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# Moclobemide and Sertraline in the Treatment of Melancholic and Nonmelancholic Major Depression: A Comparative Study

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The objectives of this study were first to compare the responses to moclobemide and sertraline in melancholic and nonmelancholic major depressive patients and secondly to compare the responses of melancholic and nonmelancholic patients in general. Sixty-three patients, with diagnosis of major depression according to the DSM-III-R criteria were included in the study. In this single blind, comparative, randomized study, 29 patients were treated with moclobemide and 34 patients were treated with sertraline for 13 weeks. A 50 per cent decrease of the HDRS (Hamilton Depression Rating Scale) is defined as response.

In intent-to-treat analysis the response rates were 69 per cent in the melancholic patients and 59·3 per cent in the nonmelancholic group. The difference is statistically insignificant. According to the intent-to-treat analysis in the nonmelancholic group the response rate of the moclobemide-treated patients was 73·3 per cent, and 41·7 per cent in the sertraline-treated patients. In the melancholic group the response rate was 82·4 per cent in the sertraline group and 50 per cent in the moclobemide group. Moclobemide was more effective in the nonmelancholic group whilst sertraline was more effective in melancholic group; but the differences were not statistically significant. Due to the small size our findings are tentative and need confirmation using more patients. © 1998 John Wiley & Sons, Ltd.

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KEY WORDS — depression treatment; melancholic depression; nonmelancholic depression; sertraline; moclobemide

## INTRODUCTION

There is some evidence that there are different phenomenological subtypes of major depression that respond preferentially to different classes of antidepressants (Preskorn, 1994). For many years, research and clinical data has shown that patients with endogenous/melancholic depression are more responsive to somatic treatment than are nonmelancholic depressed patients (Rush and Weissenburger, 1994). For example most studies indicate that depressed patients with melancholia respond better to tricyclic antidepressants (TCAs) than do patients with nonmelancholic depression. On the other hand atypical depressive patients respond preferentially to MAO inhibitors (Charney *et al*., 1995).

Since their introduction, the selective serotonin reuptake inhibitors (SSRIs) have become one of the most widely used classes of antidepressants in psychiatry. Some studies suggest that the SSRIs have different rates of efficacy for different affective syndroms (Dubovsky and Thomas, 1995). Some clinicians have suggested that SSRIs are less effective than the TCAs in treatment of severe inpatient cases of major depression; however, prospective data addressing this issue are limited (Preskorn *et al*., 1995). Sertraline is a new potent SSRI that is effective in acute depression. It is one of the SSRIs frequently chosen by the clinicians as the first-line drug in the treatment of major depression, causing significantly fewer side-effects than conventional antidepressants (Cole, 1992).

Moclobemide is the first of a new class of reversible inhibitors of monoamine oxidase (RIMA).

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In comparative trials moclobemide has proved equally effective in the treatment of depression as tricyclic antidepressants and SSRIs (such as fluoxetine) with a better side-effect profile (Youidim, 1995). According to some meta-analyses the efficacy of moclobemide appeared to be slightly more effective than imipramine in treating nonmelancholic depressive patients (Angst and Stabl, 1992).

As some clinical types of major depressive episodes may have varying responses to particular antidepressants, this study was designed to compare a RIMA (reversible inhibitor of mono amino oxidase A) antidepressant moclobemide with an SSRI (sertraline) with respect to subtypes of depression (melancholic versus nonmelancholic) in outpatients. Another aim of this study is to compare the response rates of the melancholic and nonmelancholic patients in general, regardless of the type of drug.

## METHODS

This is a prospective, randomized clinical trial conducted at the psychiatry clinic of the Social Security Hospital in Ankara. Those eligible for the study were outpatients ($n = 63$) aged 18–65 years, fulfilling the DSM III-R (APA, 1987) criteria for major depression.

Patients with a high suicidal risk, significant organic illness, alcohol or drug abuse, eating disorder, multiple drug reactions, purgative abuse, ECT within 6 months, depot neuroleptic use within the last 1 month, and women with child-bearing potential who were not using an effective form of contraception or who were pregnant/breast feeding were excluded.

