IMIPRAMINE (TOFRANIL) IN DEPRESSIVE STATES
A CONTROLLED TRIAL WITH IN-PATIENTS

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INTRODUCTION

A LARGE number of papers has been published in the last two or three years on the use of imipramine in depressive states. Much of this literature has been reviewed by Ball and Kiloh (1959) whose investigations on out-patients represents one of the remarkably few controlled trials that have so far appeared. We feel, therefore, that there is room for a report on another controlled study, this time with in-patients, in which the term "controlled" not only involved the usual "blind" procedures of administering tablets, but also included some of those elementary safeguards of reliability and validity of assessments without which uncertainty must remain concerning the meaning of any findings. Foulds (1958), for example, has presented evidence that *uncontrolled* investigations have a greater tendency to yield results supporting the hypotheses of investigations than experimentally fully *controlled* trials. In view of the claims that had been made for the efficacy of imipramine in a number of uncontrolled studies, we were primarily concerned to discover whether or not there existed valid scientific evidence of its value and, if so, in what kinds of depressive illness it appeared to be of most benefit.

MATERIAL AND METHODS

Over a five-month period consecutive admissions to Springfield Hospital of cases of depression were randomly assigned to imipramine and placebo groups. The placebo tablets were indistinguishable in appearance from the genuine ones, and the hospital pharmacist alone knew which type of tablet each patient was having. Shortly after admission each patient was interviewed and assessed independently by two of us (C.F. and M. de M.), and only when both agreed on the diagnosis of primary depression was the patient included in the series; patients in whom depressive symptoms were thought to be secondary to a schizophrenic or organic illness were excluded. In addition, a very few cases where the doctor in charge of the patient felt it would be ethically unjustifiable to withhold E.C.T. were also excluded.

Diagnosis was based on the patient's history and the clinical interview. We agreed with Lehman and others (1959) that observation, interview and history are the simplest and most reliable tools in the psychiatric diagnosis of depression, and that at present there exist no objective clinical tests on which we can base a diagnosis. Features regarded as being diagnostically significant were subjective or objective depression of mood, psychomotor retardation or agitation, feelings of guilt or unworthiness, self-reproach, suicidal ideas, insomnia with early morning waking, diurnal variation of mood, indecisiveness, and loss of interest and ability to concentrate.

In addition to the clinical interview, each patient was given a questionnaire

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designed to elicit the degree of behavioural and subjective depression. This questionnaire was constructed to serve as an outside criterion of depression—as a validity check—from items culled from several sources, including the Minnesota Multiphasic Personality Inventory. It contained 25 items to which patients had to reply either "True" or "False". (Norms were available from a control study.) The following are examples of the items in the questionnaire:

"I often feel a hopeless failure."
"I often have feelings of unworthiness."
"I feel worse in the morning."
"I have lost interest in many things lately."

Each patient was also rated independently on two rating scales. The first of these was a 5-point scale based on that of Shapiro *et al.* (1958) to assess the degree of depression clinically present. A rating of 2 would be given if the clinician found "Depression without gross depression in the patient's appearance", and a rating of 4 was given if the clinician found "Severe depression with delusions and hallucinations but in good contact". The second rating scale was the depression sub-scale of the Wittenborn Psychiatric Rating Scale (Wittenborn, 1951). The items of this scale are specifically aimed at the degree of delusional guilt and unworthiness present, e.g. "Patient tends to blame himself or refer to his unworthiness" or "Patient appears to have a delusional belief that he is an extraordinarily evil, unworthy or guilty person". The first item would be rated 2, and the second item would obtain a rating of 4.

The tablets were administered in a standardized dosage 25 mg. t.d.s. for 2 days, then 50 mg. t.d.s. for 2 days, then 75 mg. t.d.s. for 4 weeks. In the majority of cases the dosage was later reduced to 50 or 25 mg. t.d.s. when the patient had either improved or was showing side-effects which he could not tolerate.

The two rating scales and the questionnaire were re-administered at the end of the course of tablets. This was normally after 6 weeks, but in a number of cases the period of trial was shorter either because the patient became better and was discharged, or because his or her symptoms became so serious that it was considered ethically unjustifiable to keep the patient in the trial. A number of patients who had been on placebo were given a further trial on the genuine drug, following which the ratings and questionnaire were again repeated.

We feel that the traditional double-blind method is not applicable to an investigation of the pharmacotherapy of depression. When treatment is discontinued, depressive conditions do not necessarily recur when switching to a placebo, as would be expected for example in a substitution therapy (viz. B_{12} in pernicious anaemia). In addition, in a trial such as ours conducted with in-patients, remission of symptoms leads to the patient's discharge and hence a new variable is introduced into the situation.

