Papers and Originals

Clinical Trial of the Treatment of Depressive Illness

Report to the Medical Research Council by its Clinical Psychiatry Committee*

Brit. med. J., 1965, 1, 881–886

The object of the trial[1] here reported was to test the merits (and demerits) of (*a*) imipramine (5-(3-dimethylamino)-10,11,-dihydro-5 H-dibenz (b, f) azepine hydrochloride ; Tofranil) and (*b*) a monoamine oxidase inhibitor, phenelzine (β-phenylisopropylhydrazine dihydrogen sulphate ; Nardil) in the relief of depressive illness. The effects of these drugs were to be compared with those produced by (*c*) E.C.T. and (*d*) a placebo. In other words, the aim of the trial was to examine the efficacy of these drugs in comparison with E.C.T. and to assess their value in the treatment of depressive illness. It was also hoped to learn whether any response to these drugs that might be revealed by the trial occurred more often in patients with specific characteristics.

The Patients

It was recognized at the outset that depressive illness can be manifested by a wide variety of clinical syndromes. For the purposes of the trial the attributes of the patients to be admitted were defined as follows:

1. Either sex, age 40–69 years.

2. Previous duration of illness under 18 months.

3. No treatment during the previous six months by E.C.T. or by an *adequate* course of either of the drugs (as a general principle, patients having previously received imipramine (150 mg. daily) or phenelzine (45 mg. daily) continuously for periods as long as two weeks were excluded from the trial).

4. The primary manifestation and major symptom of the illness to be a persistent alteration of mood (with or without diurnal variation) which exceeds customary sadness, is evident to the examiner, and is accompanied by one or more of the following symptoms: self-depreciation with a morbid sense (or delusional ideas) of guilt ; sleep disturbance ; hypochondriasis ; retardation of thought and action ; agitated behaviour.

5. The depression to be the primary illness and not a secondary manifestation of some other psychiatric illness such as schizophrenia or an obsessional state.

6. An absence of any physical disease which would prohibit exhibition of any one of the four treatments, and of any associated major disease of a progressive nature—for example, malignancy ; no symptoms or signs at any previous time indicative of organic cerebral disease (benign uncomplicated hypertension was not a contraindication).

It was required that every patient fulfilling these criteria and whom the physician proposed to admit to the trial must be treated in hospital for the first four weeks and thereafter as an out-patient unless in the opinion of the physician there were clinical contraindications.

Treatment

Each patient brought into the trial was allocated randomly to treatment *for a minimum period of four weeks* by one of the four treatments involved—imipramine, phenelzine, E.C.T., or placebo. On ethical grounds it was held that any longer period than four weeks could not be mandatory and that at the end of that time a revision of treatment should be permissible in accordance with the previous responses of the patient. It was therefore laid down that any patient treated by a drug (including here the placebo) whose continuing illness at the end of four weeks made the exhibition of some other treatment imperative should be given a course of E.C.T. (four to eight treatments in the ensuing three and a half weeks); and, similarly, any patient who had been originally treated by E.C.T. should if necessary be given one or other of the two drugs (randomly allotted ; and no placebo to be used at this stage).

With regard to the two drugs and placebo, neither clinician nor patient was made aware of the nature of the treatment—that is, the trial was "double-blind." Participating physicians were asked to avoid as far as possible any supplementary treatment other than night sedation and aperients, but as in all controlled trials it was made clear that if at any time the clinician thought it essential in the interests of an individual patient to institute any form of treatment other than that laid down, then it was his responsibility to take such action.

Treatment Schedules.—For all patients allotted E.C.T. the required course was four to eight treatments, according to the physician's judgment, in the first three and a half weeks. For all patients allotted a drug (and remaining on it) the schedule was as follows, each tablet containing either 50 mg. of imipramine or 15 mg. of phenelzine or the placebo.

Day	1	2	3–28	29–56	57–84	85–112	113–168
No. of tablets	2	3	4	4	2	1	*

* 1 for patients born on odd dates and 0 for patients born on even dates.

Assessments of Progress.—Assessment of the patient's condition was required on prescribed forms (1) on admission to the trial ; (2) at weekly intervals during the first four weeks of treatment, while the patient was in hospital ; (3) at 8, 12, and 24 weeks, whether as in-patient or out-patient ; and (4) immediately before discharge from hospital at any point of time. It was particularly emphasized that these forms should be completed by the same psychiatrist at each successive examination of any given patient, so that an analysis could be made of the

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The trial was carried out with the aid of a research grant from the Council to Dr. R. H. Cawley, Senior Lecturer and First Assistant, Department of Psychiatry, Birmingham University.

physician's overall rating of the illness and of fifteen separate symptoms at each specified point of time—namely, depressed mood, psychomotor retardation, agitation, suicidal ideas, ideas of bodily change, ideas of reference, self-reproach, anxiety, insomnia (early, middle, and late), anorexia, fatigue, other somatic symptoms, suspiciousness, affective fluctuations, irritability. For each of these symptoms and for the overall rating a scale of severity was laid down.

