state conditions, with typical patient dosing regimens, the sustained-release quinidine gluconate tablets, in spite of lower quinidine base content, provide more systemically available quinidine than do sustained-release quinidine sulfate tablets.

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Lormetazepam and Amobarbital Sodium in the Outpatient Treatment of Insomnia: A Controlled Trial*

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ABSTRACT

In a double-blind clinical trial, 50 psychiatric outpatients with moderate insomnia (requiring daily treatment with a hypnotic drug) were treated for two weeks with lormetazepam (1 mg) or amobarbital sodium (100 mg). In interviews before and after treatment, data were collected on the patients' demographic characteristics, sleep disturbances, concomitant organic or psychiatric disorders, and opinions of the drug taken during the two-week period. During the trial the patients took notes on their use of the drug, the quality and duration of their sleep, and any adverse effects of the drug they were using.

Lormetazepam and amobarbital were equivalent in the amount of time it took patients receiving each drug to fall asleep and in the duration of the patients' sleep, but insomnia disappeared (or the condition improved) in a larger proportion of patients receiving lormetazepam, and there were fewer adverse effects (eg, hangover in the morning, sedation in the morning and during the day, and dry mouth) in patients receiving lormetazepam than in patients receiving amobarbital.

INTRODUCTION

The benzodiazepines are at present the treatment of choice for insomnia. Their advantages are obvious: marked activity, exceptional tolerance, negligible toxicity (whether taken over the long term or as an overdose in a suicide attempt), and minimal risk of drug addiction.

Although the benzodiazepines have little effect on the structure of sleep, they appreciably reduce the duration of deep slow sleep (stage IV sleep) without affecting the release of growth hormone associated with this stage—but with a compensatory increase in the duration of stage II sleep and, in general, a small reduction in the duration of REM sleep.[1]

To varying degrees all the benzodiazepines have anxiolytic and hypnotic properties. Some compounds, however, have a more specific hypnogenic or hypnotic profile close to the ideal profile[2]: rapid onset of activity (but without dangerous euphoria in susceptible subjects), physiological sleep lasting six to eight hours, with pleasant and easy

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waking, and no ill effects on the next day's activities. Moreover, the discovery of specific benzodiazepine antagonists[3,4] means that it will soon be possible to suppress the effect of the sleeping pill should the subject need to be awakened.

Lormetazepam* (Figure 1) has a useful pharmacological profile for a hypnotic drug: rapid absorption (30 minutes after oral administration the concentration in the plasma is 80% of the peak value)[5] and two-phase elimination from the plasma (a distribution phase with a half-life of about two hours and an elimination phase with a half-life of about ten hours).[6]

The drug's efficacy against insomnia has been demonstrated in several controlled trials.[7–11] The active dose is usually in the range of 0.5 to 2 mg, but in hospitalized psychiatric patients doses of up to 6 mg are sometimes necessary and can be given without causing problems of tolerance.[12]

Compared with the benzodiazepines, barbiturates have several disadvantages: a marked alteration in the structure of sleep (notably in REM sleep), high toxicity if taken in a massive dose, hepatic enzyme induction with numerous drug interactions, and possible addiction.

*Trademark: Loramet® (Wyeth Laboratories, Philadelphia, Pennsylvania).

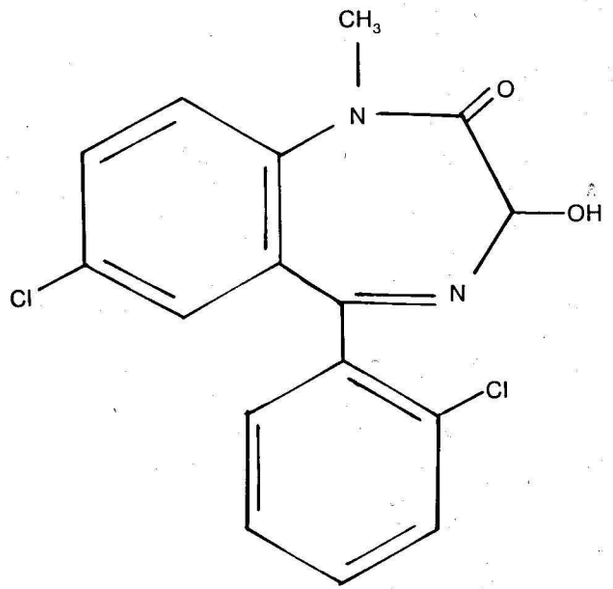

Figure 1. Chemical structure of lormetazepam.

