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# Sulpiride in Negative Schizophrenia: A Placebo-controlled Double-blind Assessment

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Twenty-four chronic schizophrenic long-stay hospital patients were identified, who had not received neuroleptic drugs for 8–30 (average 8 months) and met or exceeded a minimum criterion of severity of negative symptoms. They were randomly allocated to either sulpiride 200 mg twice daily or matching placebo, on a double-blind basis for 12 weeks. The results showed that low-dose sulpiride was significantly better than placebo in relation to improvements in negative symptoms. The changes in social behaviour were complex and not obviously related to symptom improvement; exhibited abnormal behaviour, a major factor in preventing successful return to the community, consistently improved only on the active drug.

KEY WORDS—Chronic schizophrenia, negative symptoms, sulpiride.

## INTRODUCTION

The concept of negative symptoms as a psychopathologic process (Strauss *et al.*, 1974) has been a central theme of much of the current research in schizophrenia. The two-syndrome concept (Crow, 1980) has been further strengthened by recent work (Andreasen and Olsen, 1982; Carpenter *et al.*, 1988) and negative symptoms are now considered as being distinct from affective or dysphoric states that frequently occur in schizophrenic patients (Pogue-Geille and Harrow, 1984). The predominantly negative type of schizophrenia (type II) is characterized by prominent symptoms of deficit state, structural changes in the brain and a failure to respond to conventional neuroleptic treatment (Crow, 1985). Chronic apathy and anergia, rather than the more florid signs of mental disturbance, remain the major cause of long-term social disability among schizophrenic patients. The early studies reporting improvement over a wide range of schizophrenic symptoms as a result of treatments with various phenothiazines (Goldberg *et al.*, 1963; Cole, 1964) have not been borne out by subsequent clinical experience, and more recent work (Angrist *et al.*, 1980, Johnstone *et al.*, 1987) have only been able to demonstrate therapeutic benefit for positive symptoms.

Several lines of research indicate that dopamine $D_2$ receptor activation produces an increase in certain components of behaviour in rats, such as sniffing and compulsive biting or chewing, whereas $D_1$ receptors appear to be associated with grooming behaviour which is part of the normal behavioural repertoire in many rodents (Leysen, 1982). It is suggested that a selective $D_2$ receptor blockage may allow $D_1$ receptor activation and hence potentiation of more desirable or appropriate behaviour in rats. Laboratory evidence of the effect of sulpiride, which is a highly selective $D_2$ receptor antagonist (Jenner and Marsden, 1981), suggests that it may have a favourable effect of potentiating grooming behaviour, whilst inhibiting others such as sniffing and/or compulsive biting; a differential effect not seen with any of the conventional neuroleptics (Jenner *et al.*, 1985).

Early clinical reports drew attention to alerting, activating and antidepressant effects observed in some of the patients treated with medium to low doses of sulpiride. Thus, Elizur and Davidson (1975) found a beneficial effect on apathy, withdrawal and depression in 14 schizophrenic patients who had not responded to conventional neuroleptics. In another double-blind study comparing sulpiride and chlorpromazine during an 8-week treatment of acute schizophrenics, Toru *et al.*, (1972) found sulpiride to have beneficial effects on negative symptoms. More recently Harnryd *et al.* (1984) have reported that negative symptoms, as measured by subsets of Comprehensive Psychiatric

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Rating Scale (CPRS) (Asberg *et al.*, 1978) and Nurses' Observation Scale of Inpatient Evaluation (NOSIE) (Honigfeld and Klett, 1965), responded better to sulpiride than to chlorpromazine, although the positive symptoms showed no difference. In the United Kingdom, open follow-up studies of stable chronic schizophrenics with prominent negative symptoms (Soni and Freeman, 1984; Soni, 1985) have confirmed the alerting effects of sulpiride. More recently, in another study (Petit *et al.*, 1987), two doses of sulpiride (150 mg and 1200 mg daily) were compared on a double-blind basis in a group of chronic schizophrenics with predominantly negative symptoms; there was a significantly greater improvement of negative symptoms in the low-dose group, confirming the alerting effect of this drug.

However, there are no reliable or controlled studies in the literature on the effects of sulpiride on the negative symptoms in chronic stable schizophrenics whose only or main difficulties exist in the sphere of poor social functioning due to schizophrenic deterioration ('deficit state'). Our aim in this study has therefore been to investigate, under double-blind conditions, the effects of sulpiride on chronic schizophrenic patients whose illnesses were characterized by negative symptoms and social withdrawal, and to further assess which aspects of the clinical picture, if any, responded best.

