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# A DOUBLE-BLIND COMPARATIVE TRIAL WITH MIANSERIN AND AMITRIPTYLINE IN OUTPATIENTS WITH MAJOR DEPRESSIVE DISORDERS

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**1** A double-blind trial with parallel treatment groups was conducted to compare the safety and efficacy of mianserin with amitriptyline.

**2** This was a six week trial with weekly visits. Measurements at each visit included: 21 item Hamilton Depression (HAMD) Scale, Clinical Global Impression (CGI) Scale and Treatment Emergent Symptom Scale (TESS).

**3** Mianserin and amitriptyline were comparable with respect to efficacy.

**4** More adverse experiences were reported by amitriptyline patients. The predominant amitriptyline adverse experiences were of the anticholinergic type; the predominant mianserin adverse experience was drowsiness/fatigue.

**5** The Efficacy Index (EI), a scale combining efficacy and adverse experiences, clearly demonstrated the superiority of mianserin over amitriptyline.

## Introduction

Mianserin is a tetracyclic antidepressant compound which is structurally distinct from the classical tricyclic antidepressants and from bridged tricyclics of the maprotiline type. The antidepressant effects of mianserin are comparable to those of the classical antidepressants. However, its lack of cardiotoxicity and anticholinergic effects distinguishes it from the classical tricyclic antidepressants and maprotiline subtypes. The pharmacological profile of action of mianserin is different from that of the tricyclic antidepressants. It combines presynaptic $\alpha_2$-adrenoceptor blocking activity with antihistaminic properties, but has no central anticholinergic activity, and little effect on central serotoninergic mechanisms.

The superiority of mianserin over placebo has been established in double-blind, placebo-controlled clinical trials (Murphy *et al.*, 1976; Smith *et al.*, 1978; Magnus, 1979). Also, there appears to be no difference between divided daily doses or a single night-time dose (Montgomery *et al.*, 1978). However, the customary dosing is as a single bed-time dose.

The comparable efficacy of mianserin and amitriptyline has been demonstrated in clinical trials (Coppen *et al.*, 1976; Vogel *et al.*, 1976; Jaskari *et al.*, 1977; Daly *et al.*, 1979). However, the outstanding characteristic of mianserin as an antidepressant is its relative lack of side-effects. In clinical trials, anticholinergic effects have consistently occurred more often with tricyclics than with mianserin (Buck, 1980; Pichot *et al.*, 1978; Pinder *et al.*, 1980). In addition, in cases of overdose, mianserin has had a low potential for lethality, which is in contrast to the tricyclic antidepressants (Shaw, 1980). Also, mianserin has minimal drug–drug interaction when given with propranolol (Burgess *et al.*, 1978) and phenprocoumon (Kopera *et al.*, 1978).

The objective of this study was to compare the efficacy and safety of mianserin with amitriptyline in moderately depressed outpatients.

## Methods

This was a double-blind trial with parallel treatment groups. All patients fulfilled the Feighner criteria for primary depression and the Research Diagnostic Criteria (RDC) for major depressive disorders and at baseline had a minimum total score of 19 on the 21 item Hamilton Depression Scale (HAMD).

Mianserin and amitriptyline were prepared in identical capsules containing either 30 mg mianserin or 60 mg amitriptyline. Following an initial placebo washout period the patients followed a fixed-flexible dosing schedule which is described in Table 1.

Patients were seen at weekly intervals. At each visit measurements included the HAMD, Clinical Global Impression (CGI) Scale and Treatment Emergent Symptom Scale (TESS). All patients signed an informed consent and were given a pre-

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**Table 1** Dosing schedule

| | | *Treatment days* | | | | |
|---|---|---|---|---|---|---|
| | *Washout* | *0* | *3* | *7* | *10* | *14–42* |
| Capsules | 1 | 1 | 2 | 3 | 4[a] | 5[a] |
| Mianserin | Placebo | 30 | 60 | 90 | 120 | 150 |
| Amitriptyline | Placebo | 60 | 120 | 180 | 240 | 300 |

[a]At the discretion of the investigator.
Medication administered as a single bed-time dose

and post-study physical examination and a standard laboratory panel of a CBL, UA, blood chemistry and EKG. Eighty-one patients entered the trial. The demographic profiles and study characteristics at baseline of the two groups were comparable and are described in Tables 2 and 3, respectively.