The aim of the present study was to verify the advantages of lormetazepam over a barbiturate in the treatment of sleep disturbances in psychiatric outpatients.

MATERIALS AND METHODS

The subjects were 50 men and women selected from psychiatric outpatients who had sleep disturbances that could be described as "moderate insomnia." Such insomnia was defined as requiring daily treatment with a single hypnotic drug. "Mild" insomnia was defined as requiring occasional use of a hypnotic drug, and "severe" insomnia as requiring daily hypnosis or daily treatment with more than one tablet containing the highest commercially available dose of a hypnotic drug.

The patients were randomly assigned to two groups, one given lormetazepam (1 mg) and one given amobarbital sodium (100 mg) prepared as identical tablets. The doses remained the same during the two-week trial.

Most of the patients were being seen for psychiatric disorders. They were included in the study if their insomnia was moderate, if they consented to participate in the study, and if they were sufficiently motivated to follow the investigator's recommendations and to take notes on the quality of their sleep.

Excluded from the trial were pregnant or lactating women (women who were sexually active had to use some method of contraception); patients with severe circulatory, respiratory, liver, or kidney disease; psychotic patients who were not stabilized; patients with myasthenia; alcoholics and patients with other types of addiction; epileptics; patients with sleep disturbances caused by pain; patients hypersensitive to benzodiazepines; and patients receiving tranquilizers or sedative antidepressants (doxepin hydrochloride and amitriptyline hydrochloride, in particular).

Each patient was coded and received two bottles containing tablets sufficient for two weeks of treatment. The patient was asked to take one tablet with a little water (about 100 ml) just before going to bed each night. The patient was advised not to take any alcoholic beverage or any beverage containing caffeine after 6 PM.

The clinical assessment consisted of the following stages:

1. An interview before treatment in which the investigator noted the patient's age, sex, weight, occupation, concomitant organic or psychiatric disease, and type of sleep disturbance (difficulty falling asleep; awakening during the night; premature awakening) as well as the length of time in which the symptoms had been present, any previous treatments and their results, and information on the patient's general physical condition.

2. Individual sleep assessment forms, which the patient filled in after the first night and after the first and second weeks of treatment. These forms were used to evaluate: the time of medication, how long it took to fall asleep, the duration of sleep (in absolute terms and in comparison with previous nights), the quality of sleep, the number of awakenings and their causes, the presence of dreams or nightmares, and the patient's condition on waking up in the morning and during the day. The patients were also asked to note on the forms any other medicines or alcoholic beverages taken in conjunction with the treatment, as well as any adverse

effects experienced during the night or during the day.

3. An interview after treatment designed to obtain a global evaluation: how long it took to fall asleep, the number of awakenings during the night, the duration of sleep, and the patient's opinion of the medication. The investigator also assessed the general result of treatment and the efficacy of the drug and noted the severity of any adverse effects and the possible relation of these effects to the drug tested. Any drug used previously as a hypnotic was replaced by the test drug, while other drugs required for treatment of the psychiatric or somatic disease were used throughout the trial.

RESULTS

Statistical analysis of the data revealed that the two groups of patients were homogeneous with regard to age, sex, weight, the number of patients who had previously received hypnotic treatment and the results of this treatment, the type of sleep disturbances and their duration (Table I), and the nature of the main disorder and its specific treatment (Table II).

Of the 50 patients, 48 completed the trial. In each group, one patient dropped out of treatment; the cause or causes of the attrition are not known.

After the First Night

There was no significant difference between the two groups in the length of time it took to fall asleep, the duration of sleep and the patient's assessment of the duration of sleep on one night in relation to previous nights, the quality of sleep, the number of awakenings, and the presence of pleasant or unpleasant dreams (Table III).

Waking up in the morning was easier or no different for patients taking lormetazepam than it was for patients taking amobarbital; patients receiving lormetazepam described their condition during the day as "better" or "good" whereas a larger proportion of patients receiving amobarbital reported that they had a "hangover" in the morning.

After the First and Second Weeks

There was no significant difference between lormetazepam and amobarbital for the majority of variables investigated. A hangover was associated with use of the barbiturate, however (Table IV). Data collected after two weeks of treatment revealed no significant difference between the two groups (Table V).

