Moclobemide versus Fluoxetine in the Treatment of Major Depressive Disorder in Adults

Yvon D Lapierre, MD[1], Russell Joffe, MD[2], Kevin McKenna, MD[3], Roger Bland, MB[3], Sidney Kennedy, MD[4], Peter Ingram, MD[5], Robin Reesal, MD[6], Badri G Rickhi, MD[6], Linda Beauclair, MD[7], Guy Chouinard, MD[7], Lawrence Annable, Dip Stat[8]

[1]Royal Ottawa Hospital, Ottawa, Ontario, Canada

[2]McMaster University, Hamilton, Ontario, Canada

[3]University of Alberta Hospitals, Edmonton, Alberta, Canada

[4]Clarke Institute of Psychiatry, Toronto, Ontario, Canada

[5]Seven Oaks General Hospital, Winnipeg, Manitoba, Canada

[6]Calgary General Hospital, Calgary, Alberta, Canada

[7]Allan Memorial Institute, Montreal, Quebec, Canada

[8]McGill University, Montreal, Quebec, Canada

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The objective of the present study was to compare the safety and efficacy of moclobemide versus fluoxetine in adult patients with major depressive disorder. The design of the study was a multicenter, double-blind, comparative, and randomized trial. A 1- to 2-week single-blind placebo washout phase was followed by 6 weeks of double-blind treatment with moclobemide or fluoxetine. A total of 150 patients were enrolled in the study. There were 128 patients eligible to be randomized, with 66 patients receiving moclobemide and 62 patients receiving fluoxetine. At the termination of the study, patients in the moclobemide group were receiving a mean dose of 440 mg ± 123 mg, while the mean dose in the fluoxetine group was 35 mg ± 8 mg. No significant treatment differences were found for any of the efficacy parameters. Headache and nausea were the most frequently reported adverse events in both treatment groups. Headache and blurred vision were reported significantly more often ($P < 0.05$) in the fluoxetine group, whereas significantly more dry mouth was reported ($P < 0.05$) in the moclobemide group. These results provide supporting evidence for the comparable efficacy of moclobemide and fluoxetine and the better tolerability of moclobemide when used in the treatment of major depressive disorder.

Key Words: moclobemide, fluoxetine, depression, controlled trial

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Address for correspondence: Dr YD Lapierre, Royal Ottawa Hospital, 1145 Carling Avenue, Ottawa, ON K1Z 7K4.

INTRODUCTION

Moclobemide is a reversible inhibitor of monoamine oxidase-A (RIMA) antidepressant and has been shown to be superior to placebo and comparable in efficacy and safety to other antidepressants (Fitton and others 1992). Comparisons have been made with classical monoamine oxidase inhibitors (MAOI) and tricyclic antidepressants (TCA) (Gabelic and Kuhn 1990; Rossel and Moll 1990; Bakish and others 1992b; Lingjaerde and others 1995), as well as with more recently developed 2nd-generation antidepressants (Bougerol and others 1992; Orsel Donbak and others 1995).

Fluoxetine is a selective serotonin reuptake inhibitor (SSRI) and 1 of the most widely used antidepressants. The antidepressant activity of fluoxetine has also been shown to be comparable to other antidepressants (Tollefson and others 1994). Both RIMAs and SSRIs appear to have similar efficacy and safety, even though they have different modes of action. In addition, both of these new classes of antidepressants have a different tolerability profile when compared with MAOIs and TCAs.

Recently, several studies have examined moclobemide versus fluoxetine in the treatment of major depressive episodes in randomized, double-blind comparisons (Williams and others 1993; Geerts and others 1994; Lonnqvist and others 1994; Gattaz and others 1995; Reynaert and others 1995). The efficacy results from these studies show that both of these drugs are comparable in the treatment of depression. The tolerability results from these studies show that nausea has been more frequently reported by patients receiving fluoxetine in comparison with moclobemide (Lonnqvist and others 1994), while sleep disturbances were more frequent in patients treated with moclobemide (Williams and others 1993). Other investigators have reported on the comparative efficacy and tolerability of moclobemide and another SSRI, fluvoxamine (Barrelet and others 1991; Bougerol and others 1992; Bocksberger and others 1993).

