

# AMITRIPTYLINE: A CONTROLLED TRIAL IN CHRONIC DEPRESSIVE STATES

By

ANDREW SKARBEEK  
and  
DAPHNE SMEDBERG

## INTRODUCTION

AMITRIPTYLINE HYDROCHLORIDE is 5-(3 dimethylaminopropylidene)-dibenzo (a,d) (1,4) cycloheptadiene hydrochloride. Structurally it is not related to the hydrazines and is not a monoamine oxidase inhibitor. It bears some resemblance to the phenothiazines and its chemical structure is related to imipramine, in which the central seven numbered ring is azepine, nitrogen replacing the partially unsaturated carbon of the amitriptyline cycloheptadiene ring (Dorfman, 1960; Vernier, 1961).

Its mode of action in depressive states is not clear. It has been suggested that the anti-depressant activity of imipramine may be based on the sensitization of the central nervous system to the actions of adrenergic neurohumoral transmitters, especially norepinephrine, and the same mechanism may be responsible for the effect of amitriptyline, although the evidence for this is slender (Sigg, 1959). Another hypothesis is that both drugs have a highly selective depressant effect on neural mechanisms which become hyperactive in patients with clinical depression. Both amitriptyline and imipramine exert a depressant effect on brain activity as judged by electro-encephalography, although they are less powerful than the phenothiazines in this respect (Freed, 1960).

## PATIENTS STUDIED

Patients with long-standing depression, resistant to therapy, were selected because it was felt that the response to the drug could be assessed more accurately in this type of patient than in those with more acute depression in whom spontaneous remissions are more common.

Twenty-three female patients were chosen, aged 47-78 years (average 66.6 years; median 65). All were in-patients and had been ill for 1-44 years (average 9.3 years; median 7). In four patients the duration of the illness was less than two years; in twelve between 2-10 years, and in seven more than 10 years.

All the patients were suffering from a depressive illness, and could be further subdivided into four categories:

Pure depression	...	...	...	...	...	...	11 cases
Depression with mild senile dementia	...	...	...	...	...	...	4 cases
Depression with marked hypochondriasis	...	...	...	...	...	...	4 cases
Depression with schizophrenic features	...	...	...	...	...	...	4 cases

All had been treated in the past with antidepressive drugs (imipramine and phenelzine) and fifteen had also had phenothiazines, without satisfactory improvement. E.C.T. had been given to 10 patients with moderately good but transient improvement in six and no improvement in four patients.

Eighteen patients were having sedatives at night, which were unchanged during the trial, but no other medication.

#### METHOD

The patients were seen at the same time every week by the same observer (A.S.) for sixteen weeks of the trial, and the following manifestations were each assessed on a four-point scale (0 to 3):

Feelings of depression, ideas of reference, suicidal ideas, ideas of unworthiness, hypochondriasis, initial insomnia, early waking, retardation, agitation, self-neglect, daily mood swing, constipation, anorexia, weight (Hutchinson and Smedberg, 1960)

The patients were divided into two groups, A and B, by random sampling (Bradford Hill, 1955). There were 11 patients in Group A and 12 in Group B. Group A started on amitriptyline and Group B on the placebo. The trial was divided into four periods of four weeks each, as this period was considered to be optimal for the effect of the drug to become apparent. The drug and placebo were applied twice to each group alternately, so that each group formed its own control twice.

The dose of the drug and placebo was increased weekly from 25 mgms. t.d.s. to 75 mgms. t.d.s. according to the patient's response, and during each period this procedure was repeated.

The active drug and placebo were identical in appearance, and neither the medical nor the nursing staff knew which of the patients were having the drug and which the placebo.

#### RESULTS

Analysis of item sheets for total scores of both groups show the following results:

	Before Treatment	After 1st four-week period	After 2nd four-week period	After 3rd four-week period	After 4th four-week period
Group A	175	90 (Drug)	120 (Placebo)	110 (Drug)	130 (Placebo)
Group B	175	140* (Placebo)	50* (Drug)	145* (Placebo)	45* (Drug)

\* Significant at P 0.05 level (chi-square test).

The second active treatment period of Group A shows very little response to the drug. It is the only period of active treatment in which efficacy of the drug can be in doubt. Looking, however, at the response of both groups it would appear clearly that Group A was much less responsive to the treatment than Group B and this could indicate that the groups were not homogeneous. In fact, Group A contained the four depressions with schizophrenic features and three of the four depressions with mild dementia.

#### SIDE-EFFECTS

Six patients complained of dryness of the mouth; six of dizzy feelings, headaches and shakiness; seven of blurring of vision and one developed hypomania. These side-effects subsided on changing to the placebo.

## DISCUSSION

Bearing in mind that most patients had been treated before with other anti-depressant drugs without much improvement, the results of this trial indicate that amitriptyline is a useful agent for the treatment of depression in middle-aged and elderly female patients. The beneficial effect of the drug may persist after it has been stopped, and some patients failed to show any deterioration when treatment was changed to the placebo.

Although the overall clinical picture is statistically improved by amitriptyline, because of the relatively small number of patients its influence on the individual symptoms and manifestations of the depressive state is less clear. It appears, however, that feelings of depression, retardation and agitation respond most rapidly in the first week of treatment and continue to improve less dramatically during succeeding weeks; these manifestations tend to recur when the drug is stopped.

## SUMMARY

A double blind crossover trial of a new antidepressant drug, amitriptyline, was carried out in twenty-three female patients suffering from chronic depression. The results with the drug were statistically superior to those with the placebo.

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Andrew Skarbek, M.B., B.S., L.R.C.P., M.R.C.S., D.P.M., *Research Fellow, University College, London W.C.1.*

Daphne Smedberg, M.B., Ch.B., D.P.M., *Assistant Psychiatrist, Cane Hill Hospital, Coulsdon, Surrey.*