IMIPRAMINE IN CHRONIC DEPRESSION

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IMIPRAMINE hydrochloride (N-(γ-dimethylaminopropyl)-iminodibenzyl hydrochloride, "Tofranil") has been shown by many investigators to be of value in the treatment of depressive states. The reports of Kuhn (1957, 1958) and of Kielholz and Battegay (1958) have been followed by confirmatory papers from other authors. A number of contributors to the McGill University Symposium on Depression and Allied States (1959) commented favourably on the value of imipramine in depression; Hoff, however, while agreeing that the drug is useful in acute depressions stated that he found it ineffective in chronic depression.

In Britain, Ball and Kiloh (1959) have carried out a controlled trial of imipramine in out-patients suffering from depression. They found a statistically significant response, compared with the effect of placebo tablets, in both endogenous and reactive depressions. Another trial has been reported by Leyburg and Denmark (1959). These workers treated 74 patients with depressive states and 28 per cent. made a complete recovery. The authors concluded that "the further trial of this promising drug should at this stage be primarily concerned with the chronic depressive patients of whom many remain institutionalized at present".

This paper reports the results of such a trial. The investigation was undertaken to obtain information concerning the value of imipramine in patients with long-standing depression which had been resistant to other treatments. All the patients studied had been ill for at least one year, most of them for much longer. The trial was designed as a careful clinical study of a small group of patients. The pattern of the illness was in each case well established and most of the patients had had several previous treatments under similar conditions without improvement. It seemed unlikely therefore that the mere act of presenting another new tablet would in itself bring about recovery. The study, including follow-up, has been conducted over a period of thirteen months.

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Material

Thirty-three patients were selected for study. All had been continuously depressed for at least one year.

The diagnoses were:

Endogenous depression	26
Personality disorder with depression	4
Paranoid state with depression	1
Cerebral arteriosclerosis with depression	2

Depression was the dominant symptom in all the patients.

The average duration of illness was 4·6 years (range 1 to 11), the average age 64·5 years (range 48 to 83). There were 27 females and 6 males.

All but 6 patients had had electroplexy (E.C.T.), usually several courses, but in none had the response been satisfactory. In the other six E.C.T. had been withheld because of cerebral arteriosclerosis or advanced age. In addition, 17 of the patients had had phenothiazine derivatives, 2 amphetamine, 2 iproniazid and 2 benactyzine—all without response.

Methods

Imipramine was given by mouth in three doses per day, the total daily dose being:

1st and 2nd days	100 mg.
3rd day	150 mg.
4th day	200 mg.
5th day	250 mg.
6th and subsequent days	300 mg.

Three hundred mg. daily was then administered until improvement began or—as happened frequently—side-effects dictated a reduction in dose. In three of the earlier cases a change to injection treatment was made when, after four weeks, there had been no improvement. This change was not made in later cases, as injections appeared to offer no advantage over oral administration of the drug. Imipramine was given for at least six weeks before the trial was abandoned as a failure, except in two cases. (One of these, the only one in the series with a paranoid state and depression, became so agitated and distressed that imipramine was discontinued after 17 days. The other, a man with an endogenous depression, complained bitterly of a tremulous sensation in the abdomen and became so agitated that the drug was stopped after 21 days.) No other anti-depressant treatment (E.C.T. or mono-amine oxidase inhibitors) was given to any of the patients during the trial.

In each case the mental state was assessed by frequent clinical interviews and no improvement was recorded unless there was an unequivocal amelioration of the depressive symptoms. All patients were finally assessed at the beginning of March, 1960 (9–13 months after the start of treatment), except those previously excluded from the trial because of failure to respond. In general, patients recovering were kept on a maintenance dose of imipramine of 50–100 mg. per day.

Results

Seven patients (21 per cent.) made a complete recovery, one after a period of hypomania. At the time of assessment all these had been discharged from

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hospital. In a further 8 patients (24 per cent.) there was a definite improvement. Two of these had been discharged home at the time of assessment. Eighteen patients (55 per cent.) showed no sustained response although in 3 of them there was transient improvement (lasting respectively 11, 6 and 2 months before relapse occurred). Four of these 18 developed transient hypomanic states during treatment.

