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AUTHORS' REPLY: Apparently, some aspects of our study need clarification.

Each participating psychiatrist selected some outpatients with schizophrenia who were receiving stable neuroleptic medications, and who had predominantly negative symptoms. Thus selection was based on symptom severity; whether this reflects different syndromes of schizophrenia is still a matter of discussion, in which we do not want to take a position now. After selection, patients could decide to participate, and the positive and negative symptoms were rated with the SANS and BPRS. The average ratings showed that this selection procedure was satisfactory.

The single primary parameter of this trial was change in the total SANS score at endpoint. In the ritanserin group, a larger reduction was found in the total SANS score than in the placebo group (at endpoint $P=0.012$): the 95% confidence intervals were -15.0 to -5.5 in the ritanserin group, and -7.6 to 2.5 in the placebo group.

In our paper we cited a study in which no influence of ritanserin on liver enzymes was found. Therefore pharmacokinetic interactions between ritanserin and other neuroleptics are not likely, but cannot be ruled out. The measurement of plasma concentrations of the neuroleptics and ritanserin is necessary in future investigations.

In this trial, ritanserin reduced the SANS scores (i.e. reduced negative symptoms). Could this be explained by antidepressant or anti-Parkinsonian actions? Does ritanserin reduce all negative symptoms, or only some? Answering these questions was not the primary aim of our trial, and a trial with only 33 patients cannot give conclusive evidence. But the results obtained give indications for possible answers. We do not think that the ritanserin-induced effect of this study is mainly an anti-Parkinsonian effect, since the patients had a low EPS (Simpson–Angus) scores at baseline, and the small, random changes in this score was not correlated to the larger changes in the SANS score. An antidepressant effect of ritanserin cannot be ruled out.

There is no *a priori* reason that a drug with a new mode of action (such as ritanserin) fits into existing clinical categories. The only way to evaluate is to rate its effects on a large variety of symptoms. Having found an effect on the primary parameter (total SANS), we wanted to present the changes in the various SANS items (including the statistical evaluation) – we did not use the testing of the individual items to construct a primary effect. The criticism of 'multiple testing' is therefore not appropriate. Some negative symptoms were greatly reduced in the ritanserin group, and others very little. If this finding can be replicated, the clinical actions of ritanserin are more precisely defined. The question then raised is whether negative symptoms form a unitary syndrome.

To evaluate the clinical effects of ritanserin (or drugs with a similar mode of action), changes in a variety of symptoms in a large group of patients must be tested. The number of patients in our study was too small for such conclusions, but the listed symptoms give an impression of which symptoms could be especially relevant in future larger studies.

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Tardive dyskinesia as a risk factor for negative symptoms

SIR: Liddle *et al* (*BJP*, December 1993, **163,** 776–780) conclude that there is an association between the negative symptoms of schizophrenia, orofacial tardive dyskinesia (TD), and increasing age. Their conclusions may be unwarranted, because the group of schizophrenic patients studied was atypical, and the definition of TD did not require antipsychotic treatment.

The subjects were atypical because they were long-stay patients (length of stay was not stated) and thus likely to have more severe schizophrenia and, in particular, to have prominent negative symptoms. The effects of institutionalisation are not

accounted for. The excess of men, given that TD is commoner in women (Jeste & Caligiuri, 1993), and the somewhat high prevalence of trunk and limb TD among those aged 20–39 years, further suggest that the group studied were not 'typical' schizophrenic patients. Finally, it would be reassuring to know that steps were taken to exclude neurological co-morbidity.

Tardive dyskinesia is poorly defined, and similar movement disorders have been described in the pre-antipsychotic era, and in contemporary antipsychotic-naive schizophrenic patients (Owens *et al*, 1982). However, most authorities consider that antipsychotic exposure is necessary to allow a diagnosis of TD, and some diagnostic criteria (Schooler & Kane, 1982) require treatment for three months. By these criteria the 13 patients receiving no antipsychotics, and perhaps any patients receiving less than 100 mg chlorpromazine equivalents per day, should be excluded from the analysis. Antipsychotics suppress TD symptoms and, given the impressive maximum daily antipsychotic dosage of 4380 mg chlorpromazine equivalents, this may be a further confounding factor in the present study.

Finally, Liddle *et al*'s conclusions that "in the case of orofacial dyskinesia, the prevalence increased significantly with increasing age" and that "the prevalence of trunk and limb dyskinesia did not increase significantly with age" must be treated with caution. If their younger group of subjects had a more usual prevalence of trunk and limb TD, the latter conclusion would not have been reached, while the former conclusion must be tempered by the reservations already discussed. Furthermore, we are not provided with sex ratios for the age bands used; the apparent excess of TD in older patients may be because post-menopausal women were over-represented.

Only longitudinal studies which pay attention to diagnosis, sex, organic illness, hospitalisation, and type (i.e. typical or atypical), dosage and duration of treatment with antipsychotic drugs, will unravel the links, if any, between schizophrenia, its symptoms and treatments, and TD.

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SIR: Poverty of speech and flat affect will not differentiate between primary negative symptoms of the disease process and those secondary to drug-induced Parkinsonism (DIP), a potential confounding variable (Brown & White, 1991). Perhaps this is not important, since the hypothesis Liddle *et al* tested did not concern the association between negative symptoms and TD *per se*, but rather that the presence of negative symptoms brought forward the onset of TD. However, if secondary negative symptoms had a substantive confounding effect, then the differences between patients with and without negative symptoms may have been most evident among the older patients, in whom DIP is more common (Ayd, 1961).

In the three age groups (20–39 years, 40–59 years, and 60–89 years) (Table 2) there is said to be an increasing proportion with negative symptoms (56%, 64% and 69%, respectively). This increase is most evident in the group with orofacial dyskinesia, 60% of those less than 40 years old and 73% of those older than 40 years having negative symptoms. Respective figures for patients without orofacial dyskinesia are 55% and 52%. An alternative hypothesis is that orofacial dyskinesia may bring forward the onset of negative symptoms, and this is supported (although less convincingly). Thus, in all three age groups the proportion of the TD group with negative symptoms (60%, 76%, and 71%, respectively) was greater than in the non-TD group (55%, 50%, and 58%, respectively). This excess was most marked in the middle age group, reaching statistical significance ($\chi^2=5.4$, d.f.$=1$, $P<0.05$). In view of the importance of antipsychotic medication in the development of TD, it could be argued that these medications may also facilitate the development of the type II syndrome. This would not be surprising if similar processes were responsible for both TD and negative symptoms. Indeed, it has been suggested that such common pathology need not act on anatomically distinct sites (Brown & White, 1992). Although we are familiar with the many side-effects of dopamine-blocking drugs, including secondary negative symptoms, the notion that they may interact with the disease process and age to bring forward the onset of substantive negative symptoms must be cause for concern.

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