The study was approved by the Ethics Committee of SSK Ankara Hospital. All patients gave written informed consent for their participation in the study. A physical and a neurological examination were performed on admission to the study and at the end of the treatment. An ECG and laboratory panel were done at baseline and at the end of the treatment.

Baseline measures for blood pressure, heart rate and body weight were obtained on the first visit and monitored throughout the study. No significant change was observed in these parameters throughout the study.

### *Medication*

The patients were randomized to receive either moclobemide ($n = 29$) or sertraline ($n = 34$) after the wash-out period. The subjects who were still receiving an antidepressant agent had a wash-out period of at least 1 week for TCAs, 2 weeks for MAOIs and 1 month for fluoxetine. The single blind period of the study was 13 weeks. The starting dose of moclobemide was 300 mg and that of sertraline was 50 mg/day. After 3 weeks, for patients who could not achieve a 25 per cent reduction on HDRS scores, the daily dosages were increased to 450 mg for moclobemide and to 100 mg for sertraline. The dosages, depending on their efficacy and tolerability, were increased to a maximum of 600 mg for moclobemide and to 200 mg for sertraline daily. The use of concomitant psychotropic medication was limited to benzodiazepines, analgesics and neuroleptics, if needed. During the study, patients were not required to avoid tyramine-rich food.

### *Assessment*

The subjects were all diagnosed according to DSM III-R criteria with SCID (Structured Clinical Interview for DSM III-R) (Spitzer *et al.*, 1990). Patients were assessed on admission and after 1, 2, 3, 5, 7, 9 and 13 weeks using the Clinical Global impression scale (CGI) (Guy, 1976) and the 17-item Hamilton Depression Rating Scale (HDRS) (Hamilton, 1969). The side-effects were assessed by UKU Side Effects Scale (Lingjaerde *et al.*, 1987). Patients responding to treatment were defined as having at least a 50 per cent decrease in HDRS total score between the baseline and the final visit. The raters were blind to the drug that the patient was using as the assessment of side-effects and the prescription of the drugs were performed by a clinician other than the rater group.

### *Statistical methods*

The statistical analyses were made with the SPSSwin version 5.01 statistical program. For the qualitative data, the two groups were compared with chi square tests and Fisher's exact test was used when necessary. *t*-Test was used for the comparison of mean scores. Patients who had a baseline evaluation and at least one follow-up evaluation visit were included in the intent-to-treat analysis ($n = 56$). Missing data were replaced by carrying forward the previous measurements for intent-to-treat analysis.

In this study the level of statistical significance was fixed at 0·05.

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## RESULTS

Of the 63 patients, seven were excluded from the study as they did not return to at least one follow-up assessment after the baseline visit, two were from the moclobemide group and five were from the sertraline group. Characteristics of all patients can be seen in Table 1. Of the remaining 56 patients, 30 patients completed the 13-week trial. Patients who were randomized to two treatment groups were comparable for age, gender, mean baseline HDRS scoring and CGI severity (Table 1).

### *Drug dosage*

In the moclobemide group two patients and in the sertraline group five patients completed the study with their initial doses, 300 mg and 50 mg, respectively. Five patients in the moclobemide group received the maximum dose of 600 mg at the end of the trial, whereas two patients in the sertraline group were then on the maximum dose of 200 mg. The mean daily dose of moclobemide during the last week of treatment was 461·5 mg (SD = 96·1); the corresponding dose of sertraline was 103·1 mg (SD = 49·9). In the moclobemide group, there was no dose reductions but in the sertraline group dose reductions were necessary for two patients because of adverse effects.

### *Concomitant medication*

Benzodiazepines were prescribed for a total of 12 patients for anxiety and insomnia. Seven of them were receiving moclobemide and the others were receiving sertraline. In this study no patients received lithium.

### *Efficacy*

Response to treatment was analysed using two methods. Firstly, in the standard analysis only valid cases treated for 13 weeks included ($n = 30$). In this analysis the mean total scores of the HDRS (Figure 1), CGI-severity and CGI-improvement showed a steady decline for both treatment groups. Mean HDRS scores of both treatment groups at baseline and week 13 were compared (Table 2); no statistically significant differences were found between the two groups. According to HDRS mean scores, the analysis showed a significant time effect in both treatment groups, but the difference between the two treatment groups was not significant (Table 2; Figure 1).