## METHOD

The policy in Prestwich Hospital, Manchester, of prescribing long-term maintenance neuroleptics for only those patients who demonstrably required it, had resulted in maintenance drug treatment being discontinued in a number of the long-stay patients. Such patients, aged between 18 and 65, were re-examined for conformity to the DSM-III criteria (APA, 1980) for schizophrenia, and those who in addition scored 3 or more on the sum of the two-item 'poverty of speech' and 'flattening of affect' of the Manchester Scale (Krawiecka *et al.*, 1977) (modified to score flattening and incongruity separately) were selected for the study. Those who agreed to participate were allocated randomly to treatment with either sulpiride 200 mg b.d., or matching placebo for 12 weeks. Anti-Parkinson medication was to be prescribed only if required. Patients who required other neuroleptic treatment were withdrawn from the study and the reasons noted.

Each patient was clinically assessed on entry to the study (day 1), and subsequently at the end of weeks 1, 2, 4, 8 and 12. The Manchester Scale (MS) was employed to assess general psychopathology, including both negative and positive symptoms. The negative symptom subset consisted of items 4 (flattening of affect) and 9 (poverty of speech). The positive symptom subset of this scale included four items (delusions, hallucinations, incoherence/irrelevance of speech and incongruity of affect). The Scale for Assessment of Negative Symptoms (SANS) (Andreasen, 1981) was employed for measuring change in negative symptoms to supplement the above ratings. The items included in the subset of this scale for the purpose of analysis consisted of core items from the affective flattening or blunting section viz. items 1, 2, 3, 5, 7 and 10.

The Current Behaviour Schedule (CBS) (Johnstone *et al.*, 1985) subscales 'Social Behaviour' and 'Exhibited Abnormal Behaviour' were used to assess changes in social functions and abnormal behaviour. In addition, patients were assessed on the Extrapyramidal Symptom (EPS) Checklist (Simpson and Angus, 1970), the Abnormal Involuntary Movement Scale (AIMS) (NIMH, 1975) and a side-effects inventory with item to be recorded if spontaneously mentioned by the patient and/or if evident to the investigator.

## RESULTS

Twenty-four patients, aged between 51 and 64 years (mean 59), satisfying the entry criteria, gave their consent to the study. They had been continuously in hospital for 12–49 years (mean 29) and had been taken off their maintenance medication for 8–24 months (mean 16). Twelve patients were allocated to sulpiride 200 mg twice daily, and 12 to matching placebo twice daily. There were no statistically significant differences (T-tests, two-tailed) between the two treatment groups in respect of age, sex and duration of illness or hospitalization (Table 1).

Six patients failed to complete the 12-week treatment. Three patients on placebo deteriorated with increasing self-neglect, social withdrawal and bizarre behaviour. Two patients on sulpiride who developed increasing agitation, restlessness and aggressive behaviour but no positive psychotic features had to be withdrawn from the study at 4 and 8 weeks respectively; another patient on sulpiride developed nausea, vomiting and increased sweating, and was withdrawn after 3 weeks.

The total scores for the MS negative symptom subset, the MS positive symptom subset, the SANS subscale and the CBS social behaviour and

Table 1. Demographic and clinical data

| | Placebo | Sulpiride |
|---|---|---|
| Sample size (*N*) | 12 | 12 |
| Sex (male/female) | 9/3 | 5/7 |
| Age (years) | 58·0 ± 3·7 | 59·5 ± 3·8 |
| Duration of illness (years) | 33·7 ± 6·6 | 27·0 ± 10·9 |
| Duration of hospitalization (years) | 36·3 ± 6·6 | 34·7 ± 6·2 |
| Neuroleptic-free period (months) | 13·4 ± 4·8 | 15·0 ± 6·0 |

exhibited abnormal behaviour subscales are shown as bar charts of the means and standard errors of the changes from baseline (day 1) to each subsequent assessment (day 1 minus subsequent score) in Figure 1. The pretreatment mean scores and standard errors, as well as two-tailed T-test significance values of 0·05 or less, are also indicated. It should be noted that, in contradistinction to other rating instruments, a negative change in the CBS subscales denotes improvement. Detailed analyses of the remaining items of the MS and CBS scales were not carried out since the scores remained virtually unchanged throughout.

Patients on sulpiride improved to a greater extent than those on placebo in terms of the MS negative symptom score, the difference being statistically significant at weeks 1, 4, 8 and 12. The changes in the placebo group were small and non-significant by comparison with the entry scores ($P = 0{\cdot}05$–$0{\cdot}0001$, paired T-test, two-tailed). The results on the SANS subscale also favoured the sulpiride patients, although significant differences were less marked, occurring only at weeks 4 and 8. The MS positive symptom scores did not change significantly; at 1 week a slight improvement in the placebo group and a similar deterioration in the sulpiride groups produced a statistically significant difference in favour of the former.

