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Double-blind randomized controlled study of the efficacy and tolerability of two reversible monoamine oxidase A inhibitors, pirlindole and moclobemide, in the treatment of depression

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The aim of this double-blind randomized study was to compare the efficacy and the tolerability of moclobemide (300–600 mg daily) and pirlindole (150–300 mg daily), two reversible inhibitors of MAO-A (RIMAs), in the treatment of depression. In total 116 patients were included in the trial, 111 patients (52 patients on pirlindole and 59 patients on moclobemide) were evaluable for efficacy and safety, and 77 patients completed the whole study (42 days of administration). Both treatments produced highly significant improvements in the Hamilton Depression Rating Scale (HDRS) score, the Hamilton Anxiety Rating Scale (HARS) score and the Montgomery-Asberg Rating Scale (MADRS) score from day 7 to day 42. The pattern of development of the three scores in the two groups did not differ significantly. After 42 days of treatment, an improvement of ≥50% in the HDRS score was noted in 80% and 67% of patients in the pirlindole and moclobemide groups, respectively. A total of 30 (58%) patients on pirlindole and 33 (56%) patients on moclobemide experienced side-effects that were considered to be possibly or probably related to the medication. The differences between the two drugs were non-significant for all types of side-effect, with the exception of dry mouth and tachycardia, which were significantly more frequent with moclobemide.

Key words: major depression; antidepressant; monoamine oxidase inhibitor; pirlindole; moclobemide

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Introduction

Until recently, monoamine oxidase inhibitors (MAOIs) were regarded as 'secondary drugs' for the treatment of depression relative to the tricyclic antidepressants for three main reasons. First, hepatotoxicity was a problem with the early MAOIs, such as iproniazid. The second, and probably most important, reason was the cheese effect, i.e. the interaction between MAOIs and foods rich in tyramine, leading to hypertensive episodes with eventual serious consequences, including cerebral haemorrhage or even death. Thirdly, in true depressions, MAOIs were considered to be less efficacious than tricyclic antidepressants (1). During the 1980s, controlled studies have provided evidence that MAOIs are very effective in the treatment of so-called therapy-resistant depressions, atypical depressions, phobias, panic disorders and anxiety states (2, 3). In addition, low cardiotoxicity, absence of anticholinergic side-effects, and mood-activating properties may be factors in favour of MAOIs as compared to tricyclic antidepressants (4).

The discovery of two distinct subtypes of MAO (MAO-A and MAO-B), and the resulting development of reversible (i.e. short-acting) and selective

inhibitors of MAO-A has led to a resurgence of interest in the use of MAO inhibitors for the treatment of depression (5). By competitively and selectively inhibiting MAO-A, the enzyme primarily responsible for deamination of those monoamines (noradrenaline and serotonin) that are implicated in the aetiology of depression, while leaving MAO-B unaffected, these compounds can be expected to combine antidepressant activity with a reduced risk of hypertensive crisis (6).

Among the new selective reversible inhibitors of MAO-A (RIMAs), moclobemide has certainly been the most well studied (7, 8). Its efficacy and safety have largely been demonstrated in placebo-controlled studies (1, 9) and in comparative trials vs. reference therapies (1, 10–14), and have been confirmed in clinical use (15).

Pirlindole is a tetracyclic compound that has been characterized as a potential antidepressant drug in preclinical studies (16–18), and in which interest has been shown due to its marked selectivity as a RIMA (19). In clinical trials, the efficacy and safety of pirlindole have been demonstrated compared to placebo (20) and to reference standard drugs such as maprotiline (21), imipramine (22, 23), amitriptyline (23–25), desipramine (26) and mianserin (27).

The aim of the present study was to compare the efficacy and the tolerability of pirlindole and moclobemide according to a double-blind randomized controlled design in patients suffering from monopolar (single (DSM-III-R 296.2) or recurrent (DSM-III-R 296.3) episodes) or bipolar (DSM-III-R 296.5) depression.

