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Efficacy and Tolerability of Moclobemide Compared with Imipramine in Depressive Disorder (DSM-III): An Austrian Double-blind, Multicentre Study*

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The antidepressant efficacy, tolerability, and safety of moclobemide, a reversible, monoamine oxidase-A inhibitor, were compared with those of imipramine in parallel groups of patients with a major depressive episode, in a 4-week, multicentre (17 centres), randomised study. A total of 381 patients were randomly allocated to either treatment; they were not required to avoid tyramine-rich foods. Drop-out rates were comparable in both groups at about 17%. Judged primarily on the HRSD, no significant differences in efficacy were observed between the groups, but the number of patients presenting with adverse events, as well as the total number of adverse events, was greater with imipramine. Cardiovascular tolerability was satisfactory and physical examination, body weight, and laboratory values were essentially unaffected in both groups.

Irreversible monoamine oxidase inhibitors (MAOIs) were the first drugs to be recognised as effective in the treatment of depression (Crane, 1957). However, MAOIs fell into fairly general disuse soon after their introduction, mainly because they were considered to be less effective than tricyclic antidepressants (TCAs) (West & Dally, 1959). This seemed to be particularly true for endogenous depression: phenelzine was reported to be effective in 70% of patients with depressive neurosis, but in only 18% of patients with endogenous depression (Paykel, 1971). MAOIs also became somewhat discredited because of the occurrence of hypertensive crises after exposure to foods containing tyramine (Horwitz *et al*, 1964). In recent years, reversible MAOIs have been discovered, and have attracted great interest, as the risk with them of hypertensive crisis appears to be less.

Moclobemide is a novel compound which belongs to this new class of reversible monoamine oxidase-A (MAO-A) (Da Prada *et al*, 1989). It has been shown to be a weak potentiator of the pressor effects of orally administered tyramine (Gieschke *et al*, 1988; Korn *et al*, 1988; Müller *et al*, 1988; Burgess & Mellsop, 1989) and to be more effective than placebo for the treatment of a major depressive episode (Versiani *et al*, 1989).

The question remained, however, as to whether this type of compound could be as effective as TCAs for the treatment of depression. Here, we report the results obtained in a prospective, double-blind study, comparing the antidepressant efficacy of moclobemide with that of imipramine in parallel groups of patients suffering from a major depressive episode, as defined by DSM-III.

Method

A total of 381 patients was enrolled in this double-blind, prospective, randomised, multicentre study, over a 24-month period. Patients considered for participation were men or non-pregnant and non-lactating women, over 18 years of age. Patients were required to meet the DSM-III criteria for a major depressive episode and to have a minimum baseline score of 17 on the 21-item Hamilton Rating Scale for Depression (HRSD). Once the patients were enrolled in the study, their depression was further categorised according to the ICD-9 classification, but depressive subtype did not affect either inclusion in or exclusion from the study. Patients on lithium could be enrolled in the study, providing lithium plasma levels were within the normal therapeutic range, and treatment had been stabilised for at least 4 weeks prior to entry into the study. Patients who had received antidepressant treatment (with the exception of imipramine) could be enrolled in the study after a 3–5 day washout period, providing treatment had not been effective, and/or was not well tolerated. Exclusion criteria were as follows: marked suicidal intent (because out-patients could be enrolled in the study), other psychiatric illness, alcoholism, drug abuse, and women in whom pregnancy could not be excluded during the trial. In addition, patients were required not to have the usual contra-indications to treatment with TCAs. All patients gave their consent to the study.

On inclusion (there was no run-in period), patients were randomly allocated within each study centre to either moclobemide ($n=189$) or to imipramine ($n=192$). Moclobemide, 100 mg capsules, and imipramine, 33.3 mg capsules of identical appearance were used.

