HUMAN PSYCHOPHARMACOLOGY, VOL. 10, 263–271 (1995)

A Multicentre, Double-Blind, Clomipramine-Controlled Efficacy and Safety Study of Org 3770

H. RICHOU[1]*, P. RUIMY[2], J. CHARBAUT[3], J. P. DELISLE[4], H. BRUNNER[5], M. PATRIS[6] and M. ZIVKOV[7]

[1]*Institut National Marcel Rivière, La Verrière, 78 320 Le Mesnil Saint Denis, France;* [2]*Maison de Santé Spécialisée du Roggenberg, 68130 Altkirch, France;* [3]*Centre Psychiatrique Pierre Engels, Belfort, 90800 Bavilliers, France;* [4]*Centre Hospitalier Spécialisé, 56 Avenue de Général Sarail, 5100 Chalons-sur Marne, France;* [5]*Centre Hospitalier Spécialisé, 67170 Brumath, France;* [6]*Clinique Psychiatrique, Hospices Civils, 67000 Strasbourg, France;* [7]*Medical Services Department, NV Organon, Oss, The Netherlands*

The efficacy and tolerability of the new antidepressant Org 3770 were evaluated in a multicentre, double-blind, clomipramine-controlled trial. In total, 174 patients (126 women and 48 men), aged 18–75 years, who were suffering from a moderate or severe major depressive episode, were randomly assigned to 6 weeks of treatment with either Org 3770, 20–80 mg/day, or clomipramine, 50–200 mg/day. All patients were hospitalized at the time of the trial. Depressive symptoms, assessed by 21-item HPRSD, MADRS, BPRS and GAS, improved significantly in both groups of patients after 6 weeks of treatment. Org 3770 was comparable to clomipramine with respect to improvements assessed by all the primary efficacy variables, both in moderately and severely depressed patients. Adverse clinical experiences, such as dry mouth, constipation, tremor, vertigo/dizziness, faintness on rising, and nausea, were reported by fewer patients in the Org 3770-treated group than in the clomipramine-treated group. These differences were particularly pronounced during the first 3 weeks of treatment. With respect to tremor, the difference between the two groups was statistically significant ($p_{2\text{-sided}} = 0{\cdot}03$) after both 3 and 6 weeks of treatment. This study shows that Org 3770 is as effective as clomipramine in treating moderate or severe depression, while being better tolerated.

KEY WORDS—antidepressant; Org 3770; clomipramine; depression

INTRODUCTION

Org 3770 is a new antidepressant, a member of the chemical class of piperazinoazepines, not related to any known class of psychotropic drugs. Its structure lacks the basic side-chain which is considered to be responsible for the anticholinergic activity of tricyclic antidepressants. Org 3770 has a unique pharmacological profile. Blockade of presynaptic α_2-adrenoreceptors with Org 3770 enhances noradrenergic transmission. The consequent α_1-receptor-mediated enhancement of serotonin (5-hydroxytryptamine; 5-HT) cell firing and direct blockade of inhibitory α_2 heteroreceptors located on 5-HT terminals cause an increase in extracellular 5-HT. The effect of released 5-HT is exerted only via 5-HT_1 receptors, as 5-HT_2 and 5-HT_3 receptors are blocked directly by Org 3770 (Clement *et al.*, 1992; Nickolson *et al.*, 1993; De Boer *et al.*, 1994). This dual mechanism of action on both neurotransmitter systems is thought to contribute to the antidepressant activity of Org 3770. Within the therapeutic dose range, Org 3770 follows linear pharmacokinetics, and its elimination half-life of 20–40 h justifies both once- and twice-daily dosing (Data on File).

The efficacy and safety of Org 3770 in the treatment of major depressive episodes is well documented in both hospitalized (van Moffaert *et al.*, in press; Zivkov and de Jongh, in press) and out patients (Smith *et al.*, 1990; Claghorn, in press).

Clomipramine is a tricyclic antidepressant with established efficacy in the treatment of major depression (Pecknold *et al.*, 1976; Dudley *et al.*, 1980; Lemoine *et al.*, 1981; Drago *et al.*, 1983; Kornhaber and Horwitz, 1984; Kielholtz, 1986; Moron *et al.*, 1988; Trimble, 1990). It is a preferential inhibitor of 5-HT uptake (Trimble, 1990), and affinity for central dopamine-D_2, histamine H_1 and α_1-adrenergic receptors has been shown in receptor-binding studies (McTavish

*Author to whom correspondence should be addressed.

CCC 0885–6222/95/040263–09

and Benfield, 1990). Recently, in hospitalized, depressed patients, clomipramine has been found to be more effective (in the reduction of depression and associated anxiety and sleep disturbances) but less well tolerated than the selective 5-HT reuptake inhibitors citalopram and paroxetine (DUAG, 1986, 1990), and the reversible monoamine oxidase inhibitor moclobemide (DUAG, 1993).