Parametric and non-parametric analyses were performed using SAS 79.5 (Barr *et al.*, 1979). All reported *P* values are based on either two-sided Student's *t*-tests or chi-square tests. The Efficacy Index (EI) was computed according to the method described in the ECDEU Assessment Manual for Psychopharmacology (Guy, 1976).

**Table 2** Demographic profile of patients

| | *Mianserin* | *Amitriptyline* |
|---|---|---|
| Number of patients (*n*) | 41 | 40 |
| Age in years ($\bar{x} \pm SD$) | 40.8±13.0 | 40.4±12.1 |
| Sex (%) | 83F:17M | 75F:25M |
| Social class[a] | | |
| I | 2 | 0 |
| II | 3 | 6 |
| III | 18 | 18 |
| IV | 16 | 14 |
| V | 1 | 2 |

[a]Sum of weighted occupation and education scores (ECDEU) (1976). *Assessment Man.*, p. 80

**Table 3** Study characteristics at baseline

| | *Mianserin* | *Amitriptyline* |
|---|---|---|
| Number of patients (*n*) | 41 | 40 |
| Washout days | 8.9±3.6 (4–25) | 8.0±1.7 (5–12) |
| Hamilton Depression Score | 27.3±5.4 (19–41) | 26.5±4.1 (20–34) |
| Severity of illness (CGI) | 4.6±0.7 (4–7) | 4.5±0.5 (4–5) |

Values are mean±SD (range)

## Results

Of the 81 patients entering the study, five were eliminated from the efficacy analysis. Four patients did not meet the criteria for inclusion in the efficacy analysis, and the double-blind was broken on one patient prior to the first week of measurements. All patients were included in the analysis of adverse experiences. The mean prescribed doses for each weekly interval are described in Table 4. As described in Table 1, week 1 was a fixed titration period; therefore, mean doses for that interval are not shown. For the entire study, the mean daily dose of mianserin was 105 mg/day and for amitriptyline 154 mg/day.

**Table 4** Mean prescribed dose (mg/day)

| | *Treatment week* | | | | |
|---|---|---|---|---|---|
| | *2* | *3* | *4* | *5* | *6* |
| Mianserin | 89 | 100 | 115 | 113 | 110 |
| Amitriptyline | 147 | 163 | 151 | 164 | 177 |

Based on HAMD scores, both groups throughout the trial showed a significant improvement from baseline, but there was no difference between groups. The HAMD scores across the different time-frames are described in Figure 1. Also, the number of patients with a 50%

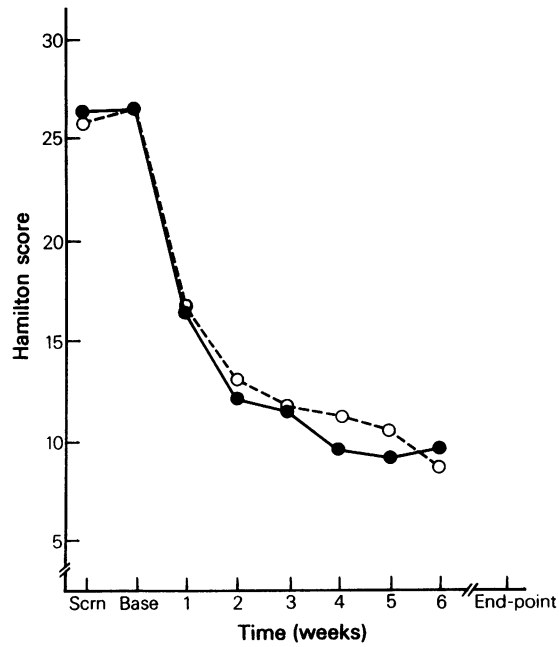


**Figure 1** Hamilton Depression scores for ● mianserin and ○ amitriptyline.

**Table 5** Number of patients with 50% reduction in Hamilton depression scores

| | *Mianserin* (*n*=37) | *Amitriptyline* (*n*=38) |
|---|---|---|
| Week 1 | 11 | 11 |
| Week 2 | 21 | 21 |
| Week 3 | 19 | 23 |
| Week 4 | 20 | 16 |
| Week 5 | 22 | 15 |
| Week 6 | 17 | 16 |
| End-point | 21 | 21 |

reduction in the baseline HAMD Scores is comparable for the two groups and is described in Table 5.