The objective of the present study was to compare the safety and efficacy of moclobemide versus fluoxetine in adult patients with major depressive disorder.

METHODS

The design of the study was a multicenter, double-blind, comparative, randomized trial. A total of 6 centers participated in the study, and each center obtained institutional research ethics committee approval to conduct the research. Informed written consent was obtained from all patients who met all criteria for entry into the study. The subjects were men and women who were aged 18 to 64 y; outpatients who had a major depressive disorder according to DSM-III-R criteria (American Psychiatric Association 1987); and subjects with a total score of at least 18 on the 1st 17-items of the 21-item Hamilton Depression Rating Scale (HDRS) (Hamilton 1960). Exclusion criteria were marked suicide risk; major depressive episode associated with mood-incongruent psychotic features; bipolar disorder; acute confusional state; epileptic or seizure disorders or mental retardation; history of unstable diabetes; the presence or history of clinically significant physical disease; known sensitivity to moclobemide, MAOIs, fluoxetine, or other SSRIs; history of drug or alcohol abuse within the last 6 mo; treatment with an MAOI within the past 2 weeks, fluoxetine within the past 5 weeks, or tri- or heterocyclic antidepressants, lithium, or daytime benzodiazepines within the past week; electroconvulsive therapy within the past 3 mo; concomitant use of medication known to affect the actions of moclobemide or fluoxetine; and the use of an investigational drug within the past 3 mo. Also excluded were pregnant or lactating women or women of child-bearing potential not using contraception.

At the initial visit, screening evaluations included medical and psychiatric history, concomitant medication use, physical examination, laboratory assessments (hematology, clinical chemistry, urinalysis), electrocardiogram, prestudy adverse events, vital signs, and some efficacy assessments. The primary efficacy parameter was the 21-item HDRS, and secondary parameters included the Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and

Table 1

Baseline patient characteristics

Characteristic	Moclobemide (n = 66)	Fluoxetine (n = 62)
Mean age (y ± SD)	41.3 ± 11.4	40.2 ± 10.7
Sex (M:F)	18:48	15:47
Weight (kg ± SD)	76.2 ± 15.9	72.3 ± 19.4
Prior psychotropic medication		
Yes (%)	27.3	35.3
No (%)	72.7	64.7
Major depressive disorder		
Single episode (%)	50.0	40.3
Recurrent episode (%)	50.0	59.7
Mean duration of episode (mo ± SD)	22.9 ± 42.7	23.6 ± 28.4
Number of previous episodes		
0 (%)	51.5	45.2
≥ 1 (%)	48.5	54.8