Material and methods

Study design

This was a multicentre, double-blind, prospective clinical trial, conducted by 6 investigators in 5 Belgian centres (Bruges, Oudenaarde, Assebroek, Kortrijk and Asse). Two randomized parallel groups of subjects (in-patients and out-patients, respectively) were treated with either pirlindole or moclobemide. The study drug was administered for 6 weeks, immediately following a washout period of 7 days.

Subjects

The subjects eligible for the study were men or women aged between 18 and 65 years, either in-patients or out-patients, who fulfilled the DSM-III-R criteria for unipolar (single (296.2) or recurrent (296.3) episodes) or bipolar (296.5) depression. A total score of $\geqslant$18 on the 17-item Hamilton Depression Rating Scale (HDRS) was also required. Patients who had been receiving lithium for more than 2 months and who showed a stable lithium plasma concentration were eligible for inclusion in the study, and could continue to receive their treatment. The exclusion criteria were as follows: psychotic disorders, other bipolar disorders (DSM-III-R 296.4, 296.6, 296.7), high risk of suicide, treatment-resistant depression, defined as the absence of response of the actual episode to two or more antidepressant drugs prescribed over a period of 21 days at a sufficient dose, equivalent to at least 150 mg amitriptyline daily, known drug or alcohol addiction, pheochromocytoma, organic brain disorder, epilepsy, hepatic tests severely disturbed (one enzyme > 3 times normal range), renal insufficiency (clearance of creatinine $\leqslant$ 80 ml min^{-1}), pregnancy, lactation or lack of efficient contraception. The study was carried out in accordance with the Declaration of Helsinki amended in Tokyo, Venice and Hong Kong. Patients were included after they had given informed consent. The study protocol was approved by the Ethical Committee of the Vrije Universiteit of Brussels.

Drug treatment

Patients received capsules, identical in appearance, containing either a 150-mg moclobemide tablet or a 75-mg pirlindole tablet and filled up with lactose. Two capsules (one in the morning and one in the evening) had to be taken on days 1 and 2, three capsules (one in the morning, one at midday and one in the evening) from day 3 to day 6, three to four capsules (one or two in the morning, one at midday and one in the evening) from day 7 to day 20, and two to four capsules (one in the morning and one in the evening, or one or two in the morning, one at midday and one in the evening) from day 21 to day 42. The relationship between medication intake and meals was not specified, and patients were not required to avoid tyramine-rich food. The use of concomitant psychotropic medication was prohibited, with the exception of lithium for patients on a previously established regimen and lormetazepam (at a maximum dose of 2 mg daily) or dipotassic clorazepate (at a maximum dose of 50 mg daily for in-patients only), if this was judged to be necessary by the investigator.

Assessments

Assessments were made at baseline (day 0) and on days 7, 14, 21, 28 and 42 of treatment. Efficacy was evaluated on the basis of scores on the 17-item Hamilton Depression Rating Scale (HDRS), the

Hamilton Anxiety Rating Scale (HARS) and the Montgomery-Asberg Depression Rating Scale (MADRS). A therapeutic index was also determined. It was a 16-point scale that combined an evaluation by the doctor, both on the therapeutic effects (4-point scale: excellent, good, poor, or no effect) and on the adverse effects (4-point scale: none, light, important, or side-effect nullifying the therapeutic benefit). Compliance was judged to be satisfactory when at least 80% of the tablets had been taken. Tolerability was evaluated on the basis of the number and severity (mild, moderate or severe) of adverse events, the likelihood of a causal relationship (possible, probable, definite or unknown) to study drugs, vital signs (supine and standing blood pressure, and heart rate), body weight, laboratory values and ECG obtained at baseline and after 42 days of treatment.