Global Assessment

The global assessment made by the investigator at the end of the study (Table VI) showed that treatment with amobarbital was accompanied by difficulty in falling asleep, hangover, sedation in the morning and during the day, and dry mouth. Patient acceptance of lormetazepam was good or excellent, and, in patients taking lormetazepam, insomnia completely disappeared or the condition greatly improved. The investigator's general impression of the drug was that it was excellent, very good, or good. There was no difference between the two groups in the time it took to fall asleep and the duration of sleep.

Figure 2 illustrates the variables that were significantly different between the two groups during this clinical trial.

Table I. Characteristics of the patient population.

	Lormetazepam (L) Group	Amobarbital (A) Group	Comparison	Estimated Mean (at 95%)
Age (years)	41.88 (n = 25)	40.91 (n = 23)	NS	41.42 ± 3.81 (n = 48)
Sex	13 M–12 F (n = 25)	10 M–13 F (n = 23)	Comparable	M 48% ± 14% F 52% ± 14% (n = 48)
Weight (kg)	64.65 (n = 23)	60.96 (n = 23)	NS	62.80 ± 3.55 (n = 46)
Concomitant disorders	23/25	20/23	Comparable	90% ± 8% (n = 48)
Associated treatment	23/23	18/20	Comparable	88% < $P \leq$ 100% (n = 43)
Difficulty in getting to sleep	25/25	23/23	—	100% (n = 48)
Waking at night	5/24	7/23	Comparable	26% ± 13% (n = 47)
Duration of insomnia	17.28 (n = 24)	14.50 (n = 22)	NS	15.95 ± 11.50 (n = 46)
Previous hypnotic treatment	22/25	15/23	Comparable	77% ± 12% (n = 48)
Unsatisfactory response	18/21	14/15	Comparable	89% ± 10% (n = 36)

Table II. Concomitant disorders in patients receiving lormetazepam or amobarbital for treatment of insomnia.

Concomitant Disorders	Lormetazepam (L) Group	Amobarbital (A) Group
Manic depressive psychosis	2	—
Depression: reactive	5	7
neurotic	4	4
involutional	3	3
melancholic	0	1
Behavioral disturbances	1	1
Disorders of concentration	1	0
Obsessive neurosis	2	0
Psychosomatic disorders	2	1
Anxiety state	1	1
Hypochondriasis	1	0
Mental deficiency	1	0
Neurotic disorders	0	1
Sexual disorders	0	1
Total	23	20

DISCUSSION

In psychiatric outpatients receiving treatment for moderate sleep disturbances, lormetazepam and amobarbital sodium were equivalent in the amount of time it took patients receiving each drug to fall asleep and in the duration of the patients' sleep.

After the first night of treatment, patients receiving lormetazepam reported easier awakening in the morning and a better condition during the day; at the end of the first week a larger proportion of the patients receiving amobarbital reported hangovers. Global assessment showed that patients in the amobarbital group had greater difficulty in falling asleep, while the lormetazepam group was distinguished by better acceptance of the drug, a more complete global response, and a more positive assessment by the investigator. A hangover and sedation in the morning and during the day were reported in 52% of the patients in the amobarbital group, whereas only one patient in the lormetazepam group complained of headaches in the morning.

These results showed that a benzodiazepine of moderate duration of action such as lormetazepam is at least as active and generally better tolerated than a barbiturate in general psychiatric outpatients.

