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Amineptine (Survector 100) in the Treatment of Depression in Brazil

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Summary: Amineptine was studied in open, simple, and comparative trials in several Latin American countries, primarily in Brazil, Uruguay, and Chile. These countries developed studies with this antidepressant in an individualized way in different centers as well as multicenter studies under single coordination. The author analyzes the results of two of these studies. Generally, amineptine showed a positive result in depression in which the inhibition symptom is predominant. This drug also showed a good tolerance: it may be prescribed to elderly patients with depression and to people who suffer from diseases for which the classic antidepressants cannot be recommended. Many other studies on this drug were developed among the general practitioners in view of its rapid onset of action and also its easy clinical handling. Many people who suffer from depression are not treated by psychiatrists; it is very important that other specialists take notice of these effective and safe antidepressants. It is also very interesting to compare these studies to others that have already been developed in several other countries so that a better comprehension of the phenomenon of depression and its treatment can be reached. **Key Words:** Amineptine—Depression—Inhibition—HARD—Neuroendocrine tests.

Amineptine is an original tricyclic molecule with a long amino acid chain; it has antidepressant properties (1–8). Amineptine itself has stimulating properties, increasing activity and acceptable social behavior. This antidepressant psychostimulant aspect may be connected to the dopaminergic neurochemical action of the molecule (9–12), primarily through inhibition of the uptake of dopamine in mesolimbic and mesocortical synapses.

To evaluate the intensity and the modalities of the thymoanaleptic action of amineptine, and to confirm its clinical and biological acceptability, we performed two open studies: a pilot, which was the first Brazilian study of amineptine; and a second one, the aim of which was to study the profile of this antidepressant and its effect on neuroendocrine tests.

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THE FIRST BRAZILIAN STUDY OF AMINEPTINE

Methods

Inclusion Criteria

Inclusion criteria comprised female or male patients, ages between 21 and 65 years, fulfilling the DSM-III criteria for depression.

Exclusion Criteria

Exclusion criteria included the following: (a) Huntington's chorea (because of the dopaminergic action of the drug); (b) severe affections: hepatic, cardiovascular, renal, severe diabetes; (c) severe asthma; (d) cancer; (e) alcoholism; (f) antecedents of acute narrow-angle glaucoma; and (g) pregnancy.

Treatment with Amineptine

This open study was held for 12 weeks, with the posology of one or two tablets per day (100–200 mg). When necessary, the dosage could be increased to the limit of 300 mg/day. The tablets were administered in the morning and (if a second tablet was necessary) after lunch.

Additional Treatments

Combined treatment with neuroleptic, anxiolytic, or nonbarbituric drugs was allowed, when necessary.

Evaluation Criteria

We used (a) the 26-item Hamilton Depression Rating Scale, (b) the Brief Psychiatric Rating Scale—BPRS, and (c) a clinical global assessment. The clinical state was evaluated regularly, according to the usual procedures used on these types of patients. The evaluation of the therapeutic effect was performed before and after the 1st, 2nd, 3rd, 4th, 8th, and 12th weeks of treatment. The main characteristics of the study are summarized in Table 1.

Results

Thirty-five observations were collected (24 female; 11 male) (Table 2). Amineptine was used as the sole psychotropic drug in 12 cases and combined with an anxiolytic in 23 cases (Table 3).

TABLE 1. *Main characteristics of the study*

Design of the study	Open study
Diagnostic criteria	DSM-III
Dosage of amineptine	200 mg/day of amineptine (range 100–300 mg) (one tablet in the morning and after lunch)
Duration of the study	12 weeks (3 months)
Assessment criteria	Hamilton Scale of Depression and BPRS
Time of assessment	Before the study, and each week until the end of the study

TABLE 2. *Description of the patients*

Number	35
Sex	
Male	11
Female	24
Mean age	38.9 (from 21 to 57 years old)
Mean initial total score of the Hamilton Scale of Depression	26.7

TABLE 3. *Additional treatments*

Amineptine	12 cases
Amineptine + benzodiazepine	23 cases[a]
Diazepam	12 cases
Flunitrazepam	8 cases
Triazolam	4 cases
Bromazepam	4 cases
Others	6 cases

[a] A patient may have been given several additional treatments.