Table 1. Demographic and clinical features according to the treatment groups

| Variables | Moclobemide | Sertraline |
|---|---|---|
| Sex *n*(%) | | |
| Men | 10 (34·5) | 13 (38·2) |
| Women | 19 (65·5) | 21 (61·8) |
| Diagnostic subtype *n* (%) | | |
| Melancholic | 16 (55·2) | 15 (44·1) |
| Nonmelancholic | 13 (44·8) | 19 (55·9) |
| Drug use in last 6 months *n* (%) | 4 (30·8) | 9 (68·2) |
| Age mean years (±SD) | 33·3 (±8·1) | 33·4 (±11·4) |
| Severity of depression HDRS mean (±SD) | 21·9 (±7·2) | 23·5 (±7·3) |
| Severity of depression CGI mean (±SD) | 4·4 (±1·0) | 4·7 (±1·0) |

Table 2. First week and week 13 mean HDRS scores (*t*-test) (Standard analysis, $n = 30$)

| | First week: HDRS Mean (±SD) | 13th week HDRS Mean (±SD) | *p* |
|---|---|---|---|
| Moclobemide | 22·6 (±6·6) | 8·6 (±5·8) | $< 10^{-3}$ |
| Sertraline | 25·2 (±6·9) | 8·8 (±8·1) | $< 10^{-3}$ |

Secondly, the response rate was calculated at the percentage of patients achieving a reduction of 50 per cent or more on the HDRS scores in comparison with pre-treatment baseline scores. In 'intent-to-treat' analysis ($n = 56$), the response rate was found to be 64·3 per cent for the total group, 63·0 per cent for the moclobemide group and 65·5 per cent for the sertraline group. The difference between the two treatment groups was not significant (chi square = 0·039, $p = 0·84$).

### *Efficacy in melancholic and nonmelancholic groups*

Of the 63 patients who entered the study, 32 fulfilled the criteria for DSM-III R melancholic type major depression (DSM-III-R Melancholic Major Depression criteria; Table 3).

In intent-to-treat analysis the response rates in the melancholic and nonmelancholic groups were 69 per cent and 59·3 per cent, respectively. The difference between groups was not statistically significant (chi square = 0·57, $p = 0·44$). In standard analysis ($n = 30$) the response rates in the melancholic and nonmelancholic groups were 82·4 per cent and 69·2 per cent (chi square = 0·70, $p = 0·39$).

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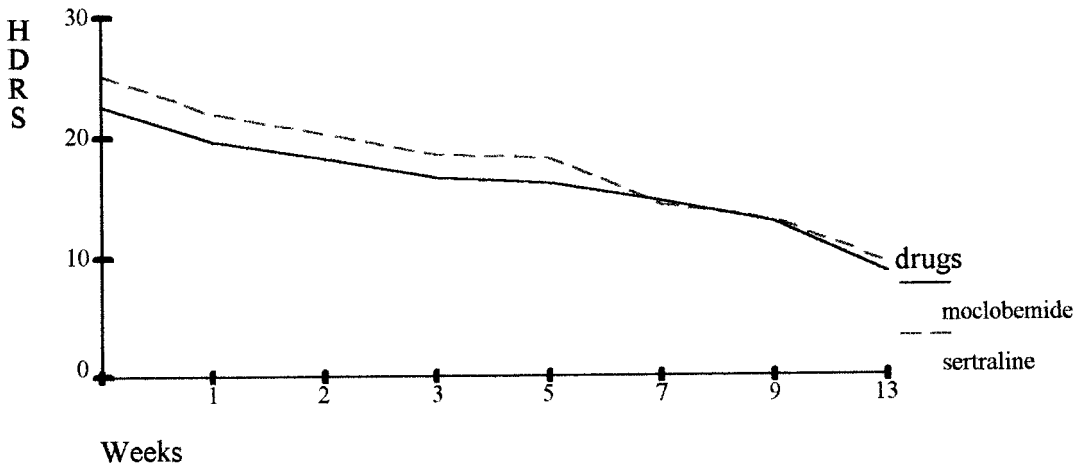