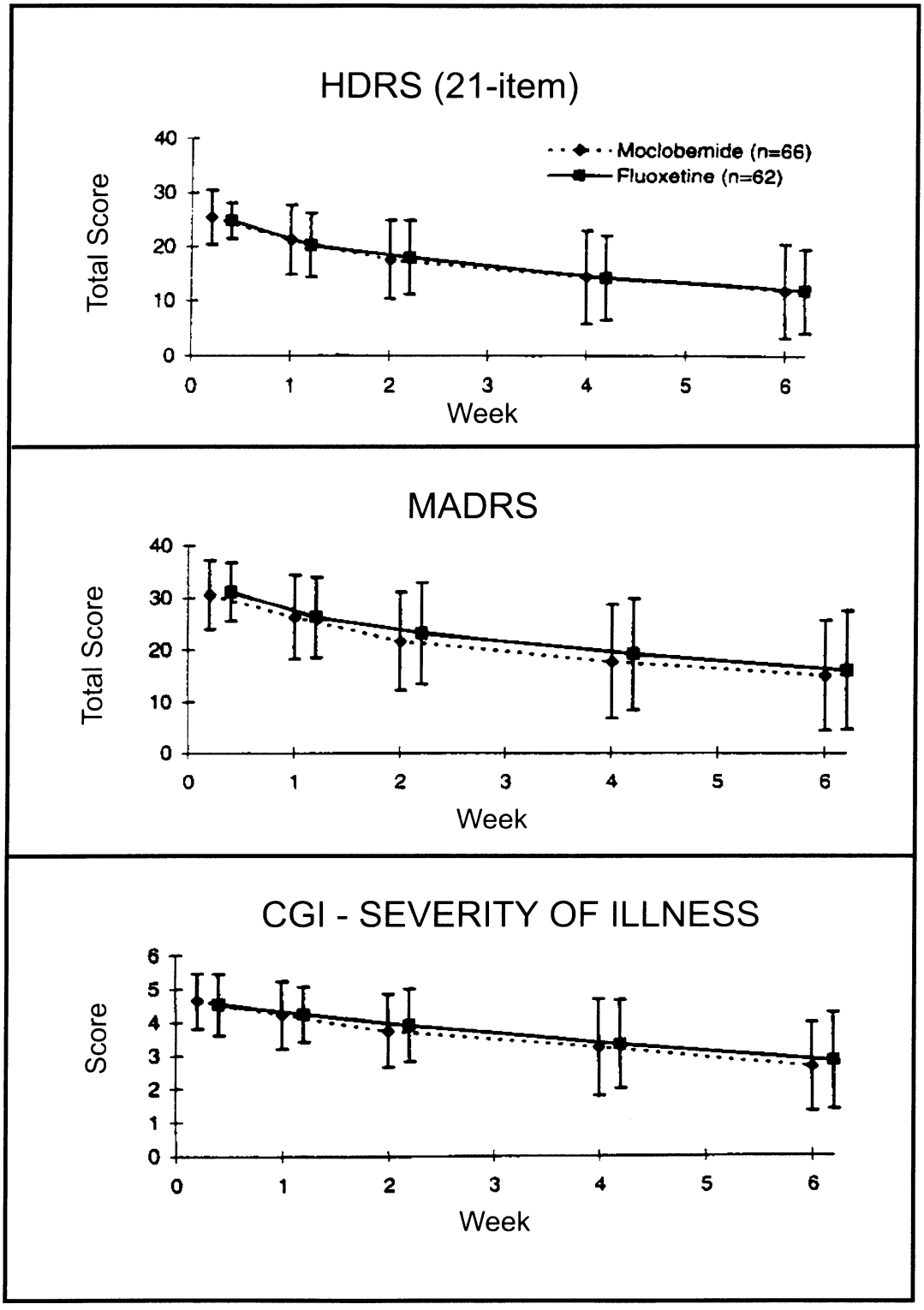

Figure 1. Assessments completed by investigators: mean and SD.