This study aimed to evaluate the efficacy and safety of Org 3770 in the treatment of major depression in hospitalized patients in a double-blind comparison with clomipramine, a tricyclic antidepressant of established efficacy.

PATIENTS AND METHODS

Study population

After obtaining written consent, 174 hospitalized patients, aged 18–75 years from seven psychiatric centres in France, entered the study. All patients had a diagnosis of major depressive episodes according to DSM III (APA, 1980) and Research Diagnostic Criteria (Spitzer *et al.*, 1978). At baseline, all patients scored $\geqslant 18$ on the 21-item Hamilton Psychiatric Rating Scale for Depression (HPRSD; Hamilton, 1967) and the duration of the present episode was between 14 days and 6 months. Patients were excluded from the study if they had had more than six depressive episodes requiring hospitalization in the past, or had had a more than 25 per cent decrease in total HPRSD score during the placebo washout period, or a history of schizophrenia or other psychoses, atypical depression, adjustment disorder, drug or alcohol abuse, drug overdose in the previous 4 months and/or active suicidal tendencies. Patients with clinically relevant renal, hepatic, cardiovascular or cerebrovascular diseases, prostatic hypertrophy, narrow angle glaucoma, unstable diabetes or seizure disorder were also excluded. At baseline, the patients could have a maximum of three abnormal laboratory variables, and no clinically relevant ECG abnormalities.

None of the patients had been treated with ECT in the previous 3 months, nor with an adequate dose of antidepressant in the month preceding the trial. Concomitant use of other psychotropic medication was prohibited, with the exception of chloral hydrate ($\leqslant 3$ g/day) or short-acting benzodiazepines for night-time sedation, the latter during the first 14 days of the study only. Women of child-bearing age were to be adequately protected against pregnancy, while mothers who were breast-feeding or within 6 months postpartum were excluded from the trial.

Study design

Eligible patients were withdrawn from their current psychotropic medication and underwent a placebo washout period for 3–7 days. Thereafter, they were randomly assigned to twice-daily, double-blind treatment with identical-looking capsules of either Org 3770 or clomipramine. The starting doses were 20 mg/day of Org 3770 or 50 mg/day of clomipramine, and these were titrated individually during two subsequent weeks up to a maximum of 60 mg/day for Org 3770 or 150 mg/day for clomipramine. During the last 3 weeks of the study, the daily dose could be further increased up to a maximum of 80 mg/day for Org 3770 or 200 mg/day for clomipramine.

Assessment instruments

The patients were assessed for severity of depressive symptoms at baseline, and after 2, 4 and 6 weeks of treatment, using the 21-item HPRSD, the Montgomery Asberg Depression Rating Scale (MADRS; Montgomery and Åsberg, 1979), the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham, 1962) and the Global Assessment Scale (GAS; Endicott *et al.*, 1976).

All patients underwent a clinical examination before starting on trial medication. Vital signs (heart rate, blood pressure, body weight and body temperature) were measured at screening, at baseline and every week throughout the study. In addition, an ECG was recorded before and after the active treatment period, while laboratory variables (haematology, serum biochemistry and urinalysis) were measured before treatment and after 3 and 6 weeks of treatment. Patients were asked about the presence of adverse clinical experiences after each week of treatment.

Statistical analysis

For the 21-item HPRSD (total score and factors) and MADRS, a per-protocol analysis was performed on all scheduled assessments. At endpoint, an intention-to-treat analysis was performed, thus including all the patients who received at least one dose of study medication

and had at least one post-baseline efficacy assessment.

Analysis of variance (ANOVA) was performed on the change from baseline, and treatments were compared for each scheduled visit and endpoint. A per-protocol analysis was performed on total scores of the BPRS (at baseline and on day 42) and the GAS (at baseline and on days 7, 14, 21, 28, 35 and 42). The frequencies of adverse clinical experiences were tested pairwise separately by means of the exact Fisher's test for days 7, 14, 21, 28, 35 and 42. All patients contributed to this analysis as far as data were available.

RESULTS

Baseline characteristics

Table 1 gives baseline characteristics for all patients entering the study. Of the 174 eligible patients, 87 were randomly allocated to treatment with Org 3770 and 87 to treatment with clomipramine. The treatment groups were well matched with respect of sex, age and baseline 21-item HPRSD, MADRS, BPRS and GAS scores. The groups were equally well matched for the percentages of patients assessed as being moderately or severely depressed, age of onset of depressive symptoms, age at first hospitalization, and the duration of the present depressive episode.