Severity of illness score for the CGI declined from a baseline value of 4.6 ($n=37$) to 3.07 ($n=29$) at week 3 for the mianserin group and from 4.5 ($n=38$) to 3.2 ($n=34$) for the amitriptyline group. At week 4, the mianserin score was 2.8 ($n=27$), and the amitriptyline score was 3.07 ($n=27$). Reasons for termination before four weeks are given in Table 6. Similarly, the Clinical Global Improvement Scores declined from a baseline value of 4.3 to 2.2 at week 3 for mianserin and from 4.6 to 2.2 for amitriptyline. At week 4, the mianserin score was 1.9 and the amitriptyline score was 2.1.

**Table 6** Reason for termination count (%)

| | *Mianserin* (*n*=37) | *Amitriptyline* (*n*=39) |
|---|---|---|
| Normal end of study | 24 (65) | 22 (56) |
| Drop-outs—Total | 13 (35) | 17 (44) |
| Did not return/ refused treatment | 1 (3) | 2 (5) |
| Adverse reaction | 2 (5) | 10 (27) |
| Lack of efficacy | 6 (16) | 5 (14) |
| Improvement | 2 (5) | 0 (0) |
| Dosage/medication violation | 1 (3) | 0 (0) |
| Administrative | 1 (3) | 0 (0) |

With respect to adverse experiences, there was a significant difference between the groups. Twenty-six of the 41 mianserin patients reported adverse experiences which were considered possibly, probably or definitely related to study medication; whereas, 39 of the 40 amitriptyline patients reported adverse experiences ($P<0.01$). The 26 mianserin patients reported 48 adverse experiences, and the 39 amitriptyline patients reported 132 adverse experiences. The number of subjects and number of adverse experiences by type are summarized in Table 7. The most commonly

**Table 7** Number of subjects (incidences) by adverse experience type

| | *Mianserin* | *Amitriptyline* |
|---|---|---|
| Cardiovascular | 0 (0) | 1 (2)[a] |
| Psychiatric | 3 (3) | 22 (25) |
| Neurological | 0 (0) | 1 (1) |
| Anticholinergic | 9 (15) | 27 (50) |
| Allergic | 0 (0) | 1 (1) |
| Gastrointestinal | 1 (1) | 4 (5) |
| Endocrine | 1 (1) | 1 (1) |
| Other[b] | 18 (28) | 32 (47) |

[a]Number of subjects (number of adverse experiences).
[b]Includes drowsiness/fatigue

reported adverse experiences for amitriptyline were anticholinergic, whereas, the most commonly reported for mianserin was drowsiness.

The Efficacy Index (EI) clearly demonstrates the superiority of mianserin over amitriptyline. At baseline, following the placebo washout period, the EI was 1.05 for the mianserin group and 1.01 for the amitriptyline group. At week 1, the mianserin EI was 1.85 and amitriptyline 1.20 ($P<0.005$). This superiority of mianserin continued throughout the trial and is illustrated in Figure 2. There were no significant differences noted in all laboratory data or EKGs taken at pre- and post-study evaluation. In addition no significant changes in physical examination status were noted.

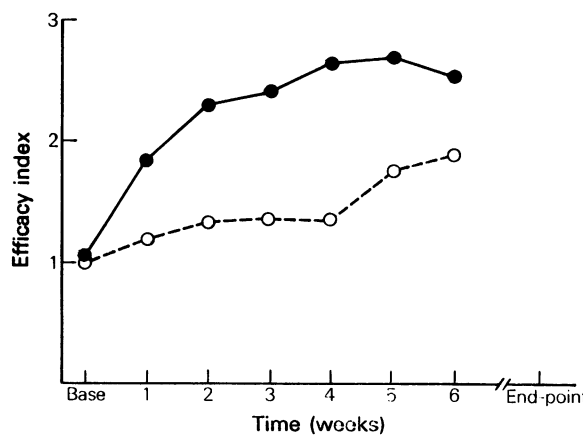


**Figure 2** Efficacy Index scores for ● mianserin and ○ amitriptyline.

## Discussion

Although mianserin and amitriptyline were comparable with respect to the efficacy data, the

outstanding finding in this study was the relative lack of mianserin-related adverse experiences as compared to amitriptyline. Of particular interest is the relatively small percentage of mianserin patients reporting anticholinergic type adverse experiences.

