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SULPIRIDE AND PLACEBO IN DEPRESSED ELDERLY OUTPATIENTS: A DOUBLE-BLIND STUDY

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SUMMARY

In a controlled double-blind study, sulpiride 100–200 mg daily or placebo was administered over a five-month period to 22 and 24 depressive elderly outpatients. The majority of the patinets in both groups were diagnosed as suffering from relatively mild degrees of depression, i.e. from dysthymic disorder (chronic depression) or atypical depression. According to the Hamilton Rating Scale for Depression, the average symptomatology decreased from 19·7 to 15·7 points in the sulpiride group and from 22·8 to 17·0 points in the placebo group. The scores of three patients in the sulpiride group and those of four patients in the placebo group decreased by 50% or more. The corresponding figures for a decrease of 25–49% were six and nine, respectively. The effect of sulpiride on depressive symptoms did not differ from the effect of placebo. The results showed that sulpiride in small doses had no antidepressant effects on elderly patients suffering from relatively mild degrees of depression, i.e. from dysthymic disorder (chronic depression) or atypical depression.

KEY WORDS—Sulpiride, substituted benzamides, depression, aged.

INTRODUCTION

Sulpiride is an atypical neuroleptic drug that belongs to the substituted benzamides. Sulpiride possesses antischizophrenic and maybe also antidepressive properties in man. Clinical studies have shown that sulpiride reduces delusions, hallucinations and states of confusion (Bratfors and Haug, 1979; Memo *et al.*, 1981). Chronic schizophrenic patients have become more interested in their surroundings and more open to contact (Blanco *et al.*, 1972; Eckmann, 1974; Elizur and Davidson, 1975; Edwards *et al.*, 1980; Härnryd *et al.*, 1984; Munk-Andersen *et al.*, 1984). Whereas the antipsychotic property of sulpiride in schizophrenic patients is well established, its use as an antidepressant drug is less convincingly documented. There is some clinical evidence that sulpiride given in low dosages might be an appropriate treatment in slightly depressed middle-aged patients (Burchard *et al.*, 1972; van Wyk and Marais, 1973; Niskanen *et al.*, 1975; Muzio *et al.*, 1975; Salminen *et al.*, 1980; Aylward *et al.*, 1981; Benkert and Holsboer, 1984), and also in depressed elderly (Müller, 1975; Waldmann, 1976).

The few laboratory studies of the effect of sulpiride in animal models of depression have indicated a neuroleptic profile of the drug but given only suggestions about a potential antidepressant activity (Vaccheri *et al.*, 1984).

Sulpiride's side-effects include extrapyramidal reactions, increased restlessness and sleep disturbances (Burchard *et al.*, 1972). Sedative and anticholinergic side-effects are rare (Niskanen *et al.*, 1975). One of sulpiride's side-effects, especially in higher doses, is the increase of serum prolactin causing amenorrhea–galactorrhea in women (Wandereycken, 1984).

The evidence about the effects of sulpiride on depression is not extensive, and there exist no controlled studies about its efficacy in depressed elderly. While depression is fairly common among the elderly, we decided to assess the

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effects of sulpiride on depression among elderly depressed outpatients.

MATERIALS AND METHODS

The material was collected from persons aged 65 years or over who on 1 November 1984 lived in either the municipality of Lempäälä or Vesilahti in southern Finland, and who received home nursing or home help or both ($N = 419$). In the first phase, depressive symptoms among this population were screened between 1 November 1984 and 31 January 1985 by postal questionnaires, which included the Zung Self-Rating Depression Scale (ZSDS) (Zung, 1965). Four men and four women moved to nursing homes, and three men and two women died before data collection. They were excluded from the material. One hundred and four (79%) men and 246 (90%) women, altogether 350 (86%) persons, returned the questionnaire.

