Efficacy of amineptine in the prevention of relapse in unipolar depression

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The clinical properties of amineptine, a mainly dopaminergic antidepressant, were assessed in a double-blind controlled study involving patients fulfilling Diagnostic and Statistical Manual of Mental Disorders (DSM-III) criteria for unipolar depression. The aim was to determine how relapses could be prevented in this frequently recurring disorder. The study was a two-phase, 12-month, multicentre trial of patients suffering from major depression or dysthymia, diagnosed using DSM-III criteria and evaluated on the Montgomery–Asberg Depression Rating Scale and the Mood, Anxiety, Retardation, Danger scale. Phase I was an open-label 3-month period, with the patients being given 200 mg amineptine per day. The second, 9-month period was a placebo-controlled prophylactic phase. A total of 458 patients were initially included in the study. Of the 376 who completed phase I, 303 (60%) were responders; 284 entered the prophylactic study, randomly assigned to two groups. Of the 134 patients in the placebo group who completed phase II, 25 (18.7%) suffered a relapse, compared with nine out of the 136 (6.6%) in the amineptine group. After resolution of an acute episode of major depression or dysthymia, long-term antidepressant therapy with amineptine significantly reduced the relapse rate.

Keywords: Unipolar depression, relapse, prevention, amineptine

INTRODUCTION

Amineptine is an antidepressant compound derived from the tricyclic antidepressants (Kamoun, 1979) with a predominant effect on the dopaminergic system (Chagraoui et al., 1989; Garattini and Mennini, 1989; Chagraoui et al., 1990). Clinically, this drug has been used in the treatment of patients with major depression or with dysthymia (Deniker et al., 1982; Ferreri et al., 1987, 1988). Controlled double-blind studies versus reference antidepressants have demonstrated that amineptine has both a wide clinical spectrum of activity and an impressive safety profile (Lemoine et al., 1980; Porot et al., 1980; Ropert et al., 1982; Jean-Louis et al., 1986). These studies have mostly indicated a rapid onset of antidepressant action, in contrast with the usual 10- to 14-day delay (Davis, 1985) and an additional disinhibiting effect (see below). Combined with good clinical tolerance, this makes the use of amineptine particularly appropriate for the maintenance of normal life in ambulatory depressives (Grivois et al., 1979; Macher and Mirabaud, 1992) and especially in high-risk patients where the delay in improvement is particularly undesirable (Ferreri et al., 1988). Deniker et al. (1981, 1982) have stressed the disinhibiting activity of amineptine, that is, mental and motor stimulation without euphoria or reactivation of anxiety, which has been found both in depressed patients and hebephrenic (disorganized) schizophrenics, as well as in opiate addicts during drug withdrawal.

Animal studies have produced data particularly relevant to long-term treatment with amineptine. Ceci et al. (1986) stated that amineptine increases dopaminergic transmission by presynaptic action, and that long-term amineptine treatment induces adaptive modifications in both pre- and postsynaptic mechanisms, which may be responsible for its pharmacological effects.

There has been increasing recognition that depressive disorders require prolonged treatment, though there is still inadequate evidence for the prophylactic efficacy of antidepressants. Since none of the established antidepressants can be considered a well validated reference compound for such investigations, most weight has been given to placebo-controlled studies (Mindham et al., 1973; Prien et
al., 1973; Coppen et al., 1978; Montgomery et al., 1988). Therefore, a placebo control group was considered necessary in our recent 12-month multicentre study carried out in France. We chose to study the most commonly treated depressive disorders, which in outpatients are major depression and dysthymia. The primary object was to test the conventional view that early cessation of antidepressant treatment, after the disappearance of overt symptoms, is clinically inadvisable. The length of the study permitted us to focus on any prophylactic effect of amineptine in preventing relapses.

PATIENTS AND METHODS

The multicentre trial was undertaken by 52 experienced psychiatrists, supervised by three regional coordinators. The trial comprised two defined periods.

Patients

Patients suffering from major depression (moderate or severe, without psychotic features) or dysthymia were diagnosed using Diagnostic and Statistical Manual of Mental Disorders (DSM-III) criteria (American Psychiatric Association, 1987). They were required to have a score of at least 20 on the Montgomery–Åsberg Depression Rating Scale (MADRS; Montgomery and Åsberg, 1979) and at least 18 on the Mood, Anxiety, Retardation, Danger (MARD) scale (Rufin and Ferreri, 1984). Each axis in the MARD scale is subdivided into three items, measured from 0 to 6, so that six clinical types of depression are generated.

Medication

In the first period (index depressive episode), treatment was open-label with 200 mg amineptine a day (one tablet of 100 mg in the morning and one at noon) for 3 months. No other concomitant psychotropic medication was allowed, with the exception of anxiolytics and non-barbiturate hypnotics.