Admissions

To secure an adequate number of patients in a reasonable space of time the trial was spread over three regions of the country—London, Leeds, and Newcastle. A total of 55 physicians participated and admitted 269 patients fulfilling in each area the conditions of admission laid down (191 in London, 43 in Leeds, and 35 in Newcastle). Three of these patients died during the trial.[2] Sixteen were lost to sight before the end of the six-months follow-up, and 250 were then adequately reported upon (222 by the physicians' own progress reports and 28 from data obtained by a psychiatric social worker specially employed in the trial). The distribution of these patients within the initial treatment groups is shown in Table I.

TABLE I.—*Number of Patients Admitted to the Trial*

Treatment Allocated for First 4 Weeks	Followed Up for 6 Months	Died.	Lost to Sight	Total
E.C.T.	65	1	8	74
Imipramine	63	1	1	65
Phenelzine	61	0	4	65
Placebo	61	1	3	65
Total	250	3	16	269

The subsequent analysis of the results of the trial is necessarily limited to the 250 patients (93% of the total) who were adequately followed-up for the required six months. With this limitation the comparability of the four treatment groups at entry is given in Table II, from which it will be seen that they were satisfactorily similar in respect of the history and social setting of the treated illness. The only differences that could call for later consideration lie in a slightly higher proportion of patients rated as severely ill in those given E.C.T. and a slightly lower proportion so regarded in those given the placebo.[3] It may be added that the four groups were also similar in characteristics less likely to affect prognosis—for example, the numbers married or single, their work status and length of absence from work before treatment, social class, and in mean heights and weights. Their comparability with respect to the presence and severity of specific symptoms is shown in subsequent tables when the progression of the illness is discussed.

TABLE II.—*Characteristics of the Four Treatment Groups at the Start of Treatment*

Characteristic at Admission	E.C.T. (65)	Imipramine (63)	Phenelzine (61)	Placebo (61)
Male/female ratio	24/41	22/41	18/43	17/44
Mean age (years)	55·4	54·8	54·7	56·3
History of a major organic illness at some earlier date	10	11	11	12
Presenting with a physical disability*	18	9	15	15
No previous affective illness	21	32	32	32
More than one previous attack	21	11	21	15
Spontaneous onset to illness	27	21	25	27
Mean duration of illness before admission (months)	3·1	4·5	4·5	4·8
No treatment before admission	32	28	31	24
Number rated as severely ill	35	27	26	20
Mean overall rating of presenting condition (0–5 scale)	3·6	3·4	3·4	3·3
Previous suicidal attempt reported	2	9	5	6

* Principally a diastolic blood-pressure over 100 mm. Hg.

[2] (1) A woman died after two weeks; allotted to E.C.T. she had one application; recorded cause of death, uraemia and myocardial infarction. (2) A man with a history of pneumoconiosis died after three weeks; allotted to imipramine to which had been added chlorpromazine; recorded cause of death, heart failure, after vomiting and aspirating food. (3) A woman died after two months; allotted to placebo, but she had been prescribed E.C.T. by the physician within the first month and had had eight applications; recorded cause of death, suicide (while still in hospital).

[3] Since the placebo was indistinguishable from the two drugs we can see no explanation for this difference except the play of chance.

Results

In analysing the results of the trial a natural division can be made between the first four weeks spent by all patients in hospital and the subsequent 20 weeks when, according to their progress, they could be either in-patients or out-patients. Thus we have a *short-term* and a *long-term* evaluation to consider.

Short-term Evaluation at Four Weeks

During the first four weeks the physicians found it necessary to change the allocated treatment in 27 of the 250 cases—either by prescribing supplementary treatment or by changing to an alternative treatment. These changes were slightly more frequent in women (12.4%) than in men (7.4%), but the difference is not statistically significant. Only nine of these 27 patients were severely ill on admission (grade 4 or 5) compared with 43% of all patients, so that presumably it was a lack of progress or actual deterioration in the patient that led the physician to his decision. On the other hand, Table III shows that the excess number in women compared with men lies in a greater recourse to other treatments in the phenelzine and placebo groups. Here (in total) changes were found necessary two to three times as often as in the E.C.T. and imipramine groups and as often with phenelzine as with a placebo. These figures we may take as a first indication of the relative merits of the four treatments.

TABLE III.—*Number of Patients Requiring Additional or Alternative Treatment During the First Four Weeks*

Treatment Allocated	No. of Patients			No. Given Additional or Alternative Treatment			
	M	F	Total	M	F	Total	%
E.C.T.	24	41	65	3	2	5	(8)
Imipramine	22	41	63	0	3	3	(5)
Phenelzine	18	43	61	2	8	10	(16)
Placebo	17	44	61	1	8	9	(15)

Of the 22 patients on a drug whose treatment was changed 16 were given E.C.T. (two on imipramine, seven on phenelzine, and seven on placebo). The five patients in the E.C.T. group received a drug in addition to their allotted treatment. Eliminating these 27 patients (and six for whom the required report at this stage was lacking[4]), the results of the four weeks of treatment are shown in detail in Tables IV, V, and VI. Column 3 of Table IV sets out the proportion of patients who according to the overall ratings of their physician on admission and after four weeks had made some progress towards recovery, and column 4 those who were judged to be wholly or almost without symptoms at this point of time. Columns 5 and 6 show the same data in terms of the numerical scale of the severity of illness. It is clear that the patients given E.C.T. had, on average, fared best with those given imipramine coming next. Those given phenelzine showed no more success than those given the placebo.[5]

[4] Two each on E.C.T. and imipramine, one each on phenelzine and placebo.

