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Evaluation of the Efficacy of Amineptine in a Population of 1,229 Depressed Patients: Results of a Multicenter Study Carried Out by 135 General Practitioners

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Summary: To assess the efficacy, tolerance, and safety of amineptine in ambulant treatment of depressive states, an open multicenter trial was performed by 135 general practitioners in a large number of depressed patients (1,229) with different nosologies and living in all areas of Portugal. The protocol included criteria of inclusion and exclusion and the full methodology was discussed with the practitioners in previous meetings coordinated by a psychiatrist. Daily dosage was 200 mg (two tablets); other psychotropic drugs were associated rarely and only when strictly necessary. Assessments were made at day 0, 7, 28, and 56, using the Clinical Global Impressions (CGI), Hamilton Depression Rating Scale (HDRS), diagram HARD, and a list of side effects. Results were analyzed statistically with calculation of statistical significance. The calculation of the correlation coefficients between the different measurement instruments was also made. There were 84 dropouts mainly due to missed appointments and intolerance of the medication. It is worth noting that 50% of the patients were treated with monotherapy, and that other psychotropics used were almost always anxiolytic drugs. Efficacy of amineptine was very good and rapid since there was a statistically significant difference in all observations with the different instruments of measurement used. Results were good in all types of depression, mainly in the neurotic and reactive ones. Moderate or severe side effects were seldom observed and transient. The acceptability was good or very good in 97.1% of the cases. **Key Words:** Amineptine—Depression.

Although the classic antidepressant drugs, tricyclics or monoamine oxidase (MAO) inhibitors, have shown great therapeutic efficacy after an initial latent period and are therefore still commonly used, their toxic and adverse effects require us to be careful when prescribing them. This justifies a continuing psychopharmacologic research to synthesize products that have a similar therapeutic

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efficacy, a better acceptability and tolerance, and also a quicker onset of action.

On the other hand, the progressive withdrawal of thymeretic antidepressants, particularly MAO inhibitors, resulted in a more difficult approach to the inhibited depressions and asthenic syndromes; this explains the interest in finding new antidepressive drugs that would be well tolerated and would have presumed activating effects. If we also take into consideration that light and moderate depressions and asthenic syndromes are often treated by general practitioners, we understand the importance of this research. Among the antidepressant drugs of the new generation, amineptine seems to fulfill these conditions.

Amineptine is a molecule that has an imipramine type of tricyclic nucleus and a long lateral chain with seven carbon atoms (1,2). This product demonstrates pharmacologic properties (3–6) that predicts a mood-elevating and activating effect, absence of cardiotoxicity, and a reduced anticholinergic action.

Many clinical studies, open and double-blind, comparing amineptine with standard products (7–20) proved the antidepressive activity with activating polarity, good acceptability, and tolerance together with a quicker onset of action.

Amineptine has dopaminergic properties (21–26), which explains its profile as an activating antidepressant drug (27,28) and its indication for depressive states, especially for neurotic depressions with marked asthenic component (29–32). These clinical characteristics of amineptine were also demonstrated in studies performed in Portugal (33–35).

Because the clinical profile of amineptine seemed to be particularly suitable for the treatment of depressive conditions of outpatients in current medical practice, we decided to carry out a large-scale clinical trial with general practitioners. The aims of this study were to confirm the safety, tolerance, and therapeutic profile of amineptine in general clinical practice; to train general practitioners in the diagnosis and classification of different types of depression; and to improve knowledge of the initial forms of depression.

To fulfill these objectives, the study was planned with the following characteristics: open multicenter trial to be performed by general practitioners all over the country; an extended number of patients from all areas of the country; a sufficiently long trial duration (2 months); and a precise protocol.

PATIENTS AND METHODS

The protocol of this multicenter study was defined in collaboration with the Portuguese Scientific Board of the "Psychiatry in Current Medical Practice" Section of the World Psychiatric Association.

This study was an open multicenter trial performed by 135 general practitioners all over Portugal. It is worth noting that all general practitioners participated in previous meetings for sensitization, with the psychiatrist who coordinated the study, to standardize the criteria of assessment and quantification.