The trial drugs were given three times daily (morning, noon, and evening). Treatment was started with 300 mg/day of moclobemide (100 mg–100 mg–100 mg) or 33.3 mg/day of imipramine (placebo–placebo–33.3 mg). Moclobemide dosage was kept constant, while imipramine dosage was increased to

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66 mg/day on day 2 (33.3 mg−placebo−33.3 mg) and to 100 mg/day on day 4 (33.3 mg−33.3 mg−33.3 mg). Between days 6 and 14, the daily target dose of moclobemide was 400 mg (200 mg−100 mg−100 mg) and of imipramine 133 mg (66.6 mg−33.3 mg−33.3 mg). Between days 15 and 28, dosage could be further increased up to a maximum of 600 mg/day of moclobemide (200 mg−200 mg−200 mg) or 200 mg/day of imipramine (66.6 mg−66.6 mg−66.6 mg), providing tolerability was satisfactory and efficacy at the prevailing level seemed to be insufficient.

The use of concomitant psychotropic medication was prohibited, with the exception of lithium, for patients on previously established lithium regime, or benzodiazepine, if judged clinically necessary by the investigator. During the study, patients were not required to avoid tyramine-rich foods.

The efficacy and safety of treatment were evaluated on study days 3, 7, 14, 21, and 28. Efficacy was judged primarily on the 17-item HRSD, and on an investigator's final overall assessment of efficacy. Tolerability was judged on the number and severity of reported and observed adverse events, on investigator's final overall assessment of tolerability, and on vital signs (blood pressure and heart rate, supine and standing; body weight). A physical examination was performed on entry to the study and at the end of treatment. An ECG and laboratory screen, including haematology (haemoglobin, erythrocytes, leucocytes, neutrophils, eosinophils, basophils, monocytes, lymphocytes, platelets), clinical chemistry (bilirubin, creatinine, urea, blood glucose, alkaline phosphatase, SGOT, SGPT, γ-GT), and urine analyses (glucose, protein, haemoglobin/erythrocytes), were performed on entry, after 2 weeks, and at the end of treatment.

Results

On entry to the study, both treatment groups were comparable for demographic and illness characteristics, as well as for baseline HRSD scores (Table I; Fig. 1). A little over half the patients were judged to suffer from endogenous-type depression (Table I). Of the 17 centres which participated in the study, two enrolled only elderly patients, explaining the relatively high proportion of patients over 60 years of age in the sample (Table I).

Drop-out rates and reasons for premature termination of treatment were comparable in both treatment groups (Table II), although there was a non-significant trend ($P = 0.082$, Fisher's Exact Test) towards more patients being withdrawn for insufficient efficacy in the moclobemide than in the imipramine group.

Approximately 65% of patients in each treatment group (119 patients in the moclobemide group and 128 patients in the imipramine group) were treated concomitantly with a benzodiazepine. In addition, seven patients in the moclobemide group and three in the imipramine group were taking lithium therapy on entry to the study, and continued to receive lithium throughout the trial.

The data from eight patients in the moclobemide group and from 13 patients in the imipramine group were excluded from the standard efficacy analysis, either because of protocol violations (having an initial HRSD score more than two points below the criterion specified in the protocol, non-fulfillment of DSM-III criteria for a major depressive episode, presence of mood-incongruent delusions or hallucinations on entry, neuroleptic co-medication) or because the patients were treated for less than 7 days.

The standard efficacy analysis included all the other patients, irrespective of their duration of treatment. Both moclobemide and imipramine were associated with a significant reduction in the depressive symptomatology as judged by total HRSD (17 items) scores (Fig. 1). No significant differences were observed between the treatment groups; it was notable that the onset of action seemed to be comparable in both groups. The mean percentage reduction of the HRSD at the end of treatment

TABLE I

Baseline demographic and illness characteristics of 381 depressed patients randomly allocated to either moclobemide (n=189) or imipramine (n=192)