Statistical analyses

Patients were randomized in blocks of six by means of randomization tables. The comparability of the two groups was assessed on day 0 using the Chi-square test for discrete variables and Student's *t*-test for continuous variables. The effects of moclobemide and pirlindole on continuous variables, such as the HDRS, HARS and MADRS, were compared using an analysis of variance for repeated measurements with the factor 'treatment', 'time' and the interaction 'time × treatment'. A standard analysis (per protocol analysis) including completer patients only, and an intent-to-treat analysis including all patients evaluable for efficacy, were performed. When the interaction was significant, *post-hoc* intra-group comparisons were made using paired *t*-tests, and between-group comparisons were made using independent *t*-tests. The effects of moclobemide and pirlindole on discrete variables, such as the therapeutic index and side-effects percentages, were compared using the Chi-square test or the Mann-Whitney test. A probability of less than 5% (two-tailed) was considered to be indicative of statistical significance. Calculations were performed using the SPSS statistical package.

Results

Description of the study population

A total of 116 patients were included in this study. Five patients were lost to follow-up between day 0 and day 7. Thus 111 patients (52 patients in the pirlindole group and 59 patients in the moclobemide group) were considered for the efficacy and tolerability analyses. In total, 34 patients (17 patients in the pirlindole group and 17 patients in the moclobemide group) discontinued the treatment prematurely. In all, 77 patients completed the 6-week treatment period (35 patients on pirlindole and 42 patients on moclobemide) (Table 1). The two groups did not differ significantly from each other with regard to the majority of baseline characteristics. However, the HDRS and the MADRS scores were significantly higher ($P<0.05$ and $P<0.01$, respectively) in the pirlindole group (Table 2).

Concomitant medication

There were no significant differences between the two groups with regard to prescription of lormetazepam or dipotassic clorazepate ($P>0.05$, Chi-square test). On day 7, 75% and 71% of patients were taking lormetazepam in the pirlindole and moclobemide groups, respectively. On day 42, these percentages were 79% and 71%, respectively. On day 7, 40% and 44% of patients (hospitalized patients) were taking dipotassic clorazepate in the pirlindole and moclobemide groups, respectively. On day 42, these percentages were 18% and 32%, respectively. In total, 17 patients were taking lithium (7 patients in the pirlindole group and 10 patients in the moclobemide group).

Efficacy

Efficacy was evaluated for completers only ($n=77$), as well as on an intention-to-treat basis including all patients evaluable for efficacy ($n=111$). Compliance was judged to be excellent in all patients.

Completers only (n=77)

Both treatment groups showed highly significant improvements in their HDRS, HARS and

Table 1. Total enrolment in the study and numbers of completers and non-completers, with reasons for withdrawal

	Pirlindole	Moclobemide	Total
Patients included	56	60	116
Patients lost to follow-up after day 0	4	1	5
Patients evaluable for efficacy and safety	52	59	111
Patients who withdrew after day 7 because of:	17	17	34
Side-effects	11	8	
Inefficacy of the treatment	5	6	
Subject felt his or her condition had improved	1	3	
Patients who completed the study	35	42	77

Table 2. Description of the study population ($n=111$)

	Pirlindole ($n=52$)	Moclobemide ($n=59$)	Probability[a]
Mean age (±SD) (years)	47.0±12.9	43.4±12.7	NS[b]
Sex			
Male (%)	35	30	NS
Female (%)	65	70	
Mean weight (±SD) (kg)	68.7±11.3	69.4±12.6	NS
Patient status			
In-patient (%)	52	54	NS
Out-patient (%)	48	46	
Mean HDRS score (±SD)	27.0±5.1	25.1±4.6	$P=0.04$
Mean HARS score (±SD)	26.0±7.0	24.6±4.8	NS
Mean MADRS score (±SD)	35.8±5.8	32.6±6.4	$P=0.007$
DSM-III-R classification			
296.2 (%)	17	9	NS
296.3 (%)	62	69	
296.5 (%)	21	22	

[a] Student's *t*-tests for continuous variables and Chi-square test for discrete variable.
[b] NS, non-significant.