One of these latter four, a woman who had been given several courses of E.C.T. without sustained improvement before the start of the trial, became elated after three weeks on imipramine. Seven weeks later she was symptom free and was discharged home on a maintenance dose. She remained well for nine months but then became depressed again. Increasing the dose of imipramine to 300 mg. daily was of no avail and she required re-admission to hospital. Another patient became hypomanic after eight weeks on imipramine. Although the drug was discontinued immediately, the hypomania took five months to subside. The patient was well for one month after this but she then became depressed again and this time did not respond to imipramine. A third patient became hypomanic in the ninth week of treatment; she rapidly entered a state of manic stupor which was only terminated by E.C.T. (After a few weeks of normal affect she once more became depressed but it was not considered advisable to start imipramine again.) The fourth patient responded well to imipramine at first, but became mildly elated after six months on the drug. During the next month the hypomania increased in severity and chlorpromazine was substituted for imipramine. This was followed (2½ months later) by a return of depression; imipramine was recommenced and two weeks later, at the end of the trial, the patient was once more improving.

At the time of final assessment 19 patients had been changed to other treatments because of unsatisfactory response to imipramine.

Side-Effects

The incidence of side-effects complained of spontaneously was:

Tremor	24
"Dizziness" and "giddiness"	10
Dry mouth	7
Flushing of skin	4
Increased agitation	4
Hyperhidrosis	3
Blurring of vision	2
Deafness (transient)	2
Dysarthria	1

There were no significant variations in blood pressure.

The most troublesome side-effect, apart from hypomania, was a fine tremor affecting most commonly the upper limbs and in some cases the lower limbs and trunk; it was present equally at rest and during voluntary movement and was not accompanied by any extra-pyramidal signs. It occurred in 73 per cent. of cases, and often necessitated reduction in dosage. In one case it was very severe indeed, affecting the whole body and persisting while the patient was asleep at night; orphenadrine 300 mg. daily did not lessen the tremor which only disappeared when imipramine was withdrawn.

Two patients (aged 57 and 78) fell and sustained fractured femurs while on imipramine. Two others developed ulceration of the mouth but white cell

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counts were normal. This latter complication was probably secondary to dryness of the mouth and disappeared with simple local treatment despite continuation of imipramine therapy.

Discussion

Our "complete recovery" rate of 21 per cent. is similar to the 28 per cent. reported by Leyberg and Denmark, and we feel it is encouraging in view of the long-standing and previously intractable nature of the cases treated. Response was best in the endogenous depressions, all the complete recoveries occurring in this group.

The development of hypomania during the administration of imipramine has been mentioned by Kielholz and Battegay (1958), Delay and Deniker (1959), Berthiaume (1959), Leyberg and Denmark (1959) and others. It is, perhaps, of interest to note that only two of our five patients had previously shown any evidence of hypomania, and in each of these it had been limited to a brief spell following E.C.T. The other three had been continuously depressed for three, five and ten years respectively without ever showing signs of hypomania. Two of these patients showed a mixed affective picture as depression gave way to hypomania.

For the most part side-effects were troublesome rather than serious. Foster and Lancaster (1959), however, have drawn attention to the incidence of disturbance of motor function during imipramine therapy. They report nine patients, three of whom fell and sustained fractures. It seems likely, therefore, that imipramine treatment may have been a contributory factor in the fractures occurring in two of our patients. One of these, however, (a 78-year old woman) was on a maintenance dose of only 25 mg. b.d. when she sustained her injury. Falls, and consequent fractures, are a definite hazard of imipramine therapy and a cautious dosage schedule is probably advisable, especially in the elderly. We now feel that the maximum dose used in this trial (300 mg. daily) is higher than is usually necessary. Two hundred–225 mg. daily is probably adequate in most cases, and in old people it may well be wiser not to exceed 150 mg. daily.

It has been our policy to keep patients responding to imipramine on a small maintenance dose, but in one patient the drug has been discontinued without ill-effect. On the other hand, two patients relapsed while on maintenance therapy. In two other cases there was a transient return of symptoms which disappeared when the maintenance dose was increased. It seems that a period of several months at least should be covered by maintenance treatment in such long-term cases as those reported here.

Summary

1. Thirty-three long-standing, previously intractable cases of depression were treated with imipramine.

2. Seven patients (21 per cent.) made a complete recovery, and a further 8 (24 per cent.) showed a definite improvement.

3. Five patients developed hypomania during treatment.

4 Disturbance of motor function was common, and two patients sustained fractured femurs. Reduced dosage and careful supervision are required when imipramine is administered to elderly patients.

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