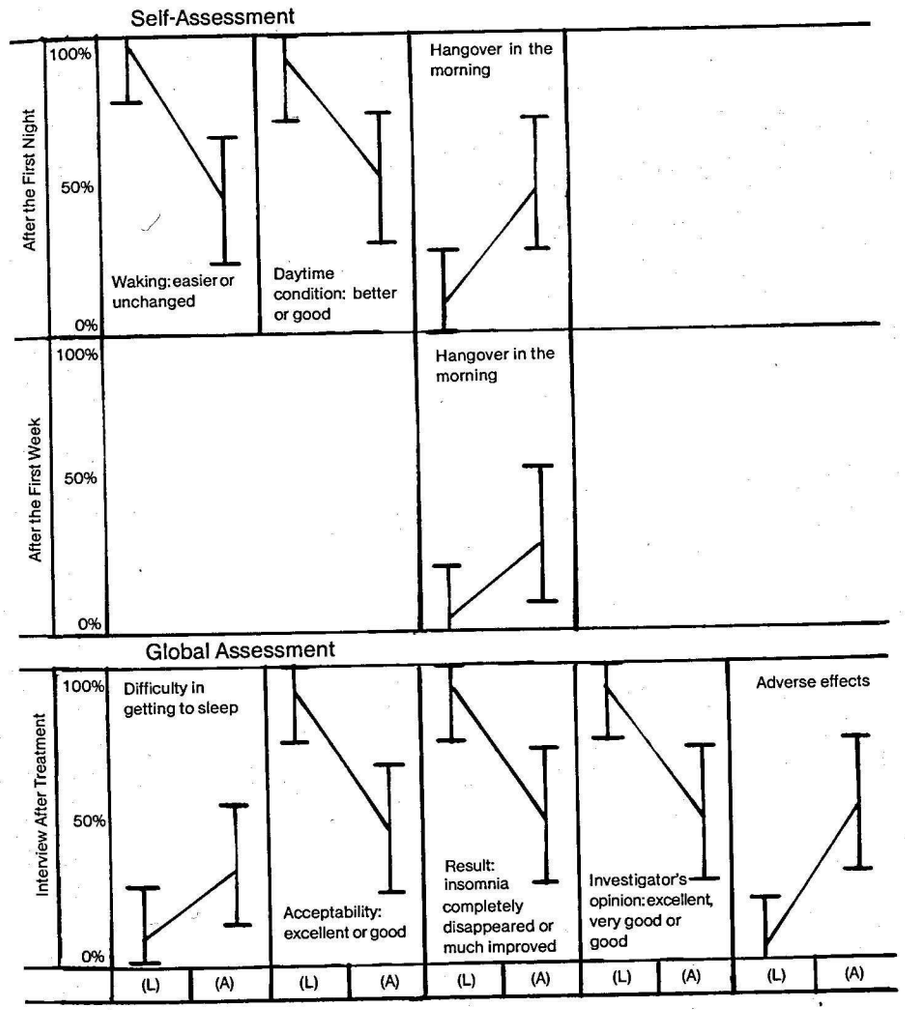

Figure 2. Lormetazepam (L) versus amobarbital (A): significant differences.

ACKNOWLEDGMENTS

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Table III. Patients' self-assessment after the first night of treatment.

	Lormetazepam (L) Group	Amobarbital (A) Group	Difference	Estimated Mean (at 95%)
Delay in getting to sleep	28min 7s (n = 24)	32min 36s (n = 23)	NS	30min 19s ± 5min 32s (n = 47)
Duration of sleep	7h 31min (n = 24)	7h 51min (n = 23)	NS	7h 40min ± 22min (n = 47)
Comparison of duration of sleep*	15 ↑↑ or ↑ 9 = ↓ or ↓↓ (n = 24)	14 ↑↑ or ↑ 9 = ↓ or ↓↓ (n = 23)	NS	↑↑ or ↑ : 62% ± 14% = ↓ or ↓↓ : 38% ± 14% (n = 47)
Quality of sleep†	14 ↑↑ or ↑ 10 = ↓ or ↓↓ (n = 24)	9 ↑↑ or ↑ 14 = ↓ or ↓↓ (n = 23)	NS	↑↑ or ↑ : 49% ± 14% = ↓ or ↓↓ : 51% ± 14% (n = 47)
Quality of waking‡	23 ↑ or = 1 ↓ (n = 24)	10 ↑ or = 13 ↓ (n = 23)	$P < 0.05$	(L) ↑ or = $78\% < P \leq 100\%$ (A) ↑ or = $24\% < P < 66\%$
Condition during the day§	22 ↑ or good 2 ↓ (n = 24)	12 ↑ or good 11 ↓ (n = 23)	$P < 0.05$	(L) ↑ or good $71\% < P < 99\%$ (A) ↑ or good $29\% < P < 73\%$
Number of awakenings	17 none 7 1 or more (n = 24)	15 none 8 1 or more (n = 23)	NS	none: 68% ± 13% 1 or more: 32% ± 13% (n = 47)
Presence of dreams	8/24	3/23	NS	23% ± 12% (n = 47)
Disturbing dreams	1/8	1/3	NS	$3\% < P < 54\%$ (n = 11)
Hangover in the morning	2/24	11/23	$P < 0.05$	(L) $1\% < P < 27\%$ (A) $27\% < P < 71\%$

* ↑↑ much longer; ↑ longer; = no change; ↓ shorter; ↓↓ much shorter
† ↑↑ much better; ↑ better; = no change; ↓ worse; ↓↓ much worse
‡ ↑ easier; = no change; ↓ more difficult
§ ↑ better; ↓ worse.

Table IV. Patients' self-assessment after the first week of treatment.

