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Amitriptyline in Depressive States

A Controlled Trial in India

By ROSHEN S. MASTER

Amitriptyline, 5-(3 dimethylaminopropylidine)-dibenzo (a,d) (1,4) cycloheptadiene hydrochloride, though chemically and pharmacologically related to imipramine (Barsa and Saunders, 1961) has a tranquillizing effect which is absent with imipramine (Pressman and Weiss, 1961; Bennett, 1961); it acts simultaneously as an antidepressant through its influence on the "anxiety factor" (Freed, 1960; Dorfman, 1960). In contrast to imipramine and the monoamine oxidase inhibitors, amitriptyline has very little influence on the circulatory system and blood pressure (Jensen, 1961) and less proneness to exacerbate the symptoms of schizophrenia (Barsa and Saunders, 1961). Dunlop (1961) noticed a reduction in other symptoms, such as gastro-intestinal distress, hyperventilation and vasomotor dysfunction for which amitriptyline was not primarily administered. This he attributed to an anticholinergic side-effect on the central nervous system.

Depression is a symptom-complex that can occur in any diagnostic category, from normal mourning to depressive reactions in schizophrenia. It may show a clinical picture of a complexity of symptoms or just a few of them. For an appraisal of chemotherapy for depression it is therefore important to ascertain which of the "target symptoms" specifically respond to each particular drug (Freyhan, 1960), and which symptoms could be better treated with another drug or by one of the older physical methods.

In view of the above, Hamilton's Rating Scale for Depression (1960) was used for this trial, as it provides both the target symptoms as well as an agreed rating scale.

Methodology

The trial was conducted in the out-patient practice of an Indian hospital serving an area approximately the size of Wales. It is important that this should be borne in mind, as under these conditions irregularity of attendance and a high proportion of drop-out during the trial are inevitable.

Every patient, irrespective of age or sex, who conformed to the criteria of depression, in the sense described above, was included in the trial, thus avoiding "selection". Inert tablets identical in colour, shape and size to amitriptyline tablets were used for control purposes, and all tablets were given uncrushed to avoid recognition by taste. To eliminate errors due to suggestion, anticipation or bias in reporting or recording of clinical changes the trial was fully blind and the code of random numbers was broken only after the whole trial was completed.

As accurate matching of psychiatric patients is virtually impossible because of the various aetiological and environmental factors, duration of illness, etc.—even more so under out-patient conditions—it was decided to use each patient as his own control.

A complete physical examination and laboratory investigation was given to each patient.

In view of the past clinical experience of the author, as well as information gleaned from the literature, that mood elevators show their maximal effect at the end of three weeks, the assessment and rating was made at the end of 3, 6, 9 and 12 weeks, and the drug and inert tablets were switched over at the end of each period. A similar assessment and rating was made before each patient was included in the

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trial. The allocation of the tablets for the first tri-weekly period was also done at random. The dosage given was 1 tablet (25 mg. amitriptyline or placebo) t.i.d. for the first week, followed by 2 tablets t.i.d. for the two subsequent weeks.

Results

Of the 61 patients who were started on the trial, only 12 completed the full 12 weeks, the rest gradually falling out. Of these, it was later found that 2 had been assigned the placebo first (Group A) while 10 had been put on amitriptyline in the initial three-week period (Group B). The average overall ratings of these patients are shown in Table I.

As there were only 2 patients in Group A, no statistical test was carried out. For the B Group "t" tests were carried out for comparison of the successive averages. The overall improvement due to amitriptyline proved to be significantly higher than the improvement due to the placebo for the first 3 weeks, while subsequent improvements were not significant.

Separate analysis for each of the 17 symptoms was carried out with the help of the large sample approximation of the Mann-Whitney "U" Test (corrected for ties). This test was selected in preference to the normal "t" test since the scores were such that they could not be said to have come from a normal population.

In the first analysis, the ratings at the end of 3 weeks were compared with the pre-trial ratings. As can be seen from Table II, in three symptoms, viz. Depressed mood, Guilt, and Delayed Insomnia, the improvement due to amitriptyline was considerably more (at 1 per cent. level of significance) than with the placebo. Five other symptoms, viz. Work and Interests, Retardation, Agitation, Psychic Anxiety and Hypochondriasis, showed a significant improvement (at 5 per cent. level). The improvements for the rest of the symptoms did not differ significantly.

The overall improvement with the active drug proved to be significantly higher (at 1 per cent. level) than that with the inert tablets, by both the "U" and the "t" tests.