The patients were selected by inclusion and exclusion criteria (Table 1). The inclusion criteria were as follows: patients of both sex, between 18 and 75 years of age, ambulatory or hospitalized, requiring antidepressive treatment. The pa-

TABLE 1. *Criteria of patient's selection*

Inclusion criteria
Both sexes
18 to 75 years old
Ambulatory or hospitalized
HDRS > 18
HARD > 20
"R" POLE > 5
Exclusion criteria
Severe brain pathology
Gastrointestinal, liver, or kidney diseases
Pregnancy
Huntington's chorea
Association with MAO inhibitors

tients were selected if they had a score higher than 18 in Hamilton's depression scale and a score higher than 20 in HARD scale with a minimum of 5 in retardation item (R) in this scale.

These criteria, as well as the exclusion criteria (severe brain pathology; gastrointestinal, liver, or kidney diseases; pregnancy; Huntington's chorea; and association with MAO inhibitors) enabled us to select 1,229 depressed patients living in all areas of the country (Fig. 1), 973 females and 256 males, with a mean age of 43.9 ± 12.9 years for women and 42.2 ± 12.7 for men. Ages ranged from 17 to 71 years. These patients were divided into six diagnostic groups, according to the psychiatric classification of depression used in Portugal, as shown in Table 2, mostly suffering from neurotic and reactive depressions.

There was a total of 84 dropouts (Table 3), mainly in the first week of the trial, the majority of them due to missed appointments; the dropouts caused by side effects were 26 (2.1% of the population) and were mainly due to symptoms such as excitement, palpitations, trembling, and headaches. Thus, our final sample was made up of 1,145 depressed patients. The patients were treated for 2 months with 200 mg of amineptine (two 100-mg tablets per day, one at breakfast and one at lunch).

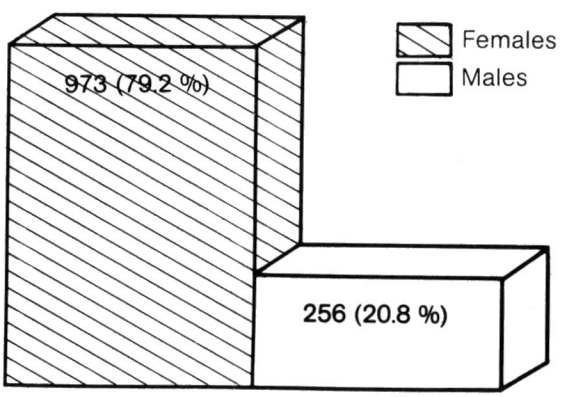

FIG. 1. General characteristics of the sample (n = 1,229). Mean age: females, 43.9 years ± 12.9; males 42.2 years ± 12.7. Range: 17 and 71 years.

TABLE 2. *General characteristics of the sample (N = 1,229)—distribution of patients according to diagnosis*

	Number of patients	Percentage
Neurotic depression	447	36.37
Reactive depression	637	51.83
Unipolar endogenous depression	94	7.65
Bipolar endogenous depression	13	1.06
Involutional depression	31	2.52
Not classified	7	0.57

With the exception of other antidepressant drugs, use of other psychotropic drugs was allowed only when strictly necessary. In many cases the investigators used drug association with anxiolytics (54.8%), as shown in Table 4; we must emphasize, however, that 42.5% of patients took amineptine in monotherapy.

The patients were examined four times during the trial: at D0 (before active treatment) and at the 7th (D7), 28th (D28), and 56th (D56) days of treatment. To assess the efficacy, tolerance, and safety of amineptine we used the following measuring instruments; Clinical Global Impressions (CGI); Hamilton Depression Rating Scale (HDRS) (36); HARD scale (37) in its Portuguese version (38), and a list of side effects.

To assure the correctness of the observations, the concurrent validity between the different instruments of measurement, the Pearson correlation coefficient, was used. The results were statistically analyzed (means, percentages, and analysis of variance—two tailed—$p < 0.05$). Statistical significance ($p < 0.05$) was calculated between the first and following observations in order to appreciate the global therapeutic efficacy and its rapidity of action.

