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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

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