Doses

The investigators were able to titrate, in a double-blind fashion, the medication for individual patients in order to optimize the ratio of efficacy to adverse clinical experiences within the dosing regimens previously described. The mean doses during the whole study period were 47·3 mg/day for Org 3770 and 113·7 mg/day for clomipramine. During the fixed-dose period of the study (last three weeks), the doses were 53·5 mg/day of Org 3770 and 121 mg/day of clomipramine. Fifty-one Org 3770-treated patients and 47 clomipramine-treated patients took short-acting benzodiazepines during the first 2 weeks of the study, which was allowed by the protocol.

Dropouts and protocol violators

A total of 51 (29·3 per cent) patients terminated the trial prematurely (24 and 27 patients in the Org 3770- and clomipramine-treatment groups, respectively) (Table 2). There were no significant differences between the treatment groups with respect to the reason for premature termination, although more clomipramine-treated patients dropped out due to lack of efficacy (8·0 per cent versus 4·6 per cent, respectively) or patient improvement (6·9 per cent versus 4·6 per cent, respectively).

Table 1. Demographic characteristics and rating scale scores at baseline (group means ± SD)

Number of patients	Org 3770	Clomipramine
Patients randomized to treatments	87	87
Patients acceptable for ITT analysis	87	86
Patients acceptable for per-protocol analysis	82	81
Sex (*n*)*		
Male	24	23
Female	58	58
Age (years)*		
Mean age	51·8 ± 12·0	49·5 ± 12·7
Range	21–73	21–74
Body weight (kg)*	63·5 ± 10·8	64·9 ± 14·1
Height (cm)*	164·6 ± 7·0	163·3 ± 8·6
21-item HPRSD*	28·0 ± 5·5	27·1 ± 5·2
21-item HPRSD†	27·7 ± 5·7	26·7 ± 5·4
MADRS*	35·3 ± 6·9	34·2 ± 6·7
MADRS†	35·2 ± 6·9	33·8 ± 6·8
GAS*	37·8 ± 8·7	38·1 ± 8·1
BRPS*	22·0 ± 8·6	22·0 ± 8·3
NEDRS*	8·2 ± 1·6	8·0 ± 1·5
Baseline severity of depression (*n*)†		
Moderate	39	44
Severe	48	42

* Per-protocol analysis.
† Intention to treat (ITT) analysis.

Table 2. Patients prematurely terminating the study (number and percentage)

	Org 3770 (*n* = 87)	Clomipramine (*n* = 86)
Lack of efficacy	4 (4·6)	7 (8·0)
ACEs	9 (10·3)	8 (9·3)
Inadequate compliance/ refusal	6 (6·9)	4 (4·6)
Much improved	4 (4·6)	6 (6·9)
Not related to treatment	1 (1·1)	2 (2·3)
Total	24 (27·6)	27 (31·0)

ACEs = adverse clinical experiences.

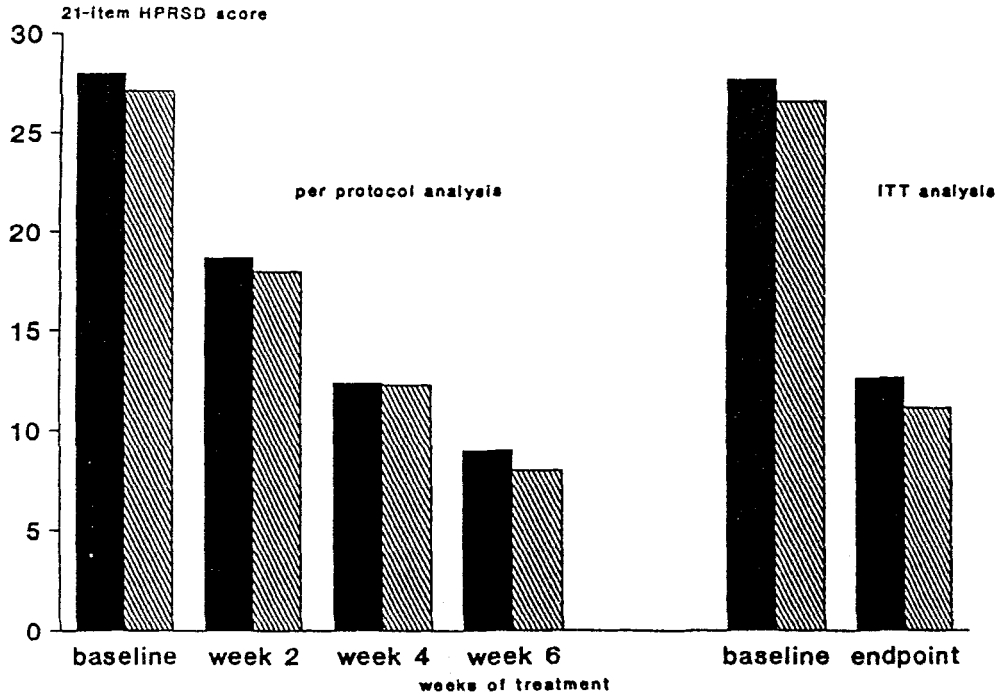

Figure 1. 21-Item HPRSD scores (per-protocol and ITT analysis) during 6 weeks of treatment with Org 3770 or clomipramine. Black bars = Org 3770; hatched bars = clomipramine

Comparable percentages of patients in both groups dropped out due to development of adverse clinical experiences (10·3 per cent versus 9·3 per cent, respectively). However, one patient, treated with clomipramine, 150 mg/day, developed the 'serotonin syndrome' (Sternbach, 1991) on day 32, with confusion, agitation, trembling, sweating and hyperthermia.