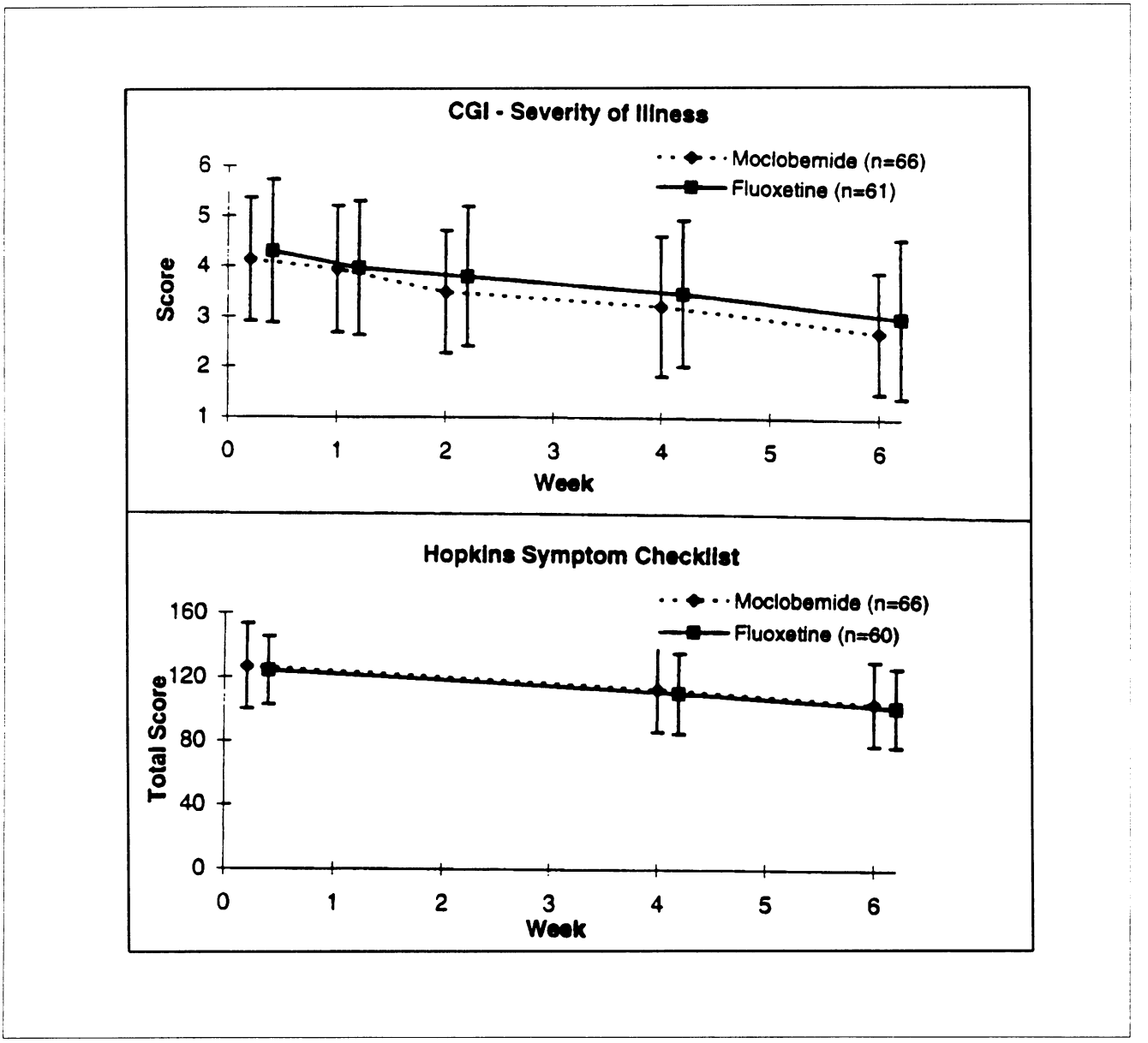

Figure 2. Patients' self-assessments: mean and SD.

Asberg 1979), physician-completed Clinical Global Impression (CGI), patient-completed CGI, 58-item Hopkins Symptom Checklist (HSCL) (Derogatis and others 1974), and the Physician Global Assessment Scale of efficacy and tolerability. The treatment response for each group was defined in the protocol as a termination HDRS total score of less than 10 plus a reduction from the baseline HDRS total score of at least 50%. Efficacy of treatment was determined by the response from patients who received active study medication for at least 2 weeks.

All eligible patients were dispensed single-blind placebo at the initial visit for a 1-week period. Placebo was administered as 2 capsules in the morning and 1 capsule at noon. If patients had an improved HDRS total score of 20% or more after 1 week of single-blind placebo, they were allowed to receive single-blind placebo for an additional week to be reassessed for eligibility.

