A CLINICAL TRIAL OF IMIPRAMINE ("TOFRANIL") ON DEPRESSED PATIENTS

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RECENTLY many new anti-depressive drugs have flooded the market, the objective being initially to assist and finally to replace E.C.T. as the treatment of choice for depressive states. One such preparation is Tofranil (N-(γ-Dimethyl-aminopropyl)-iminodibenzyl hydrochloride or imipramine). It was first favourably reported on by Azima (1) and Kuhn (2).

This drug was tried on a series of chronic depressed patients at Barnwood House, most of them being sufficiently unchanging in their depression to make it likely that little change was to be expected spontaneously over a period of some months.

METHOD

The "double-blind method" was used with placebo tablets exactly resembling the Tofranil ones. The tablets were issued by the dispenser in such a manner that neither patients nor the assessing physician knew which were being given.

Every patient was given a full course of the placebo and a similar one on Tofranil, the following sequence of 25 mg. tablets being strictly adhered to:

1	tablet	t.d.s. for	3 days
2	tablets	t.d.s. for	3 days
3	tablets	t.d.s. for	3 days
4	tablets	t.d.s. for	3 days
3	tablets	t.d.s. for	3 days
2	tablets	t.d.s. for	42 days
1	tablet	t.d.s. for	7 days

A week without tablets was left between the two courses, each of which was of nine weeks' duration. When a patient was included in the series, the question as to whether Tofranil or placebo should be given first was decided by chance.

The assessment of each patient's clinical condition was carried out by means of a standardized scale which was duly completed at the following times:

1. Before the first course;

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2. Just before the end of the first course, while the patient was still on the drug (or placebo);
3. At one week after the end of the first course (this occasion being also "Before the second course");
4. Just before the end of the second course;
5. At one week after the end of the second course.

A copy of the standardized rating scale is attached (Appendix I); it assessed the patient's state according to:

1. Degree of depression.
2. Amount of activity, as retardation or agitation.
3. The presence of delusions.
4. The presence of hallucinations.
5. The amount of sleep, either with sedative or without.
6. Amount of appetite.
7. Range of interests.
8. Degree of sociability.
9. Amount of nursing required.

Each of these nine variables was assessed at one degree of normality and four degrees of abnormality. One point for each degree of abnormality in each of the nine criteria gave a scale varying from 0 to 36 points measuring the "degree of clinical abnormality". We are satisfied, from practical experience of it, that it gave an estimate of as much accuracy as can reasonably be expected in psychiatric practice.

The markings at the five assessments are shown in Tables I and II below. Fifteen patients only completed the clinical trial out of twenty-two who were originally selected. Of the number who failed to complete the trial three died of causes quite unrelated to the treatment, and four refused to continue because of side-effects. This small group will be discussed separately.

TABLE I

	Assessment				
	First	2	3	4	Final
Patients receiving Tofranil first	10	7	12	14	6
	12	10	9	10	10
	11	11	11	10	11
	18	15	11	16	10
	4	5	2	2	3
	9	10	9	7	8
	14	11	13	13	11

TABLE II

	First	2	3	4	Final
Patients receiving placebo first	7	11	4	1	12
	18	11	15	11	16
	18	11	14	13	12
	8	10	15	14	12
	11	10	10	12	10
	14	14	19	18	15
	15	13	12	10	10
	18	16	13	15	14

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As stated above, only fifteen patients completed the clinical trial. In the Tables, their order has been re-arranged so as to bring together all those who had Tofranil first (Table I) and those who had placebo first (Table II). Each row in the Tables refers to one patient, and the score records "degrees of clinical abnormality", so that a decrease corresponds to an improvement in the clinical condition.

In addition to this objective but somewhat insensitive method of scoring, one of us (G.H.C.) kept regular records of the patients' general clinical condition, while also remaining ignorant of the type of tablet which was being given.

The Results

Simple inspection of the Tables shows that no factors are grossly effective, although the final readings of all the patients who were given Tofranil first (Table I) were uniformly lower than those at the first assessment, indicating some terminal improvement over the whole course. In Table II the final assessments were less frequently lower than the ones made at the initial assessment. The exact statistical significance of these differences between the two groups is uncertain, so we proceed to more sensitive statistical tests for changes on the average.