Figure 1. Mean values of total HDRS scores for completers over 13 weeks

*Efficacy of drugs in nonmelancholic patients*

According to the intent-to-treat analysis in the nonmelancholic group the response rate of the moclobemide-treated patients was 73·3 per cent and 41·7 per cent in the sertraline-treated patients (Figure 2; Table 4). The two groups showed no difference statistically ($p = 0{\cdot}96$, chi square $= 2{\cdot}76$). According to the standard analysis in the nonmelancholic group, 87·5 per cent of the moclobemide patients and 40 per cent of the sertraline patients were identified as responders after 13 weeks. The difference was again statistically insignificant ($p = 0{\cdot}07$, chi square $= 3{\cdot}25$).

*Efficacy of drugs in melancholic patients*

In intent-to-treat analysis the treatment response in the melancholic group was 50 per cent and 82·4 per cent for moclobemide and sertraline, respectively. The difference was not significant ($p = 0{\cdot}06$; chi square $= 3{\cdot}44$) (Figure 2; Table 4). If we compare the incidence of responders in standard analysis, again sertraline is more efficient (91·7 per cent versus 60 per cent $p = 0{\cdot}19$; chi square $= 2{\cdot}43$); however there is no statistically significant difference between moclobemide and sertraline.

Table 3. DSM-III-R diagnostic criteria for melancholic type major depression

The presence of at least five of the following

(1) Loss of interest or pleasure in all, or almost all, activities
(2) Lack of reactivity to usually pleasurable stimuli
(3) Depression regularly worse in the morning
(4) Early morning awakening
(5) Psychomotor retardation or agitation
(6) Significant anorexia or weight loss
(7) No significant personality disturbance before first major depressive episode
(8) One or more previous major depressive episodes followed by complete or nearly complete, recovery
(9) Previous good response to specific and adequate somatic antidepressant therapy, e.g. tricyclics, ETC, MAOI, lithium

*Premature termination*

A total of 26 patients terminated treatment prematurely. There were 14 (53·8 per cent) in moclobemide group and 12 (46·2 per cent) in sertraline group. The difference between groups in respect to age, gender, mean baseline HDRS scores and CGI severity were not significant. Furthermore, there were no differences regarding their response

Table 4. Response rate according to the depression subtypes (chi-square) (Intent-to-treat analysis, $n = 56$)

| | Moclobemide *n*(%) | | Sertraline *n*(%) | | |
|---|---|---|---|---|---|
| Subtypes of depression | Responders | Non-responders | Responders | Non-responders | *p* |
| Melancholic ($n = 29$) | 6 (50·0) | 6 (50·0) | 14 (82·4) | 3 (17·6) | 0·063 |
| Nonmelancholic ($n = 27$) | 11 (73·3) | 4 (26·7) | 5 (41·7) | 7 (58·3) | 0·096 |

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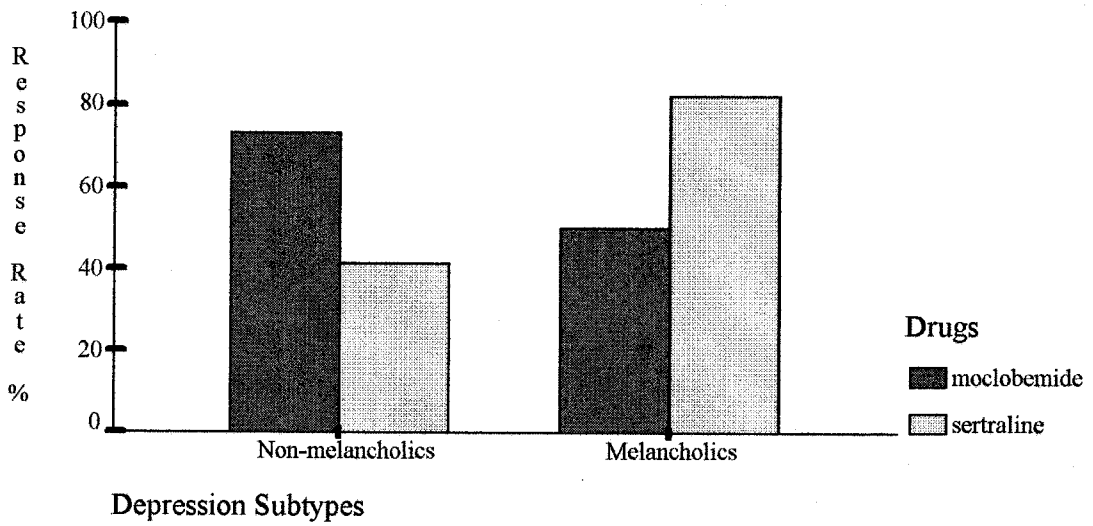