In addition, one patient in the clomipramine group was a baseline dropout and was excluded from ITT analyses, while five patients in the Org 3770-treated group and six patients in the clomipramine-treated group were excluded from the per-protocol analyses due to protocol violations. The use of prohibited psychotropic medication did not occur during the study.

Clinical efficacy

After 6 weeks of treatment with Org 3770 or clomipramine, significant improvements of depressive symptoms were evident on the 21-item HPRSD, MADRS, BPRS and GAS rating scales (Figures 1 and 2, and Table 3). There were no significant differences between the two groups at any of the assessments and at endpoint. At week 6, a similarly high response to treatment, defined as a decrease of baseline HPRSD scores of at least 50 per cent, was observed in 80 per cent of patients treated with Org 3770 and in 86 per cent of patients treated with clomipramine (Figure 3). In addition, similar improvements of HPRSD factors (anxiety/somatization, cognitive and sleep disturbances, retardation depression, weight, diurnal variation and Bech melancholia factor) were evident in both treatment groups (Table 3). A separate analysis of HPRSD scores was performed in subgroups of moderately (Org 3770, $n = 39$; clomipramine, $n = 44$) and severely (Org 3770, $n = 48$; clomipramine, $n = 42$) depressed patients. The treatments with Org 3770 and clomipramine were equally effective in both subgroups of patients, resulting in a progressive reduction of mean HPRSD scores (Figure 4).

Corresponding results were observed on the MADRS and BPRS scales: both treatment groups improved to a similar extent, with no statistically significant differences between treatments. An improvement in global functioning was reflected in the increased GAS scores of both treatment groups at the end of the trial.

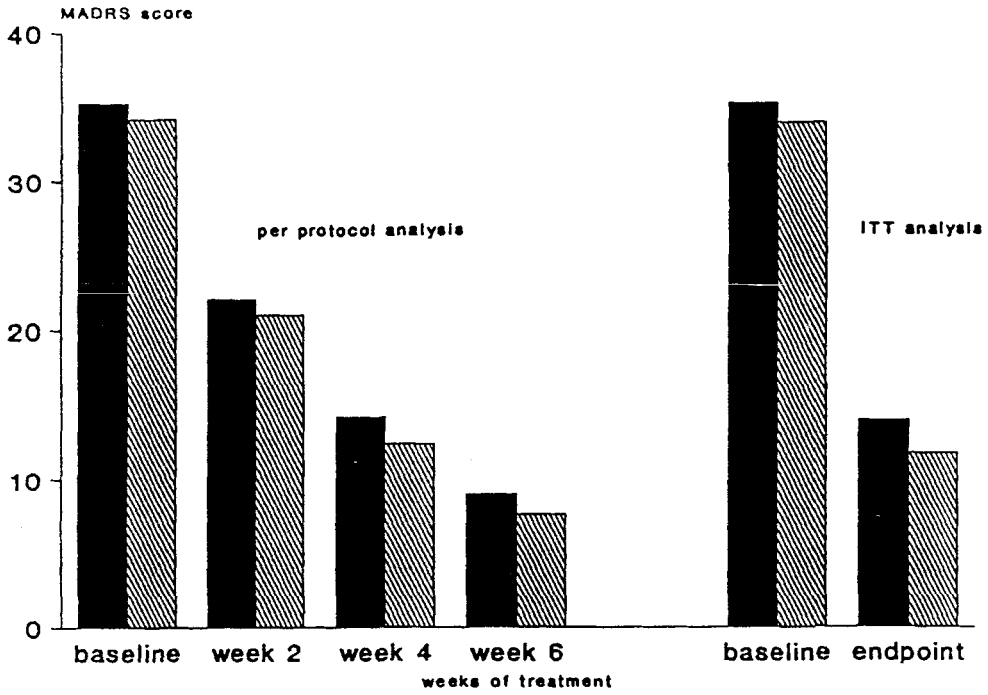

Figure 2. MADRS scores (per-protocol and ITT analysis) during 6 weeks of treatment with Org 3770 or clomipramine. Black bars = Org 3770; hatched bars = clomipramine