An analysis of the ratings for the second tri-weekly period showed an improvement on amitriptyline for only two symptoms, viz. Depressed mood (at 1 per cent. level of significance) and Insomnia—middle (at 5 per cent. level). There was no statistically significant improvement in the other symptoms. The overall improvements did not differ significantly.

This second analysis was undertaken with a stringent assumption that the improvement in this period was solely due to the tablets given in the second tri-weekly period and the ratings at the end of the first tri-weekly period would have remained stable over the next period even if no drug was administered. Therefore, this analysis must be considered only as a subsidiary analysis in view of the above assumption which may or may not be true.

In the analysis after the first 3 weeks, amitriptyline was more efficient than the placebo for all but 2 symptoms and statistically significant for as many as 8 of them, while in the second period it was more efficient for only 6 of the 17 symptoms and statistically significant for only 2 of them. The reason for this apparent anomaly appears to be that even though the placebo was being administered in the second period, the effect of the amitriptyline was carried over from the previous period.

As assumptions of the above type would

Table I

Average Ratings of Patients Who Completed the Trial

Group	No. of Cases	Average Overall Ratings				
		Pre-trial	After 3 Weeks	After 6 Weeks	After 9 Weeks	After 12 Weeks
A	2	25·0	19·0	17·c	15·0	11·0
B	10	18·2	7·2	4·9	2·1	2·7

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TABLE II

Mean Improvement Scores on Ratings

No.	Symptom	After 3 Weeks		After 6 Weeks	
		Amitriptyline n=33	Placebo n=28	Amitriptyline n=21	Placebo n=25
1	Depressed mood	3·122*	0·462	2·286*	−0·294
2	Guilt	0·094*	0·0	0·0	0·0
3	Suicide	0·452	0·308	0·0	0·0
4	Insomnia, initial	0·960	1·083	0·400	0·125
5	Insomnia, middle	0·742	0·500	0·400†	−0·125
6	Insomnia, delayed	0·355*	0·167	0·0	−0·125
7	Work and interests	1·576†	0·615	0·0	0·687
8	Retardation	0·594†	0·307	0·0	0·375
9	Agitation	0·848†	0·307	0·142	0·059
10	Anxiety, psychic	1·697†	0·462	0·286	−0·176
11	Anxiety, somatic	0·303	0·615	0·286	0·235
12	Somatic symptoms, gastrointestinal	0·152	0·0	0·0	0·0
13	Somatic symptoms, general	0·219	0·154	−0·286	0·176
14	Genital symptoms	0·065	0·0	0·0	0·0
15	Hypochondriasis	0·515†	−0·077	0·0	0·471
16	Loss of insight	0·273	0·0	0·0	0·0
17	Loss of weight	0·182	0·167	0·0	0·0
	Total improvement	12·760*	3·870	4·200	1·000

* Statistically significant at 1 per cent. level.
† Statistically significant at 5 per cent. level.

become more and more stringent at each subsequent cross-over of the tablets, similar analysis of further data was not carried out, as it would have been invalid.

SIDE-EFFECTS

Amitriptyline does not seem to have any severe side-effects. Dryness of the mouth and constipation were frequently complained of. But it seems to provoke hallucinatory excitation, and 2 of the depressed schizophrenic patients developed this symptom which entailed their immediate withdrawal from the trial.

CONCLUSIONS

The trial with 61 patients, studied under outpatient conditions, shows that amitriptyline is a useful addition to the already existing number of antidepressant drugs with very few side-effects; in fact amitriptyline represents a clear advance in the chemotherapy for depression.

As a point of further interest, it may be mentioned that nine of the twelve patients who went through the trial, and have continued to remain under clinical observation, have remained completely symptom-free for a period of 5 months after the withdrawal of the drug.

SUMMARY

A double-blind crossover trial of amitriptyline confirmed its overall effectiveness as an antidepressant.

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References

Barsa, J. A., and Saunders, J. C. (1961). *Amer. J. Psychiat.*, **117**, 739.

Bennet, D. (1961). *Lancet*, 7189, 1287.

Dorfman, W. (1960). *Psychosomatics*, **1**, 155.

Dunlop, E. (1961). *Dis. Nerv. Syst.*, **22**, 46.

Freed, H. (1960). *Amer. J. Psychiat.*, **117**, 455.

Freyhan, F. A. (1960). *Ibid.*, **116**, 1057.

Hamilton, M. (1960). *J. Neurol. Neurosurg. Psychiat.*, **23**, 56.

Jensen, E. (1961). Paper presented at 5th International Congress of Psychotherapy in Vienna on 26 August, 1961.

Pressman, M. D., and Weiss, L. B. (1961). *Amer. J. Psychiat.*, **118**, 74.

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