

## THERAPY WITH AMINEPTINE, A DOPAMINE REUPTAKE INHIBITOR, IN PATIENTS WITH MAJOR DEPRESSION

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### ABSTRACT

*The original tricyclic antidepressant drugs are consistently underused in major depression because of side effects, delayed onset of action, and potential for overdose. In an open study of 6 weeks' duration, we studied the efficacy and acceptability of amineptine, a dopamine reuptake inhibitor, at fixed dose of 200 mg per day in 50 patients with major depression.*

*Intention-to-treat analysis showed a patient response rate of 64% (95% CI 77-50) in HDRS, 62% (95% CI 75-48) in MADRS, 46% (95% CI 59-32) in ZUNG scale, 52% (95% CI 66-38) in Social Activity scale, and 26% (95% CI 38-14) in CGI-severity of illness after 7 days treatment. Response in CGI-global improvement was 38% (95% CI 51-25), and in CGI-efficacy index 48% (95% CI 62-34) after 14 days of treatment. With continued therapy, only CGI-severity of illness showed a significant increase in response rate after 42 days. The treatment effect of amineptine was reflected in a significant and progressive improvement in all depression, social activity, and CGI rating scale scores throughout the study period. Somatic symptoms and side effects assessed by AMDP-5 showed significant improvement at each assessment.*

*The clinically useful response in depression which occurred by the first week of treatment, favourable side effect profile, and the convenience of a fixed dose could make amineptine a suitable first line alternative for the treatment of major depression.*

*Key Words : Indian patients, major depression, amineptine*

In the past 30 years there have been major changes in the diagnosis and treatment of depression (Potter et al., 1991). The original tertiary and secondary amine tricyclic antidepressant drugs, which have been the drugs of choice for major depressive disorders, suffer from lack of pharmacologic specificity, a delayed onset of action, a potential for fatal overdosage, and side effects (Michel et al., 1993). Epidemiologic studies have constantly found that these drugs are underused in those who meet the criteria for major depression (Shapiro et al., 1983).

Amongst the newer antidepressant agents, amineptine (7-5 amino-(10, 11-dihydro

(a,d) dibenzocycloheptenyl) heptanoic acid hydrochloride) is a tricyclic antidepressant drug that selectively decreases dopamine reuptake without affecting other neurotransmitters (Ceci et al., 1986). In controlled studies, it is as effective as amitriptyline (Van Amerogen, 1979), trimipramine (Vauterin and Bazot, 1987), and fluoxetine (Dalery et al., 1992). It has a rapid onset of action, and is devoid of the disadvantages of the original tricyclic antidepressant drugs (Deniker et al., 1982). These features may favour the use of amineptine as a first line drug in the treatment of major depression, and improve the compliance with treatment of patients seen in

everyday clinical practice.

In a detailed open study we assessed the efficacy and acceptability of amineptine in Indian patients with major depression (single or recurrent episode), and work impairment.

## MATERIAL AND METHOD

The protocol was approved by the institutional ethics committee. To be eligible for the study patients had to be between 18 and 65 years of age, with major depression (single or recurrent episode, with or without seasonal pattern or melancholia) diagnosed by DSM III-R criteria (American Psychiatric Association, 1987), a Montgomery and Asberg depression rating scale (MADRS) score of 20, a Hamilton depression rating scale (HDRS) score of 18; and with work or academic impairment (DSM III-R criteria). Patients were excluded if they had psychotic symptoms, dysthymia during the preceding 2 years, a previous history of inadequate work or academic performance epilepsy, severe hepatic, cardiovascular, or neurologic disease, cancer, Huntington's chorea or hypersensitivity to amineptine, if they were non responders to two antidepressants after 4 weeks of treatment with each at full therapeutic dose, hospitalised due to suicidal risk, under treatment before inclusion for 7 days with MAOI, 15 days with reversible MAOI, or 1 month with fluoxetine, pregnant or breast feeding, of child bearing potential without contraception, or dependent on alcohol or drugs; or if their condition required treatment with ECT.

