Brit. J. Psychiat. (1967), **113**, 659–665

Treatment of Depression

A Comparative Trial of Imipramine and Desipramine

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Desipramine (Pertofran) is the monomethyl analogue of imipramine (Tofranil) and is marketed as a potent anti-depressant agent. The literature on this drug has already been adequately reviewed by Rose *et al.* (1964) and Waldron *et al.* (1965). It is therefore sufficient to note that earlier reports claiming a more rapid action than imipramine have not been supported by more recent investigations. This paper reports a double-blind controlled comparison of imipramine and desipramine, designed to investigate the relative effectiveness, speed of action and side-effects of these two drugs.

Method

The 60 subjects were 51 in-patients and 9 out-patients of a psychiatric unit in a large general hospital. All were suffering from a primary depressive illness, defined as a sustained primary mood disturbance leading to subjective or objective inefficiency of mental activities, experienced in a mood of sadness and usually with a diffuse, persistent lowering of interest and activity (Mayer-Gross, 1954). No selection was made regarding severity of illness, but patients over the age of 65 were excluded in order to minimize the possibility of organic factors due to ageing being present. Patients who had received electroconvulsive treatment in the preceding six months or anti-depressant drugs in the preceding four weeks were not included in the trial.

In obtaining the usual clinical and social history, particular attention was directed towards a family history of psychiatric disorder, the number of previous attacks and the duration of the present illness. An assessment of the personality was made with regard to the presence of neurotic (anxiety, hysteria, inadequacy), obsessional and psychopathic traits. The patients were classified into reactive and endogenous depressions on aetiological grounds only, i.e. depending on the presence or absence of relevant precipitating factors.

Each patient was assessed independently by two clinicians, using an appropriate rating scale for depression (Hamilton, 1960), the sum of the assessments being taken as the score for the patient. Assessments were made initially and after 1, 2, 3 and 6 weeks of treatment.

A double-blind controlled technique was employed, using tablets containing either 25 mg. imipramine or 37·5 mg. desipramine. Imipramine was given 75 mg. daily for one week, thereafter 150 mg. daily. Desipramine was given 112·5 mg. for one week, thereafter 225 mg. daily; clinical experience with desipramine is still limited and this higher dosage was chosen to ensure full therapeutic effect. Since many patients with depression have considerable anxiety or agitation, it is a common practice of the authors to give a tranquillizer as well as an anti-depressant drug; all patients, therefore, received thioridazine (Melleril) 150 mg. daily in addition. Sixteen patients (7 imipramine, 9 desipramine) were removed from the trial after the third week of treatment because of unsatisfactory clinical response. Simple psychotherapy was given where indicated.

Results*

1. *Initial Similarity of the Two Treatment Groups*

Similarity of the two groups as regards sex, in-patient–out-patient status and type of depression was secured by a stratified randomiza-

* Abridged results only are recorded here. Full details are available on request to the authors.

tion procedure in allocating entrants to the imipramine and desipramine groups. That the procedure was successful is demonstrated in Table I. The slight differences are not statistically significant. No steps were taken to ensure that the two groups were similar as regards other relevant features, but in the event, as shown in Table I, no significant differences could be demonstrated.

2. *Overall Outcome*

Table II shows the rating scale scores before and after treatment. The patients have a mean initial score of 43·9 points; the mean 3 and 6 week scores are 10·1 and 6·6 respectively, which indicates considerable improvement in the group as a whole. Regarding the two treatments, none of the scores at any assessment differs at a significant level, although the desipramine group has some advantage at the final week. Comparison of the percentage reduction in the scores, taking the initial score as 100, also shows no significant difference between the two groups.

Since 16 patients left the trial after the third week, the final sixth week assessment is not on "all fours" with earlier assessments. For this reason, the data based on the 44 patients who completed the full trial were examined separately for both the raw scores and the percentage reduction. Again no significant differences are found, although the desipramine group shows a slight advantage at the third and sixth week assessments.