Eligible patients were randomized at the baseline visit to receive a starting dose of 300 mg/d of moclobemide or 20 mg/d of fluoxetine after the placebo washout phase was

Table 2

Premature terminations

Variable	Moclobemide (n = 66)	Fluoxetine (n = 62)
Completed study	53	54
Reason for discontinuation		
Adverse events	6	7
Lack of efficacy	1	0
Noncompliance	1	0
Lost to follow-up	5	0
Overdose[a]	0	1

[a]Overdose with nonstudy drug.

Table 3

Dosage levels at end of study

Moclobemide (weeks 4 to 6)			Fluoxetine (weeks 4 to 6)		
Dosage	N	%	Dosage	N	%
300 mg	16	24.24	20 mg	29	46.77
400 mg	14	21.21	40 mg	33	53.23
500 mg	18	27.27			
600 mg	18	27.27			
Total	66	100.00	Total	62	100.00

Table 4

Efficacy

Patients	Moclobemide (n = 61)	Fluoxetine (n = 60)
Patients with final HDRS[a] score < 10 and ≥ 50% improvement over baseline	47.4%	38.4%
Patients with final HDRS[a] score ≥ 50% improvement over baseline	54.2%	55.1%

[a]Improvement based on 17-item HDRS.

completed. The allowable dosage titration range for moclobemide was 200 to 600 mg/d and 20 mg every other day to 40 mg/d for fluoxetine. Patients received double-blind active medication for 6 weeks. At the initiation of active treatment, 200 mg of moclobemide was administered in the morning and 100 mg at noon. Fluoxetine 20 mg was administered in the morning, and placebo was given at noon. Study medications were supplied in identical capsules, and compliance was assessed by a pill count at each visit.

Study visits were scheduled at randomization (week 0) and at the end of weeks 1, 2, 4, and 6 of active treatment. Efficacy parameters were repeated at all visits except the Hopkins Symptom Checklist, which was completed at weeks 0, 4, and 6, and the Physician Global Assessment, which was completed only at week 6. Adverse events and vital signs were recorded at every assessment period. Laboratory parameters and electrocardiogram were repeated at weeks 2 and 6. All efficacy and safety assessments required at week 6 were completed at the time that a patient prematurely left the study.

Data analysis was carried out using Statistical Analysis System (SAS) 6.09. Categorical outcome measures were analyzed by the Mantel-Haenszel procedure, with stratification by center. Total and factor scores of the rating scales were submitted to multivariate analysis of variance for repeated measures, including tests for treatment, center, and time main effects and treatment × center and treatment × time interactions. In addition, an analysis of covariance using baseline values as covariates was carried out on the endpoint values, with the last observation carried forward. An intention-to-treat analysis was carried out on all randomized patients, and an efficacy analysis was conducted for all patients except those lost to follow-up or excluded for administrative reasons during the 1st 2 weeks of treatment. All tests were 2-tailed, with the level of type I error set at 0.05.

RESULTS

A total of 150 patients were enrolled in the study. All were outpatients. There were 22 patients who did not qualify for randomization into the study at the end of the placebo washout period. The reasons for nonrandomization were placebo response, intercurrent illness, loss to follow-up, lack of compliance, abnormal laboratory tests or electrocardiogram, and adverse events with placebo. Intent-to-treat and safety analyses were conducted on 128 patients randomized to active treatment, with 66 patients in the moclobemide group and 62 patients in the fluoxetine group. Efficacy analysis was conducted on data from 121 patients.

Baseline patient characteristics are shown in Table 1. The moclobemide group included 18 males and 48 females with a mean age of 41.3 y ± 11.4 y (range 18 to 61 y). The fluoxetine group included 15 males and 47 females with a mean age of 40.2 y ± 10.7 y (range 18 to 64 y). Patients in both groups had comparable prior psychotropic medication use and depression history.

