Brit. J. Psychiat. (1967), **113**, 195–199

Amitriptyline and Perphenazine in Depressive Illness A Controlled Trial

By IJAZ HAIDER

This paper describes a "double-blind" trial comparing 'Triptafen' tablets—each containing amitriptyline hydrochloride 25 mg. and perphenazine 2 mg.—with a matching placebo in the treatment of depressive illness.

Such a trial seems worthwhile on two counts. Firstly, there is still considerable need for controlled studies of drugs used in psychiatry—a field in which, perhaps more than in any other, the results of uncontrolled studies are vulnerable to bias on the part of observer and patient alike. The need for proper controls is particularly true of drugs used in the treatment of depressive illness whose self-limiting nature may result in a drug being given credit for improvement which would have taken place anyway. Secondly, it is usually helpful to add a tranquillizer to the antidepressant drugs in order to control the anxiety or agitation that so often form part of a depressive illness and sometimes cause as much difficulty as the depressed mood itself does.

Although some reports on the clinical use of Triptafen have been published (Ernst, 1963; Martins, 1966; Mattey, 1963; and Smith 1963), none of these was adequately controlled. It was therefore of interest to study the effects of this preparation on depression and agitation under controlled conditions.

Methods

Population

All the patients included in this trial presented with depressive illness. There were 39 out-patients and 90 in-patients. Of these, 67 were diagnosed as suffering from primary depressive disorders. Patients obviously so severely ill that immediate recourse to E.C.T. was felt to be essential were excluded.

Patients above the age of 65 years showing depressive features were also included, as they were the ones who usually showed marked anxiety or agitation and required a tranquillizer in addition to an antidepressant. Some of these were true cases of depression in old age, whereas others manifested depressive symptoms in the setting of cerebral disease, especially arteriosclerotic psychosis.

Dosage Schedule

An individual bottle containing a month's supply of Triptafen tablets or placebos was dispensed for each patient. The dose prescribed was one tablet three times a day during the first week, increasing to two tablets three times a day from the second week onwards. The distribution of active and placebo tablets was in accordance with a random code which was not known to the clinical or nursing staff at the hospital. The use of a completely random distribution lessened the risk that the "blind" nature of the trial might be compromised by systematic observation of therapeutic or side-effects. All patients in the trial were also given supportive psychotherapy and occupational therapy; barbiturate hypnotics were administered at night according to the needs of individual patients. In-patients who had not had any previous antidepressant therapy were left for 2 to 4 days without any medication except night sedation, to give them time to settle down in the ward. This period was longer for those who had had antidepressant drugs immediately prior to admission.

Rating

Patients were assessed by the author on the Medical Research Council rating scale (1965) for their depressive symptoms at the time of entry into the trial and again after three weeks. The two assessments were made independently on two separate sheets at two special interviews.

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On the second occasion a clinical assessment was also made according to the following scale: Greatly Improved, Improved, No Change, or Worse.

Side-Effects

To avoid any bias in favour of the drug by a knowledge of the side-effects, the clinical assessment was made first and then the side-effects were assessed at the end of the trial period with each patient.

Results

One hundred and twenty-nine patients took part in the trial. When the treatments had been decoded it was found that 66 patients had received Triptafen and 63 placebo. Distribution of patients in the two groups by age and sex is shown in Table I.

There was, as might be expected, a preponderance of female patients in the trial, and this preponderance was more marked in the Triptafen-treated group, but the difference in distribution by sex does not quite achieve statistical significance.

Table I

	Male	Female
Triptafen	15	51
Placebo	25	38
$\chi^2_1=3\cdot6$: $0\cdot1>p>0\cdot05$		

	Age in years			
	<40	40–49	50–59	60+
Triptafen	9	10	13	34
Placebo	5	9	7	42
$\chi^2_3=3\cdot7$: $p>0\cdot2$				

When the results of treatment were analysed according to the overall assessments, it was found that more patients had improved on Triptafen than on the placebo (Table II). The difference is statistically highly significant ($p<0\cdot001$).