After giving their informed consent, patients received 200 mg of amineptine (*survector*) daily, in two divided doses at 8 A.M. and 12 noon for 6 weeks. Anxiolytic therapy with oxazepam was allowed in a dose of less than 50 mg per day. No other psychotropic medication was given. Treatment for associated disease, excluding those known to affect depression, were recorded at baseline and at each assessment. After baseline assessment, patients were seen on the 7th, 11th, 14th, and 21st day and at weekly intervals until the end

of the 6 weeks study period.

Assessments were made by trained psychiatrists. In most cases each patient's condition was evaluated by the same person throughout the study. Thirteen clinical variables were evaluated: MADRS, HDRS, ZUNG Self Rating Depression Scale (ZUNG), Social Adjustment Self Reporting Questionnaire (SAS), Hamilton Anxiety Rating Scale (HARS), Clinical Global Impression (CGI) - severity of illness, CGI-global improvement, CGI-efficacy index, physical examination, blood pressure, heart rate, and weight. The primary outcome measures were the MADRS & HDRS.

The following tests were performed at baseline: total haemoglobin, haematocrit, RBC, WBC, platelet counts, and WBC differential count; total bilirubin, SGPT, gamma GT, SGOT, alkaline phosphatase, blood glucose, and serum creatinine; and ECG. Side effects were assessed at baseline and at 1st, 2nd, 4th, and 6th week with the AMDP-5 somatic scale, by asking patients about somatic complaints and side effects.

Response to treatment in outcome variables was analysed on an intention-to-treat basis, and categorical data expressed as a proportion with its standard error. Difference in response between assessments was tested by the  $\chi^2$  test. Change in outcome variables between assessment was compared by the paired 't' test. Significance was defined as a two tailed p value of less than 0.05.

## RESULTS

Fifty consecutive patients who met the eligibility criteria entered the study and received treatment with amineptine. The baseline characteristics of these patients are summarised in Table 1. The mean (SD) age was 32.3(10.3) years, and the majority were male with major depression of moderate severity. Twenty three (46%) had recurrent depressive episodes, and the mean (SD) duration of illness was 5.4 (3.8) months. Among those enrolled, 35 patients completed the 6 week regimen of study

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medication. The timing and reasons of the 15 patients who withdrew from the study medication before 6 weeks are shown in Table 2. One patient had to be withdrawn because of severe anxiety.

**TABLE 1**  
**BASILINE CHARACTERISTICS OF PATIENTS**

<b>Age</b> (Years)		32.3±10.3
<b>Sex</b> (Male)		34 (68)
<b>Clinical</b>		
duration of illness (months)		5.4±3.8
recurrent depressive episodes		23 (48)
weight (kg)		62.2±7.3
blood pressure		
systolic		123±12.0
diastolic		79.1±9.5
<b>Haematology</b>		
haemoglobin (gme%)		13.4±1.7
total WBC (x100/mm <sup>3</sup> )		77.1±16.3
platelet count (x10 <sup>6</sup> /mm <sup>3</sup> )		20.7±7.5
<b>Biochemistry</b>		
total bilirubin (mg%)		0.67±0.22
gamma GT (mU/ml)		17.8±6.3
SGOT (mU/ml)		23.7±6.7
SGPT (mU/ml)		23.7±10.6
alkaline phosphatase (mU/ml)		99.6±26.2
serum creatinine (mg%)		0.85±0.18
fasting blood glucose (mg%)		82.5±11.9

± values are means ±SD. All other values are numbers of patients followed in parentheses by the percentage of the group

The proportion of patients who showed improvement in the depression, SAS, and CGI-severity of illness scale is shown in Figure 1. The intention-to-treat analysis showed that