Evaluation

During the index depressive episode, the patients were seen weekly to assess their clinical states: assessments were made with the MADRS and MARD scales before treatment (day 0), and after 1, 2 and 3 months. The trial design is shown in Fig. 1.

To enter the second, prophylactic phase, the subjects had to have recovered clinically during the first 2 months, as well as maintaining a symptom-free period without relapse for the following month. The criteria used to define clinical recovery were a MADRS score of 20 or less, a MARD score of 18 or less, a decrease of at least 50% of the initial MADRS score and a favourable clinician’s evaluation. The subjects who responded according to these criteria and entered the prophylactic period were then randomly assigned to double-blind treatment with either amineptine (100 or 200 mg a day) or placebo. When a relapse

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Fig. 1. Design of the multicentre study

S40 International Clinical Psychopharmacology • Vol 12, Suppl 3 • 1997
occurred, the patient was immediately treated with active antidepressant medication. Relapse was defined as a depressive syndrome satisfying the same diagnostic and severity criteria as for entrance to the study (a score of at least 20 on the MADRS scale and of at least 18 on the MARD scale).

After entering the prophylactic period, the patients were regularly seen and evaluated clinically; if there was evidence of relapse, this was treated by an antidepressant, as required. Assessments were made after 3, 6 and 9 months, or at the appearance of a relapse.

Tolerability of the drugs was assessed during both the initial treatment period and the prophylactic phase, through a symptom check-list and clinical surveillance.

Ethical issues
Verbal informed consent was obtained before entrance to the double-blind controlled period. Ethical approval was obtained from the Ethical Committee of Saint-Antoine Hospital.

RESULTS
Subjects
A total of 458 patients were treated openly with amineptine: 284 women (62%) and 174 men (38%), with a mean (SD) age of 44 ± 0.6 years and diagnosed with major depression (74%) and dysthymia (26%). At inclusion (day 0), the mean (SEM) MARD score was 37.7 ± 0.4 and the MADRS score was 33.8 ± 0.3. In their previous history, 54.7% of the patients had suffered from earlier depressive episodes, and 10.6% had shown suicidal behaviour. The duration of the present episode was less than 6 months for 42.5% of the patients, between 6 months and 1 year for 20.5% and more than 1 year for 37%.

The typology of the depression was assessed with the MARD scale, and the subjects allocated to the following categories: 34.9% anxious-retarded, 32.3% pure depressive, 11.1% inhibited, 5.9% asthenic depressive, 5% anxious depressive, 3.7% anxious somatic. This typology shows that retardation was a dominant symptom in 91.2% of the sample and confirms that mental and psychomotor retardation is a primary expression of depressive illness (Wildöcher, 1983a,b).

During the first period of the trial, anxiolytics were co-

prescribed in 90.8% of the subjects, in accord with the usual clinical practice in France.

The demographic characteristics of the sample showed that 64.8% were in active employment, 23.9% had no occupation, 5% were retired, and 6.1% unemployed; moreover, 58.2% were married, 22% single, 11.6% divorced and 8.1% widowed. Thus, the sample was consistent with the characteristics of depressed patients in general, in France.

Outcome
At the end of phase I, 376 subjects had completed the protocol. Of these, 303 (81%) were responders and 73 (19%) non-responders (response being defined as a decrease of at least 50% of the MADRS initial score). Thus, 303 responded out of 458 entrants to the study (66%). Early study termination occurred with 82 patients. In 66 of these patients, the treatment was not effective or the clinical picture deteriorated; five patients dropped out because of side effects, and 11 did so giving other reasons.