A total of 13 patients (20%) from the moclobemide group and 8 patients (13%) from the fluoxetine group prematurely left the study (Table 2). Adverse events were the main reason

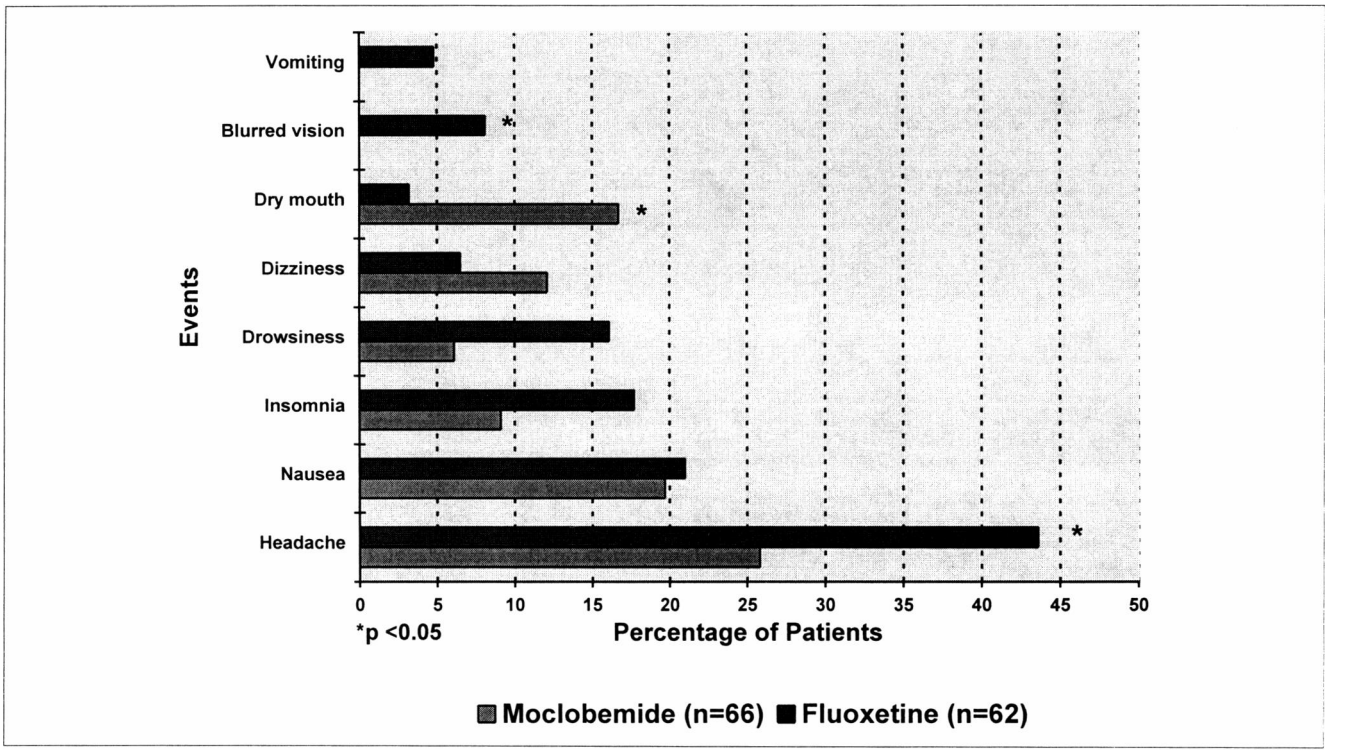

Figure 3. Most frequently reported adverse events (excluding events unrelated to study medication).

for premature departure in both treatment groups. Of the 13 patients who left the moclobemide group prematurely, 5 patients were lost to follow-up when they failed to return for study visits. Further review of these cases revealed that there was no common reason for patients to leave the study, and it was unclear why the frequency of termination differed between the treatment groups.

Table 3 shows the proportion of patients taking specific dose levels at the end of the study. Dosage titration occurred during the 1st 2 weeks of treatment, and only 1 dosage decrease was allowed during the last 4 weeks of the study. Titration decisions were clinician-based and aimed at achieving optimum balance between therapeutic response and medication tolerance. At the termination of the study, patients in the moclobemide group were receiving a mean dose of 440 mg ± 123 mg while the mean dosage in the fluoxetine group was 35 mg ± 8 mg. Patient compliance in both treatment groups was 97% over the 6-week study.