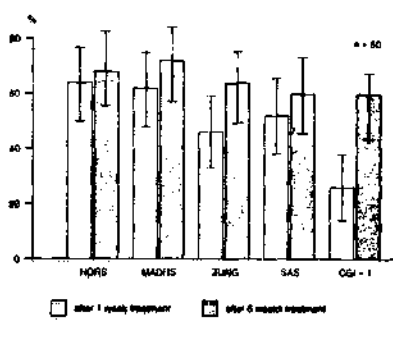
**TABLE 2**  
**REASONS FOR EARLY WITHDRAWAL OF PATIENTS FROM THE STUDY**

Reason	No. of patients	Mean no. * of weeks
Lack of efficacy	4	3
Adverse reaction	1	1
Refusal to continue	10	3
All	15	-

\* After start of study treatment

† Due to severe anxiety

Figure 1 Patients showing improvement in depression, social adjustment and severity of illness after 1 and 6 weeks of treatment (intention to treat basis)



Open represent 95% confidence interval

† Significant difference relative to 1st week

HDRS = Hamilton Depression Rating Scale; MADRS = Montgomery & Asberg depression rating scale; ZUNG = Zung self-rating depression scale; SAS = Social adjustment self-report questionnaire; CGI-1 = Clinical Global Impression - severity of illness

about half the patients responded after one week of treatment and that this response rate did not significantly change at 6 weeks, except for CGI-severity of illness, in which improvement was significantly greater at 6 weeks compared to the 1st week. The number (%; 95 percent confidence interval [CI]) of patients with improvement after the first week of treatment relative to baseline, was for depression, 32 (64, 95% CI 77-50) in HDRS, 31 (62, 95% CI 75-48) in MADRS, and 23 (46, 95% CI 59-32) in the ZUNG scale; for social activity 26 (52, 95% CI 66-38) in the SAS scale; and for severity of illness 13 (26, 95% CI 38-14) in the CGI scale. At the end of 6 weeks treatment, scores of less than 8 were observed

**TABLE 3**  
**TREATMENT OUTCOMES WITH AMINEPTINE ON DEPRESSION, SOCIAL ACTIVITY, CLINICAL GLOBAL IMPRESSION, SOMATIC, AND ANXIETY SCALES DURING 6 WEEKS OF STUDY**

Outcome	Baseline score	Reduction in score from baseline after treatment (mean±S.D.)			
		1st week (n=45)	2nd week (n=42)	3rd week (n=41)	6th week (n=35)
<b>Depression</b>					
HDRS	24.3±5.7	4.3±6.3*	9.5±7.5*	12.4±8.0*	15.9±9.1*
MADRS	32.7±5.5	6.9±9.5*	11.8±11.1*	16.5±11.5*	22.4±9.9*
ZUNG	58.2±6.4	4.6±8.2*	9.7±12.3*	13.5±13.4*	21.8±15.2*
<b>Social adjustment</b>					
SAS	78.2±24.0	6.4±18.0*	13.1±18.1*	18.6±18.2*	21.3±22.4*
<b>Clinical global impression</b>					
Severity of illness	3.6±0.7	0.3±0.7*	0.8±1.0*	1.3±1.2*	2.0±1.4*
Global improvement +	2.3±0.1	-	0.5±1.0*	0.8±1.0*	1.1±1.4*
Efficacy index +	22.6±2.6	-	6.8±9.4*	9.5±10.0*	12.3±10.7*
<b>Somatic symptoms and side effects</b>					
AMDP-5	17.2±5.6	3.4±6.2*	6.4±6.3*	-	11.0±6.2*
<b>Anxiety</b>					
HARS	14.0±5.1	-	-	-	7.8±7.3

\* Reduction in score is significant as compared to score at previous assessment + Baseline assessment after 1st week of treatment