[5] Taking the percentage improved, E.C.T. and imipramine at one end of the scale, and phenelzine and placebo at the other, do not differ significantly from each other. On the other hand, the differences between E.C.T. and phenelzine and placebo are four to five times their standard errors and the corresponding differences with imipramine are three to four times their standard errors. Taking the proportion showing no or slight symptoms, the difference between E.C.T. and imipramine is just over twice its standard error (19 ± 8.9), and the differences between E.C.T. and phenelzine and placebo are three to four times their standard errors. Imipramine differs significantly from phenelzine (22 ± 9.2) but not from the placebo (13 ± 9.5), and the latter do not differ significantly from one another.

TABLE IV.—*Result of Treatment for 4 Weeks (in Patients in Whom the Allocated Treatment was Maintained) According to Physician's Overall Rating*

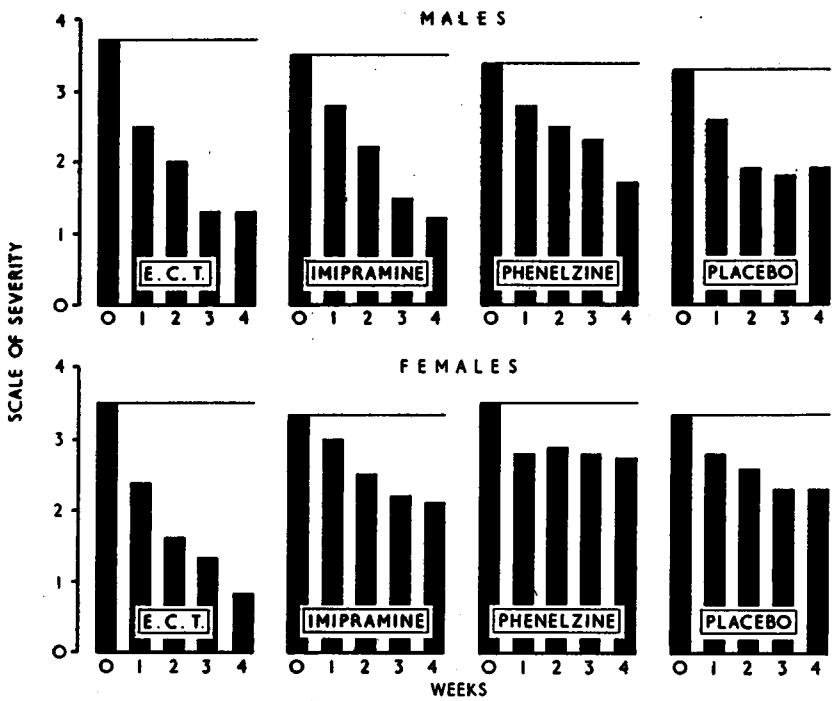
Treatment (and No. of Patients)	No. of Patients		Percentage Improved			Percentage with No or Only Slight Symptoms			Average Overall Rating			
									Entry	4 Weeks	Entry	4 Weeks
(1)	M (2)	F (2)	M (3)	F (3)	Total (3)	M (4)	F (4)	Total (4)	M (5)	M (5)	F (6)	F (6)
E.C.T. (58)	21	37	71	92	84	67	73	71	3·7	1·3	3·4	1·0
Imipramine (58)	22	36	82	67	72	68	42	52	3·5	1·2	3·4	2·0
Phenelzine (50)	15	35	60	29	38	40	23	30	3·4	1·8	3·5	2·9
Placebo (51)	15	36	53	42	45	43	36	39	3·3	1·8	3·3	2·1

Division of these results by sex, however, suggests one difference—that while men in these early weeks had fared equally well on E.C.T. or imipramine, women had shown a similar degree of response to E.C.T. but substantially fewer successes on the drug. The numbers involved are, however, small and the difference between the sexes with imipramine is only just twice its standard error (26% ± 12.9 for the proportion with no or slight symptoms).

In Table V the rate of loss of symptoms shown in Table IV is studied in relation to the severity of the illness at admission. In those most severely ill the results with E.C.T. are outstanding while with those moderately ill at admission imipramine also shows to some advantage. It is noticeable that with phenelzine and the placebo the moderately ill reveal no greater response than the severely ill, a feature which might suggest no specific value in the treatment. The figure of some 40% shown by the placebo group may indicate the spontaneous short-term response to be expected in these patients.