Originally 67 patients were included in the investigation. Of these 17 dropped out because they either discharged themselves or had to be given alternative treatment. Of the remaining 50 patients, all completed at least 4 but more often 6 weeks on either placebo or imipramine, while 6 completed a full trial on imipramine as well as placebo. It was not found possible to obtain all the necessary questionnaire and rating data on testing or retesting for all these 50 patients because of precipitate discharges, the death of one patient, and various administrative reasons. Thus second assessments on the depression questionnaire were obtained for only 47 patients, one of the raters completed pre- and post-treatment rating on 49 patients, and the other 43. Pre- and post-

treatment ratings from both raters are available for 42 of the 50 patients. In the final analysis of the results, only those 36 cases are considered where the raters agreed in the direction of post-treatment changes.

We do not intend to discuss in this paper the question of the classification of depressive illness. Recent literature ranges from total rejection of sub-groups in depression, viewing depressive conditions as a continuum on a quantitative scale, to various sub-groupings according to assumed aetiology, physiopathology or psychodynamic concepts. There is, however, almost general agreement that for therapeutic purposes it is expedient to classify depression as endogenous, involutional and reactive. On the whole therapeutic tests have justified such a distinction (Roth, 1959).

We classified our cases as follows: cases were regarded as endogenous when all or some of the following features were present; history of previous attacks, marked diurnal variation of mood, marked psychomotor retardation, or evidence of hereditary factors; cases were regarded as involutional when the first attack of depression had occurred in the involutional period, and was associated particularly with agitation rather than retardation, and with obsessional personality traits; the remainder were regarded as reactive. According to these criteria the sample contained 26 endogenous cases, 11 involutionals, and 13 reactive depressions.

Results

The formal hypothesis to be tested was that the drug imipramine would be more successful in effecting improvements in depressive disorders than a placebo despite the therapeutic efficacy of placebos that has been demonstrated in many studies. The hypothesis was confirmed. Our calculations are based on 36 cases in which the two raters were in agreement in their post-treatment ratings as to the direction of change of clinically observable depression (Shapiro *et al.*, 1958). Of these, 17 patients were actually receiving imipramine, while 19 were on placebo. The sex distribution was 9 men between the ages of 52 and 62 (mean age=56·9, S.D.=11·8) and 27 women between the ages of 32 and 76 (mean age=56·9, S.D.=16·1). The difference in ages between those receiving imipramine and those on placebo was not statistically significant, though the mean of the former group was somewhat higher.

TABLE I

	Imipramine	Placebo	Total
Improved	11	4	15
Not improved or worse ..	6	15	21
Total	17	19	36

Table I shows that patients on imipramine had a significantly greater chance of improving than patients on the placebo (chi-square=5·353, p=0·02 approx. with df=1).

TABLE II

	Endogenous	Involutional	Reactive	Total
Improved	6	3	2	11
Not improved or worse	3	1	2	6
Total	9	4	4	17

Considering now only the 17 patients receiving imipramine, Table II shows that endogenous and involutional depressions have a greater chance of benefiting from the drug than reactive depressions. For reasons already given, the total

number of patients involved in the investigation was small, and the numbers given in Table II are actually too small to carry out statistical evaluations. The trends are, however, fairly clear.

When examining the two raters' post-treatment ratings of clinically observable depression separately, it was found that a more substantial contribution to the positive finding was made by the ratings of one than by the other. With the Wittenborn Scale as a rating device no significant results were obtained either with cases where inter-rater agreement on improvement had been obtained or when taking the ratings of the two raters separately. Considering the 6 cases who were put on imipramine after showing no improvement on placebo, and on whom post-treatment ratings were available, 4 showed improvement while 2 did not respond.

Discussion

The significant improvement following imipramine treatment, and the relative lack of improvement following placebo, shown by means of the rating scale evidence of depression (Shapiro *et al.*, 1958) was supported by the change in scores on the depression questionnaire.

Table III

Group	Assessment	N	Mean Scores on Depression Question-naire	S.D.	Range
Controls	—	26	6·62	4·05	2–20
Present total sample	Pre-treatment	50	15·50	4·12	5–23
Imipramine	Pre-treatment	23	15·87	3·97	5–23
Imipramine	Post-treatment	23	8·74	4·10	0–21
Placebo	Pre-treatment	24	16·50	4·14	10–23
Placebo	Post-treatment	24	13·79	4·06	0–22

Table III indicates (*a*) that both the groups used in the present study scored much higher on this device, aimed deliberately at behavioural and subjective evidence of depression, than a normal control group, (*b*) that the two randomly obtained imipramine and placebo groups were well equated for depression as measured by this questionnaire prior to differential medication, and (*c*) that the imipramine group's depression score fell significantly following treatment ($p = < 0 \cdot 01$), whereas the placebo group's scores did not fall significantly.