Adverse clinical experiences

The frequencies of reported adverse clinical experiences in both treatment groups are presented in Table 4. All of them were reported in less than 20 per cent of patients, except for dry mouth and tremor in the clomipramine-treated patients. In the Org 3770 treatment group, adverse clinical experiences were reported with a low frequency at the beginning of the trial, and continued to

Table 3. HPRSD factors, BPRS and GAS scores (per-protocol analysis)

HPRSD factors	Org 3770		Clomapramine	
	Baseline	Week 6	Baseline	Week 6
Anxiety/somatization factor	1·26±0·44	0·49±0·42	1·25±0·45	0·43±0·41
Cognitive disturbance factor	0·82±0·33	0·23±0·20	0·77±0·33	0·17±0·19
Retardation-depression factor	2·37±0·44	0·79±0·59	2·36±0·48	0·68±0·50
Sleep disturbance factor	1·43±0·51	0·38±0·41	1·28±0·54	0·41±0·40
Weight factor	0·66±0·74	0·02±0·13	0·68±0·77	0·09±0·35
Diurnal variation	1·04±0·76	0·42±0·50	1·06±0·68	0·39±0·49
Bech melancholia factor	13·5±2·6	4·8±3·3	13·3±2·6	3·6±2·9
BPRS score	22·0±8·6	7·2±5·2	22·0±8·3	6·0±4·9
GAS score	37·8±8·7	74·1±12·6	38·1±8·1	75·7±14·3

Anxiety/somatization factor: mean of items 10–13, 15 and 17.
Cognitive disturbance factor: mean of items 2, 3, 9 and 19–21.
Retardation-depression factor: mean of items 1, 7, 8 and 14.
Sleep disturbance factor: mean of items 4, 5 and 6.
Weight factor: item 16.
Diurnal variation: item 18.
Bech melancholia factor: sum of items 1, 2, 7, 8, 10 and 13.

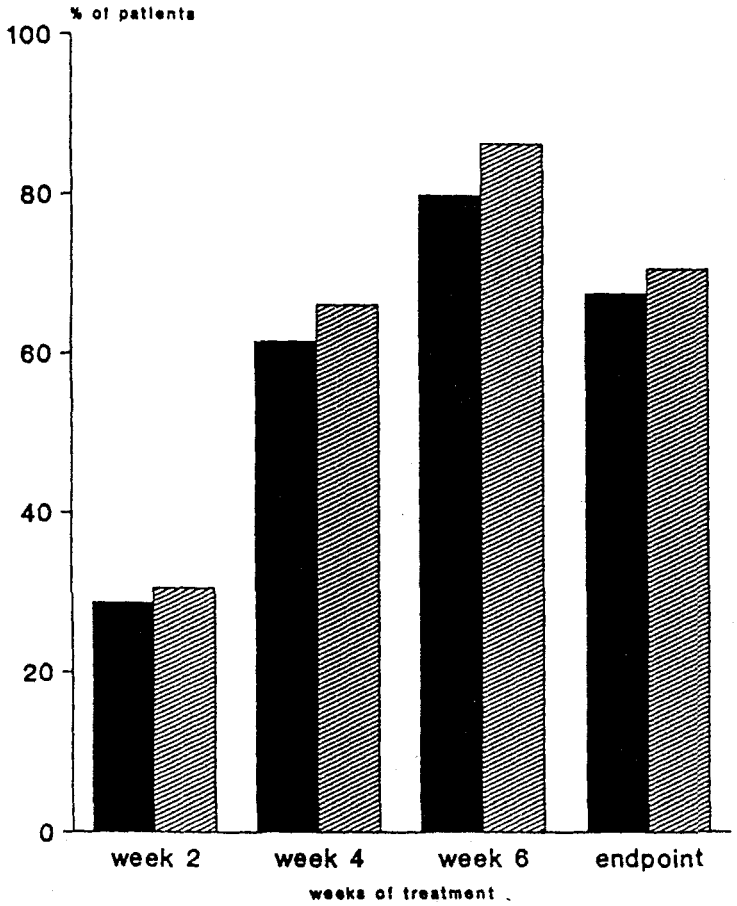

Figure 3. Responder rates (ITT analysis) during 6 weeks of treatment with Org 3770 or clomipramine. Black bars = Org 3770; hatched bars = clomipramine

decrease until the end. In the clomipramine-treated patients, dry mouth, constipation, tremor, vertigo/dizziness, faintness on rising and nausea were registered at week 3 in substantially more patients than in the Org 3770 group.