TABLE V.—*Results of Treatment for Four Weeks in Relation to Severity of Illness on Admission*

Treatment	No. of Patients Severely Ill on Admission	Percentage with No or only Slight Symptoms at 4 Weeks	No. of Patients Moderately Ill on Admission	Percentage with No or only Slight Symptoms at 4 Weeks
E.C.T.	32	66	26	77
Imipramine	26	42	32	59
Phenelzine	23	30	27	30
Placebo	16	44	35	37



Severity of illness on admission to the trial and at weekly intervals (mean values).

Table VI shows the progression of those symptoms which had relatively high average values at entry and may therefore be accepted as important components of the illness. The close similarity of the four groups at entry will be noted. In their progression over the next four weeks it is again apparent that the greatest degree of improvement was reported for treatment by E.C.T. and that imipramine appeared to be associated with more improvement than either phenelzine or the placebo. These same trends were also generally apparent in the less frequently reported presenting components of the illness, such as agitation and ideas of reference, suspiciousness, and somatic symptoms.

The weekly assessments of the severity of the illness during these early stages are shown in the Chart. With men the E.C.T. and imipramine groups show closely similar average degrees of improvement by the end of the four weeks, but the change is obviously rather more rapid on E.C.T. Those on imipramine, in fact, were not better than those on phenelzine or placebo until quite late in the month. With women the improvement on E.C.T. is both marked and rapid. The value of imipramine compared with the other tablets is, as previously noted, much less distinct than with men, and the group on phenelzine did singularly badly.

In summary of the short-term evaluation, it appears that: (1) in these first four weeks of the trial E.C.T. was in both sexes the most effective treatment (in this instance, however, the assessments of the patients were inevitably not blind). (2) Under treatment by the drugs there may be a difference between men and women. Thus in reduction or loss of symptoms the men showed almost as favourable a picture with imipramine as with E.C.T. and no appreciable difference between phenelzine and the placebo. With the women the response to imipramine appeared much less distinct and their response to phenelzine unexpectedly poor (though with the numbers involved it does not differ significantly from the placebo). (3) From the response to the placebo it would seem (counting those whose treatment was changed as failures) that

TABLE VI.—*Mean Rating of Principal Symptoms at Entry and at 4 Weeks*

Treatment (No. of Patients)	Depressed Mood		Psychomotor Retardation		Suicidal Ideas		Self-reproach		Anxiety		Insomnia*		Anorexia		Fatigue	
	At Entry	At 4 Weeks	At Entry	At 4 Weeks	At Entry	At 4 Weeks	At Entry	At 4 Weeks	At Entry	At 4 Weeks	At Entry	At 4 Weeks	At Entry	At 4 Weeks	At Entry	At 4 Weeks
E.C.T. (58)	2·6	0·6	1·6	0·3	1·0	0·1	1·3	0·2	1·9	0·8	1·3	0·3	1·1	0·2	1·1	0·4
Imipramine (58)	2·4	1·3	1·4	0·5	1·0	0·2	1·4	0·6	1·9	0·9	1·0	0·7	0·9	0·4	1·0	0·5
Phenelzine (50)	2·5	1·7	1·6	1·0	1·2	0·6	0·9	0·8	1·8	1·4	1·0	0·5	1·2	0·5	1·0	0·5
Placebo (51)	2·5	1·4	1·2	0·6	1·2	0·5	1·2	0·6	1·8	0·9	1·0	0·6	1·0	0·5	1·2	0·6

* Insomnia was differentiated as early, middle, or late. The late form gave the highest rating at entry and has been used here.

about a third of these patients had wholly, or almost wholly, lost their symptoms within the first four weeks without any specific treatment apart from the general care given in hospital. (4) E.C.T., it seems, may have rather more than doubled this short-term rate of improvement and more specifically in women than in men ; imipramine, on the other hand, revealed a similar advantage to men but relatively little to women, and phenelzine appeared to assist neither sex.

These conclusions are supported by the decisions taken by the physicians at the end of the fourth week. At this stage of the trial, it may be recalled, the physician was empowered to change the allocated treatment if he thought such a change was necessary in the interests of the patient. Such changes were in fact regarded as necessary in approximately one-third of the patients given E.C.T. (30%) or imipramine (32%) and in as many as one-half of those given phenelzine (59%) or the placebo (48%).[6] That in general it is reasonable (as was anticipated in the design of the trial) to ascribe such a change of treatment to a failure of that particular treatment is shown in Table VII.

TABLE VII.—*Change in Symptoms (Averages of the Scales Employed) in (1) Patients Whose Treatment was Changed During the Second Month and (2) Patients Remaining on the Allotted Treatment*

		Overall Rating		Depression		Psychomotor Retardation		Suicidal Ideas	
		(1)*	(2)†	(1)	(2)	(1)	(2)	(1)	(2)
E.C.T.	Admission	3·7	3·5	2·9	2·5	2·2	1·3	1·2	1·0
	4 weeks	2·0	0·6	1·3	0·4	0·4	0·2	0·3	0·0
Imipramine	Admission	3·5	3·4	2·5	2·4	1·4	1·4	0·9	1·1
	4 weeks	2·9	1·1	2·3	0·8	1·1	0·2	0·5	0·03
Phenelzine	Admission	3·6	3·4	2·5	2·4	1·7	1·5	1·2	1·2
	4 weeks	3·3	1·8	2·3	1·2	1·5	0·5	1·1	0·2
Placebo	Admission	3·3	3·3	2·6	2·4	1·3	1·3	1·3	1·3
	4 weeks	3·2	1·3	2·3	0·7	1·2	0·3	1·3	0·1

*(1) Group whose treatment was changed in the second month.
†(2) Group who continued on originally allotted treatment.