The CBS social behaviour scale failed to show a consistent pattern of changes, non-significant improvements occurring in both treatment groups at 2 and 4 weeks, and significant improvements on placebo at weeks 8 and 12 ($P = 0{\cdot}04$ and $0{\cdot}02$), the difference between the treatments being marginally significant in favour of placebo at week 8. In contrast, the CBS exhibited abnormal behaviour scale showed a consistent pattern of greater improvements on active drug on the four occasions from week 2 onwards (no change occurred in either group at week 1); the difference between the treatments being marginally significant in favour of sulpiride at the final assessment (week 12).

The EPS scores were virtually zero throughout. Five patients had definite abnormal involuntary movements on entry to the study (total AIMS body movements score range 2–11); four of these were allocated active drug, of whom three improved and one remained unchanged, as did the only patient allocated placebo. Other side-effects were trivial on both placebo and sulpiride.

## DISCUSSION

The question of whether conventional neuroleptics benefit the negative symptoms of schizophrenia remains controversial almost 30 years after the original NIMH report claimed that they were beneficial (Andreasen, 1985; Goldberg, 1985). Much of the difficulty in deciding the issue arises out of the problem of agreeing on what constitutes negative symptoms, as well as of having a precise operational definition of them. Studies which have employed more inclusive and broader criteria have tended to find more favourable results for drug treatment than those using a narrower range of symptoms more precisely defined. We chose the latter strategy in this trial, since sulpiride has been differentiated from conventional neuroleptics partly as a result of clinical experience of its beneficial effect on negative schizophrenia, and a stringent test of this claim was clearly required. Accordingly we chose the measure used in the original study (Johnstone *et al.*, 1985), which challenged the findings of the NIMH with regard to negative symptoms, viz, the sum of the scores of the two items of the Krawiecka scale for chronic schizophrenia, 'poverty of speech' and 'flattening of affect'.

Whilst considering these to be the core symptoms of what may turn out to be an aetiologically distinct category of schizophrenic illness, in order that the results be of relevance to patient management as well as of research interest, the patients were also assessed on a wide range of psychopathological, behavioural and social measures on the SANS and CBS. The SANS subscale assessed the core symptoms of 'affective flattening' and 'poverty of speech' in more detail than the MS, and produced a broadly similar result, confirming the greater improvement on active drug.

As expected from the selection criteria, the MS positive symptom scores were low, averaging about 20 per cent of the maximum possible; there was no consistent change in either drug or placebo

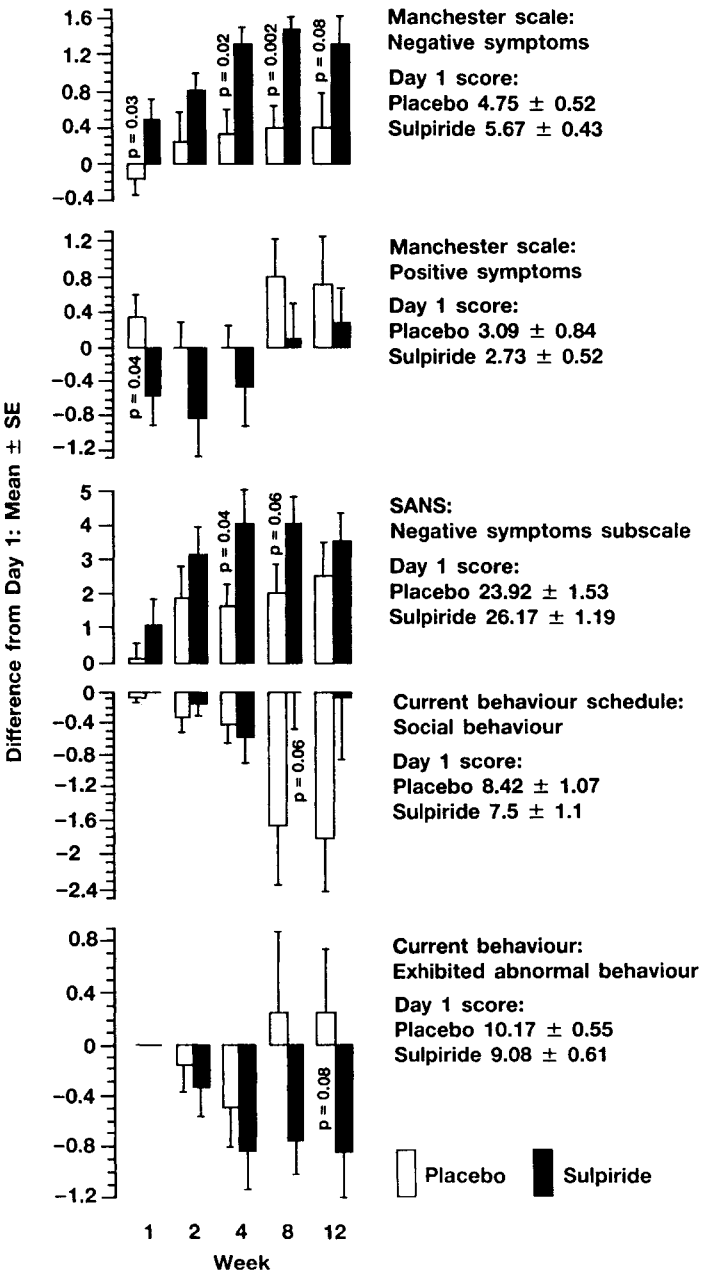


Figure 1.