Figure 1 shows the results of the investigator-completed HDRS, MADRS, and CGI, while Figure 2 shows the patient-completed CGI and HSCL. As shown in both of these figures, no significant treatment differences were found on any of the efficacy parameters. In addition, no significant differences were found on any efficacy parameter factor scores.

All efficacy parameters were found to decrease significantly over time ($P < 0.001$), regardless of treatment. The percentage of patients in each treatment group who were both eligible for an efficacy analysis and who met the criteria as treatment responders is shown in Table 4. A total of 47.4% of the patients in the moclobemide group and 38.4% of patients in the fluoxetine group had a final HDRS score of less than 10 as well as a greater than 50% improvement over baseline. When the changes were assessed using the single response criterion of 50% reduction in HDRS, the response rate to moclobemide was 54.2% and to fluoxetine, 55.1%. The frequency of treatment responders was not significantly different between the treatment groups according to either analysis.

The most frequently reported adverse events are shown in Figure 3. The Physician Global Assessment Scale of tolerability indicated that moclobemide was generally better tolerated, having fewer side effects than fluoxetine, as shown in the side effect profile. There were a total of 172 adverse events reported in the moclobemide group and 186 events in the fluoxetine group. At least 1 adverse event was reported by 88% of patients in the moclobemide group and by 94% of patients in the fluoxetine group. Headache and nausea were the most frequently reported adverse events in each treatment

Table 5

Side effects burden[a]

Side effect	Week 1	Week 2	Week 4	Week 6	Total
Headache					
Moclobemide[b]	11	12	13	8	44
Fluoxetine[c]	20	28	23	28	99
Nausea					
Moclobemide	7	8	10	3	28
Fluoxetine	5	8	9	12	34
Insomnia					
Moclobemide	9	7	6	11	33
Fluoxetine	15	14	11	18	58
Drowsiness					
Moclobemide	1	2	1	4	8
Fluoxetine	5	9	10	14	38
Dizziness					
Moclobemide	3	5	6	4	18
Fluoxetine	1	4	2	4	11
Dry mouth					
Moclobemide	10	10	12	10	42
Fluoxetine	3	2	1	1	7
Blurred vision					
Moclobemide	0	0	0	0	0
Fluoxetine	4	2	4	4	14

[a]Side effect burden was calculated by multiplying the frequency of each event by its severity, where mild severity = 1, moderate = 2, and severe = 3.
[b]n = 66.
[c]n = 62.

group. Significantly more patients in the fluoxetine group reported headache and blurred vision ($P < 0.05$), while dry mouth was reported by significantly more patients in the moclobemide group ($P < 0.05$). Nausea, insomnia, drowsiness, and vomiting were reported more frequently in the fluoxetine group, and dizziness was more frequent in the moclobemide group, although these differences were not statistically significant. The side effect burden for each treatment group is shown in Table 5. Side effect burden was calculated at each assessment period by multiplying the frequency of each event by its severity, where mild severity equals 1, moderate equals 2, and severe equals 3. According to this assessment, the headache, insomnia, drowsiness, and blurred vision experienced with fluoxetine were more burdensome than the effects experienced with moclobemide. By contrast, dry mouth was more burdensome with moclobemide than with fluoxetine.

No treatment differences were found with regard to blood pressure, heart rate, body weight, physical examination, electrocardiogram, and laboratory parameters at the end of the study. The overall frequency of concomitant medication use was comparable, with analgesics being the most common medication in both treatment groups. Chloral hydrate, which was allowed during the study for treatment of insomnia, was dispensed to 17 patients in the fluoxetine group and 11 patients in the moclobemide group. The daily dose of chloral hydrate ranged from 500 to 1000 mg and was prescribed as required and administered at bedtime in both treatment groups.