Here two groups of patients are distinguished: (1) those whose treatment was changed at the end of the first month, and (2) those whom the physician was content to leave on the originally allotted treatment. In the overall rating of their condition and in three main components of it the two groups were remarkably similar at the start of the trial. At the end of four weeks they are quite different. Those remaining on the allotted treatment show a considerable (average) degree of recovery ; those changed to another treatment show very little improvement indeed.

Long-term Evaluation up to Six Months

As pointed out in the previous section, the number of changes of treatment at the end of the four-week period was very considerable. Of the 250 patients admitted and observed for six months 223 had remained on their allotted treatment over the four weeks spent in hospital. At the end of this time, however, 72 were given an alternative treatment as prescribed in the trial and another 20 received other treatment as prescribed by the physician. Over the subsequent five months an alternative treatment was given for a further 33 patients. In short, the number of patients having no additional or alternative treatment throughout the whole six months was only 98 (39%).

In the treatment of these depressive illnesses such a sequence of events may well have proved unavoidable, but at the same time it clearly makes impossible any direct comparison of the progress made by the four original treatment groups. Some other form of comparison must be sought, and we have taken the time of discharge from hospital as the most informative.

Discharge of the patient from hospital was, it may be recalled, required at the end of the four-week period or as soon thereafter as the physician thought proper. This event therefore necessarily becomes a criterion of improvement if not recovery. To this we may make two provisos: (*a*) that after discharge the patient was not readmitted within the six-month period, and (*b*) that he or she did not receive treatment by E.C.T. as an out-patient.

In individual cases the decision whether or not to discharge a patient may, of course, depend in part upon social and other circumstances not directly reflecting the patient's mental state. On the other hand, it can safely be assumed that patients for whom admission to hospital was originally required are likely to have revealed considerable improvement at the time at which prolongation of in-patient care was regarded as unnecessary. Any other factors influencing the time should, by the play of chance, operate equally in the four treatment groups. In what follows, therefore, *we shall regard discharge from hospital as indicative of a substantial degree of recovery from the illness—provided that no readmission took place and that no E.C.T. was administered on an out-patient basis during the six-month period.*[7] This outcome we shall term "final discharge," and we have considered the frequency with which it had taken place in each treatment group at four points of time—namely, at the end of 5, 8, 12, and 24 weeks.

We may first make reference to the 106 patients regarded as wholly or almost without symptoms after four weeks of trial treatment (physicians' overall rating 0 or 1). The proportions finally discharged by the end of 5, 8, 12, and 24 weeks respectively were 43, 63, 73, and 87%. For the 111 patients who remained ill at the end of four weeks (overall rating >1) the corresponding proportions were 5, 26, 56, and 79%. A higher proportion of patients in this latter group had received additional or alternative treatment prior to their discharge. These figures show that, although earlier discharge was likely for patients rated as symptom-free at four weeks, nevertheless many of them required a further period in hospital. Hence, if treatment is to be assessed adequately it is important, as was anticipated in the design of the trial, to follow progress of patients beyond the first few weeks. The results at the later dates are shown in Table VIII (all patients), Table IX (men), and Table X (women).

TABLE VIII.—*Number of Patients, Men and Women, Finally Discharged from Hospital* in Relation to Treatment Given Before Discharge*

Final Discharge by End of Week:	Treatment Group†	Treatment Given by Time of Final Discharge					
		Allotted Treatment Only	Allotted Treatment +E.C.T.	Allotted Treatment + Anti-depressants	Allotted Treatment + Some Other Treatment	Total Discharged	
						No.	%
5	E.C.T. ..	25	—	—	2	27	*42*
	Imipramine	12	1	—	—	13	*21*
	Phenelzine	4	3	—	—	7	*11*
	Placebo ..	13	2	—	—	15	*25*
8	E.C.T. ..	31	—	—	4	35	*54*
	Imipramine	23	3	—	—	26	*41*
	Phenelzine	12	11	—	1	24	*40*
	Placebo ..	17	9	1	—	27	*44*
12	E.C.T. ..	34	—	2	5	41	*63*
	Imipramine	34	11	—	—	45	*71*
	Phenelzine	12	21	—	1	34	*56*
	Placebo ..	19	18	1	1	39	*64*
24	E.C.T. ..	35	6	5	6	52	*80*
	Imipramine	34	19	1	—	54	*85*
	Phenelzine	13	31	—	2	46	*75*
	Placebo ..	22	28	2	2	54	*88*

* Final discharge was defined as discharge from hospital with no readmission before the end of the six months of the trial and with no treatment by E.C.T. as an out-patient.
† Total numbers : E.C.T. 65; imipramine 63; phenelzine 61; placebo 61.