	Treatment group	
Characteristic	*Moclobemide*	*Imipramine*
Age (mean ± s.d.) years:	53.4 ± 17.8	55.6 ± 16.7
range	23–97	20–96
No. of patients		
under 60 years	128	116
over 60 years	61	76
Sex:		
no. of males/age range	48/23–88	49/20–74
no. of females/age range	141/24–97	143/21–96
Weight (mean ± s.d.) (kg)	68.3 ± 13.3	68.4 ± 13.1
No. of:		
in-patients	122	120
out-patients	37	36
in- and out-patients	30	36
No. of patients with[1]:		
endogenous monopolar depression	93	97
endogenous bipolar depression	18	15
neurotic/reactive depression	46	41
organic/symptomatic depression[2]	27	32
other[3]	5	7
Mean (± SD) total score on the first 17 items of the HRSD	25.0 ± 5.7	24.3 ± 5.9

1. Patients were enrolled in the study on a diagnosis of a major depressive episode (DSM-III). Once they were enrolled in the study the investigator categorised their depression according to the ICD-9 classification, but depressive subtype did not influence either inclusion in or exclusion from the study.
2. This was seen predominantly in geriatric patients, and was associated with cerebral atherosclerosis or a history of stroke.
3. Moclobemide: post-psychotic depression in schizophrenia (2), neurasthenia (1), endo-reactive depression (1), chronic depression unspecified (1).
Imipramine: post-psychotic depression in schizophrenia (4), neurasthenia (3).

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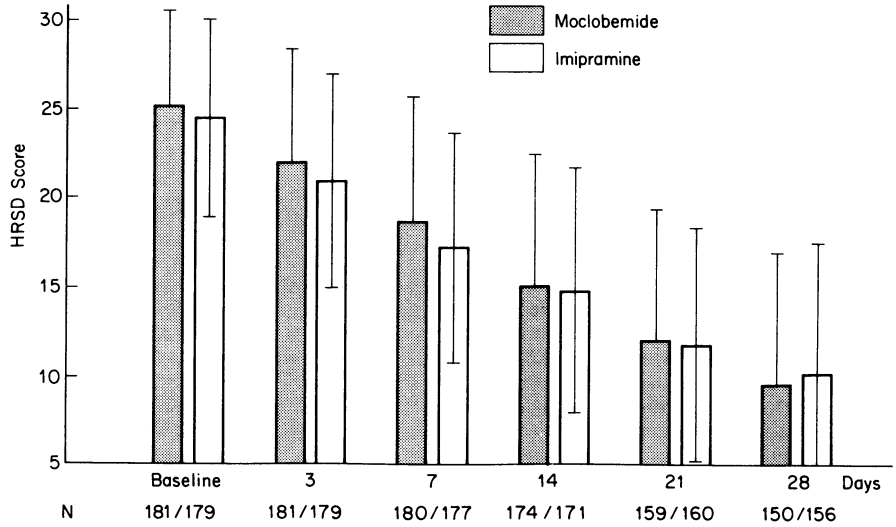

FIG. 1 Mean (±s.d.) total scores on the first 17 items of the HRSD throughout the study for 360 depressed patients during treatment with either moclobemide or imipramine.

TABLE II

Reasons for premature termination of treatment in 381 depressed patients treated either with moclobemide (n=189) or with imipramine (n=192)

Reason	*Treatment group*	
	Moclobemide No. (%)	*Imipramine No. (%)*
Recovery	2 (1.1)	2 (1.0)
Manic switch	1 (0.5)	—
Suicidal attempt	1 (0.5)	2 (1.0)
Suicidal ideation	1 (0.5)	1 (0.5)
Insufficient efficacy	15 (7.9)	7 (3.6)
Poor tolerability	9 (4.8)	7 (3.6)
Intercurrent disease	1 (1.1)	—
Other[1]	5 (2.6)	11 (5.7)
Total	35 (19)	31 (16)

1. Failure to return, or drug refusal.

was 51.7% in the moclobemide group and 52.1% in the imipramine group. Factorial evaluation of the HRSD (Fig. 2) failed to show any substantial difference between the efficacy of moclobemide and that of imipramine on any of the four factors.