The outcome of phase I is summarized in Fig. 2 and Table 1. The therapeutic activity of amineptine was manifest in all axes of assessment, and this was statistically significant at every timepoint of measurement (Table 1). This improvement was manifest on all axes of the MARD scale, as well as in the global scores of the two evaluation scales. The clear-cut reduction in scores on the danger and depressed mood axes between day 0 and 3 months (−71.2 and −68.9%, respectively) and the substantial improvement on the other two subscores, retardation (−67%) and anxiety (−58.2%), are important features.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>No. patients</th>
<th>Day 0</th>
<th>Month 1</th>
<th>Month 2</th>
<th>Month 3</th>
<th>Time effect (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mood</td>
<td>369</td>
<td>10.6 ± 0.1</td>
<td>6.7 ± 0.2</td>
<td>4.4 ± 0.1</td>
<td>3.3 ± 0.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anxiety</td>
<td>369</td>
<td>9.8 ± 0.1</td>
<td>6.7 ± 0.1</td>
<td>5.0 ± 0.1</td>
<td>4.1 ± 0.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Retardation</td>
<td>370</td>
<td>10.6 ± 0.1</td>
<td>6.6 ± 0.2</td>
<td>4.5 ± 0.2</td>
<td>3.5 ± 0.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Danger</td>
<td>366</td>
<td>6.6 ± 0.2</td>
<td>3.8 ± 0.1</td>
<td>2.5 ± 0.1</td>
<td>1.9 ± 0.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Global</td>
<td>365</td>
<td>37.7 ± 0.4</td>
<td>23.7 ± 0.5</td>
<td>16.2 ± 0.5</td>
<td>12.7 ± 0.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MADRS global score</td>
<td>370</td>
<td>33.8 ± 0.3</td>
<td>21.2 ± 0.4</td>
<td>14.7 ± 0.4</td>
<td>11.9 ± 0.5</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are means ± SEM. For all parameters listed, Newman–Keuls' test: a = 1%; day 0 | months 1, 2, 3; month 1 | months 2, 3; month 2 | month 3.
During the initial treatment period, the tolerability of amineptine was very good. Only 5.2% of early terminations were due to side effects. The adverse events exceeding a frequency of 1% in the first month were tachycardia, dry mouth, nausea, tremor and digestive pain.

Prophylactic phase

A total of 284 patients (62% of the initial population) entered the 9-month prophylactic study. They were randomly assigned to two groups, 141 to amineptine and 143 to placebo. The principal reason given by patients for agreeing to enter this phase of the trial was fear of relapse. The two groups were homogeneous in terms of diagnosis, sociodemographic status, and initial MÅDRS and MARD scores.

Altogether, there were 42 drop-outs in phase II: five were lost to follow-up (two after 6 months and three after 9 months), 22 stopped because of a subjective feeling of recovery (14 after 6 months and eight after 9 months), and 15 dropped out for other reasons (nine after 6 months and six after 9 months). The percentage of drop-outs (14.7%) was small for a trial of this length.

Complete data were missing for nine patients from the initial placebo group and five from the initial amineptine group. Of the 270 patients for whom complete data were available, 34 suffered a relapse in the form of a depressive episode during the 9-month study. Of the 134 patients in the placebo group, 25 (18.7%) relapsed, compared with nine of the 136 (6.6%) in the amineptine group ($P = 0.003$ versus placebo). Of the nine patients who relapsed in the amineptine group, three were treated with 200 mg a day, five with 100 mg a day, and for the one remaining patient, the dose was not recorded. There was no significant difference between the two doses, possibly because of the small number of patients in each of these groups.

Table 2 summarizes the relapses at each timepoint of phase II. The mean (SEM) MÅDRS score of the patients who relapsed was 34.9 ± 1.2, and their mean (SEM) MARD score was 37.1 ± 1.4.

At the end of this 9-month period, a highly significant advantage of amineptine in reducing the rate of relapse was evident. The reduction achieved, compared with placebo, was 64%; this advantage was significant both at 6 and 9 months.

Prediction criteria for relapse

In an attempt to establish prediction criteria for relapse, the main characteristics of both groups were examined. At the end of phase II, the characteristics of the patients who suffered a relapse were compared with those of patients who did not have a further depressive episode. None of the characteristics summarized in Table 3 was helpful in predicting a relapse.

**DISCUSSION**

The design of this long-term multicentre trial attempted to take into account some of the problems that had emerged in earlier studies of the prophylactic efficacy of antidepressant medication (Mindham et al., 1973; Prien et al., 1973). We were aware that long-term treatment with placebo is not devoid of clinical and ethical problems (Woggon, 1992), but close surveillance of the patients and monitoring of the study minimized any possible danger to the patients' health or life. Lithium was not used as a reference drug, although it is well known to have prophylactic efficacy in bipolar depression (Prien et al., 1973). Schou (1973) recommended lithium as a prophylactic medication in unipolar depression, but Prien et al. (1984) believed that there was no positive evidence of its efficacy.

The prophylactic efficacy of antidepressants is more assumed than scientifically proved. Klerman et al. (1974) emphasized the need to distinguish clearly between the definitions of ‘relapse’ (an early return of the symptoms of an ongoing episode) and ‘recurrence’ (a later new epi-
weeks: only those responders who remained symptom-free during this period were eligible for entry to phase II. The 9-month period of phase II can be regarded as sufficient to study prophylactic efficacy. A longer period of controlled placebo treatment would place outpatients at risk, making follow-up extremely difficult. Previous studies (Prien and Kupfer, 1986) reported a considerable rate of relapse on placebo in the early months of long-term trials.