MADRS scores over time ($P<0.001$, ANOVA), the decrease being significant from day 7. However, the pattern of development of the three scores in the two groups did not differ significantly ($P>0.05$, ANOVA) (Figs 1–3). After 42 days of treatment, an improvement of ≥50% in the HDRS score was measured in 80% and 67% of patients in the pirlindole and moclobemide groups, respectively ($P>0.05$, Chi-square test). The same improvement in the HARS score was measured in 74% and 67% of patients in the pirlindole and moclobemide groups, respectively ($P>0.05$, Chi-square test). The same improvement in the MADRS score was measured in 74% and 71% of patients in the pirlindole and moclobemide groups, respectively ($P>0.05$, Chi square test). Taking into account the therapeutic index, the efficacy of the treatment was judged to be good or excellent in 85% and 76% of patients in the pirlindole and moclobemide groups, respectively ($P>0.05$, Mann-Whitney test).

Intent-to-treat analysis (n=111)

Similar results with regard to reduction in mean total HDRS, HARS and MADRS scores were obtained when all patients evaluable for efficacy were included (Figs 4–6). At the endpoint, an improvement of ≥50% in the HDRS score was measured in 62% and 56% of patients in the pirlindole and moclobemide groups, respectively ($P>0.05$, Chi-square test). The same improvement in the HARS score was measured in 50% and 58% of patients in the pirlindole and moclobemide groups, respectively ($P>0.05$, Chi-square test). The same improvement in the MADRS score was measured in 54% and 61% of patients in the pirlindole and moclobemide groups, respectively ($P>0.05$, Chi-square test).

Tolerability (n=111)

A total of 30 (58%) patients on pirlindole and 33 (56%) patients on moclobemide experienced adverse effects that were considered to be possibly or probably related to administration of the study drug. The difference between the two groups was non-significant ($P>0.05$, Chi-square test). Table 3 shows the frequencies of side-effects in both treatment groups. Pirlindole tended to induce more

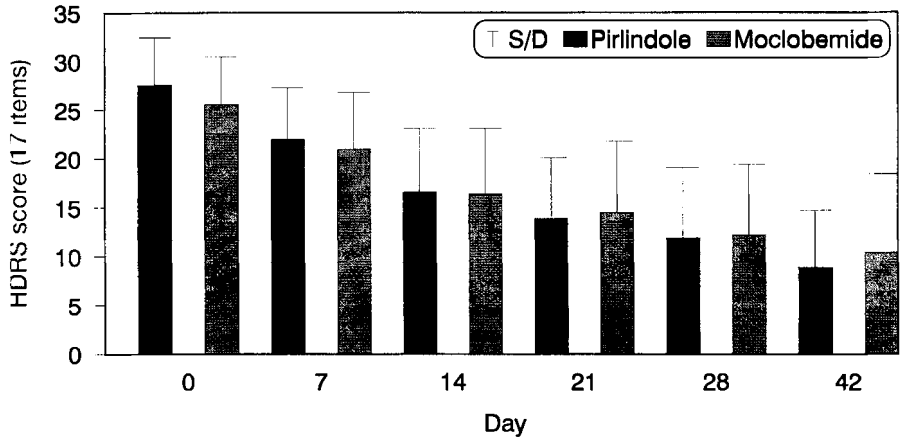

Fig. 1. Change of the HDRS score (17 items) for completer patients ($n=77$; pirlindole, $n=35$; moclobemide, $n=42$). Results are expressed as mean values ± SD. All of the differences vs. baseline were statistically significant from day 7 to day 42 in both groups ($P<0.01$; ANOVA for repeated measurements followed by paired *t*-tests).