Dry mouth, the most frequent complaint at the beginning of the study in both treatment groups, decreased over time to 12·3 per cent in the Org 3770 patients, while remaining at 17·9 per cent in the clomipramine-treated patients until the end of

Table 4. Adverse clinical experiences with frequency ⩾3 per cent (percentage of patients at any time during the study)

	Week 3		Week 6	
	Org 3770	Clomipramine	Org 3770	Clomipramine
Dry mouth	20·0	23·7	12·3	17·9
Constipation	11·3	17·1	5·3	5·4
Tremor	8·7	22·0*	3·5	16·1*
Vertigo/dizziness	2·5	7·9	5·3	5·3
Faintness on rising	1·3	6·6	0·0	0·0
Nausea	1·3	6·6	0·0	0·0

*p = 0·03, Org 3770 versus clomipramine.

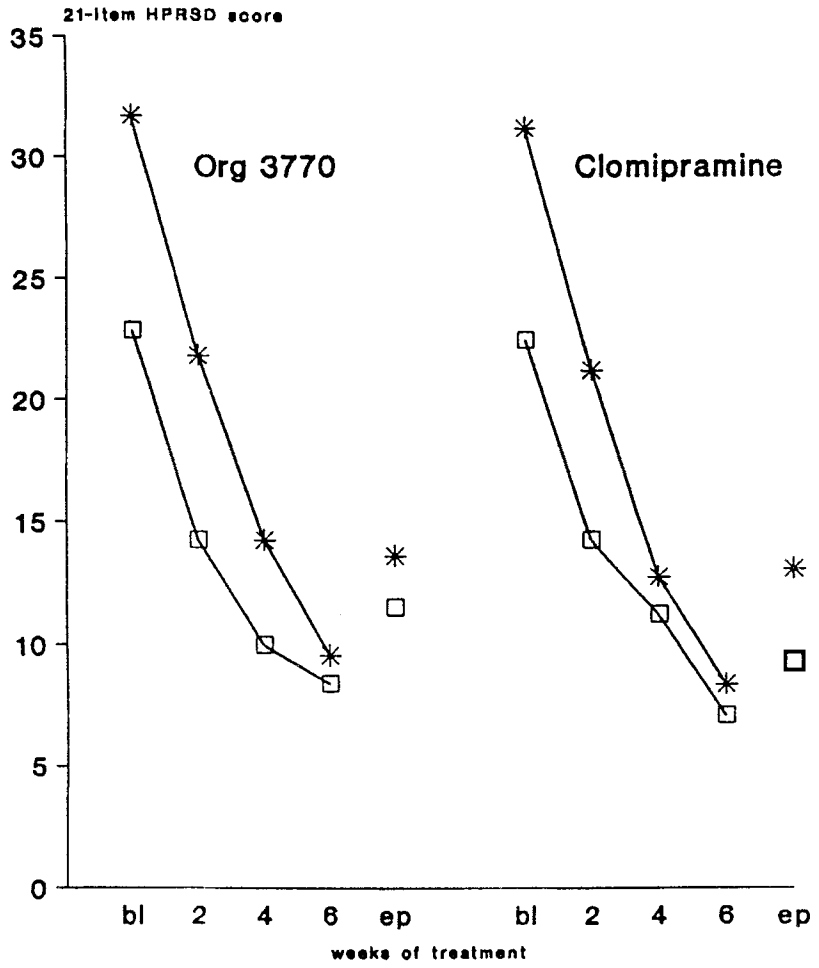

Figure 4. 21-Item HPRSD scores in subgroups of moderately or severely depressed patients treated with Org 3770 or clomipramine. (asterisk = severely depressed patients; squares = moderately depressed patients)

the trial. At week 3, constipation was more common in the clomipramine-treated patients, but decreased over time in both groups to a similar degree.

Significantly more clomipramine-treated patients ($p_{2\text{-sided}} = 0{\cdot}03$) were complaining of tremor at weeks 3 and 6. At week 3, 22·0 per cent of clomipramine-treated patients and 8·7 per cent of Org 3770-treated patients complained of tremor; at week 6, these percentages were 16·1 per cent and 3·5 per cent, respectively. Moreover, five out of eight patients prematurely terminating the treatment with clomipramine due to development of adverse clinical experiences complained of tremor.

Serious adverse clinical experiences were reported in six patients. There were two suicide attempts (one in each treatment group); a patient with a history of seizures suffered a grand mal seizure while receiving Org 3770 at 80 mg/day; in one patient, elevated levels of SGOT (80 U/l) were detected at week 3 and returned to normal during further treatment with the same dose of Org 3770 (60 mg/day). One patient, treated with Org 3770, failed to drink for 3 days and became severely dehydrated. There were no clinically relevant effects on vital signs or ECG in both treatment groups. Biochemical, haematological and urinary variables remained within the range of normal clinical values.