	Lormetazepam (L) Group	Amobarbital (A) Group	Difference	Estimated Mean (at 95%)
Delay in getting to sleep	29min 21s (n = 23)	32min 48s (n = 16)	NS	30min 46s ± 5 min 23s (n = 39)
Duration of sleep	7h 32min (n = 23)	7h 50min (n = 16)	NS	7h 40min ± 18min (n = 39)
Comparison of duration of sleep*	4 ↑ 20 = ↓ or ↓↓ (n = 24)	5 ↑ 12 = ↓ or ↓↓ (n = 17)	NS	↗ : 22% ± 13% = ↓ or ↓↓ : 78% ± 13% (n = 41)
Quality of sleep†	4 ↑ 20 = ↓ or ↓↓ (n = 24)	3 ↑ 14 = ↓ or ↓↓ (n = 17)	NS	↗ : 17% ± 11% = ↓ or ↓↓ : 83% ± 11% (n = 41)
Quality of waking‡	22 = 1 ↓ (n = 23)	15 = 2 ↓ (n = 17)	NS	=: $85\% < P \leq 100\%$ ↓ : $15\% > q \geq 0\%$ (n = 40)
Condition during the day§	22 ↗ or good 2 ↓ (n = 24)	14 ↗ or good 3 ↓ (n = 17)	NS	↗ or good: 88% ± 10% ↓ : 12% ± 10% (n = 41)
Number of awakenings	14 none 10 1 or more (n = 24)	11 none 6 1 or more (n = 17)	NS	none: 61% ± 15% 1 or more: 39% ± 15% (n = 41)
Presence of dreams	3/24	2/17	NS	12% ± 10% (n = 41)
Disturbing dreams	1/3	1/2	NS	$8\% < P < 80\%$ (n = 5)
Hangover in the morning	1/24	5/17	$P < 0.05$	(L) $0\% \leq P < 22\%$ (A) $10\% < P < 55\%$

* ↑↑ much longer; ↑ longer; = no change; ↓ shorter; ↓↓ much shorter
† ↑↑ much better; ↑ better; = no change; ↓ worse; ↓↓ much worse
‡ ↑ easier; = no change; ↓ more difficult
§ ↑ better; ↓ worse

Table V. Patients' self-assessment after the second week.

	Lormetazepam (L) Group	Amobarbital (A) Group	Difference	Estimated Mean (at 95%)
Delay in getting to sleep	29 min 22s (n = 24)	31 min 00s (n = 15)	NS	30 min 00s ± 4 min 57s (n = 39)
Duration of sleep	7h 33min (n = 24)	7h 49min (n = 15)	NS	7h 39min ± 19min (n = 39)
Comparison of duration of sleep*	2 ↗ 20 = 2 ↘ or ↘↘ (n = 24)	0 ↗ 17 = 0 ↘ or ↘↘ (n = 17)	NS	↗ : 0% ≤ P < 12% = ↘ or ↘↘ : 100% ≥ q > 88% (n = 41)
Quality of sleep†	6 ↗ 18 = ↘ or ↘↘ (n = 24)	1 ↗ 16 = ↘ or ↘↘ (n = 17)	NS	↗ : 17% ± 11% = ↘ or ↘↘ 83% ± 11% (n = 41)
Quality of waking‡	23 = 0 ↘ (n = 23)	15 = 2 ↘ (n = 17)	NS	=: 88% < P ≤ 100% ↘ : 12% > q > 0% (n = 40)
Condition during the day §	22 ↗ or good 2 ↘ (n = 24)	16 ↗ or good 1 ↘ (n = 17)	NS	↗ or good: 85% < P ≤ 100% ↘ : 15% > q ≥ 0% (n = 41)
Number of awakenings	16 none 8 1 or more (n = 24)	10 none 7 1 or more (n = 17)	NS	none: 63% ± 15% 1 or more: 37% ± 15% (n = 41)
Presence of dreams	6/24	2/17	NS	20% ± 12% (n = 41)
Disturbing dreams	4/6	1/2	NS	24% < P < 90% (n = 8)
Hangover in the morning	4/24	4/17	NS	20% ± 12% (n = 41)

* ↗↗ much longer; ↗ longer; = no change; ↘ shorter; ↘↘ much shorter
† ↗↗ much better; ↗ better; = no change; ↘ worse; ↘↘ much worse
‡ ↗ easier; = no change; ↘ more difficult

Table VI. Global assessment of lormetazepam and amobarbital.