Clinical Global Assessment

The clinical global assessment by the investigator is listed in Table 4. Sixty percent of the results were considered very good and good; 94.3% were considered positive.

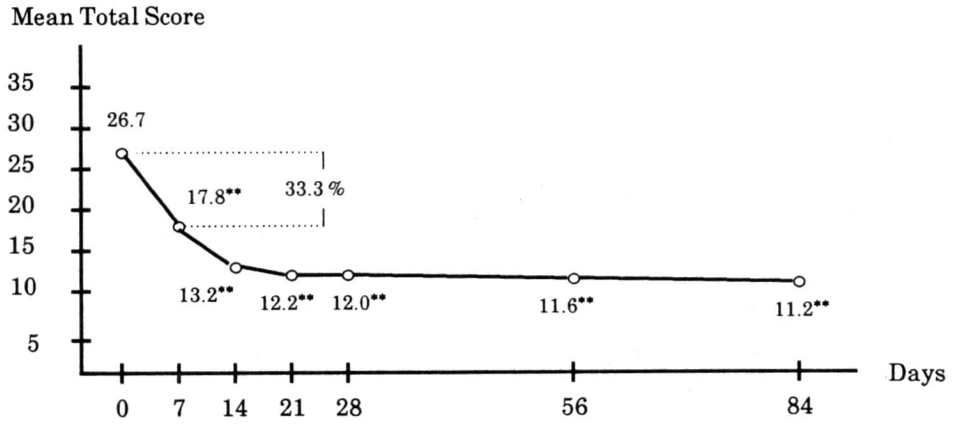
Quantitative Evaluation of the Results

Quantitative evaluation of the results was standardized by the use of Hamilton Scale of Depression (Figs. 1 and 2). The initial mean score was of 26.7; a rapid onset of action was observed, as shown by a decrease of 33.3% in the global score on the 7th day ($p < 0.01$). This rapid onset of action showed great efficacy, for up to the 28th day the global score was 12 (decrease of 55% in relation to the 10th day) ($p < 0.01$).

Regarding the BPRS (Fig. 3), the decrease in the scores was similar to that of the Hamilton scale. The mean initial score was 42.3 and decreased rapidly. In the group of patients who have shown a good and very good clinical evolution

TABLE 4. *Global clinical evaluation of the results after 12 weeks of treatment with amineptine*

Very good results	11 cases	(31.4%)	60%	94.3% *Positive*
Good results	10 cases	(28.6%)		
Fair results	12 cases	(34.3%)		
Nil	1 case	(2.9%)		
Poor results	1 case	(2.9%)		



** $p < 0.01$ (when compared with D0)

FIG. 1. HDRS—Time course in patients treated with amineptine.

(60%), BPRS score decreased from 40.2 (day 0) to 19.3 (day 14) ($p < 0.001$). The Hamilton depression score was higher in cases of endogenous depressions; the efficacy of amineptine was shown to be slower in these patients than in cases of reactive depressions. However, with respect to the percentages, the results were almost equivalent.

Discontinuations of Treatment and Acceptability

Three patients abandoned the study: one left due to a worsening of the symptoms on the 7th day, a second attempted suicide on the 7th day, and the third did not attend the assessment on the 14th day. Ten patients demonstrated moderate

