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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?

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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