Figure 2. Response rates in nonmelancholic and melancholic patients

rate to treatment between the groups at week 3 (chi square = 1·9, $p = 0{\cdot}17$). These patients were included for analysis considering efficacy in intent-to-treat analysis.

*Safety and tolerance*

As the primary tolerability parameter, we compared the two treatment groups in terms of frequency of newly emerging side-effects throughout the 13-week therapy period using the UKU scale. The most frequent side-effects for moclobemide were dry mouth ($n = 15$), headache ($n = 13$), insomnia ($n = 12$) and tremor ($n = 11$), while for sertraline they were dry mouth ($n = 17$), headache ($n = 15$), nausea ($n = 14$), anorexia ($n = 13$), tremor ($n = 13$), insomnia ($n = 12$), and sweating ($n = 12$). Compared to the moclobemide group constipation ($n = 5$ in the sertraline group, $p = 0{\cdot}03$) and sweating ($p = 0{\cdot}02$) were seen more frequently statistically significantly in the sertraline group. Tolerance in general was better in the moclobemide group, mainly due to a lower frequency of gastrointestinal side-effects. The overall side-effect profile of moclobemide and sertraline is shown in Figure 3.

## DISCUSSION

The first finding of this study was that the response rate of melancholic patients was comparable to the nonmelancholic patients. Despite the common belief in the literature that 'melancholics are particularly responsive to somatic treatment', there is no definite research confirming this. Peselow *et al.* examined the effects of somatic treatment and placebo in patients with and without DSM-III endogenous/melancholic depression and concluded that depressed patients with melancholia were not particularly different from depressed patients without melancholia in their responses to antidepressant medication (Peselow *et al.*, 1992).

The second objective of our study was to compare the efficacy of moclobemide and sertraline in melancholic and nonmelancholic depressive patients.

In our study, moclobemide was more effective in the nonmelancholic group in contrast to sertraline which was more effective in melancholic group; the fact that the differences were not statistically significant may be due to the small size of the groups. Also the small sample size of our study and the large number of patients who failed to complete the study significantly reduces the validity of the findings. In our recent study the antidepressant efficacy of sertraline and moclobemide in depressive patients was closely comparable (Orsel-Donbak *et al.*, 1995). The samples of this study comprised mixed minor depressive (dysthimic, depression NOS, depressive adjustment disorder) and major depressive patients. The response rate of melancholic patients to moclobemide was evaluated by means of some meta-analysis. Angst and Stabl (1992) performed a meta-analysis of different