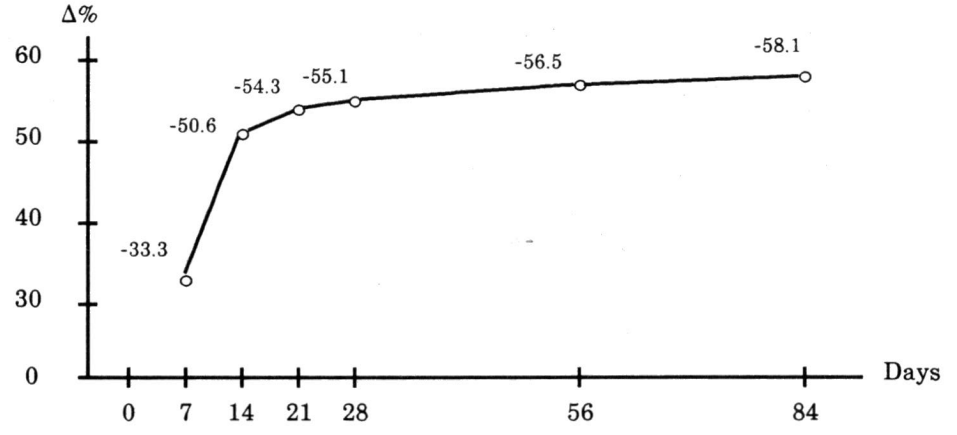


FIG. 2. HDRS—Percentages of decrease in the total score.

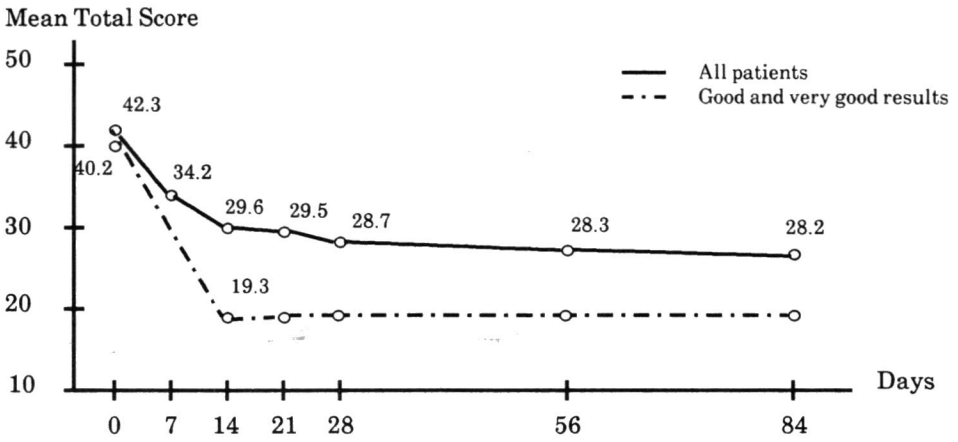


FIG. 3. BPRS—Time course in patients treated with amineptine.

adverse reactions. Six patients showed these symptoms only during the first 2 weeks of treatment. The clinical acceptability was very good; none of the patients requested the discontinuation of treatment (Table 5).

Discussion and Conclusion

With regard to the antidepressant efficacy, the clinical global evaluation demonstrated 94% positive results in depressed patients. The statistical analysis of the time course of scores of Hamilton Scale of Depression and of the BPRS Scale showed significant decreases as soon as the 7th day of treatment. Amineptine was shown to be quickly effective; its action was maintained until the end of treatment.

Using a checklist, we conducted a systematic search for all side effects. This exhaustive research allowed us to demonstrate the slight incidence of side effects. Cardiovascular, urinary, and ocular alterations were not reported; however a 42-year-old patient showed transient accommodation alterations during the last week of the treatment. This study confirmed the good clinical acceptability of amineptine.

TABLE 5. *Side effects observed on amineptine*

Symptoms	Moderate	Intense	Absent
Dry mouth	4	0	31
Fatigue	3	0	32
Agitation	2	0	33
Drowsiness	2	0	33
Tachycardia	2	0	33
Weakness	1	0	34
Photosensitization	1	0	34
Constipation	1	0	34
Disturbance of accommodation	1	0	34

It may be objected that an open study may be subject to criticism. However, it was the first study we performed in Brazil to evaluate the antidepressant action of amineptine, knowing that controlled studies have already been done in other countries and that many others are in progress to compare amineptine with placebo and with other well-known antidepressants. Nevertheless, the results of this first study of amineptine are not very different from the others published in literature.