In the second phase, the patients and clients scoring at least 45 raw sumpoints on the Zung scale were interviewed and investigated by a primary health care physician skilled in diagnosing depression among the elderly. The interviews included a semistructured interview based on the Hamilton Rating Scale for Depression (HRSD) (Hamilton, 1960) and a semistructured interview used in diagnosing depressive disorder according to the DSM III classification (American Psychiatric Association, 1980).

A total of 40 men and 93 women scored 45 sumpoints or more on the Zung scale. Two men and five women did not want to participate in the clinical examination, and we failed to contact three women. Thus, 38 men and 85 women were investigated. Depression was diagnosed in 26 men and 62 women, or in 26% of the patients and clients returning the questionnaire. The procedure and the results of this prevalence study have been described in detail elsewhere (Kivelä *et al.*, 1986).

A double-blind trial technique was used in the clinical pharmacological trial. Patients were randomly divided into two groups: one group received sulpiride (Suprium®, Orion, Finland) and the other placebo. The code was known only to the drug manufacturer. Demented, severely agitated or psychotic patients were excluded, as were those who had bipolar manic depressive disorder, breast cancer or liver, kidney or blood disorders. All subjects who participated in the trial were physically impaired volunteers. Drugs that the patient had been receiving for somatic diseases were continued. Home nursing and home help were continued as earlier. Supportive psychotherapy by the general practitioner was part of every patient's treatment.

The trial started on 10 December 1984. The patients were treated with sulpiride or placebo in randomised order for five months. The initial dose of sulpiride was 100 mg daily in one dose in the morning. After three months, the dosage was increased to 200 mg daily in one dose in the morning. One active tablet contained 100 mg sulpiride. The placebo was identical as regards the composition of inert constituents. Two participants did not want to take two tablets and remained on one tablet during the whole period. One of them belonged to the sulpiride group and one to the placebo group.

The patients were assessed before initiation of the treatment and three weeks, six weeks, three months and five months later. The last two assessments were made in order to detect the persistence of the possible effects. The assessments were based on clinical interviews and ratings by the same general practitioner who carried out the initial investigations. The status of the patients was scored in the HRSD consisting of 22 variables (range 0–65 sumpoints) (Hamilton, 1960). Furthermore, the general practitioner assessed the presence or absence of depressive disorder according to the DSM III classification.

In addition to the total HRSD a subscale consisting of 11 items was used in the analysis. The items of the subscale were: depressed mood, suicidal ideas, difficulties to get sleep, difficulties to sleep, lack of interest in activities and hobbies, psychomotor retardation, psychic anxiety, somatic anxiety, gastrointestinal symptoms, general somatic symptoms and hypochondriasis (range 0–36 sumpoints).

At the beginning of the trial 66 depressed patients participated. During the study 20 patients dropped out: 46 patients continued to the end of the trial. When the codes were opened at the end of the trial, it was found that 22 patients had been in the sulpiride treatment group and 24 in the placebo group (Table 1). The groups did not differ with respect to age, class and duration of present depression.

In analysing the results, the points on the HRSD and the HRSD subscale were individually

Table 1. Description of the patients in different treatment groups

	Treatment group	
	Sulpiride	Placebo
Age (yr)		
Mean ± SD	76·8 ± 5·1	74·5 ± 5·9
Range	69–86	65–84
Sex (*N*)		
Men	7	7
Women	15	17
Total	22	24
Detection of depression (*N*)		
Before screening	2	9
During screening	20	15
Total	22	24
Class of depression (*N*)		
Major depression	1	0
Melancholia	1	3
Dysthymic disorder (chronic depression)	13	13
Cyclothymic disorder	0	0
Atypical depression	7	8
Total	22	24
Duration of present depression (*N*)		
Less than 1 yr	5	4
1–2 yr	1	1
More than 2 yr	16	19
Total	22	24

computed for every participant. The significance of the difference between the means in a transversal design was tested by the Mann–Whitney U-test. The two-tailed *t*-test, the Friedman analysis and Anova II were used in testing the significance of the difference between the individual means in a longitudinal design. The percentage decrease in the HRSD scores between the beginning, the third week and the fifth month of treatment was also computed for each individual patient.