The response rate, defined as the percentage of patients whose total score on the first 17 items of the HRSD was reduced by 50% at the end of treatment, appeared to be comparable in the two groups; subgroup analyses recording type of depression, sex, and age, did not reveal any relevant differences between the treatment groups (Table III). Interestingly, the response rate was lower, in both treatment groups, in the patients who had received benzodiazepines than in those who had not received benzodiazepines. The investigator's final overall assessment of efficacy (Table IV) yielded results which were in good agreement with those obtained by analysing the response rate on the HRSD.

Treatment tolerability and safety were judged on reported and observed adverse events, an investigator's final overall assessment of tolerability, vital signs, physical examination, ECG, and a laboratory screen. Adverse events were reported and observed in significantly more patients taking imipramine (69%) than moclobemide (56%; $P = 0.008$, Fisher's Exact Test). The investigator's overall judgement on tolerability also significantly favoured moclobemide over imipramine ($P = 0.005$, Stucky-Vollmar Test; Table V). The total number of adverse events, irrespective of severity, was higher with imipramine than with moclobemide (total: 286 v. 189; mild and moderate: 215 v. 150; severe: 71 v. 39). The difference in tolerability between imipramine and moclobemide appeared to be due mainly to the higher incidence of anticholinergic adverse events with imipramine (Fig. 3).

Therapy with first-generation MAOIs has been reported to induce a typical pattern of central nervous system side-effects characterised by insomnia, irritability, agitation, motor restlessness, and hypomania (see e.g. Kline & Cooper, 1980). In this study, the adverse events induced by moclobemide were mainly sleep disturbances and restlessness; the incidence of these, however, seemed to be comparable in both treatment groups (Table VI). Autonomic side-effects observed with first-generation MAOIs included dry mouth, constipation, dizziness, orthostatic hypotension, and delayed ejaculation, but in this study, the incidence of these effects was greater with imipramine than with moclobemide (Table VI). Cardiovascular tolerability was satisfactory in both groups, tachycardia and hypotension being reported a little more frequently with imipramine than with moclobemide (Fig. 3). ECG anomalies (a conductance defect) developed in one patient taking imipramine. One 53-year-old, female in-patient taking moclobemide was reported to have an asymptomatic 40 mmHg increase in systolic blood pressure values 2 h after her morning dose of moclobemide on study day 7. Her blood pressure values

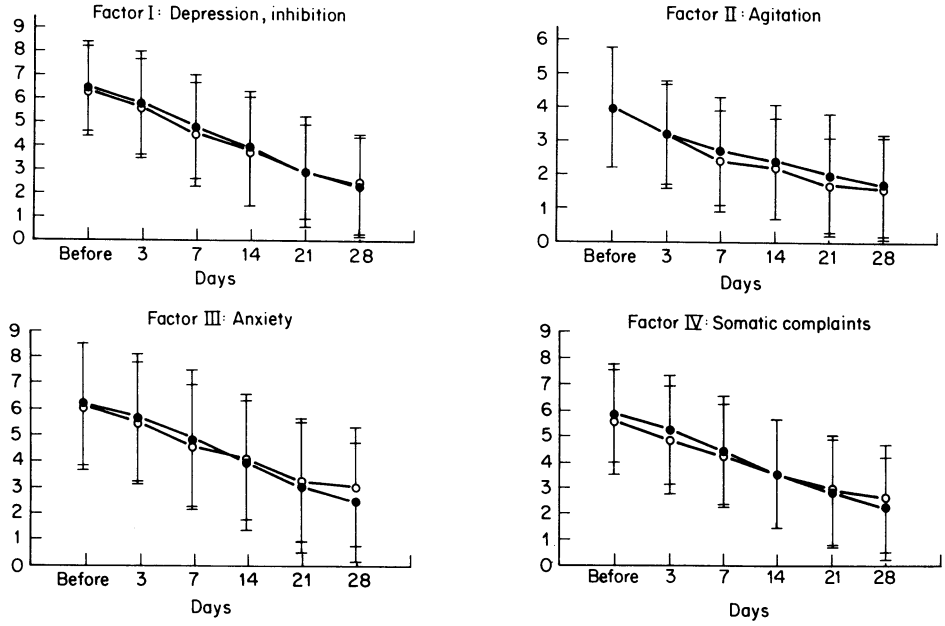

FIG. 2 Mean (±s.d.) values on the four factors of the HRSD throughout the study for 360 depressed patients during treatment with either moclobemide (●—●) or imipramine (o—o).