HDRS= Hamilton depression rating scale; MADRS=Montgomery & Asberg depression rating ; ZUNG-Zung self-rating depression scale; SAS=social adjustment self report questionnaire; HARS=Hamilton anxiety rating scale

in 23 (46, 95% CI 59.8-32.0) on HDRS and in 19 (38, 95% CI 51.5-24.5) on MADRS scales. Significant increase in improvement relative to that at the 1st week, was observed only in severity of illness, in 17 (34%, p<0.001) patients on the CGI scale. The number (percent, 95% CI) of patients who responded after 2 weeks treatment, relative to baseline, in global improvement was 19 (38, 95% CI 51-25), and in efficacy index 24 (48, 95% CI 62-34) on the CGI scale, with no further significant change upto 6 weeks. The number (percent, 95% CI) of patients with improvement in anxiety after 6 weeks treatment compared to baseline was 29 (58, 95% CI 72-44) on the HARS.

There was significant treatment effect with amineptine in all clinical outcome

measures at each assessment, as summarised in Table 3. After 1 week of treatment, compared to baseline, mean (SD) improvement in scores was 4.3 (6.3, p<0.001) in HDRS, 6.9 (9.5, p<0.001) in MADRS, 4.6 (8.2, p<0.001) in ZUNG scale, 6.4 (17.6, p<0.01) in SAS, and 0.3 (0.7, p<0.01) in CGI-severity of illness. Between the 1st and 2nd week of treatment, mean (SD) improvement was 4.0 (5.2, p<0.001) in HDRS, 5.4 (6.7, p<0.001) in MADRS, 4.0 (7.8, p<0.001) in ZUNG scale, 7.7 (15.3, p<0.001) in SAS, and 0.5 (0.9, p<0.002) in the CGI-severity of illness. The mean (SD) improvement in scores between the 2nd and 3rd week of treatment was 3.0 (4.91, p<0.001) in HDRS, 4.6 (6.84, p<0.001) in MADRS, 4.0 (7.8, p<0.01) in ZUNG scale, 5.6 (11.69, p<0.01) in SAS, 0.5 (0.7, p<0.001) in the CGI-severity of illness and

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0.39 (0.7,  $p < 0.001$ ) in CGI-global improvement. Between the 3rd and 6th week of treatment mean (SD) improvement in scores was 3.5 (4.1,  $p < 0.001$ ) in HDRS, 6.1 (1.9,  $p < 0.001$ ) in MADRS, 2.4 (6.3;  $p < 0.05$ ) in ZUNG scale, 2.7 (11.3,  $p < 0.01$ ) in SAS, and 0.7 (0.7,  $p < 0.01$ ) in CGI-severity of illness. There was no significant change in CGI-global improvement. HARS scores showed a mean (SD) improvement of 7.71 (7.28,  $p < 0.001$ ) after 6 weeks treatment relative to baseline.

The effect of treatment on side effects assessed by the AMDP-5 scale and the efficacy of amineptine assessed by the CGI-efficacy index are shown in Table 3. Mean (SD) scores in AMDP-5 improved by 3.38 (6.2,  $p < 0.001$ ) between baseline and the 1st week, by 2.83 (6.5,  $p < 0.01$ ) between the 1st and 2nd week, by 3.6 (5.54,  $p < 0.01$ ) between the 2nd and 4th week, and did not change significantly between the 4th and 6th week of treatment. The mean (SD) scores in CGI-efficacy index improved by 2.6 (10.07,  $p < 0.001$ ) between the 1st and 2nd week, by 2.6 (6.4,  $p < 0.01$ ) between the 2nd and 3rd week, and by 2.8 (5.6,  $p < 0.01$ ) between the 3rd and 6th week. There were no significant changes in heart rate or blood pressure after 6 week of treatment compared to the baseline.