DISCUSSION

Org 3770 is a novel type of antidepressant that is both structurally and pharmacologically different from the tricyclic antidepressants, selective 5-HT re-uptake inhibitors or monoamine oxidase inhibitors. In the present clinical trial, the efficacy and tolerability of Org 3770 were compared with those of clomipramine. Over the course of the study, improvements in depressive symptoms in both Org 3770- and clomipramine-treated patients were indicated by progressive decreases in mean group scores of all assessment instruments used (21-item HPRSD, MADRS and BPRS). This is further confirmed by increases in GAS scores, indicating improvements in global functioning. The improvements were sustained throughout the course of the trial in both treatment groups, with no statistically significant differences between the treatments neither at any of the assessments nor at endpoints, and approximately 80 per cent of patients in each group classified as responders according to the HPRSD criterion. The therapeutic effect was evident both in moderately and severely depressed patients in both treatment groups. Given that the two groups were well matched for the severity of depressive disorder on 21-item HPRSD, MADRS, BPRS and GAS at baseline, the similar improvements and response rates that were observed after 6 weeks of treatment demonstrated that Org 3770 and clomipramine have comparable efficacy in the treatment of major depressive episodes.

Depressed patients often present with symptoms of anxiety, and the symptomatological overlap between depression and anxiety is widely accepted, with a reported range of between 19 per cent and 91 per cent (Bowen and Kohout, 1979; Fawcett and Crawitz, 1983; Hillier *et al.*, 1989). Sleep disturbances are also one of the major complaints of patients with depression; it is estimated that four out of five depressed patients suffer from sleep disturbances, usually as a difficulty in falling asleep (Hamilton, 1989). In this study, an analysis of the HPRSD factors showed that Org 3770 and clomipramine had favourable and equal effects on symptoms associated with depression, such as anxiety and sleep disturbances.

There was no significant difference between the Org 3770- and clomipramine-treated groups in terms of the reasons for premature discontinuation. The overall percentage of dropouts (about 30 per cent) was not unexpected in a population of hospitalized patients (DUAG, 1990).

Adverse clinical experiences occurred less frequently in the patients treated with Org 3770 than in those treated with clomipramine, especially at the beginning of treatment. The most common adverse clinical experience at the beginning of treatment in both groups was dry mouth. However, in patients treated with Org 3770, it decreased over time, while remaining present in 17·9 per cent of the clomipramine-treated patients — the majority of whom complained of dry mouth throughout the whole course of the study.

Significantly more clomipramine-treated patients reported tremor at weeks 3 (22·0 per cent and 6 (16·1 per cent), and this symptom was also reported by five out of eight patients prematurely terminating the treatment due to development of adverse clinical experiences. This is not unexpected, because tremor is a common complaint during clomipramine treatment. It affects 6–42 per cent of patients (McTavish and Benfield, 1990; Lejoyeux *et al.*, 1993), and is considered to be related to the increased levels of 5-HT and serotonergic activity in the brain during clomipramine treatment (McTavish and Benfield, 1990). In the Org 3770-treated patients, tremor was virtually absent during the study.

This trial has shown that Org 3770 is effective in the treatment of hospitalized patients with severe or moderate depression, in whom a combination of robust efficacy and good tolerability is particularly desirable. As such, Org 3770 was as effective as clomipramine, but had a better tolerability profile. The results of the present study suggest that Org 3770 is a promising new antidepressant, especially in the treatment of severely depressed patients.

ACKNOWLEDGEMENTS

This study was supported by a grant from N.V. Organon, Oss, The Netherlands.

REFERENCES

American Psychiatric Association (APA) (1980). *Diagnostic and Statistical Manual of Mental Disorders*, 3rd edn. American Psychiatric Association, Washington DC.

Bowen, R. C. and Kohout, J. (1979). The relationship between agoraphobia and primary effective disorders. *Canadian Journal Psychiatry*, **24**, 317–322.

Claghorn, J. L. (in press). A double-blind, placebo-controlled study of Org 3770 in depressed outpatients,. *Journal of Affective Disorders.*

Clement, H. H, Gemsa, D. and Weseman, W. (1992). The effect of adrenergic drugs on serotonin metabolism in the nucleus raphe dorsalis of the rat, studies by *in vitro* voltametry. *European Journal of Pharmacology*, **217**, 43–48.

Danish Antidepressant University Group (DUAG (1986). Citalopram: Clinical effect profile in comparison with clomipramine: A controlled multicentre study. *Psychopharmacology*, **90**, 131–138.

Danish Antidepressant University Group (DUAG) (1990). Paroxetine: A selective serotonin reuptake inhibitor showing better tolerance, but weaker antidepressant effect than clomipramine in a controlled multicenter study. *Journal of Affective Disorders*, **18**, 289–299.

Danish Antidepressant University Group (DUAG) (1993). Moclobemide: A reversible MAO-A-inhibitor showing weaker antidepressant effect than clomipramine in a controlled multicenter study. *Journal of Affective Disorders*, **28**, 105–116.

Data on File, NV Organon, Scientific Development Group, Oss, The Netherlands.