DISCUSSION

Since SSRIs have, for many disorders, become the most commonly prescribed antidepressants, we felt that a more direct comparison of the RIMA moclobemide with fluoxetine would help establish moclobemide more firmly in the therapeutic spectrum of antidepressants. As both drugs have demonstrated their individual efficacy and safety as

Table 6

Double-blind comparative trials of moclobemide and fluoxetine

Study	Number of patients	Mean final dose (mg)[a] (dose ranges in mg)		Percent response[b]	
		Moclobemide	Fluoxetine	Moclobemide	Fluoxetine
Williams and others 1993	92	505.1 (300 to 600)	26.5 (20 to 40)	81	71
Lonnqvist and others 1994	209	366.1 (300 to 450)	28.7 (20 to 40)	67	57
Geerts and others 1994	28	340.0[c] (300 to 600)	24.6[c] (20 to 40)	67	77
Reynaert and others 1995	80	402.6[c] (300 to 600)	25.2[c] (20 to 40)	47	48

[a]Treatment duration 28 to 42 d.
[b]Response: final HDRS score < 10 or ≤ 50% of baseline score.
[c]Dosages in these studies were either 300 mg or 600 mg for moclobemide and 20 mg or 40 mg for fluoxetine.

antidepressants, the differences that may exist between them may be discernible by this study. The use of a placebo control, therefore, was not considered as necessary as it was for the earlier trials.

A stricter criterion of efficacy was considered by adding the requirement of a final HDRS score of less than 10 in addition to the 50% reduction in total score so that the proportion of patients who could be considered as virtually recovered could be more closely determined. In this study, the 2 drugs were quite comparable on the 50% improvement criteria, but the HDRS score criterion favored moclobemide slightly. The improvement profile observed in the various parameters confirmed the similarity of therapeutic profile between the 2 antidepressants noted in previous studies (Table 6) (Williams and others 1993; Geerts and others 1994; Lonnqvist and others 1994; Reynaert and others 1995). The response rates for moclobemide were also comparable to those yielded by placebo-controlled moclobemide studies using similar dosage ranges (Versiani and others 1989; Ucha Udabe and others 1990; Bakish and others 1992a). The mean moclobemide dose of 440 mg/d used in this study, though lower than in some previous studies (Versiani and others 1989), has been demonstrated to have therapeutic efficacy in several placebo-controlled studies (Cassachia and others 1984; Ucha Udabe and others 1990).

The side effect profile of fluoxetine in this study was congruent with, though not exclusive to, the side effect profile usually associated with SSRI treatment (Goodwin 1996). Headaches and blurred vision were more predominant for fluoxetine and dry mouth for moclobemide. In fact, headache was the most common side effect for both drugs. The sleep disturbances encountered with fluoxetine, especially insomnia, explained the need for more chloral hydrate in this group of patients. Nausea, common to most SSRIs, was also quite predominant for fluoxetine in this study. This finding differs slightly from the profile reported in other studies, where insomnia was equally problematic with both drugs (Lonnqvist and others 1994) or even more so with moclobemide (Williams and others 1993), where nausea and gastrointestinal disturbances were equally frequent (moclobemide) or more frequent (fluoxetine) than headache (Lonnqvist and others 1994), and where dry mouth was greater for fluoxetine (Lonnqvist and others 1994). Also in contrast to our study, Reynaert and others (1995) found no statistically significant difference between the side effect profiles of moclobemide and fluoxetine.

The side effect burden experienced by patients in both groups was, to a certain extent, similar. The profile of this burden, however, differed markedly between the 2 drugs. Headaches and blurred vision were significantly common with the SSRI, whereas dry mouth was so with the RIMA.

The results of this study provide further data supporting the comparable efficacy of moclobemide and fluoxetine. They do suggest, however, that moclobemide may have a better tolerability with fewer discomforting side effects than fluoxetine in the treatment of major depression.

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