RESULTS

Scores on the Hamilton Rating Scale for Depression

The total HRSD score before the treatment varied from 11 to 26 in the sulpiride group and from 14 to 32 in the placebo group. The mean score tended to be higher in the placebo group, but no statistically significant difference was found ($p > 0{\cdot}05$) (Fig. 1).

In the sulpiride group, statistically significant differences were found between the mean score before the treatment and the mean assessed three months later ($p < 0{\cdot}05$) and between the mean before the treatment and the mean assessed five months later ($p < 0{\cdot}05$). ANOVA II also showed a significant decrease in the mean points during the whole period of the trial ($p < 0{\cdot}01$).

In the placebo group, statistically significant differences were found between the mean before the treatment and the mean three weeks ($p < 0{\cdot}01$), six weeks ($p < 0{\cdot}01$), three months ($p < 0{\cdot}01$) and five months ($p < 0{\cdot}01$) later. Here again, ANOVA II showed a significant decrease in the mean points during the whole period ($p < 0{\cdot}001$).

Among the population receiving sulpiride, a steady decrease was found in the mean score of the Hamilton subscale until the end of the trial. Measured by the two-tailed *t*-test, the difference between the first and the last measurement was not significant ($p > 0{\cdot}05$), but ANOVA II showed the decrease to be significant ($p < 0{\cdot}05$).

In the placebo group, the *t*-test showed a significant difference between the mean score on the HRSD subscale measured before the treatment and the mean measured three weeks ($p < 0{\cdot}05$), six weeks ($p < 0{\cdot}01$), three months ($p < 0{\cdot}01$) or five months ($p < 0{\cdot}01$) later. Also ANOVA II revealed a significant decrease in the mean points on the subscale ($p < 0{\cdot}001$).

Response rates

Six patients in the sulpiride group and nine patients in the placebo group could not be classified as having a depressive syndrome at the end of the trial.

After the first three-week period, a decrease of 25% or more in the HRSD scores was noticed among only four patients in the sulpiride group but among 13 in the placebo group (Table 2). Also after the treatment period of five months more subjects in the placebo group than in the sulpiride group had significantly decreased scores on the HRSD.

Reasons for discontinuation and adverse effects

Altogether 13 patients in the sulpiride group and seven patients in the placebo group dropped