A STUDY OF THE ANTIDEPRESSANT PROFILE OF AMINEPTINE

Aim of the Study

The aim of this second study with amineptine was to evaluate its clinical profile of action in depressed patients with inhibition using the HARD Scale (13), and its neuroendocrine action by the means of two neuroendocrine tests (Dexamethasone Suppression Test and TRH/TSH Test).

Methods

This open study included 40 depressed patients.

Inclusion Criteria

To enter this trial, the subjects had to be depressed outpatients, between the ages of 18 and 70 years, requiring an antidepressant drug therapy. Furthermore, they had to have a global score of at least 20 in the HARD Scale and a score of at least 5 in the item Inhibition of this rating scale. These scores were used to include depressions with moderate or severe intensity and retardation.

Noninclusion Criteria

The usual noninclusion criteria for amineptine were used (Huntington's chorea, pregnancy, current severe organic diseases, treatment with monoamine oxidase inhibitors within 2 weeks before the study).

Dosage and Duration of the Treatment

The patients were treated by two tablets of 100 mg amineptine per day for 2 months.

Combined Treatment

The following additional treatments could be used, if necessary: antianxiety drugs, nonbarbiturate hypnotics, or neuroleptics. These treatments had to be previously prescribed.

Assessment Criteria

The evaluation of the depression used included the following: (a) the clinical global judgment by the investigators; and (b) the HARD scale—total score and

four subscores related to the intensity of mood, anxiety, inhibition, and suicidal risk. These assessments were performed prior to and 7, 21, and 60 days after the first administration of amineptine. Furthermore, all side effects were searched for carefully; two laboratory tests (Dexamethasone Suppression Test and TRH/TSH Test) were performed prior to, and 60 days after, the first administration of amineptine.

Results

Forty depressed patients (20 female and 20 male) were included. Their mean age was 38.6 ± 6.3 years (range: 19–58).

Their mean scores according to HARD Scale were as follows:

H = "Humeur" (Mood)	13.3 ± 0.3
A = "Anxiété" (Anxiety)	8.5 ± 0.5
R = "Ralentissement" (Inhibition)	13.1 ± 0.4
D = "Danger" (Suicidal risk)	6.4 ± 0.5
T = Total (H + A + R + D)	41.3 ± 1.4

These scores indicated a medium severity of depression with mainly a "depressive inhibition."

Combined Treatment

Six of the patients were treated by amineptine alone; the others received antianxiety drugs or hypnotics, besides amineptine.

Clinical Global Evaluation

The clinical global evaluation included 39 patients (Table 6), among whom 21 obtained very good or good results (54%).

Statistical Analysis

All the HARD items were analyzed using a two-way (time, subject) analysis of variance; in cases of a significant time effect, a further Newman-Keuls test of multiple comparison of means two-by-two was performed. The results are showed in Table 7.

TABLE 6. *Clinical global judgment*

Very good results	10 cases	(26%)	54%	72%
Good results	11 cases	(28%)		
Fair results	7 cases	(18%)		
Nil	11 cases	(28%)		
Without interpretation	1 case			

TABLE 7. *HARD—Time course of total score*

	D0	D7 Significance/D0	D21 Significance/D0	D60 Significance/D0
Total score $n = 31$	40.8 ± 1.6	24.2 ± 2.4[a]	17.1 ± 2.6[a]	14.4 ± 2.7[a]

[a] $p \leq 0.01$.

A statistically significant decrease in the total score of HARD Scale was observed ($p < 0.001$). This improvement was shown as soon as the 7th day of treatment ($p \leq 0.01$) and increased until the end of treatment. A statistically significant ($p < 0.001$) improvement of the four items of HARD Scale was noted, as soon as the 7th day of treatment ($p \leq 0.01$).

Generally speaking, the treatment with amineptine was very effective as shown by the following data: (a) in 54% of the cases, the clinical judgment was good (72% of the results were considered very good, good, and fair); (b) the HARD diagram showed a significant statistical decrease in its global score and scores of each item (Table 8).

Clinical Acceptability

In total, the clinical acceptability was considered very good.

The following adverse reactions were observed: (a) tachycardia—two cases; (b) tachycardia and excitement—one case; (c) tachycardia and anxiety—one case. None of these transient adverse reactions required a corrective treatment. There was no significant modification of blood pressure.