RESULTS

From the investigators' clinical global evaluation of a trial extended to 1,145 patients, we found a clinical efficacy similar to those verified in previous trials in different countries. As shown in Fig. 2, the treatment with amineptine led to very positive results (''very good'' and ''good'') in 89% of the cases.

TABLE 3. *Dropouts (N = 84)*

	D7	D28	D56	Total
Missed appointments	33	5	—	38
Side effects	22	4	—	26
Inefficacy	8	6	1	15
Intercurrent situations	3	2	—	5

TABLE 4. *Additional treatments (%)*

None (amineptine in monotherapy)	42.5
Amineptine + anxyolytics	54.8
Amineptine + hypnotics	2.4
Amineptine + neuroleptics	0.3

These results show a good efficacy of amineptine (Fig. 3); the significant decrease in the mean total scores between D0 and D56 of the HDRS and the HARD scale proved that amineptine was effective in treating the various depressions. Furthermore, amineptine had a rapid onset of action (from 7th day of treatment), and its efficacy increased until the 56th day of therapy, as demonstrated by the decrease in the mean total scores in both scales, statistically significant between D7 and D28 and between D28 and D56.

With respect to the clinical global evaluation in different diagnoses of depression (Fig. 4) it was shown that in nonpsychotic depressions (neurotic or reactive), amineptine was active in 90% of cases and seemed particularly well suited to the treatment of this type of depression, which are the most frequently treated by the general practitioners. With regard to endogenous depressions (unipolar and bipolar) and involutional depression, "very good" or "good" results were observed in 79, 69, and 73% of the cases. These results confirm that amineptine has antidepressive action, with efficacy similar to that of classic antidepressant drugs. Concerning tolerance (Table 5), the side effects were less numerous and tended

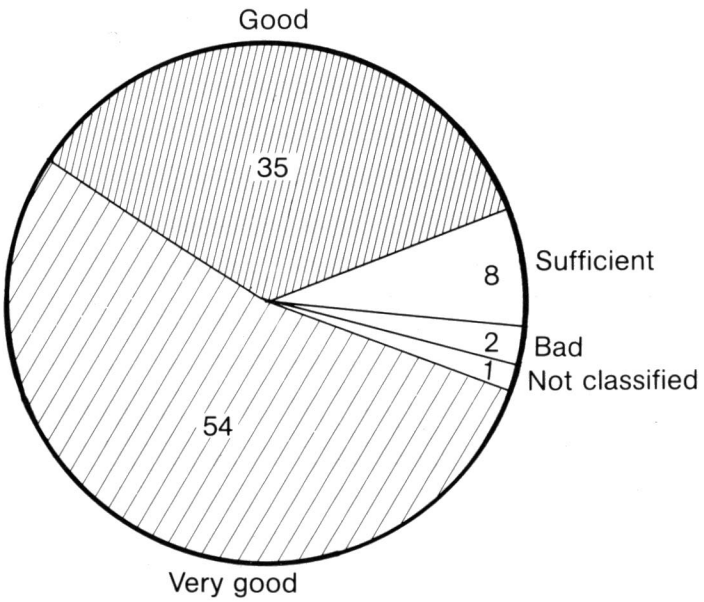

FIG. 2. Clinical global impression at D56, according to diagnosis in the 1,145 depressed patients (percentages).