Examination shows that the most evident effect is that caused by just putting the patients on to "a tablet", for, though hardly significant, the first assessment (column 1) made before the patients actually commenced treatment, has a somewhat higher average than those of the others. The averages are, respectively:

$$12{\cdot}5,\ 11{\cdot}0,\ 11{\cdot}3,\ 11{\cdot}1,\ 10{\cdot}7$$

(The slight lack of orthogonality is not sufficient to cause appreciable disturbance here.)

This drop in the score of "degrees of clinical abnormality", suggests that clinical improvement invariably followed after administration of a tablet, regardless of whether this was Tofranil or placebo.

In view of this effect, which was at least as large as any other detectable effect, it seems simplest to compare the effects of Tofranil and placebo in the following ways:

(*a*) The two compared for the effects produced during the first seven weeks of the first course, i.e. by columns 1 and 2.

(*b*) The two compared for the effects produced during the first seven weeks of the second course, i.e. by columns 3 and 4.

In this way we obtain two independent comparisons, each in fairly homogeneous conditions. By making each patient his own control, the heterogeneity in the levels of depression (some patients with high scores throughout, some with low) can be eliminated. The *changes* induced by the tablets, all in the first course, were then as follows:

(*a*) Due to Tofranil: $-3, -2, 0, -3, +1, +1, -3.$

(*b*) Due to placebo: $+4, -7, -7, +2, -1, 0, -2. -2.$

The two distributions may both be displaced from zero by all those factors that make the second column different from the first, but the *difference* between their means can only be due to the drug difference t proves to be $+0{\cdot}21$, so there is no significant difference.

The same comparison can be made for the second course, and here the changes were:

(*a*) Due to Tofranil: −3, −4, −1, −1, +2, −1, −2, +2,

(*b*) Due to placebo: +2, +1, −1, +5, 0, −2, 0.

t is −1·50—again the effect is not of great significance, though in the right direction.

As the series is small and no main effect can be seen, further analysis lacks justification.

The method of assessment, however, tends to be somewhat insensitive and the more delicate perceptions of the clinician have more to report. Of the fifteen patients who completed the trial, eight were reported by him as "more settled" when on Tofranil, but none were reported as being clinically improved while on placebo. Treatment with Tofranil was continued with good effect on the eight patients noted above after the end of the clinical trials.

Side-Effects

These were complained of by four patients in the group and all discontinued treatment within three weeks of commencement. It is to be noted that three of these cases were in the same ward, were friendly, and were in close contact with each other. One after the other within a period of a few days they all made similar complaints, namely of dryness of the mouth, tachycardia, and tremulousness of the lower limbs affecting their gait. All were over seventy years of age. The fourth patient was much younger and refused to continue the tablets after 3–4 days, claiming that they made her giddy.

Summary

Fifteen depressed patients were given a nine-weeks course of Tofranil, on a double-blind system with a similar course on facsimile placebo tablets. Some were given the placebo course first and some the Tofranil.

Survey of the results suggests that the drug had some effect in making the patients more settled. The effect, however, could not be shown significantly on a planned marking scale.

Mention is also made of the side-effects which were encountered.

Acknowledgments

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References

1. Azima, H., and Vispo, R. H., *Amer. J. Psychiat.*, 1958, **115**, 245.
2. Kuhn, R., *ibid.*, 1958, **115**, 459.

APPENDIX I

Depression Rating Scale

Name..... Age..... Date of Marking.....

Depression	Absent	Slight	Moderate	Severe	Remarks
Activity:					
(*a*) Retardation ..	Absent	Slight	Moderate	Severe	
(*b*) Agitation ..	Absent	Slight	Moderate	Severe	
Delusions	Absent	Slight	Moderate	Severe	
Hallucinations ..	Absent	Slight	Moderate	Severe	
Sleep:					
(*a*) With drugs ..	Over 7 hours	5–7 Hours	3–5 Hours	0–3 Hours	
(*b*) Without drugs	Over 7 hours	5–7 Hours	3–5 Hours	0–3 Hours	
Appetite	Normal	Poor	Needs coaxing	Has to be fed	
Interests	Normal	Limited	Needs coaxing	None	
Sociability	Normal	Reserved	Withdrawn	Inaccessible	
Nursing required ..	None	Slight	Consider-able	Constant	
Suicidal	No			Yes	

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