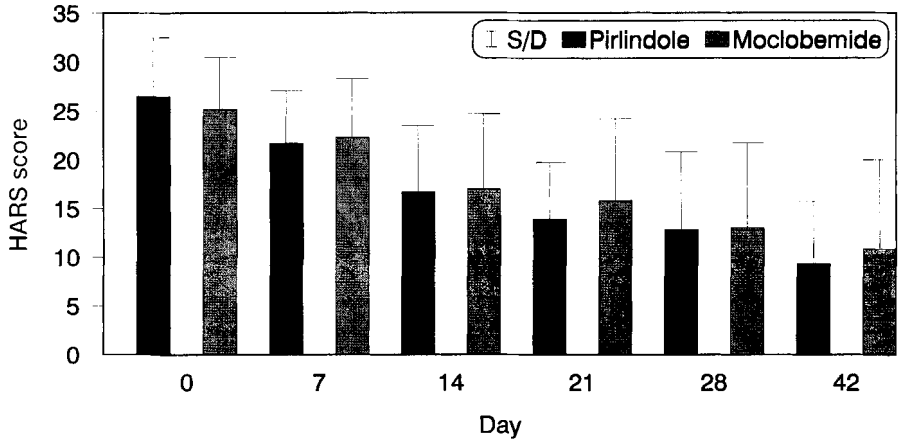

Fig. 2. Change of the HARS score for completer patients (n=77; pirlindole, n=35; moclobemide, n=42). Results are expressed as mean values ± SD. All of the differences vs. baseline were statistically significant from day 7 to day 42 in both groups (P<0.01; ANOVA for repeated measurements followed by paired t-tests).

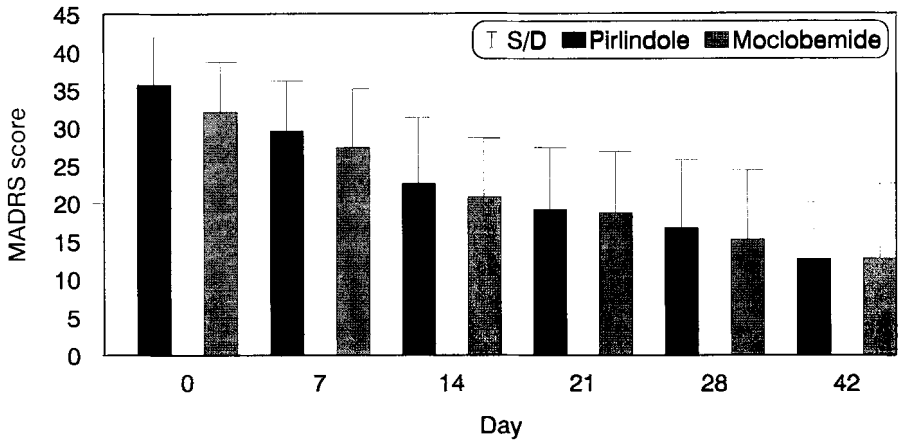

Fig. 3. Change of the MADRS score for completer patients (n=77; pirlindole, n=35; moclobemide, n=42). Results are expressed as mean values ± SD. All of the differences vs. baseline were statistically significant from day 7 to day 42 in both groups (P<0.01; ANOVA for repeated measurements followed by paired t-tests).

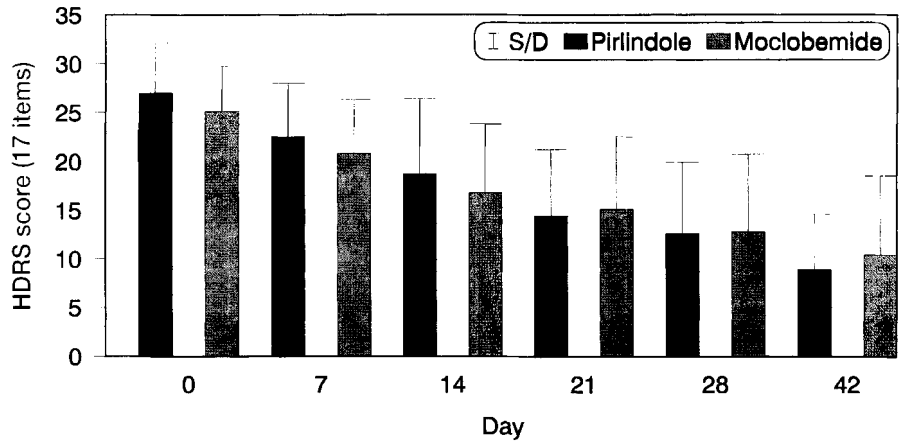

Fig. 4. Change of the HDRS score (17 items) for all patients evaluable for efficacy on an intent-to-treat basis (n=111; pirlindole, n=52; moclobemide, n=59). Results are expressed as mean values ± SD. All of the differences vs. baseline were statistically significant from day 7 to day 42 in both groups (P<0.01; ANOVA for repeated measurements followed by paired t-tests).