Stage I, at end of five weeks.—At the end of the first five weeks E.C.T. shows (significantly) the highest rate of final discharge (42%). There is nothing at all to choose between imipramine (21%) and the placebo (25%), but treatment with phenelzine has been singularly unsuccessful, with only 7 (11%)

[6] The differences between E.C.T., imipramine, and phenelzine are three times their standard errors, but with the placebo they are barely twice the standard errors.

[7] There were only five such cases—one on imipramine, two on phenelzine, and two on placebo.

discharges, in three of which the treatment had already been supplemented by E.C.T. This early advantage of treatment by E.C.T. and disadvantage of phenelzine is, however, limited to women (Table X); no difference at all between the four treatment groups is apparent in men (Table IX).

Stage II, at end of eight weeks.—At the end of eight weeks E.C.T. retains some slight advantage with a final discharge rate of 54% (Table VIII), and it is noticeable that 31 of the 35 patients concerned had had no other treatment. With the three groups on drugs the rate of discharge had risen in each to some 40%, but nearly half the patients on phenelzine (11 out of 24) and a third of those on the placebo (9 out of 27) had received E.C.T. in addition to their allotted treatment before their final discharge by this date. The sex difference, however, appears to continue. With men imipramine (54%) has given a slightly better result than E.C.T. (42%) and has required no supplementation. The patients on phenelzine and the placebo fared equally well but supplementation by E.C.T. was made in some of them. With women, on the other hand, E.C.T., unsupplemented except in one case, remains the method of choice (61%), and to bring the final discharge rate of the three groups on drugs up to only about half this level the frequent addition of treatment with E.C.T. has been regarded as necessary.

Stage III, at end of 12 weeks.—By the end of 12 weeks the final discharge rates for all patients do not differ appreciably, but once again it is necessary to consider the sexes separately. With men the most favourable picture is given by imipramine, in which group 19 out of the 22 patients (86%) had reached final discharge; for only two of these had the drug been supplemented by E.C.T. Treatment by E.C.T. alone reveals a relatively poor response—no better than phenelzine and the placebo. Yet with women it continues to show the most favourable results and phenelzine the poorest.

Stage IV, at end of 24 weeks.—At the end of the period of the study it had proved possible to discharge approximately four-fifths of the patients. In total, E.C.T. and imipramine have been equally effective, 35 and 34 patients having remained on them throughout, and a further 17 and 20 having reached discharge after the use of an additional treatment (E.C.T., antidepressants, etc.). Unsupplemented imipramine in men and E.C.T. in women have shown the most favourable rates. With men, indeed, those on E.C.T. have not come to final discharge any more frequently than those on phenelzine and the placebo (whether supported or unsupported by additional treatment). Here the contrast with women is striking. Of the 34 women originally allotted E.C.T. and given a final discharge by the end of the trial only nine had had additional treatment. This figure compares with 18 out of 35 on imipramine, 27 out of 30 on phenelzine, and 24 out of 38 on the placebo.

TABLE IX.—*Number of Men Finally Discharged from Hospital in Relation to Treatment Given Before Discharge*

Final Discharge by End of Week:	Treatment Group*	Treatment Given by Time of Final Discharge: Allotted Treatment Only	Allotted Treatment + E.C.T.	Allotted Treatment + Anti-Depressants	Allotted Treatment + Some Other Treatment	Total Discharged: No.	Total Discharged: %
5	E.C.T. ..	4	—	—	2	6	*25*
	Imipramine	6	—	—	—	6	*27*
	Phenelzine	3	1	—	—	4	*22*
	Placebo ..	6	—	—	—	6	*35*
8	E.C.T. ..	7	—	—	3	10	*42*
	Imipramine	12	—	—	—	12	*54*
	Phenelzine	10	2	—	—	12	*67*
	Placebo ..	7	2	1	—	10	*59*
12	E.C.T. ..	9	—	—	3	12	*50*
	Imipramine	17	2	—	—	19	*86*
	Phenelzine	10	3	—	—	13	*72*
	Placebo ..	7	3	1	1	12	*71*
24	E.C.T. ..	10	4	—	4	18	*75*
	Imipramine	17	2	—	—	19	*86*
	Phenelzine	10	6	—	—	16	*89*
	Placebo ..	8	5	1	2	16	*94*

* Total numbers: E.C.T. 24; imipramine 22; phenelzine 18; placebo 17.