### DISCUSSION

Patients with moderate to severe major depression and work or academic impairment had clinically significant improvement when treated with amineptine. As shown in Figure and Table 3, the benefits were consistent for all clinical outcomes which included the depression rating scales (HDRS, MADRS and ZUNG), social adjustment scale (SAS), clinical global improvement scales (severity of illness, global improvement, and efficacy index), somatic symptoms and side effects scale (AMDP-5), and anxiety scale (HARS). The intention-to-treat analysis (Figure) showed a patient response rate in depression of 60-70%, to fixed dose of amineptine (200mg per day), which occurred within the 1st week, which increased

significantly to about 60% by the 6th week.

The extent of improvement with amineptine (Table 3) is progressive over time in all depression, social adjustment, and CGI scales, with significant reduction in scores occurring at each assessment compared to the previous one, from the 1st to the 6th week of treatment. Somatic symptoms and side effects related to sleep, gastrointestinal, cardiovascular, neurologic and autonomic systems, assessed by the AMDP-5 scale (Table 3) did not increase but showed a significant decrease at each assessment from the 1st to the 4th week of treatment. The balance between therapeutic benefits and side effects with amineptine therapy assessed by the CGI-efficacy index (Table 3) also showed significant increase in therapeutic benefits at each assessment from the 2nd to 6th week. Anxiety assessed by the HARS (Table 3) improved significantly after 6 weeks of treatment. The lack of effect of amineptine on heart rate and blood pressure is consistent with previous studies (Boral et al., 1989).

In major depression, the traditional drugs (such as imipramine and amitriptyline) continue to be the treatment of choice (Potter et al., 1991). However, there are several problems related to their use. With standard treatments, even when pushed to deliver the equivalent of 200-300 mg imipramine per day, only 70-80% of patients show clinical response (Michel et al., 1993). In those who respond only 50-60% show clinical improvement before 4 weeks of treatment (Potter et al., 1991). The anticholinergic, antihistaminergic, sedative, orthostatic hypotensive, and cardiotoxic properties related to their use (U' Prichard et al., 1978), and potential for fatal overdose (Milne et al., 1993) result in about 30% of patients not complying with treatment at all, and about 25% being treated with inadequate doses (Harrison, 1994).

Studies in depression, Parkinson's disease and animal models of depression, suggest an aetiological role of dopamine deficiency in major depression (Kapoor and Mann, 1992). Amineptine, a recent antidepressant drug in India, selectively inhibits dopamine reuptake without affecting other neurotransmitters (Ceci et al., 1986). In

controlled and large open studies, its antidepressant efficacy is equal to traditional tricyclic drugs (Van Amerongen, 1979; Deniker et al., 1982; Vauterin and Bazat., 1987) and serotonin reuptake inhibitors (Dalery et al., 1992). The frequency of side effects is low, with a withdrawal rate of 3.5% due to anxiety, nausea, and palpitations, and no withdrawals due to unacceptable anticholinergic, antihistaminergic, orthostatic or cardiotoxic event (Deniker et al., 1982), even in the elderly (Reignier, 1983). It has no effect on liver and renal function or body weight (Boral et al., 1989).

Our protocol which included 3 different measures each for depression, and clinical global impression, and one measure each of social adjustment, anxiety, somatic symptoms and side effects, provides a detailed evaluation of the efficacy and safety of amineptine, although the absence of a control group is a limitation. From our results, the usefulness of therapy with amineptine can be evaluated from different perspectives. Symptoms of major depression improved rapidly in a high proportion of patients; the dosage was fixed requiring no titration reflecting ease of prescription especially for out patients and general practitioners; and social adjustment improved with depression which may allow patients an early resumption of work and a normal life style. The withdrawal rate was low, major side effects, adverse haemodynamic events, and cardiotoxicity were absent, and somatic symptoms improved. This could result in better patient compliance. Many believe that an increased compliance of just 6% represents a recovery of 4-5% of depressed patients (Harrison, 1994). In the short term amineptine may be suitable as a first line drug for major depression seen in every day clinical practice. Long term follow up is required to assess whether benefits are maintained, and if toxicity is increased.

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