Previously conducted clinical trials have demonstrated that adverse experiences occurred less frequently with mianserin than with other antidepressants. In a review of six clinical trials of mianserin with either amitriptyline or imipramine (Peet, 1977), the total adverse experiences increased from baseline in patients receiving the tricyclic compounds and decreased in the mianserin treated patients. One should note that the adverse experiences data reported in this study were the actual incidences reported during the trial and do not include a correction for the pretreatment incidences of these events. This suggests that the lack of such a correction in these data may have resulted in an overestimation of the true drug-related adverse experiences. If one assumes a random distribution of the pretreatment occurrences of these adverse experiences, then one would expect an equal pretreatment correction for both mianserin and amitriptyline. Such a correction would only increase the relative incidence of amitriptyline adverse experiences compared with mianserin.

The advantages of the decreased anticholinergic effects of mianserin are quite evident. Tricyclic antidepressants have been reported to produce micturition difficulties, constipation and blurred vision. In a patient population of advancing age, these side-effects may constitute a contraindication for the use of the compounds. Inasmuch as mianserin has a relatively low incidence of these adverse experiences, it is particularly suited for elderly depressed patients.

An interesting finding in this study was the lack of cardiovascular adverse experiences reported with both mianserin and amitriptyline. In previous clinical trials, cardiovascular effects have consistently been more prevalent with tricyclics than with mianserin (Peet *et al.*, 1977; Hoc, 1978; Pichot *et al.*, 1978; Buck, 1980; Montgomery, 1980; Pinder *et al.*, 1980). No changes in EKG, nor cardiovascular side-effects were observed in 50 depressed patients who were treated with mianserin (90 mg/day) for one week (Songar, 1979). The same was reported for patients treated for up to eight months (Conti *et al.*, 1979). No differences were observed between the effects of mianserin 30 or 60 mg daily for three weeks or placebo on the EKGs and heart rates of 54 patients with cardiac disease (Coppen & Kopera, 1978; Kopera & Schenk, 1978). Moreover, the lack of cardiotoxicity of mianserin is supported by the lack of cardiac arrhythmias in 44 patients taking overdoses of mianserin (Drykoningen *et al.*, 1979).

The relatively low incidence of cardiovascular effects observed in this trial may be partially attributed to the study design, EKG recordings were obtained pretreatment and post-treatment, and weekly recordings were not obtained. Therefore, some of the earlier effects one would expect with the tricyclic may have subsided by the final visit. However, this does not fully explain the absence of cardiovascular effects in those patients who discontinued early in the study. This suggests the need for a well conducted trial in depressed cardiovascular patients utilizing the technique of continuous Holter monitoring.

Drowsiness/fatigue has been the side-effect most commonly reported during clinical trials with mianserin. In some studies drowsiness was more frequent with mianserin than with tricyclics (Wheatley, 1975; Jaskari *et al.*, 1977; Buck, 1980), but this was not confirmed in other studies (Daly *et al.*, 1979; Blaha *et al.*, 1980). In this study drowsiness/fatigue accounted for 50% (24 out of 48) of the mianserin adverse experiences and only 25% (33 out of 132) of the amitriptyline adverse experiences. This particular side-effect results in mianserin being well suited for bed-time use.

Although the actual incidences of drowsiness/fatigue (24 for mianserin, 33 for amitriptyline) are comparable, the large number of psychiatric and anticholinergic type adverse experiences reported by the amitriptyline group decrease the relative percentage of drowsiness/fatigue adverse experiences. Once again, this illustrates that the predominant adverse experiences reported by mianserin patients tend to be less clinically significant than those reported by the amitriptyline patients.

This study demonstrates that mianserin is a safe and effective treatment for patients with moderate depression. Moreover, compared to amitriptyline mianserin has fewer and less clinically significant adverse effects.

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