TRIAL OF IMIPRAMINE

By

VERA HOLDWAY, B.A., M.R.C.S., L.R.C.P., D.P.M.
Senior Assistant Psychiatrist, Middlewood Hospital, Sheffield

ALTHOUGH in the majority of cases E.C.T. is swiftly effective in the treatment of morbid depression there are some who regard it with repugnance, and have long hoped for drugs which would obviate its use. It was that hope which prompted this trial of imipramine ("Tofranil").

The subjects of the trial were forty women in-patients of Middlewood Hospital, thirty-four of whom had been admitted recently whilst the remaining six had been in hospital for a considerable period. Their ages varied between forty-two years and seventy-five years and nineteen of these were aged over sixty years.

Whilst all suffered from a depressive state the primary condition in four was a chronic schizophrenia, in another paraphrenia and in another a personality disorder, and in four others dementia. The six long-term patients were amongst this number. The remaining thirty patients suffered from involutional melancholia.

Physical disabilities were common. Nine suffered from hypertension—diastolic pressure above 110 mg. of mercury—four suffered from cardiac disease, two from marked arteriosclerosis and four from a moderately severe anaemia.

TECHNIQUE

Before treatment commenced each patient was assessed on a five-point scale by Sister C. Winterbottom, Sister N. L. Simpson, and by Dr. Vera Holdway, for various aspects of the depressed condition. A controlled technique was used—half the patients being given Tofranil and half a placebo. When treatment had proceeded for about two weeks another assessment was made. The information as to which patients were having Tofranil and which the placebo was then divulged by the Chief Pharmacist. From then on, all patients received Tofranil with the exception of those who recovered whilst taking the placebo.

DOSAGE

On the 1st day Tofranil 50 mg. t.d.s. was given, increasing on the 2nd day to 75 mg. t.d.s. and on the third day to 100 mg. t.d.s. This dose remained unchanged for the following 10 days after which it was reduced by 25 mg. daily until a maintenance dose of 50 mg. was reached. Those patients who made a satisfactory response continued with this dose for a few weeks after discharge from hospital.

RESULTS

The correlation between the assessments made by the Sisters and Dr. Holdway was found to be as high as ·8 and this despite the fact that each

https://doi.org/10.1192/bjp.106.445.1443 Published online by Cambridge University Press

looked only at her own assessment and did not discuss the patients in relation to them.

The first and second assessments were compared statistically (chi-square test using Yate's correction where appropriate) for both groups. The results are tabulated below:

Aspects of Depression	χ^2 Tofranil	χ^2 Placebo
1. General impression on observer of depression	8·56†	2·76
2. Facial expression of depression	2·7	0·02
3. Retardation	0	0
4. Agitation and tension	1·8	0
5. Activity	5·44*	2·7
6. Sociability	2·8	0·46
7. Extent to which deluded	5·34*	0
8. Ability to be interested	6·72†	1·5
9. Emotional liveliness	1·88	1·44
10. Expressions of guilt	1·0	0
11. Hopelessness	4·0*	0
12. Hypochondriasis	0	0

* = significant at a 0·05 level.
† = significant at a 0·01 level.

It was hoped to demonstrate in those taking Tofranil a general trend towards recovery that was stronger than could be accounted for by the natural sequence of events. We think that it can be fairly claimed that the result does so demonstrate the action of Tofranil in relieving depression.

As treatment progressed beyond the first two weeks it became necessary in some cases to give E.C.T. When patients appeared to be quite well, both to themselves, their relatives and to the hospital staff, or when all treatment failed to produce any further improvement, the cases were divided into three categories in relation to their response to Tofranil. Response was "good" when the patient appeared to be recovered from depression without resort to E.C.T. It was "fair" when a few E.C.T.s were needed to obtain a satisfactory result. Response was "poor" when a relatively large number of E.C.T.s had to be given.

Two patients on the placebo alone recovered on commencing treatment. The remaining thirty-eight were divided as follows:

	Good	Fair	Poor
Patients on Tofranil from the onset	8	4	8
Patients initially on the placebo	5	5	8
	13	9	16

In one or two instances improvement was noted whilst the patient was taking the larger doses of Tofranil, but the final recovery occurred suddenly when the patient had been on a maintenance dose for some weeks and when hope of further improvement had been almost abandoned.

https://doi.org/10.1192/bjp.106.445.1443 Published online by Cambridge University Press

Influence of Other Mental or Physical Illness

The question arose as to what extent the results were influenced by the presence of other mental illness or by the presence of physical disability in the subjects of the trial.