group, and in particular no evidence of activation of symptoms was found after 12 weeks treatment on low-dose sulpiride. A drawback of severity as a criterion for selection is that, even if there is no actual treatment effect, random fluctuations in individual scores will produce an apparent tendency to improve (regression to the mean), at least in the short term; hence between-group comparisons are likely to be more informative than within-group changes with respect to the measures of negative schizophrenia. Clearly this should not have affected the MS positive symptom scores, and it is

Table 2. Scores on clinical rating scales

| | | Baseline | Week 1 | Week 2 | Week 4 | Week 8 | Week 12 |
|---|---|---|---|---|---|---|---|
| Manchester Scale (MS) | P | 4·8 ± 1·8 | 4·9 ± 1·8 | 4·5 ± 1·5 | 4·4 ± 1·7 | 4·1 ± 1·4 | 4·1 ± 1·2 |
| (negative subset) | A | 5·7 ± 1·5 | 5·2 ± 1·6 | 4·8 ± 1·5 | 4·2 ± 1·1 | 4·0 ± 1·4 | 3·8 ± 1·7 |
| Scale for Assessment of Negative | P | 23·9 ± 5·3 | 23·8 ± 4·3 | 22·0 ± 2·9 | 22·3 ± 4·8 | 20·7 ± 4·9 | 18·7 ± 1·5 |
| Symptoms (SANS) | A | 26·2 ± 4·1 | 25·1 ± 3·6 | 23·0 ± 3·7 | 21·3 ± 3·6 | 20·8 ± 3·4 | 21·6 ± 4·4 |
| Current Behaviour Schedule (CBS) | P | 8·4 ± 3·8 | 8·5 ± 3·7 | 8·8 ± 3·7 | 8·8 ± 3·4 | 10·6 ± 3·0 | 11·6 ± 3·3 |
| (social behaviour) | A | 7·5 ± 3·8 | 7·5 ± 3·8 | 7·7 ± 3·8 | 8·8 ± 3·0 | 7·5 ± 3·6 | 8·7 ± 2·5 |
| Current Behaviour Schedule (CBS) | P | 10·2 ± 1·9 | 10·2 ± 1·9 | 10·3 ± 1·9 | 10·7 ± 1·2 | 9·8 ± 2·3 | 10·5 ± 1·9 |
| (exhibited abnormal behaviour) | A | 9·1 ± 2·1 | 9·1 ± 2·1 | 9·4 ± 2·5 | 9·8 ± 2·8 | 9·9 ± 1·8 | 10·0 ± 1·8 |
| Manchester Scale (MS) | P | 3·1 ± 2·8 | 2·7 ± 2·5 | 3·1 ± 2·5 | 3·1 ± 3·2 | 2·3 ± 2·1 | 2·5 ± 2·3 |
| (positive subset) | A | 2·7 ± 1·7 | 3·3 ± 1·9 | 3·6 ± 1·4 | 3·6 ± 1·4 | 2·6 ± 1·3 | 2·5 ± 1·4 |

All figures are mean ± standard deviation. P = placebo. A = active drug.

possible that the placebo effect would have diminished in the longer term, leaving a small but significant benefit for patients on active treatment. As with Breier *et al.*,'s study of oral fluphenazine, we found no correlation between the individual changes in positive and negative symptoms induced in each treatment group.

The CBS social behaviour scale showed more complex changes, which were not correlated with the changes in either positive or negative symptoms. This underlines the difficulty of defining improvement in terms of psychotic symptoms alone. The improvement of the social behaviour score on placebo at weeks 8 and 12 was related mainly to improvement in two patients, but the Krawiecka and SANS scores remained unchanged in one patient and improved slightly in the other at these times. However, the exhibited abnormal behaviour subscale of the CBS improved consistently only in the patients on the active drug. This scale includes items such as posturing/mannerisms, laughing or muttering to oneself and incoherence, which are likely to have a major influence on successful reintegration into the community.

The study thus provides some evidence of a beneficial effect of sulpiride on negative symptoms and socially detrimental abnormal behaviours in chronic schizophrenic patients, whilst highlighting some of the uncertainties in both assessment and interpretation in this field. Whether the benefit would be maintained in the longer term remains a question for further research.

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