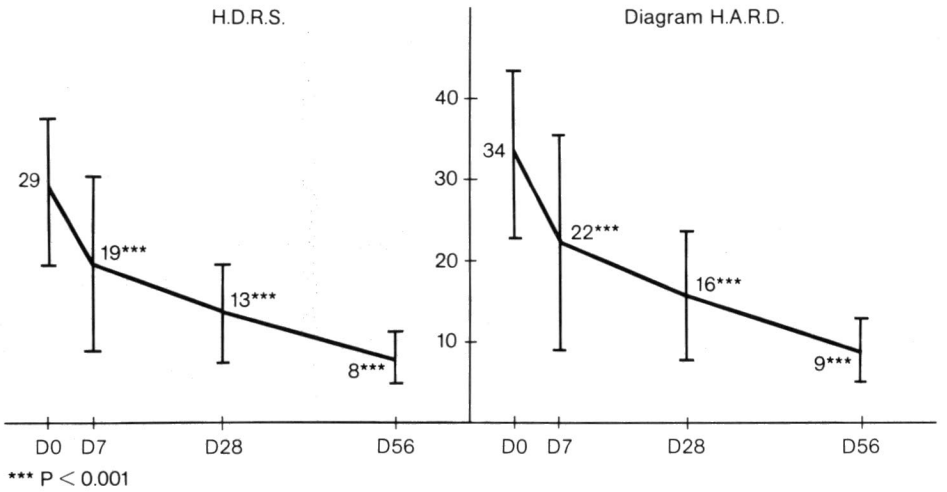

FIG. 3. Time course of the HDRS and diagram HARD mean total scores at D0, D7, D28, and D56.

to decrease as treatment continued, and in a great majority did not lead to its interruption. The acceptability of the treatment with amineptine was therefore considered "very good" and "good" by the investigators in 97.1% of the cases (Table 6).

DISCUSSION

It is important, at this point, to evaluate the reliability of the highly significant results obtained with the Hamilton's and HARD scales during the treatment and

TABLE 5. *Side effects (N = 1,145)*

	Moderate or severe	
	D7	D56
Headaches	40 (3.5%)	12 (1.0%)
Insomnia	38 (3.3%)	10 (0.9%)
Confusion	22 (1.9%)	—
Excitement	21 (1.8%)	4 (0.3%)
Dry mouth	21 (1.8%)	8 (0.7%)
Dizziness	18 (1.6%)	1 (0.1%)