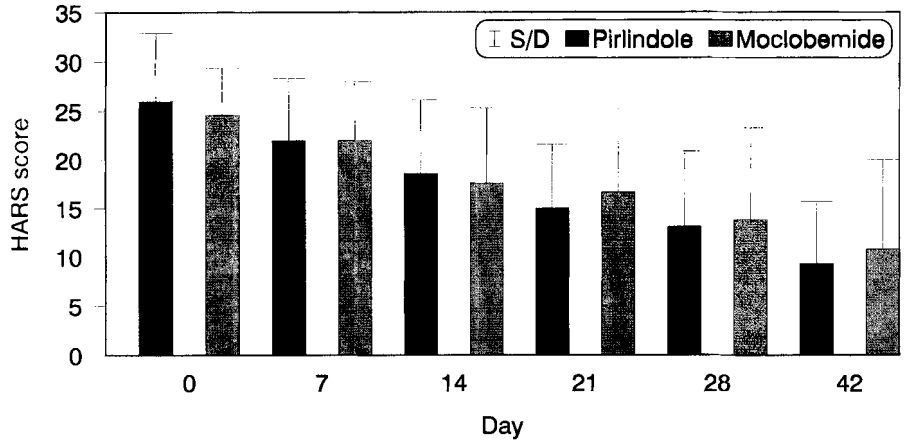

Fig. 5. Change of the HARS score for all patients evaluable for efficacy on an intent-to-treat basis (n=111; pirlindole, n=52; moclobemide n=59). Results are expressed as mean values ± SD. All of the differences vs. baseline were statistically significant from day 7 to day 42 in both groups (P<0.01; ANOVA for repeated measurements followed by paired t-tests).

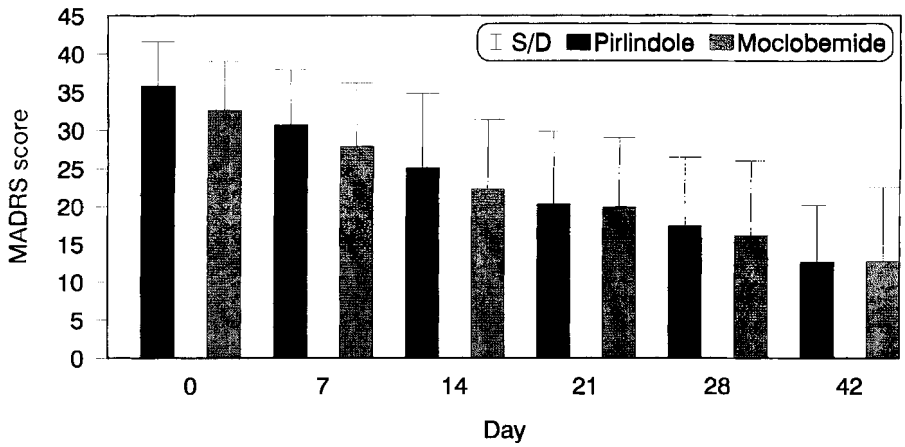

Fig. 6. Change of the MADRS score for all patients evaluable for efficacy on an intent-to-treat basis (n=111; pirlindole, n=52; moclobemide, n=59). Results are expressed as mean values ± SD. All of the differences vs. baseline were statistically significant from day 7 to day 42 in both groups (P<0.01; ANOVA for repeated measurements followed by paired t-tests).

agitation (31% vs. 27% for moclobemide), headache (23% vs. 19% for moclobemide), tremor (10% vs. 5% for moclobemide) and nausea/vomiting (23% vs. 19% for moclobemide), while moclobemide tended to induce more confusion (5% vs. 2% for pirlindole), fatiguability (12% vs. 4% for pirlindole), sedation (5% vs. 0% for pirlindole), insomnia (17% vs. 13% for pirlindole), dizziness (12% vs. 6% for pirlindole), constipation (10% vs. 4% for pirlindole) and sweating (14% vs. 4% for pirlindole). All of these differences were non-significant (P>0.05, Chi-square test). However, moclobemide caused dry mouth (P<0.05) and tachycardia (P<0.05) significantly more often than pirlindole. There was no relevant modification of mean systolic or diastolic blood pressure (standing or supine) during the trial, and there was no evidence of clinically important drug-related changes in laboratory values. Physical examination findings and body weight were not affected to a clinically and statistically relevant degree in either treatment group.