The findings are tabulated below and the importance of their bearing on the results was ascertained by chi-squared.

Result	Mental Illness Complicating Depression	
Good	None	
Fair	Paraphrenia	1
	Schizophrenia	1
Poor	Demented	4
	Schizophrenia	3
	Inadequate Personality	1

$\chi^2 = 7{\cdot}3$ (Significant at a 0·05 level)

The physical conditions considered were hypertension, marked arterio-sclerosis, cardiac disease and anaemia.

Result	Number Suffering from Physical Disability
Good	5
Fair	8
Poor	8

$\chi^2 = 1{\cdot}8$

Thus in this series the chances of a good recovery were prejudiced by the presence of mental illness other than depression, but were not significantly affected by the presence of cardio-vascular disease or anaemia.

Duration of Hospitalization

Considerable pressure is exerted on the part of patients and their relatives in favour of short-term treatment.

If Tofranil is to provide an alternative to E.C.T. in the treatment of depression the question of duration of hospitalization is important. The average length of stay in hospital for those who received Tofranil from the outset was 12·1/3 weeks. This period was rather longer than that required for the recovery of patients receiving E.C.T. alone, but there is some evidence that the prolongation was in part due to physical conditions.

Out-Patients

A study was also made of twenty-one out-patients suffering from relatively mild conditions of depression. A controlled technique was used for twelve of these, but was abandoned because in practically every case it was easily apparent which patient had had Tofranil and which the placebo. Those receiving the placebo showed no improvement. Of those taking Tofranil four showed no improvement and of these three were neurotic and the other had an inadequate personality whilst three did not persevere with treatment.

Of the fourteen patients who did well one suffered from reactive depression, three from endogenous depression and ten from involutional melancholia.

The ages varied between 32 years and 76 years and the doses of Tofranil used ranged from 50 mg. t.d.s. to 75 mg. t.d.s.

https://doi.org/10.1192/bjp.106.445.1443 Published online by Cambridge University Press

One patient who recovered rapidly from her depression had been ill for twelve months and during that time most of the anti-depressant drugs and some of the tranquillizers had been prescribed with little effect. There was an exacerbation of symptoms when this patient was taking the placebo, but a rapid response when Tofranil was given.

Side-Effects

1. Dryness of the mouth was a very common complaint and in two cases this led to a stomatitis progressing in one of these to a parotitis.

2. Sweating was complained of by about one-third of the cases treated.

3. Transitory loss of power in limbs was complained of by two neurotic patients.

4. Rashes developed in two patients and in both cases subsided without withdrawal of the drug.

5. Trembling of hands was noticed frequently in the older patients.

6. Acute mania of sudden onset and sudden subsidence and lasting about twelve hours occurred in one patient.

7. A feeling of remoteness and detachment was complained of in a few instances.

8. The blood-pressure appeared to be little affected.

9. Dizziness was a relatively rare complaint.

10. Two cases of gastro-enteritis may have been attributable to Tofranil.

Summary

A trial of impramine was made using a controlled technique with forty in-patients suffering from morbid depression. The results were ascertained by chi-squared and demonstrated a definite improvement in those patients taking Tofranil.

A second study was made of twenty-one out patients suffering from moderately severe conditions of depression. On clinical assessment relief from depression was found to have occurred in a number of patients who received Tofranil but no improvement occurred in those taking the placebo.

There were indications that in some cases significant improvement did not occur until late in the course of treatment.

Results were not good when the depression was complicated by other mental illness, but appeared unaffected in the presence of anaemia or cardio-vascular disease.

Side-effects were variable but the most important were dryness of the mouth stomatitis and parotitis and probably gastro-enteritis.

This trial series ended in September, 1959, and only one patient who received Tofranil alone returned to hospital with a recurrence of depression in the subsequent four months.

https://doi.org/10.1192/bjp.106.445.1443 Published online by Cambridge University Press