TABLE X.—*Number of Women Finally Discharged from Hospital in Relation to Treatment Given Before Discharge*

Final Discharge by End of Week:	Treatment Group*	Treatment Given by Time of Final Discharge: Allotted Treatment Only	Allotted Treatment + E.C.T.	Allotted Treatment + Anti-depressants	Allotted Treatment + Some Other Treatment	Total Discharged: No.	Total Discharged: %
5	E.C.T. ..	21	—	—	—	21	*51*
	Imipramine	6	1	—	—	7	*17*
	Phenelzine	1	2	—	—	3	*7*
	Placebo ..	7	2	—	—	9	*20*
8	E.C.T. ..	24	—	—	1	25	*61*
	Imipramine	11	3	—	—	14	*54*
	Phenelzine	2	9	—	1	12	*28*
	Placebo ..	10	7	—	—	17	*39*
12	E.C.T. ..	25	—	2	2	29	*71*
	Imipramine	17	9	—	—	26	*63*
	Phenelzine	2	18	—	1	21	*49*
	Placebo ..	12	15	—	—	27	*61*
24	E.C.T. ..	25	2	5	2	34	*83*
	Imipramine	17	17	1	—	35	*85*
	Phenelzine	3	25	—	2	30	*70*
	Placebo ..	14	23	1	—	38	*86*

* Total numbers: E.C.T. 41; imipramine 41; phenelzine 43; placebo 44.

In summary of this long-term evaluation it appears that:

1. At the end of 24 weeks approximately one-third of patients have had a satisfactory outcome on a placebo alone (22 out of 61). This figure was increased to slightly more than one-half after the exhibition of E.C.T. alone (35 out of 65) or imipramine alone (34 out of 63). It was not increased after the exhibition of phenelzine (13 out of 61).

2. The action of imipramine is slower than that of E.C.T., which appeared to be the more effective treatment in the first two months. Thus the numbers of patients in the E.C.T. and imipramine groups who were discharged without any additional treatment were respectively 25 and 12 at the end of five weeks, 31 and 23 at the end of eight weeks, and 34 and 34 at the end of 12 weeks. However, it should be emphasized that approximately one-third of the patients originally on imipramine subsequently received E.C.T., to which about one-half of these patients responded. This would suggest a specific response to E.C.T. by some patients. The design of the trial made it impossible to determine whether imipramine could be regarded as a specific form of treatment for a subgroup of depressed patients.

3. Almost half of the placebo patients discharged by the end of 12 weeks (18 out of 39) had received E.C.T. compared with only a quarter (11 out of 45) of the patients given imipramine (a difference of 22% ± 10.2). Thus the exhibition of imipramine was associated with a reduction of the number of patients for whom E.C.T. was finally required. On the other hand, with phenelzine over half (21 out of 34) were judged to have needed further treatment by E.C.T., a figure at least as unfavourable as that shown by the placebo group.

4. When subdivided by sex the numbers of patients involved become relatively small, particularly for men (81 in total compared with 169 women). What they suggest is that in the patients admitted to this trial imipramine was of the greatest value in men, of whom 17 out of 22 (77%) were discharged by the end of the 12th week, having had no other treatment. At this point of time as many as 41% of men had shown a satisfactory outcome on the placebo alone, and this figure was not significantly different with phenelzine (56%) or E.C.T. (38%). On the other hand, only 27% of the women had a satisfactory outcome by the end of 12 weeks on the placebo alone, and this figure was increased to 61% with E.C.T. alone and to 41% with imipramine alone. For phenelzine it was only 7% (3 out of 43). It is noticeable that after the exhibition of E.C.T. to patients who had failed to respond to imipramine the final discharge rate of men by the end of the trial had increased from 17 to 19 (out of 22) whereas in women it had increased from 17 to 34 (out of 41).

5. In general the proportion of women with a successful outcome by the end of the trial who had originally been allotted to drugs and who in the opinion of the physicians subsequently needed E.C.T. (65 out of 103) greatly exceeded the corresponding proportion of men (13 out of 51).

In short, it appears that for the patients in our series imipramine was superior to both phenelzine and a placebo in both sexes, that men responded better to tablets of whatever kind than women and noticeably less well to E.C.T., and that women responded singularly poorly to phenelzine. It would

also seem that by the end of approximately 12 weeks one-quarter (27%) of women had responded to the placebo alone, that a further seventh had responded to imipramine (41%), and a further fifth to E.C.T. (61%).

We have not been able to identify any factors associated with the specific therapeutic responses; evaluation of demographic, social, and clinical characteristics revealed disappointingly little basis as reliable prognostic indicators. Thus there was no association between outcome as measured by final discharge from hospital and age, history of previous affective illness, and type of onset, previous duration, and clinical severity of the treated illness.

Summary and Conclusions

In 250 patients aged 40–69 years (81 men and 169 women) a comparison has been made between different treatments of depressive illness as specifically defined for the purpose of the trial. The treatments employed were E.C.T., imipramine, a monoamine oxidase inhibitor (phenelzine), and, for a short period of time, a placebo. These treatments were randomly allotted, and comparable groups thus set up and their progress assessed for six months. Many changes of treatment were made during the later stages of the trial period.

On both a short-term basis (after four weeks' treatment in hospital) and on a long-term basis (up to six months) it appears that E.C.T. and imipramine increased the frequency of recovery over and above the spontaneous rate shown by patients on the placebo. This drug, it appears, was specially effective in men and E.C.T. specially effective in women. For these patients, as defined by clinical condition and age, phenelzine revealed no advantage over the placebo in the treatment of men and gave even less favourable results than the placebo in women. Imipramine showed a slower action than E.C.T., but its use certainly reduced the total number of patients for whom E.C.T. was finally regarded as necessary.

