, L., *et al* (1997) Efficacy and safety of two new methods of rapid intravenous detoxification in heroin addicts previously treated without success. *British Journal of Psychiatry*, **171**, 340–345.

Rabinowitz, J., Cohen, H., Tarrasch, R., *et al* (1997) Compliance to naltrexone treatment after ultra-rapid opiate detoxification: an open label naturalistic study. *Drug and Alcohol Dependence*, **47**, 77–86.

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Moclobemide in social phobia

Sir: The claim made by Schneier *et al* (1998) that moclobemide is not indicated as a first-line therapy in social phobia should be challenged. Social phobia is a relatively common anxiety disorder, which rarely presents to psychiatrists even when there is marked impairment in occupational and social functioning (Weiller *et al*, 1996). Thus, a first-line therapy for social phobia should be effective, well tolerated and suitable for prescription within primary care.

Addressing the latter two issues, moclobemide has a simple dosing regime and is well tolerated; Schneier *et al* found eight-week drop-out rates were 24% on moclobemide *v.* 25% on placebo. Their most serious objection to the use of moclobemide

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