Evidence of the validity of the questionnaire is obtained not only from the great discrepancy between the mean scores on the scale of an unhospitalized, heterogeneous sample of the population and the hospitalized sample, but also from the correlations between the questionnaire and the rating scales. These correlations, shown in Table IV, are all statistically significant at better than the 0·01 level.

Table IV

Correlations Between Questionnaire and Rating Scales

Questionnaire	Scales: Overt Depression (Shapiro *et al.*, 1958)	Scales: Wittenborn (1951)
Rater I:		
Pre-treatment	0·48	0·54
Post-treatment	0·77	0·69
Rater II:		
Pre-treatment	0·57	0·55
Post-treatment	0·74	0·78

The fact that the pre-treatment correlations are consistently lower than the post-treatment correlations might at first sight suggest that the questionnaire we were using is more valid as a post- than a pre-treatment measuring instrument. That this is a misleading impression is shown by the variations in inter-rater reliability in Table V.

TABLE V

Inter-Rater Reliability

	Scales	
	Overt Depression (Shapiro *et al.*, 1958)	Wittenborn (1951)
Pre-treatment	0·46	0·66
Post-treatment	0·75	0·62

These figures suggest that the apparently lower correlation between scores on the depression questionnaire and ratings on overt depression particularly, may be due in part to lower pre-treatment rating reliability. This suggests that the assessment of freedom from symptoms may be easier and less susceptible to subjective bias, than the assessment of the absolute severity of depression.

Our findings support those of other studies (e.g. Ball and Kiloh, 1959) which demonstrated the therapeutic effects of imipramine. In our study, improvement in all depressive states following imipramine is consistently about 65 per cent., taking each rater separately, or taking only those cases where both raters agree in the degree of improvement, stability or worsening of symptoms.

We feel it should be emphasized, however, that of 8 patients whose illnesses were characterized by the presence of frank delusions of guilt or unworthiness, and who were clearly the most severely ill cases in our series, none showed any significant response to Tofranil, while 5 of them subsequently responded to E.C.T.

Our experience in this investigation illustrates some of the difficulties inherent in therapeutic trials in psychiatric illness in general, and in depressive illness in particular. Firstly, the influence of psychological and interpersonal factors, which were quite distinct from any effects attributable to a drug, was clearly operating in some cases, and caused difficulty in assessing results. The methods of assessing patients were even themselves occasionally responsible for producing emotional changes in the patient, thus making rating difficult. Secondly, in carrying out a therapeutic trial on depressive illness ethical questions become particularly serious in view of the availability of a treatment, i.e. electroplexy, which is generally believed to produce rapid relief of symptoms in most cases. Doctors tend therefore to be unwilling sometimes to keep patients for weeks on a possibly ineffective tablet, particularly in severe cases where there is a risk of suicide.

With regard to side-effects, like other investigators we found that Tofranil produced in many patients an atropine-like effect of mild degree. Many patients complained of dryness of the mouth and this was more disturbing in patients with obsessional features. Many patients showed increased perspiration during the treatment period. Other symptoms complained of were dizziness, weakness, lassitude, lack of energy, feeling of pressure in the head, tremor of hands, disturbances of visual accommodation, and in one case an erythematous eruption. Side-effects were more pronounced during the first four or five days of treatment and receded as the treatment went on. We did not observe jaundice or any Parkinsonian symptoms. Because of the side-effects it is of psychological

interest that one patient developed increased perspiration and nausea and was then found to have been on placebo. It was also of interest that hypomania, a complication which has been reported by a number of observers, developed in one patient, and he too was on placebo. In one ward there was amongst the nursing staff and patients some degree of prejudice against Tofranil, and in this ward all the patients whether on the genuine drug or on the placebo developed side-effects for a time.

We think that it is extremely difficult to carry out controlled experimentation where the needs of the patients and the demands of scientifically valid procedure are equally satisfied. It may be considered that the present study, though based on relatively small numbers, at least took into account some of the more elementary validity and reliability safeguards, which are often absent from investigations claiming to have been "controlled".

Summary and Conclusions

1. A controlled trial of Tofranil in the treatment of 50 cases of depression admitted to Springfield Hospital is described.

2. In addition to the usual random distribution of cases into active drug and placebo groups, special reliability and validity safeguards were used.

3. Taking all cases of depression together, it was found that patients on Tofranil had a significantly greater chance of improving than patients on placebo.

4. Endogenous and involutional depressions benefited more from the drug than reactive ones, but the most severe cases, whatever their classification, failed to respond to the drug.

5. Some of the difficulties inherent in therapeutic trials in depressive illness are discussed.

6. It is concluded that Tofranil is of value in the treatment of less severe depressions, but in severe cases it would appear to be inferior to E.C.T. (Further comparisons between E.C.T. and Tofranil are indicated.)

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