	Lormetazepam (L) Group	Amobarbital (A) Group	Difference	Estimated Mean (at 95%)
Hypnotic action	23/25	22/23	NS	87% < P ≤ 100% (n = 48)
Difficulty in getting to sleep	2/25	7/23	P < 0.05	(L) 1% < P < 26% (A) 13% < P < 53%
Delay in getting to sleep	32 min 48s (n = 25)	35 min 25s (n = 23)	NS	34 min 03s + 6 min 05s (n = 48)
Awakening at night (number of times)	16 none 9 1 or more (n = 25)	14 none 8 1 or more (n = 22)	NS	none: 64% ± 14% 1 or more: 36% ± 14% (n = 47)
Duration of sleep	7h 33min (n = 25)	7h 54min (n = 23)	NS	7h 43min ± 20min (n = 48)
Global assessment of the drug (by patient)	14 excellent 9 good 2 passable/nil (n = 25)	2 excellent 8 good 13 passable/nil (n = 23)	P < 0.05	(L) Excellent/good: 74% < P < 99% (A) Excellent/good: 24% < P < 66%
Global results (by investigator)*	14 c.d. 9 m.i. 2 l.i./n.i. (n = 25)	4 c.d. 7 m.i. 12 l.i./n.i. (n = 23)	P < 0.05	(L) c.d./m.i.: 74% < P < 99% (A) c.d./m.i.: 27% < P < 71%
Global assessment of the drug (by investigator)	14 excellent 9 very good/good 2 fair/poor (n = 25)	2 excellent 9 very good/good 12 fair/poor (n = 23)	P < 0.05	(L) Excellent/very good/good: 74% < P < 99% (A) Excellent/very good/good: 27% < P < 71%
Adverse effects	1/25	12/23	P < 0.05	(L) 0% ≤ P < 21% (A) 29% < P < 73%

*c.d. = insomnia completely disappeared; m.i. = insomnia much improved; l.i. = insomnia little improved; n.i. = insomnia not improved.

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Treatment of Depression with Maprotiline Hydrochloride: Multicenter Evaluation of Efficacy and Tolerability*

ABSTRACT

A multicenter, noncomparative evaluation of the antidepressant effects and tolerability of maprotiline hydrochloride was undertaken. The drug was given to 134 patients between the ages of 17 and 83 years who had either a dysthymic disorder or a major depressive disorder. In most cases, the starting dosage was 75 mg/day with a mean of 71.6 mg/day. The mean final dosage was 144.7 mg/day. Mean dosages were considerably lower in patients aged 65 and over.

Patients were given maprotiline for six weeks and were evaluated before treatment and one, two to three, four to five, and six or more weeks after starting use of the drug. Efficacy was judged on the basis of overall improvement, compared with the patient's condition before using maprotiline, and reductions in the specific symptoms of disturbed sleep, anxiety, depressed mood, and lack of drive. The results indicate that maprotiline is a highly effective antidepressant drug with a rapid onset of action in some cases. By the final week of treatment, 89% of the evaluated patients had marked or moderate improvement in their overall condition.

Fifty-three patients had one or more side effects, which were mostly mild or moderate. Only one patient complained of a severe side effect, lethargy. Anticholinergic effects, notably dry mouth (19%), and sedation (16%) were the predominant side effects. There was no greater incidence of side effects in patients 65 years of age and older than in younger patients. It is thus concluded that maprotiline is a safe and effective antidepressant agent for adults of all ages.

*The following physicians participated in the multicenter study: David A. Baron, M.D., USC/LAC Department of Psychiatry, Pasadena, California; Dennis Caffrey, M.D., Henry Ford Hospital, Detroit, Michigan; Joseph T. DiBianco, M.D., Misericordia Hospital Medical Center, Bronx, New York; John P. Hutton, M.D., and R. Bergman, R.N., Shawnee Hills Community Mental Health Center, Charleston, West Virginia; S. Idupuganti, M.D., Maimonides Medical Center, Brooklyn, New York; Laurence C. Miller, M.D., St. Vincent's Hospital, Staten Island, New York; J. S. Moreno, M.D., St. Joseph's Hospital, Paterson, New Jersey; Shamin Qureshi, M.D., Foster McGaw Hospital, Chicago, Illinois; Deepak Sankholkar, M.D., Lincoln Hospital, Bronx, New York; Michael Shehi, M.D., Smolian Psychiatric Clinic, University of Alabama/Birmingham School of Medicine, Birmingham, Alabama; and Susan J. Stagno, M.D., and Nicholas Votolato, Pharm. D., Ohio State University, Columbus, Ohio.