When these groups are further analysed by sex (Table III) it is seen that the difference in response is most striking in the female group,

Table II

	Greatly Improved	Improved	No Change	Worse	Total
Triptafen	36	16	5	9	66
Placebo	9	10	25	19	63
$\chi^2_3=34\cdot3$: $p<0\cdot001$					

Table III

	Greatly Improved	Improved	No Change	Worse	Total
Female:					
Triptafen ..	27	14	3	7	51
Placebo	4	3	17	14	38
$\chi^2_3=35\cdot25$: $p<0\cdot001$					
Male:					
Triptafen ..	9	2	2	2	15
Placebo	5	7	8	5	25

Because of the small numbers in some of the cells, the "Greatly Improved" category only has been used for statistical comparison.

$\chi^2_1=4\cdot95$: $p<0\cdot05$

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nearly half of the males showing some degree of improvement on the placebo.

Table IV shows the changes that took place in major individual symptoms between the initial and final assessments. The figures represent the mean of the scores for all patients in the group, each symptom being assessed on the scale:

Severe =3
Moderate=2
Mild =1
Absent =0

It will be seen that at the beginning of the trial the Triptafen-treated group was on the whole more severely ill than the control group. This was due to chance, as no selection could have taken place. The differences at this time do not achieve statistical significance.

In the final assessment the Triptafen-treated group showed marked improvement in all symptoms studied, except fatigue. In the placebo-treated group little improvement took place and two symptoms, anxiety and late insomnia, became worse. It is rather surprising that late insomnia became worse in the placebo group, in marked contrast to those on the active preparation, as hypnotics were being administered at night to all.

Fig. 1 illustrates graphically the group mean scores for main symptoms at the start of the trial and after three weeks.

Side-Effects

They were noted as present or absent, and rated according to the scale:

0=none
1=slight
2=moderate
3=severe

Table V shows the incidence and severity of side-effects.

More patients in the Triptafen-treated group experienced side-effects than in the control group. It seemed of interest, therefore, to see whether patients with side-effects were assessed as "improved" more often than those without side-effects, in order to test the hypothesis that the author's assessment might have been influenced by the indication thus given of which treatment the patient had received. As seen in Table V, patients assessed as "not improved" consistently reported side-effects more frequently than those assessed as "improved". This was true of patients receiving placebo as well as of those receiving the active preparation.

Discussion

This controlled study demonstrates that, over a three-week treatment period, Triptafen (amitriptyline HCl 25 mg.+perphenazine 2 mg.) relieved most of the symptoms of depressive illness more effectively than did a matching placebo. This combination seems to provide a satisfactory means of treating depressive illness, especially in patients with marked anxiety or agitation in addition to depression.

The number of patients who improved while receiving placebo seems to have been unusually low in this trial. Men showed a better response to placebo than did women.

Table IV

	Initial		Final	
	Triptafen Group	Placebo Group	Triptafen Group	Placebo Group
Depressed Mood	2·04	1·83	0·76	1·56
Retardation ..	1·89	1·67	0·77	1·51
Agitation	2·41	1·95	0·62	1·51
Anxiety	1·59	1·16	0·53	1·25
Insomnia (early) ..	1·56	1·21	0·77	1·14
Insomnia (late) ..	1·12	0·89	0·52	1·10
Fatigue	1·08	0·90	0·83	0·89

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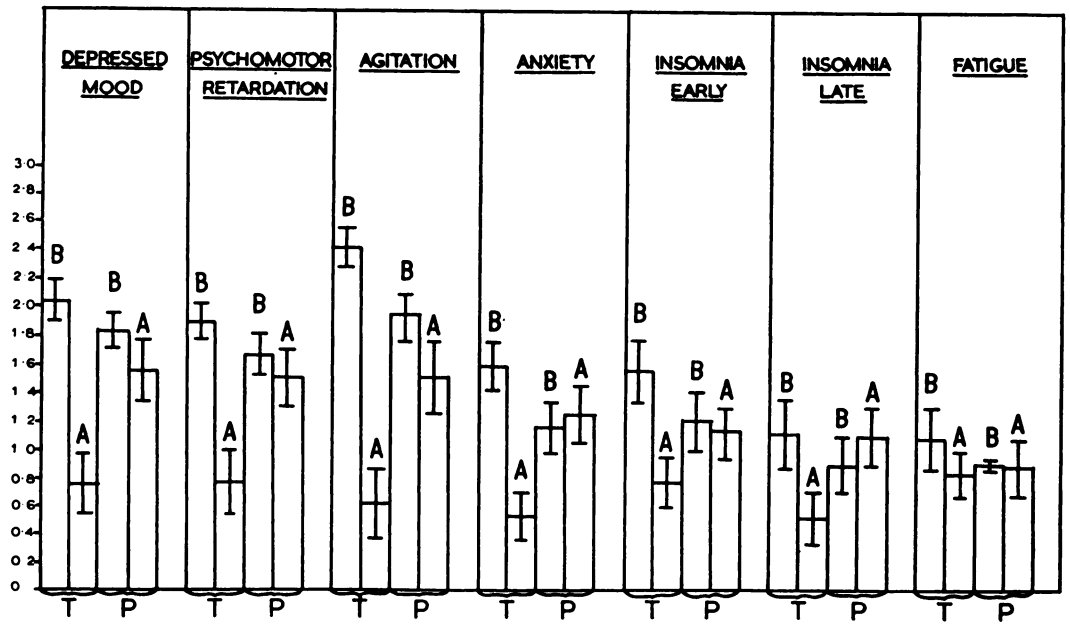