TABLE 6. *Acceptability (%)*

Very good	52.3	97.1
Good	44.8	
Sufficient	2.7	
Bad	0.2	

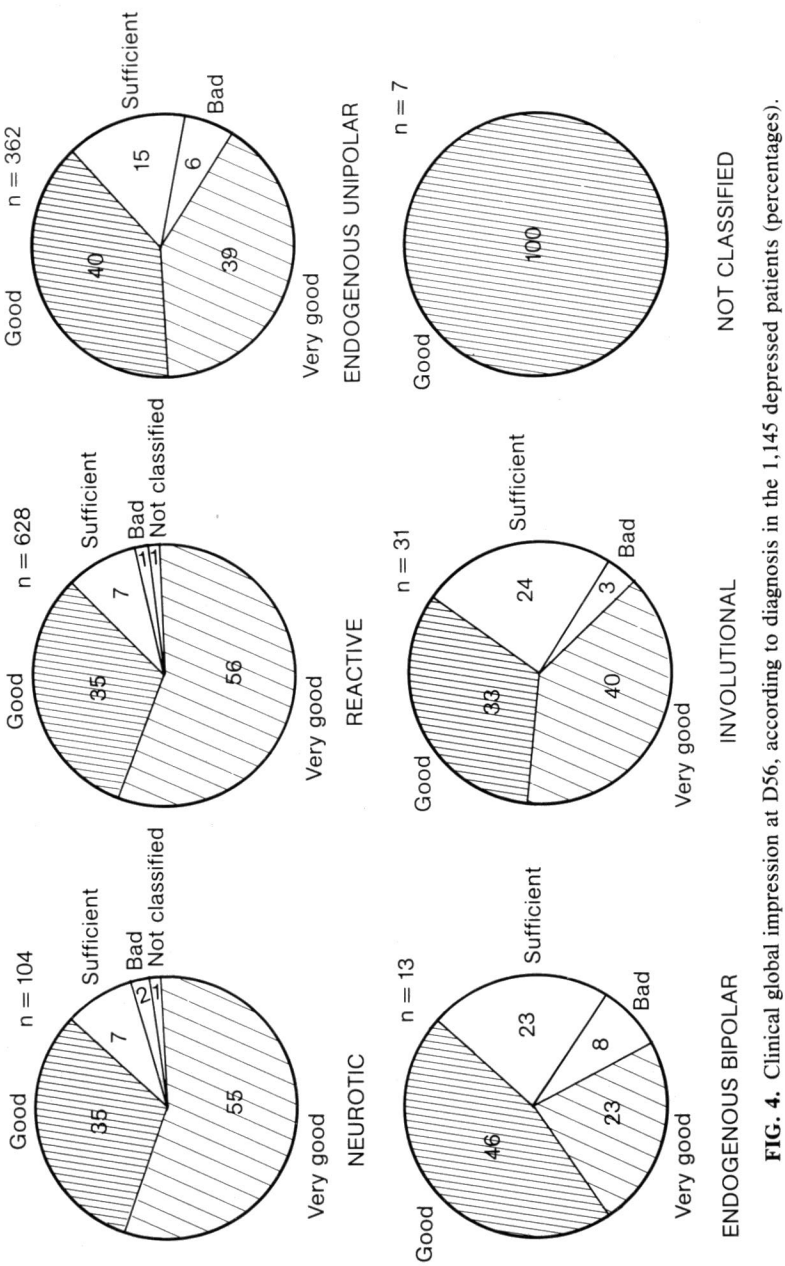

FIG. 4. Clinical global impression at D56, according to diagnosis in the 1,145 depressed patients (percentages).

TABLE 7. *Correlation between the measurement instruments at D0, D7, D28 and D56*

	D0		D7			D28			D56		
	HDRS	HARD	HDRS	HARD	CGI	HDRS	HARD	CGI	HDRS	HARD	CGI
HDRS	100	23	100	80	76	100	53	60	100	63	57
HARD	23	100	80	100	78	53	100	68	63	100	63
CGI	—	—	76	78	100	60	68	100	57	63	100

confirmed by the clinical global impression of the investigators. Therefore, we studied the concurrent validity evaluation between the different instruments of measurement, using Pearson's correlation coefficient. This validity was positive in the second, third, and fourth assessments submitted to active treatment (Table 7). This positive correlation is also important because these instruments measuring psychiatric states, require certain experience and previous psychopathologic knowledge, and because the investigators were all general practitioners.

If we compare the results of this study to a previous multicenter trial performed by psychiatrists only (35), in which the correlations between assessment instruments were evaluated from the beginning, it is not surprising to find the less important correlations at D0. These values can be explained by the difficulty that general practitioners have in using instruments that are used primarily by psychiatrists. That is why the training, whereby they became acquainted with the meanings of psychopathological symptoms and their quantitative assessment, led to improvement in the correlations between the instruments at the second and following observations. This fact demonstrates the interest of trials of this kind to improve general practitioners postgraduate formation.

The clinical global impression of the general practitioners that performed this study was slightly superior to that obtained by psychiatrists in the similar previous trial. These results can be explained by the fact that the general practitioners do not usually treat major depressions; it is more likely that they deal with neurotic-reactive depressions, which are more easily treated.

The depressive pathology of this trial performed by general practitioners was similar to the depressive pathology treated by psychiatrists, with a similar distribution of the patients according to the different diagnoses. The results confirm the efficacy, the rapid onset of action, and good tolerance of amineptine, which was also obtained in a great number of cases in previous trials, such as the ones carried out in Portugal by psychiatrists (33–35).

CONCLUSIONS

This multicenter trial with 1,229 patients created by 135 general practitioners was performed with maximum guarantees of reliability, because of the utilization of a strict protocol and previous working meetings with all the investigators and ongoing follow-up by the psychiatrist who coordinated this trial.

Besides the improvement in the knowledge of the diagnosis and treatment of a depressive pathology gained by the general practitioners, this extensive trial permitted the confirmation of antidepressive efficacy and the good acceptability of amineptine, used at the dosage of two tablets a day, in the great majority of depressive states. Concerning the antidepressive efficacy, the global clinical evaluation done by the investigators proved 89% positive results for all the treated depressions, and better results in the neurotic-reactive ones. Regarding the quick action of amineptine, the statistical analysis of evolution of mean total scores of both scales showed that amineptine acts rapidly (as soon as the 7th day of treatment), and that its efficacy increases until the end of the treatment. The rarity of side effects and their tendency to disappear with the continuation of the treatment shows the good tolerance and excellent general acceptability of amineptine, confirmed here in a great number of cases. In fact, the side effects that led to interruption were only noted in 2.1% of the population.

Because of its characteristics of efficacy, rapid action, safety, and tolerance, amineptine seems to be particularly well suited to the maintenance of an active life and, therefore, to ambulatory treatment in current medical practice.

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