De Boer, T., Nefkens, F. and van Helvoirt, A. (1994). The α2-antagonist Org 3770 enhances serotonin transmission *in vivo*. *European Journal of Pharmacology*, **253**, R5–R6.

Drago, F., Motta, A. and Grossi, E. (1983). Intravenous maprotiline in severe and resistant primary depression: a double-blind comparison with clomipramine. *Journal of International Clinical Research*, **11**, 78–84.

Dudley, D. I., Volberding, N. and Loebel, J. P. (1980). Intravenous clomipramine and refractory depression. *Gen Hosp Form*, **2**, 61–64.

Endicott, J., Spitzer, R. I., Fleiss, J. I. and Cohen, J. (1976). The Global Assessment Scale: A procedure for measuring overall severity of psychiatric disturbance. *Archives of General Psychiatry*, **33**, 766–771.

Fawcett, J. and Crawitz, H. M. (1983). Anxiety symptoms and their relationship to depressive illness. *Journal of Clinical Psychiatry*, **44**, 8–11.

Hamilton, M. (1967). Development of a rating scale for primary depressive illness. *Journal of Social and Clinical Psychology*, **6**, 278–296.

Hamilton, M. (1989). Mood disorders: Clinical features. In: *Comprehensive Textbook of Psychiatry/V*, Kaplan, H. I. and Sadock, B. J. (Eds), Williams and Wilkins, Baltimore, pp. 891–913.

Hillier, W., Zaudig, M. v. and Bose, M. (1989). The overlap between depression and anxiety on different levels of psychopathology. *Journal of Affective Disorders*, **16**, 223–231.

Kielholtz, P. (1986). Treatment for therapy-resistant depression. *Psychopharmacology*, **19** (suppl. 2), 194–200.

Kornhaber, A. and Horwitz, I. M. (1984). A comparison of clomipramine and doxepin in neurotic depression. *Journal of Clinical Psychiatry*, **45**, 337–341.

Lejoyeux, M., Rouillon, F. and Ades, J. (1993). Prospective evaluation of the serotonin syndrome in depressed inpatients treated with clomipramine. *Acta Psychiatrica Scandinavica*, **8**, 369–371.

Lemoine, P., Achaintre, A., Balvay, G., Bonnet, H., Burgat, R., *et al.* (1981). Double-blind trial of amineptine and clomipramine in the treatment of depression. *Current Medical Research and Opinion*, **7**, 234–240.

McTavish, D. and Benfield, P. (1990). Clomipramine: An overview of its pharmacological properties. *Drugs*, **39**, 136–153.

Montgomery, S. A. and Åsberg, M. A. (1979). A new depression rating scale designed to be sensitive to change. *British Journal of Psychiatry*, **134**, 382–389.

Moron, P., Besancon, G., Carrier, G., Cordier, B., Degiovanni, A., *et al.* (1988). Fluoxetine versus clomipramine in endogenous depression and melancholia — multicentric study (Abstract). *Psychopharmacology*, **96**, (suppl.), 286.

Nickolson, V. J., Radhakishun, F., Sitsen, J. M. A. and Van Delft, A. M. L. (1993). Remeron® (Org 3770), an atypical antidepressant with 'typical' efficacy. Abstract No. 109. The 9th World Congress of Psychiatry, Rio de Janeiro.

Overall, J. E. and Gorham, D. R. (1962). The Brief Psychiatric Rating Scale (BPRS). *Psychological Reports*, **10**, 799–812.

Pecknold, J. C., Bratton, L. and Ban, T. A. (1976). Systematic clinical studies with clomipramine in depressed psychiatric patients, number 3: standard controlled clinical trial. *Psychopharmacological Bulletin*, **12**, 26–27.

Smith, W. T., Glaudin, V., Panagides, J. and Gilvary, E. (1990). Mirtazapine vs amitriptyline vs placebo in the treatment of major depressive disorder. *Psychopharmacology Bulletin*, **26**, 191–196.

Spitzer, R. L., Endicott, J. and Robins, E. (1978). Research diagnostic criteria: rationale and reliability. *Archives of General Psychiatry*, **35**, 773–783.

Sternbach, H. (1991). The serotonin syndrome. *American Journal of Psychiatry*, **148**, 705–713.

Trimble, M. R. (1990). Worldwide use of clomipramine. *Journal of Clinical Psychiatry*, **51**, 8 (suppl.), 51–54.

van Moffaert, M., de Wilde, J., Vereecken, A., Dierick, M., Evrard, J. L., Wilmotte J. and Mendelwicz, J. (in press). Mirtazapine is more effective than trazodone. A controlled study in hospitalised patients with major depression. *International Clinical Psychopharmacology*.

Zivkov, M. and de Jongh, G. D. (in press). Org 3770 vs amitriptyline: a 6-week randomised double-blind multicentre trial in hospitalised depressed patients. *Human Psychopharmacology*.