TABLE I

Initial Similarity of the Two Treatment Groups

Characteristics	Imipramine	Desipramine	Significance Level
Males	7 (23%)	9 (30%)	·80> P>·70
Females	23	21	
In-patients	25 (83%)	26 (87%)	P>·95
Out-patients	5	4	
Endogenous depression	16 (53%)	17 (57%)	P>·95
Reactive depression	14	13	
Mean age	42·6 years	41·9 years	·90> P>·80
No. of previous attacks: 0	17 (57%)	19 (63%)	
1	9	9	χ^2=·069
2	3	1	n =1
3	1	1	·80> P>·70
	13 (43%)	11 (37%)	
Mean duration of disease	5·4 months	6·1 months	·70> P>·60
Family history present	13 (43%)	12 (40%)	P>·95
Neurotic traits clearly present	3 (10%)	4 (13%)	P>·95
Obsessional ,, ,, ,,	11 (37%)	18 (60%)	·70> P>·50
Psychopathic ,, ,, ,,	1 (3%)	— (—)	

TABLE II

Overall Comparison of the 2-Drug Groups

	Imipramine	Desipramine	Total
No. of cases	30	30	60
Mean Initial Scores	44·6	43·2	43·9
Mean 1 week Scores	19·6	20·1	19·8
Mean 2 week Scores	12·7	11·9	12·3
Mean 3 week Scores	10·3	9·9	10·1
Mean 6 week Scores	(23) 8·2	(21) 4·8	(44) 6·6

The figures in parenthesis are the number of cases at the 6 week assessment.

https://doi.org/10.1192/bjp.113.499.659 Published online by Cambridge University Press

3. *Outcome of the Diagnostic Groups*

In Table III the two drug groups are compared with regard to diagnostic classification, by the method of analysis of variance. No differences at a significant level are found between the groups, although endogenous depressions treated with desipramine have the best final response. The outcome of the diagnostic groups was further investigated by comparing all possible pairs of groups, using the Student t-test; none of the six tests at each assessment shows a significant difference. Similar examination of the percentage reduction in the scores and of the data based on the 44 "non-leavers" also reveals no significant differences between the diagnostic groups.

4. *Comparison of the Individual Symptoms*

Although the overall scores of the two drug groups show little or no divergence throughout the trial, this result might mask differences between the groups in regard to one or more of the 17 symptoms which contributed to the overall score. The individual symptoms were therefore examined separately, using the data for all 60 patients up to the three-week assessment.

As a first approach to this aspect, the proportions contributed to the overall score by each symptom at each assessment were compared. At no assessment was any significant difference found between the two drug groups.

Next, the two groups were compared by expressing the actual amount of improvement as a percentage of that initially possible. No significant differences between the improvements of the two groups could be demonstrated in regard to any one symptom at any assessment, but for three items the differences approached significance level ($\cdot 1 > P > \cdot 05$). These were "insomnia-early", for which at three weeks, the desipramine group had improved 70 per cent. of the initial improvement possible, whilst the imipramine group improved 85 per cent.; "insomnia-middle" showed a similar difference at two weeks, but for "insomnia-late" at three weeks the desipramine group showed some advantage, improving 68 per cent. as against 48 per cent. in the imipramine group. To illustrate the general pattern of this comparison of the individual symptoms, the three-week results may be briefly summarized as showing a slight advantage to the imipramine group in regard to 8 symptoms, a similar advantage to the desipramine group for 7 symptoms and no difference whatsoever for the remaining 2 symptoms; this is precisely the type of result which could be expected to occur by chance if there were no difference in the efficacy of the two drugs.

The outstanding feature using both methods of examination was the enormous improvement, as early as one week, of the symptom "depression-suicide" in both drugs groups. Thus at one week this symptom had improved 91 per cent. of the possible improvement; at two weeks improvement to 96 per cent. occurred and no further improvement was made after three weeks of treatment.

TABLE III

Comparison of the Diagnostic Groups

	Imipramine				Desipramine			
	Endogenous		Reactive		Endogenous		Reactive	
No. of cases	16		14		16		14	
Mean Initial Scores ..	46·2		42·9		42·4		44·1	
Mean 1 week Scores ..	18·9		20·3		20·1		20·1	
Mean 2 week Scores ..	12·6		12·8		13·3		10·4	
Mean 3 week Scores ..	10·4		10·2		10·7		8·9	
Mean 6 week Scores ..	(12)	8·6	(11)	7·8	(11)	3·2	(10)	6·5

The figures in parenthesis are the number of cases at the 6 week assessment.

https://doi.org/10.1192/bjp.113.499.659 Published online by Cambridge University Press

5. *Prediction of the three-week Outcome from the one-week Scores*

The possibility of predicting the three-week outcome from the response after one week of treatment was studied. Three aspects were examined; to predict the three-week score from:

(*i*) Actual score at one week.
(*ii*) Absolute reduction in the score at one week.
(*iii*) Relative (percentage) reduction in the score at one week.