TABLE III

Percentage of patients with a ≥50% decrease of their total score on the first 17 items of the HRSD at end of treatment as a function of diagnostic and demographic characteristics, or of concomitant treatment

	Treatment group			
	Moclobemide		*Imipramine*	
Patient group	*No.*	*Responders (%)*	*No.*	*Responders (%)*
All patients[1]	180	58	179	58
Patients with:				
endogenous monopolar depression	90	64	92	71
endogenous bipolar depression	17	53	15	60
neurotic/reactive depression	44	55	40	55
organic/symptomatic depression	25	52	28	25
Patients:				
over 60 years	54	52	67	52
under 60 years	126	61	112	62
Males	45	67	46	76
Females	135	55	133	52
Patients taking benzodiazepines[2]	112	50	121	55
Patients not taking benzodiazepines	68	69	58	66
Patients taking lithium	7	28	3	100

1. Eight patients in the moclobemide group and 13 patients in the imipramine group were excluded from the standard efficacy analysis (for further details, see Results); one patient in the moclobemide group was treated for 7 days, but not assessed.
2. In most patients the benzodiazepines were either nitrazepam or diazepam given throughout the study.

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TABLE IV
Investigator's final overall assessment of efficacy in 359 depressed patients treated with either moclobemide or imipramine

Investigator's assessment	*Treatment group*	
	Moclobemide (n=181)[1] No. (%)	*Imipramine (n=178)[1] No. (%)*
Very good	53 (29)	41 (23)
Good	60 (33)	66 (37)
Moderate	41 (23)	53 (30)
No change or worse	27 (15)	18 (10)

1. Number of patients/group; eight patients in the moclobemide group and 13 patients in the imipramine group were excluded from the standard efficacy analysis (for further details, see Results); one patient in the imipramine group was not assessed.

TABLE V
Investigator's final overall assessment of tolerability in 379 depressed patients treated with either moclobemide or imipramine

Investigator's assessment	*Treatment group*	
	Moclobemide (n=189)[1] No. (%)	*Imipramine (n=190)[1] No. (%)*
Very good	96 (51)	63 (33)
Good	61 (32)	79 (42)
Moderate	18 (10)	31 (16)
Poor	14 (7)	17 (9)

1. Number of patients/group; two patients in the imipramine group were not assessed.

returned to normal within a few hours without any particular treatment, and the patient continued to be treated with moclobemide without any other increases in blood pressure.

Physical examination, body weight and laboratory values were not affected in a clinically relevant fashion in either treatment group.

Discussion

This study shows that the antidepressant efficacy of moclobemide is comparable to imipramine in patients suffering from a major depressive episode. However, the tolerability of moclobemide was superior to that of imipramine.

On entry to the study, both treatment groups were comparable for demographic and illness characteristics, affording valid comparisons between the groups. One of the major criticisms, however, which could be made of this study, is that a high proportion of patients (approximately 65%) were treated concomitantly with a benzodiazepine. This reflects the habit, in certain European countries, of prescribing a benzodiazepine together with an antidepressant drug, but does not simplify the interpretation of results. Efficacy was judged primarily on the HRSD and on the investigator's final global assessment of efficacy. No significant differences between the two treatment groups were observed, yet the number of patients enrolled in each group (i.e. 189 in the moclobemide group and 192 in