FIG. 1.—Mean severity of symptoms (± 2 standard errors) before (B) and after (A) Triptafen (T) and Placebo (P).

TABLE V

	Triptafen Group								Placebo Group							
	Improved					Not Improved					Improved					Not Improved				
Severity	0	1	2	3	% Incidence	0	1	2	3	% Incidence	0	1	2	3	% Incidence	0	1	2	3	% Incidence
Drowsiness	31	10	10	1	40·4	5	–	4	5	64·3	17	–	2	–	10·5	36	4	4	–	18·2
Dry Mouth	38	12	2	–	26·9	7	3	3	1	50·0	17	2	–	–	10·5	38	6	–	–	13·6
Dizziness	41	8	2	1	21·2	7	3	2	2	50·0	16	2	1	–	15·8	40	3	1	–	9·1
Hypotension	48	3	–	1	7·7	12	2	–	–	14·3	19	–	–	–	Nil	43	–	–	1	2·3
Extrapyramidal	49	2	–	1	5·8	10	2	2	–	28·6	19	–	–	–	Nil	43	1	–	–	2·3
Skin Rash	52	–	–	–	Nil	13	1	–	–	7·1	19	–	–	–	Nil	41	2	1	–	6·9
Gastrointestinal	38	12	12	–	26·9	8	3	3	–	42·8	15	4	–	–	21·0	28	5	8	3	36·4
Paraesthesia	52	–	–	–	Nil	14	–	–	–	Nil	19	–	–	–	Nil	43	1	–	–	2·3

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Side-effects of one kind or another were experienced by most (77 per cent.) of patients receiving Triptafen; but they were mostly of a trivial nature, and this apparently high incidence should be interpreted in the light of the fact that more than half (54 per cent.) of patients receiving placebo also reported side-effects. It seems possible that the method of inquiry was at fault, and encouraged reporting of trivial or irrelevant symptoms.

It is, of course, not possible to state with any certainty what effect, if any, can be attributed to the perphenazine component of Triptafen, although anxiety and agitation improved more than one would have expected with amitriptyline alone.

Summary

A "double-blind" trial of Triptafen (amitriptyline hydrochloride 25 mg.+perphenazine 2 mg.) was carried out in 129 patients with depressive illness. After three weeks' treatment, 79 per cent. of patients receiving Triptafen were improved or greatly improved as compared with 30 per cent. receiving placebo. The combination seems to be most useful in depressive illnesses with marked anxiety and agitation.

Acknowledgments

I should like to express my thanks to Dr. Russell Barton, Physician-Superintendent, Severalls Hospital, Colchester, for his permission to conduct this trial and for much encouragement and advice; to my colleagues, Dr. E. M. Cheongvee and Dr. D. Sarbadhikary, for allowing me to include their cases in this study; to the Nursing Staff and Pharmacy Staff for their co-operation, and to Dr. J. V. Deakin of Allen and Hanburys Ltd. for generous supplies of identical tablets of Triptafen and placebo.

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Ijaz Haider, B.A., B.Sc., M.B., B.S.(PB)., *Registrar, St. Francis and Hurstwood Park Hospitals, Haywards Heath, Sussex; formerly Registrar, Severalls Hospital, Colchester, Essex*

(*Received 2 May, 1966*)

https://doi.org/10.1192/bjp.113.495.195 Published online by Cambridge University Press