Complementary Hormone Tests

Dexamethasone suppression test (DST). The test was performed by intramuscular administration of 2 mg of dexamethasone and measurement of plasmatic cortisol

TABLE 8. *HARD—Time course of the items*

	D0	D7 Significance/D0	D21 Significance/D0	D60 Significance/D0
Item H Mood ($n = 31$)	13.5 ± 0.3	8.2 ± 0.8[a]	6.0 ± 0.9[a]	5.5 ± 1.0[a]
Item A Anxiety ($n = 31$)	8.1 ± 0.5	4.2 ± 0.5[a]	2.5 ± 0.5[a]	2.1 ± 0.4[a]
Item R Inhibition ($n = 31$)	13.1 ± 0.4	8.5 ± 0.9[a]	6.4 ± 1.0[a]	5.0 ± 1.0[a]
Item D Suicidal risk ($n = 31$)	6.2 ± 0.6	3.3 ± 0.5[a]	2.2 ± 0.4[a]	1.6 ± 0.4[a]

[a] $p \leq 0.01$.

at 4:00 p.m. and at 11:00 p.m. the next day. The test was performed in all the patients on day 0 and was positive (nonsuppression) in 19 patients. On the 60th day, a second test was given to 33 patients who had been treated for 60 days. Among the 19 patients with positive results on day 0, we observed suppression in 9 patients and nonsuppression in the remaining 10 patients.

Relation with clinical data. Among the nine patients with nonsuppression on day 0 and suppression on day 60, the following clinical results were noted: (a) very good results—three patients; (b) good results—five patients; (c) fair results—one patient.

Among the 10 patients with nonsuppression on day 0 and nonsuppression on day 60, the following clinical results were noted: (a) very good results—three patients; (b) good results—two patients; (c) fair results—two patients; (d) nil—three patients.

In conclusion, the 19 observations showed that the clinical assessment was in agreement with the results of DST in 12 cases, whereas in 7 cases contradictory results were found.

TRH/TSH test. An injection of 100 mg of TRH was performed; TSH was measured before and 20 min and 60 min after injection.

(a) On day 0, the TRH test was performed on 40 patients. In nine patients this test was positive (blunted TSH response to TRH).

(b) On the 60th day a second test was performed in 33 patients (patients were in treatment for 60 days). Among the nine patients with positive results on day 0, the following results on the 60th day were noted: (1) Negative test—six patients; (2) Positive test—one patient. (Two patients discontinued treatment before the test.)

(c) Relation with clinical data: Among the six patients with a positive test on day 0 and a negative one on day 60, the following clinical results were obtained: (1) Very good results—two patients; (2) Good results—four patients. The one patient with a positive test on day 0 and on day 60 demonstrated a good clinical result.

In conclusion, among these seven patients in six cases the clinical judgment was in agreement with the results of the test while in one case we found contradictory results.

CONCLUSION

The objective of this open study was to assess the action of amineptine in depressed and inhibited patients and to evaluate its action on two neuroendocrine tests. Forty outpatients (20 male and 20 female; mean age 38.6 ± 6.3 years) received two 100-mg tablets per day of amineptine for 2 months. The mean profile of depression was defined as "depression with depressive inhibition," according to the HARD Scale.

The efficacy of amineptine was satisfactory: 54% had very good or good results and 72% had positive results. The statistical analysis of HARD Scale confirmed the efficacy of the drug in these depressed and inhibited patients. The total score

and the score of each single item were statistically decreased, and this improvement increased regularly with time.

The acceptability of amineptine was good. We noted infrequent adverse reactions, which were not important. The measurement of blood pressure demonstrated an excellent cardiovascular acceptability of amineptine.

The evolution of the DST and the TRH/TSH test was studied in these patients treated with amineptine. The results of DST were moderately in agreement with some results of literature (14) but the results of TRH/TSH test were more conclusive. Anyway, these results may confirm that the interest of these two tests is questionable in depression, as already shown by other authors in other studies.

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