The Committee is greatly indebted to the 55 physicians (see below) who admitted patients to this trial and completed the records so carefully; to William R. Warner and Co. Ltd., and Geigy Pharmaceutical Company Ltd., who kindly supplied specially prepared indistinguishable tablets; to Dr. W. J. Martin and Miss B. Hafner for much of the statistical work; to Mrs. B. Grant, who traced many patients after their discharge; to Miss K. M. Blick for secretarial assistance; and to Professor M. Hamilton, Dr. L. G. Kiloh, and Dr. M. W. Carney, who assisted the trial in Leeds and Newcastle.

Special recognition is made of the work of Dr. R. H. Cawley, who co-ordinated the trial and provided invaluable assistance at every stage of the investigation.

The following were the participating hospitals and physicians:

Leeds Region.—Dr. D. E. Munro (Clifton), Dr. E. A. M. Wood (Leeds General Infirmary), Dr. J. C. Little, Dr. J. M. Roberts (St. James), Professor Max Hamilton, Dr. A. Spellman, Dr. J. M. White (Stanley Royd), Dr. D. K. Bruce, Dr. J. E. Dessart, Dr. A. L. Smith (Storthes Hall).

London Region.—Dr. E. Roderic-Evans (Cane Hill), Dr. A. Mezey (Claybury), Dr. R. C. Gledhill (Goodmayes), Dr. J. D. Morrissey, Dr. J. Towers (Graylingwell), Dr. S. Benaim, Dr. E. H. Larkin (Halliwick), Dr. D. Rice, Dr. R. Maggs (Hellingly), Dr. S. Catterall, Dr. G. V. Stephenson (Hill End), Dr. B. A. J. C. Gregory (Horton), Dr. F. Letemendia, Dr. B. M. Mandelbrote (Littlemore), Dr. L. J. Clein, Dr. H. Conitzer (Long Grove), Dr. D. L. Davies, Dr. J. P. Dewsbery, Dr. J. G. Hamilton, Dr. E. H. Hare, Dr. W. Linford Rees, Dr. M. Shepherd (Maudsley and Bethlem Royal), Dr. A. N. Edwards, Dr. G. S. Gladstone (Napsbury), Dr. N. Farnan, Dr. M. J. Raymond (Netherne), Dr. C. M. Xavier (Oakwood), Dr. P. H. Mitchell (St. Augustine's), Dr. R. H. Wheeler (St. Francis), Dr. I. A. Horton, Dr. D. C. Watt (St. John's), Dr. I. C. Lodge-Patch, Dr. M. Markowe (Springfield), Dr. C. F. Allfrey (Warley).

Newcastle Region.—Dr. G. A. Fitzpatrick, Dr. A. Gillis, Dr. C. F. Lascelles (Cherry Knowle), Dr. D. W. Kay, Dr. F. A. Whitlock (Newcastle General), Dr. L. G. Kiloh, Professor M. Roth (Royal Victoria Infirmary), Dr. J. Blackburn, Dr. D. D. Webster (St. Luke's), Dr. J. R. Roy (St. Nicholas), Dr. J. R. Hawkings (Winterton).

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Auto-antibody Studies in Interstitial Pulmonary Fibrosis

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Brit. med. J., 1965, 1, 886–891

Interstitial pulmonary fibrosis ("fibrosing alveolitis," Scadding, 1964) designates in terms of morbid anatomy a group of lung diseases which, although possibly not aetiologically homogeneous, is nevertheless characterized by similarity of microscopical, clinical, radiographic, and physiological features (see review by Livingstone *et al.*, 1964).

Briefly, the condition presents most commonly in middle age and the sexes are affected equally. The presenting symptom is dyspnoea and the course is variably progressive but usually extends over years; the rapidly progressive illness described by Hamman and Rich (1944) is seen only occasionally. On examination of patients with moderately advanced disease central cyanosis is usually present, especially on exercise. Characteristic showers of fine rales are often heard and finger-clubbing is common. The radiographic changes vary from widespread "ground-glass" shadows to fine or coarse mottling, often denser at the bases, and as the disease advances small translucent cystic areas appear. The bronchographic appearances consist in condensation of the peripheral bronchioles with narrowing of the normal peripheral unfilled zone (Scadding, 1960). Physiological studies show small lung volumes, hyperventilation without airway obstruction, and diminution of carbon-monoxide uptake, indicating deficient gas-exchange. Hypoxia develops on exercise, and, as the disease progresses, is present also at rest, but hyperventilation maintains the carbon dioxide at low or normal levels. The compliance is reduced. The earliest pathological changes are thickening of the alveolar wall and an intra-alveolar exudate containing macrophages. With progressive fibrosis the normal alveolar architecture is destroyed and there is gross condensation of tissue leading to areas of scarring separated by cystic spaces. There is now general agreement with Scadding (1960) that the clinical pattern of the condition is often sufficiently characteristic to warrant diagnosis without resort to lung biopsy.

Although in many cases the lung changes occur in the absence of other diseases, the syndrome is well recognized in association with rheumatoid arthritis (Ellman and Ball, 1948),

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