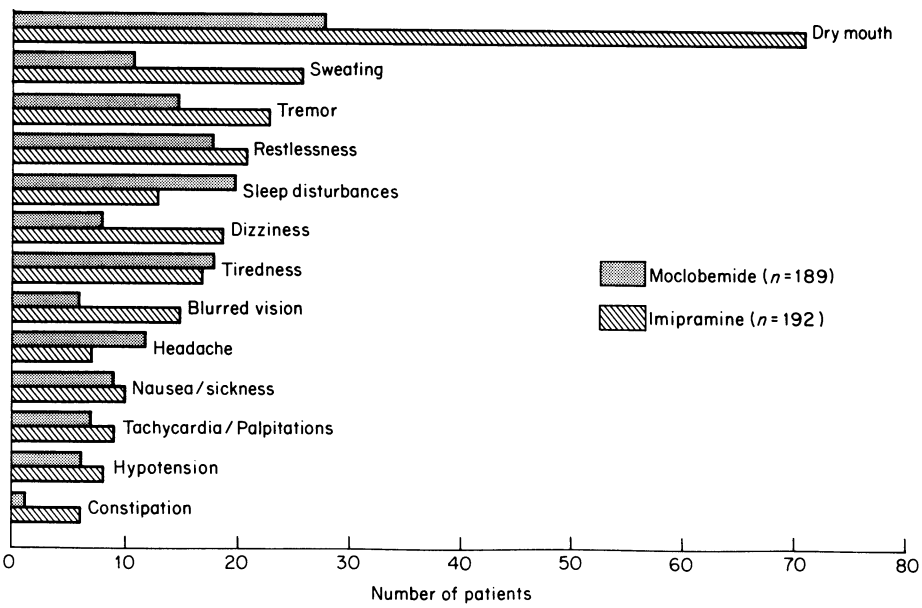

FIG. 3 Most commonly reported and/or observed adverse events in 381 depressed patients treated with either moclobemide or imipramine.

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TABLE VI
Incidence of classical CNS and autonomic MAOI-type adverse events in 381 depressed patients treated with either moclobemide (n=189) or imipramine (n=192)

Reported and/or observed adverse effects	*Treatment group*	
	Moclobemide No. (%)	*Imipramine No. (%)*
CNS		
sleep disturbances	20 (10.6)	13 (6.8)
irritability/excitation	1 (0.5)	1 (0.5)
agitation (increased)	1 (0.5)	2 (0.5)
restlessness/nervousness	18 (9.5)	21 (10.9)
hypomania	2 (1.0)	1 (0.5)
Autonomic		
dry mouth	28 (14.8)	71 (37.0)
constipation	1 (0.5)	6 (3.0)
dizziness	8 (4.2)	19 (9.9)
hypotension (orthostatic)	6 (3.2)	8 (4.2)
delayed ejaculation	—	1 (0.5)

the imipramine group) would have been sufficient to detect a >12% difference in response rate ($2\alpha = 0.05$, power = 80%, N1 = N2 = 190, response rate = 60%). Thus, it can be concluded that the antidepressant efficacy of moclobemide is unlikely to be very different from that of imipramine.

First-generation MAOIs have been reported not to be effective in endogenous depression (West & Dally, 1959; Paykel, 1971; Davidson *et al*, 1978; Robinson *et al*, 1978) but in the present study, moclobemide was not shown to differ from imipramine in efficacy in such cases. This result should, however, be interpreted with caution, because analysis of the subgroups was retrospective and the diagnosis of depressive subtypes was based only on the ICD-9 classification.

The tolerability of moclobemide was found to be significantly superior to that of imipramine; this seemed to be mainly due to the higher incidence of anticholinergic adverse events with imipramine. Moclobemide did not induce the typical spectrum of central and autonomic nervous system side-effects which is characteristic of first-generation MAOIs. The cardiovascular tolerability of both drugs was comparable, and no typical acute elevations of blood pressure were reported, even though no dietary restrictions had been given to the patients.

In conclusion, moclobemide, an MAOI which differs from first-generation MAOIs by the fact that it is reversible and selective for MAO-A, was not shown to differ in efficacy from imipramine in the treatment of depression, including endogenous depression, but was significantly better tolerated. Moreover, moclobemide does not induce the typical side-effect profile observed with first-generation MAOIs.

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