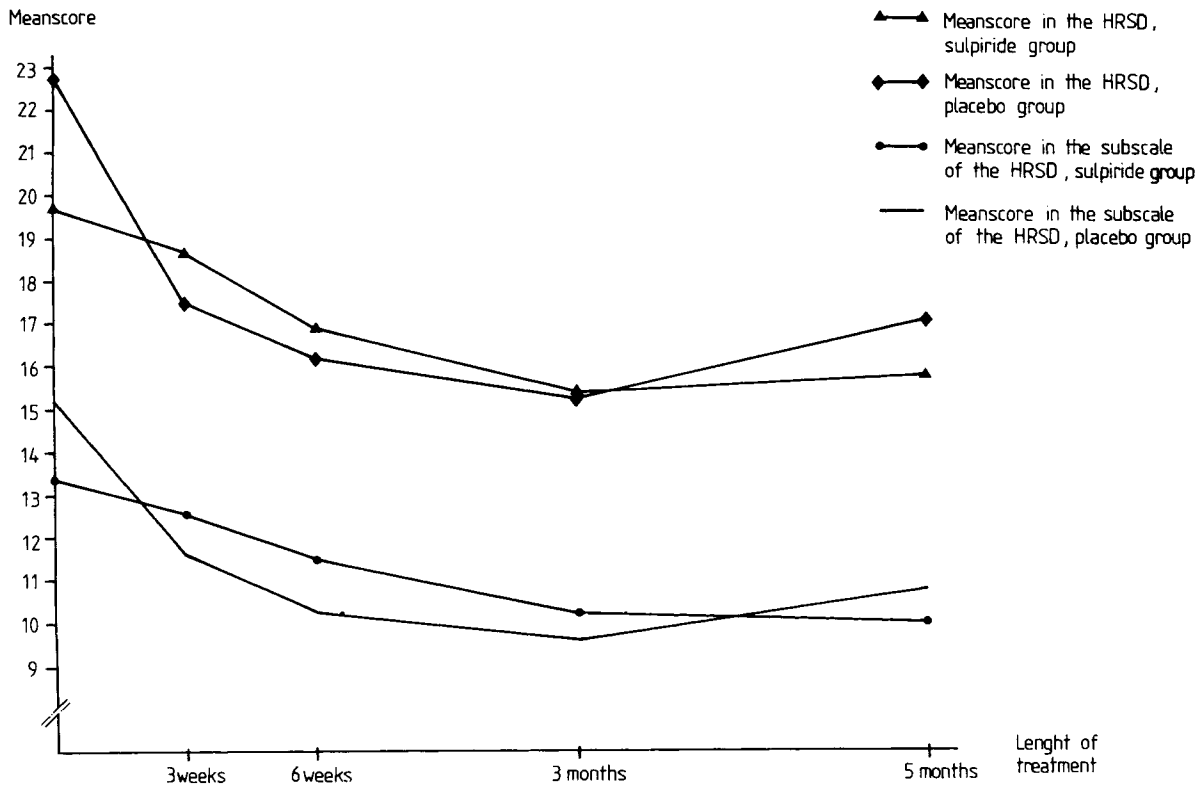

Fig. 1. Starting values and changes in the mean scores on the HRSD and the subscale of the HRSD in different treatment groups

Table 2. Number of patients in different treatment groups by change in the Hamilton scores

	Sulpiride *N*	Placebo *N*
Change between start and 3 weeks		
Decrease 50% or over	0	2
Decrease 25–49%	4	11
Decrease 1–24%	8	6
No change	1	1
Increase	9	4
Total	22	24
Change between start and 5 months		
Decrease 50% or over	3	4
Decrease 25–49%	6	9
Decrease 1–24%	7	7
No change	2	2
Increase	4	2
Total	22	24

out during the study. The main reasons for discontinuing the medication were unwillingness to take tablets or to visit the health centre, admission to another hospital and reported side-effects. The reported side-effects that led to discontinuation in the sulpiride group were confusion and ulcer in oral mucosa, and in the placebo group vomitus and tiredness. The mental status of the confused patient improved after ceasing the treatment. The confusion was most probably provoked by sulpiride. No other adverse effects were noticed.

Altogether seven patients in the sulpiride group and five in the placebo group reported some side-effect. In addition to those mentioned above in the sulpiride group, they mainly included tiredness and weakness. Similar side-effects were also reported by the placebo group.

DICUSSION

The home nursing or home help personnel made

regular visits to the patients' homes and it was possible to check whether the medication was taken regularly. Irregularity was reported only in relatively few cases.

A double-blind trial technique was used, and the patients were randomly divided into sulpiride and placebo groups. Earlier studies have used either other control groups than placebo or even an open-study model. The difference between the method of this study and the methods of earlier studies in this respect may be one reason for the differences between the results.

The majority of the participants in this study suffered from dysthymic disorder (chronic depression) or atypical depression and only a few cases of major depression were included. Due to the small number of cases, effects of sulpiride were not analysed separately on different classes of depression. This differs from earlier studies, the materials of which have mainly consisted of persons suffering from major depression. Another difference is age: the material of this study consisted of elderly, disabled persons. These facts may partly explain the differences between the results of this study and earlier studies. The results of this study are relevant as to the effects of sulpiride on depressive symptoms and depression of disabled elderly persons, who suffer from relatively mild degrees of depression.

The decrease in scores was evident among both the sulpiride and the placebo group. The response rates were modest among both groups: every third responded well. Because detecting and treating depression among the elderly decreased the occurrence of depressive symptoms, we may also conclude that diagnosing depression and supporting depressive elderly gives more positive than negative results and, therefore, it is worth while.

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