Table IV gives the correlation co-efficients for these three measures and the three-week score. These are all substantial and significant at the ·01 level, indicating a definite relation between the score at the three-week assessment and the three variables above. The negative signs for the absolute and relative reductions in the scores were of course expected, since the greater the reduction in the first week, the smaller one would expect the three-week score to be.

The regression co-efficients and regression equations were then calculated, and the actual values of the three variables for each of the 60 patients were used to obtain the predicted three-week scores. From this it was seen that the regression line of the actual one-week score gave the best prediction, closely followed by the percentage reduction in the score. It may be argued, though, that instances where the actual three-week score was below the predicted value should be considered as successes as far as treatment is concerned. In Table V, therefore, all instances where the three-week score was less than the "predicted value plus 4" are treated as successes. This shows that successful prediction thus defined was attained in 77 per cent. of patients by all three variables—slightly higher (80 per cent.) in the desipramine group and slightly lower (73 per cent.) in the imipramine group.

Clinicians, however, cannot be expected to calculate predicted values from regression equations. Given that by week one the patient has a score of x_1, or has reduced it by x_2 points or by x_3 per cent., they will ask what the score is likely to be at week 3 and the probability of the answer being correct. Whilst it is hardly feasible to provide a complete list of predicted three-week scores for every possible value of one-week scores or reduction in scores, an abbreviated form is attempted in Table VI, in which a successful prediction is given where the actual three-week score does not exceed the

TABLE IV

Correlation Coefficients of the 1-week Measures and 3-week Score

	Imipramine	Desipramine	Total
Actual 1-week score ..	+·763	+·707	+·726
Absolute reduction of initial score at 1 week	−·716	−·618	−·652
Percentage reduction of initial score at 1 week	−·780	−·685	−·722

TABLE V

Predicted 3-week Successes

	Imipramine		Desipramine		Total	
	No.	%	No.	%	No.	%
Actual 1-week score ..	22	73	24	80	46	77
Absolute reduction of initial score at 1 week ..	23	77	24	80	47	78
Percentage reduction of initial score at 1 week ..	22	73	24	80	46	77

https://doi.org/10.1192/bjp.113.499.659 Published online by Cambridge University Press

TABLE VI

Predicted 3-week Scores and Successes

	Imipramine		Desipramine		Total	
	Predicted 3-week score	Percentage successes	Predicted 3-week score	Percentage successes	Predicted 3-week score	Percentage successes
Actual 1-week score:						
0–9	0–4	100	0–4	100	0–4	100
10–19	5–10	86	5–9	86	5–10	86
20–29	11–16	50	10–14	88	10–15	67
30–54	17–27	67	15–27	50	16–28	60
Absolute reduction in 1-week score:						
0–9	20–26	50	18–23	60	19–24	57
10–19	14–20	71	12–17	67	13–18	62
20–29	8–13	82	7–12	78	7–12	85
30–41	1–7	80	0–6	90	1–7	65
Percentage reduction in 1-week score:						
0–9	21–27	50	19–24	50	20–25	50
20–49	13–21	100	11–19	71	12–20	73
50–69	7–12	92	6–11	67	7–12	81
70–91	1–6	75	1–6	100	0–6	89

upper limit of the predicted one. Comparing the three variables: actual one-week score, absolute reduction in the score and relative reduction in the score, it appears that the former provides the best indication of the three-week score. The following generalizations may be made:

(*i*) 91 per cent. of patients whose one-week score is less than 19 can be expected to have a three-week score of below 10.

(*ii*) 75 per cent. of patients who reduced their score in the first week of treatment by 20 to 40 points can be expected to have a three-week score of 12 or less.

(*iii*) 85 per cent. of patients who reduced their score by 50 per cent. or more can be expected to have a three-week score of below 12.

Therefore, if any of the above three events occur in a particular patient, the prognosis would seem excellent, although there may be a small percentage of failures.

6. *Side-Effects*

Included here are only those conditions spontaneously complained of by the patients or observed by the nursing and medical staff. Table VII summarizes the results. Side-effects occurred in 30 patients (50 per cent.), but on the whole interfered little with treatment. With imipramine, 18 patients had side-effects; 2 cases needed a temporary reduction in dosage. With desipramine, 12 patients had side-effects; 3 cases needed a temporary reduction in dosage. Most of these effects occurred on maximum dosage and some were multiple. With imipramine, not only were more patients affected,

TABLE VII

Comparison of Side-Effects

Side-Effect	Imipramine	Desipramine
Tremor	9	3
Faintness	3	8
Dry mouth	4	1
Syncope	3	1
Paraesthesia	2	1
Blurred vision ..	2	—
Drowsiness	2	—
Constipation	1	—
Total	26	14
No. of patients ..	18	12

https://doi.org/10.1192/bjp.113.499.659 Published online by Cambridge University Press

but side-effects were relatively more numerous, in spite of a dosage lower than desipramine. Tremor of the limbs and faintness were common effects in both drugs.