The present study provides evidence for the prophylactic efficacy of amineptine in unipolar depression. The results of phase I confirmed its efficacy and safety in the treatment of acute unipolar depressive episodes, while phase II showed that the long-term use of amineptine reduced the relapse ratio by 64%. Depressive illness is frequently a recurring disorder (Davis, 1995); evidence for the prophylactic action of amineptine strongly suggests that this drug is efficacious in preventing the recurrence of new episodes, after the 6-month relapse period.

In these long-term studies, considerable attrition of the number of patients must be expected, due to drop-outs or relapses. However, in the present study, there was only a small percentage of drop-outs in each phase. This reflects the careful design, which allowed only complying, motivated responders to enter the prophylactic period, and probably also the good safety and tolerance of amineptine, which causes fewer side effects than classical antidepressants (Kamoun, 1979; Deniker et al., 1982). The fact that most subjects who terminated the trial early felt that they had recovered seems to be important. This design also introduced a possible bias by excluding refractory depressives, but efficacy can best be demonstrated in non-treatment-resistant patients (Woggon, 1992). The MARD scale, by measuring the ‘danger’ axis, is of value in the follow-up of depressed outpatients, especially in relation to the risk of suicide. In outpatient treatment, alleviation of a depressed mood and retardation are much appreciated by patients, but clinicians must also pay attention to the danger axis, in order to predict and prevent suicidal behaviour. The stimulating effect of amineptine can be seen in the strong improvement in the retardation axis of the MARD scale at the end of the trial. This effect is helpful to outpatients in maintaining a normal way of life.

During the past 30 years, it has become increasingly clear that depression should be viewed in longitudinal terms, rather than simply in terms of treatment of an acute episode (Deniker, 1989). However, it has not yet been possible to demonstrate whether treatment corrects the postulated underlying disorder, therefore shortening the depressive episode, or whether it merely suppresses acute symptoms until the episode runs its natural course. Therefore, long-term treatment is to be advised for at least 4 months after the disappearance of acute symptoms, that is, for as long as a depressive episode would be expected to last if it

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**Table 3. Search for predictive criteria of relapse**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>No relapse (n = 236)</th>
<th>Relapse (n = 34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SEM) age (years)</td>
<td>43.4 ± 0.8</td>
<td>46.2 ± 2.1</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>83</td>
<td>15</td>
</tr>
<tr>
<td>Female</td>
<td>153</td>
<td>19</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major depression</td>
<td>176</td>
<td>25</td>
</tr>
<tr>
<td>Dysthymia</td>
<td>60</td>
<td>9</td>
</tr>
<tr>
<td>Past history of depression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>115</td>
<td>17</td>
</tr>
<tr>
<td>No</td>
<td>115</td>
<td>16</td>
</tr>
<tr>
<td>Past history of suicide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>16</td>
<td>4</td>
</tr>
<tr>
<td>No</td>
<td>207</td>
<td>29</td>
</tr>
<tr>
<td>Baseline score (day 0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MARD</td>
<td>36.8</td>
<td>37.1</td>
</tr>
<tr>
<td>MADRS</td>
<td>33.3</td>
<td>32.9</td>
</tr>
<tr>
<td>Duration of current depressive episode</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;6 months</td>
<td>105</td>
<td>18</td>
</tr>
<tr>
<td>6–12 months</td>
<td>49</td>
<td>9</td>
</tr>
<tr>
<td>1–2 years</td>
<td>26</td>
<td>4</td>
</tr>
<tr>
<td>2–3 years</td>
<td>20</td>
<td>1</td>
</tr>
<tr>
<td>&gt;3 years</td>
<td>35</td>
<td>2</td>
</tr>
<tr>
<td>Employment status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Actively employed</td>
<td>158</td>
<td>25</td>
</tr>
<tr>
<td>Unemployed</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td>Retired, inactive</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>With no profession</td>
<td>47</td>
<td>6</td>
</tr>
</tbody>
</table>

MARD, Mood, Anxiety, Retardation, Danger scale; MADRS, Montgomery–Åsberg Depression Rating Scale. Numbers do not add up to the full number of patients in all cases because data were missing for some patients. No comparisons were significant.
was left untreated (Georgotas, 1985; Prien and Kupfer, 1986).

The results of this double-blind multicentre trial concur with those of previous well designed and well conducted trials in confirming the general usefulness of long-term treatment in unipolar depression. It is clear from this study that long-term medication prevents relapses, and there are suggestive findings that recurrence is also reduced. Treatment with amineptine appears to reduce the chance of a relapse for at least 9 months after resolution of an acute depressive episode followed by a symptom-free period. This finding of a significant prophylactic effect with amineptine, compared with placebo, is comparable to those found with selective serotonin reuptake inhibitors, which have the ability to prevent new episodes in recurrent unipolar depression (Montgomery et al., 1988).

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REFERENCES