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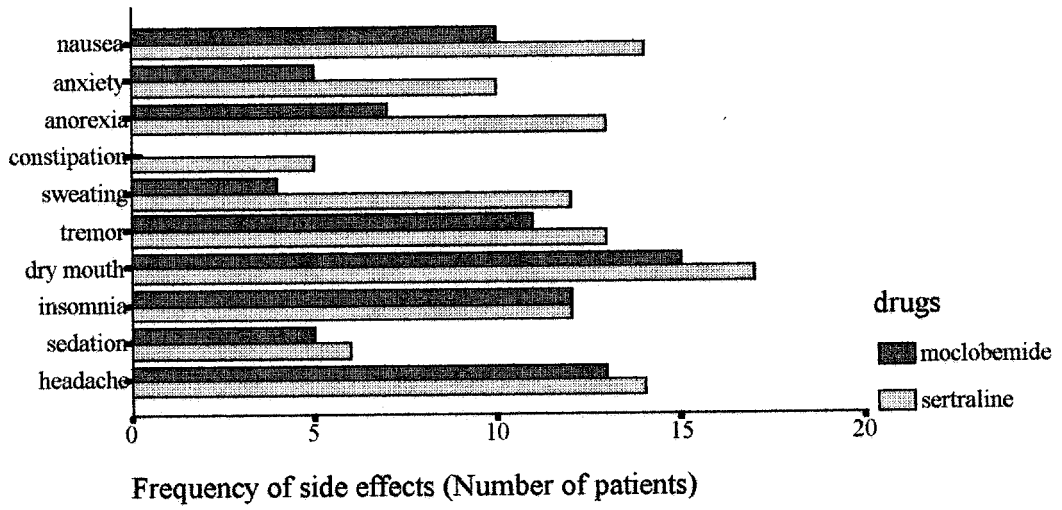


Figure 3. Side-effect profile

studies comparing moclobemide and reference drugs, based on a total of 1405 patients. According to the DSM-III-R melancholia criteria in the moclobemide group the percentage of responders (at CGI — very good and good) was slightly higher in the nonmelancholic (62·7 per cent) compared with the melancholic patients (59·6 per cent). In imipramine-treated patients, the difference was reversed (61·8 per cent responders in melancholic and 55·3 per cent in nonmelancholic patients). Moclobemide has been reported by one group to be less efficacious than clomipramine in difficult-to-treat populations of patients (Danish University Antidepressant Group, 1993). But some studies did not find a difference in response rate with regard to melancholic subtyping. Lecrubier and Guelfi (1990) compared moclobemide and clomipramine in non-endogenous depressive patients and the two drugs were found to produce equivalent degrees of improvement. In a double-blind randomized trial, moclobemide was compared with clomipramine in patients suffering from endogenous depression (according to the ICD-9 and Newcastle scale). No significant differences in efficacy were seen between the treatment groups (Guelfi *et al.*, 1992).

This efficacy profile of moclobemide which was seen in Angst and Stabl's (1992) analysis is similar to our study. We have no data to explain this efficacy profile. Maybe the difference in the mechanism of action of the drugs plays a role. Another explanation for this tendency can be the different tolerability of the drugs. When compared to sertraline and imipramine (Baldwin and Rudge, 1994) moclobemide appears to be a relatively well tolerated drug. This can be an important point for the nonmelancholic patient. May be poor tolerance has a negative effect on the response rate in nonmelancholic patients; on the other hand side-effects of drugs was not as important as in melancholic patients.

Contrary to the general belief that SSRIs are less effective in severe cases of major depression, another interesting finding of our study was that sertraline proved to be more efficient in the melancholic depressed group, although the results revealed no significant difference. There are conflicting findings about the efficacy of SSRIs in melancholic patients. Two studies of clomipramine versus paroxetine or citalopram for the treatment of hospitalized endogenous major depression found this TCA to be superior to the comparative SSRI (Danish University Antidepressant Group, 1986, 1990). There is another study which compares the responses to fluoxetine and nortriptyline of older patients with severe depression. As a result of this study fluoxetine appeared to be significantly less effective than nortriptyline (Roose *et al.*, 1994). We have no data comparing the efficacy of moclobemide and setraline in melancholic patients. But in a published meta-analysis of four studies on sertraline, there was no difference between the response rate of DSM-III melancholic and nonmelancholic patients (Burton, 1993). Also of interest is the Norwegian study comparing sertraline and mianserin; sertraline was found to be

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significantly superior to placebo in patients with melancholia, whereas there was no significant difference between mianserin and placebo in this respect (Malt, 1995).

In conclusion our study implies that sertraline and moclobemide may have different spectra of efficacy in respect to the DISM-III-R melancholic–nonmelancholic subtypes of major depression. Because of the small sample size of our study group, our findings are tentative. For this reason, further large-scale double-blind studies are needed to determine whether these two drugs have unique spectra of efficacy with respect to the melancholic–nonmelancholic dichotomy.

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