It must be remembered that all patients received thioridazine in addition to the anti-depressant drug, and therefore any side-effects should strictly be regarded as resulting from the combined therapy.

Discussion

Examination of both the overall scores and the individual symptom scores showed no significant difference in outcome of treatment between imipramine and desipramine. Our findings here are similar to those of previous reports.

Desipramine is the monomethyl analogue of imipramine. Brodie *et al.* (1961) and Sulser *et al.* (1962) have provided evidence that it is an active metabolite of imipramine, to which the latter may owe its anti-depressant effect; on this basis it has been suggested that desipramine might have a more rapid onset of action than imipramine, and some early reports have supported this view. However, in this investigation the outcome of treatment in both drug groups is very similar throughout the whole period of observation, and particularly so in the first three weeks of treatment. It appears then, that neither drug offers any practical advantage over the other in speed of onset of action. This finding is in line with more recent controlled trials (e.g. Waldron and Bates, 1965) and throws doubt on the view that desipramine is the active metabolite of imipramine.

On the Hamilton rating scale, a score of not more than 10 points (with two assessors) can usually be regarded as a very satisfactory response to treatment. On this basis, adequate clinical improvement appears to occur with both imipramine and desipramine after three weeks of treatment, although it is true that further improvement was recorded at the sixth week assessment. It must be noted, however, that all the subjects also received thioridazine, and that most of them were in-patients and as such benefited from therapeutic measures in addition to drugs.

One interesting point is the very similar outcome in the two types of depression. Previous reports (e.g. Ball and Kiloh, 1959, and Kiloh, Ball and Garside, 1962) have stressed the superior response to imipramine of the endogenous or severe depression as opposed to the reactive or neurotic type. However, it must be noted that the majority of our patients were sufficiently ill to warrant admission to hospital, and they could therefore be regarded as a selective group in respect of severity of depression. Furthermore, the diagnostic classification was made on aetiological grounds only and is thus not strictly comparable to one made on symptomatology; in this respect, the report by Fleminger and Groden (1962) that the presence or absence of precipitating stress was not significantly related to the result of treatment with imipramine, is probably relevant.

From the statistical point of view the response after one week of treatment has good prognostic value. Thus the majority of patients with a one-week score of less than 19 or with a reduction in their score of 50 per cent. or more showed adequate clinical improvement after three weeks. This finding is very similar to that reported by Waldron and Bates (1965). However, it does not follow that a poorer early response necessarily indicates an unsatisfactory outcome. Thus, 10 out of 18 patients with a one-week score of 20 to 29 reduced it to 12 or less by the third week, whilst 5 out of 10 patients with a one-week score as high as 30 to 54 reduced it to 20 or less two weeks later. With regard to the individual patient, therefore, prediction of the final outcome is probably of limited practical value.

Regarding side-effects, desipramine appears to have some moderate advantage, in spite of the higher dosage employed. Not only were fewer patients affected (12 as against 18), but the total number of side-effects was less than with imipramine (14 as against 26). However, since all patients received thioridazine in addition, some caution must be used in interpreting these results.

Summary

Imipramine was compared with desipramine in a double-blind controlled trial on 60 patients suffering from primary depressive disorders and

classified aetiologically into reactive and endogenous depressions. All the patients received thioridazine in addition to specific antidepressive therapy, and were assessed initially, and after one, two, three and six weeks of treatment, using an appropriate rating scale.

Examination of both the overall scores and the individual symptom scores showed imipramine and desipramine to be similar in antidepressant potency and provided no evidence that either drug had any advantage with regard to speed of action; the latter result raises doubt on the view that desipramine is the active metabolite of imipramine.

The response after one week of treatment was shown to be a good indication of the three-week outcome. Reactive and endogenous depressions responded equally well to either drug. Side-effects were similar in nature and were less numerous in patients treated with desipramine.

ACKNOWLEDGMENT

Thanks are due to Dr. Cyril Maxwell, of Geigy Pharmaceuticals Ltd., for supplying the drugs and providing help with the statistical calculations.

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(*Received 26 July, 1966*)