Discussion

The present study was designed to evaluate the efficacy and tolerability of pirlindole compared to moclobemide (two selective reversible MAO-A inhibitors) in the treatment of major depression. A marked antidepressant effect was noted in both treatment groups from day 7 to day 42 of administration. However, the treatment results in the two groups showed no difference in any of the rating methods used (HDRS, HARS and MADRS). These results tend to corroborate those obtained

Table 3. Incidence of adverse events in the 111 'intent-to-treat' patients

	Side-effects (%)		
	Pirlindole ($n=52$)	Moclobemide ($n=59$)	Probability[a]
Concentration difficulties	4	5	NS[b]
Confusion	2	5	NS
Fatiguability	4	12	NS
Sedation	0	5	NS
Insomnia	13	17	NS
Dizziness	6	12	NS
Agitation	31	27	NS
Aggressiveness	2	0	NS
Headache	23	17	NS
Tremor	10	5	NS
Nausea/vomiting	23	19	NS
Diarrhoea	6	3	NS
Constipation	4	10	NS
Dry mouth	6	19	$P=0.04$
Accommodation disturbances	4	2	NS
Tachycardia	4	15	$P=0.04$
Sweating	4	14	NS
Hypertension	0	2	NS
Hypotension	4	5	NS
Sexual dysfunction	0	0	NS
Nasal congestion	2	0	NS
Rash	0	0	NS
Pruritus	0	0	NS

[a] Chi-square test.
[b] NS, non-significant.

in previous double-blind and open studies with pirlindole, demonstrating that it is an efficacious antidepressive drug comparable to amitriptyline (23), imipramine (22), desipramine (26), maprotiline (21) and mianserin (27). They also corroborate the recognized antidepressant efficacy of moclobemide (1, 10–14). Furthermore, it is interesting to note that both pirlindole and moclobemide produced a significant decrease in the HARS score that attests to their efficacy in treating the anxious components of depression.

So far as tolerability is concerned, the global frequency of side-effects that were probably or possibly related to the medication did not differ significantly between the two treatment groups. Pirlindole tended to induce more agitation, headache, tremor and nausea/vomiting, while moclobemide tended to induce more confusion, fatiguability, sedation, insomnia, dizziness, constipation and sweating, but these differences were non-significant. However, the frequency of dry mouth and tachycardia was significantly greater in the moclobemide group (19% and 15%, respectively) compared to the pirlindole group (6% and 4%, respectively). These results confirm the findings of the most recent study conducted with pirlindole vs. placebo, in which the frequency of dry mouth and tachycardia associated with pirlindole treatment was 2% and 0%, respectively (20). They also confirm the findings of the majority of studies conducted with moclobemide, in which the frequency of tachycardia ranges from 5% (28) to 11% (29), and the frequency of dry mouth ranges from 17% (30) to 33% (29). In global terms, the frequency of anticholinergic side-effects (dry mouth, constipation and sweating) was lower in the pirlindole group than in the moclobemide group.

In conclusion, this clinical trial confirms the potential of RIMAs such as moclobemide and pirlindole for the treatment of unipolar (single or recurrent episodes) and bipolar depression. It also demonstrates that pirlindole has an antidepressant effect comparable to that of moclobemide. The global adverse events frequencies were comparable. The frequency of dry mouth and tachycardia associated with pirlindole treatment was significantly lower than that related to moclobemide treatment. The incidence of all other side-effects was not significantly different between the two drugs.

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