Imipramine and "Drinamyl" in Depressive Illness: A Comparative Trial

E. H. HARE,* M.D., D.P.M.; C. McCANCE,† M.B., M.R.C.P., D.P.M.
W. O. McCORMICK,‡ M.B., M.R.C.P., D.P.M.

Brit. med. J., 1964, 1, 818-820

It is surprising that, so far as we can ascertain, no trial has been reported in which the efficacy of a modern "antidepressive" drug has been compared with that of a combination of drugs (dexamphetamine and amylobarbitone) widely used in the treatment of depressive illness before the newer drugs were introduced five or six years ago. Proprietary mixtures of dexamphetamine and amylobarbitone are still advertised as of value in depression, and the lack of any comparative trial is perhaps more surprising when it is remembered that the basic cost to the National Health Service of a week's treatment with the ingredients of such mixtures (dexamphetamine sulphate 5 mg. and amylobarbitone sodium 50 mg. t.i.d.) is 5d., while that of the currently most popular antidepressant (imipramine hydrochloride ("tofranil") 50 mg. t.i.d.) is about 11s. 6d.

In this paper we report a controlled comparative trial of imipramine and a proprietary mixture of dexamphetamine and amylobarbitone ("drinamyl"), in the treatment of depressive illness.

Method

Selection of Patients.—The trial was restricted to patients who (1) were in-patients or day-patients, (2) were diagnosed as suffering from a primary depressive illness, without evidence of schizophrenia or organic psychosis, (3) had not received electric convulsion therapy during the previous three months, and (4) had not had antidepressive drug treatment during the previous two weeks.

Drugs.—The drugs given were imipramine 25 mg. t.i.d. for three days, then 50 mg. t.i.d.; and drinamyl (each tablet containing amylobarbitone sodium 50 mg. and dexamphetamine sulphate 5 mg.), 1 tablet t.i.d. It proved impracticable to have identical-looking tablets of imipramine and drinamyl. Accordingly, each patient received both orange and purple pills throughout the trial; these were either imipramine with placebo–drinamyl, or the reverse. Patients received each drug for a period of three weeks, the two periods being consecutive. The drug order was randomized; and until each subject completed his trial his drug order was known only to the pharmacist.

Subjects.—Of the 106 patients who entered the trial, eight had to be withdrawn during the first three-weeks period and 20 during the second three-weeks period. Of these 28 failures 15 were receiving imipramine and 13 drinamyl at the time of withdrawal. The causes of withdrawal were: other treatment considered necessary due to change in the nature or severity of the illness (13 cases); left against advice (9); complications, possibly due to the drugs (4); and technical failure (2). Of the 78 subjects who completed the trial 32 were male and 46 female. The median age was 45 years (18 were under 35, 16 were 35–44, 25 were 45–54, and 19 were 55 or over). There was a family history of depressive illness in 19, a history of previous depressive illness in 42, and a history of previous in-patient treatment in 37. The duration of present illness was three months or less in 48. Causative exogenous factors were rated as strong in 13, moderate in 21, mild in 13, and absent in 31. The number of subjects receiving imipramine during the first period was the same as that receiving drinamyl (39 each). Thirty-one subjects were in-patients at Bethlem Hospital, 26 were day-patients at the Bethlem Day Hospital, and 21 were in-patients at the Royal Mental Hospital, Aberdeen.

* Physician, Bethlem Royal and the Maudsley Hospitals, London.
† Consultant Psychiatrist, Royal Mental Hospital, Aberdeen.
‡ Senior Registrar, Bethlem Royal and the Maudsley Hospitals, London.

Assessment and Analysis

The clinical state of subjects was assessed at entry to the trial and at the end of each three-weeks period. Aspects of the clinical state were rated on a five-point scale (absent, mild, moderate, marked, severe). These aspects were: depression, agitation, anxiety, retardation, hypochondria, paranoid attitude, insomnia, and overall clinical state. The observations on which the assessments of depression, agitation, and anxiety were based have been described (Hare *et al.*, 1962). Hypochondria was assessed in terms of a morbid belief in the presence of physical disease or undue preoccupation with physical symptoms and the possibility of disease. Insomnia was rated solely on the subject's statement, no account being taken of whether or not he was receiving hypnotics. In addition, the subject's weight was recorded at the time of the assessment.

Each assessment was based on a clinical interview conducted mainly by the first assessor, at which the second assessor and others present were free to ask the patient questions. Each assessor recorded his ratings before there was any discussion of the case. Assessors have been classed as "first" and "second." The first assessors were those with longest experience in clinical psychiatry; the second assessors were, so far as was possible, the registrars concerned with the day-to-day management of the case. For 69 of the 78 subjects completing the six-weeks trial, the first assessor was the consultant in charge of the case (E. H. H. or C. McC.). A second observer was present for 70 subjects, and in 62 of these he was the registrar concerned with the case. Altogether there were 18 second assessors.

The assessments provided data for a self-controlled series which was analysed by the sequential method (Armitage, 1960). A subject's ratings at the end of the first period were compared with those of the second period and the results expressed in terms of the severity of a clinical manifestation in one period being "better than," "equal to," or "worse than" that in the other period. Also, where there was a change in weight of more than 2 lb. (0.9 kg.), the period with the greater weight was considered "better than" the other period as regards weight increase. These comparisons were then assumed to represent the comparative clinical effect of the drugs given during the periods.

Results

Figs. 1 and 2 show the results for the first assessors. The sequential charts (Armitage, 1960) are constructed so that the

outer boundaries correspond to the 5% level of significance: if the two treatments being compared are equally good the outer boundaries would be reached by chance only in 5% of trials; and if one treatment is better than the other to the extent that 80% of comparisons are in its favour then the corresponding boundary has a 95% chance of being reached. Only positive comparisons between the two drugs—"better than" or "worse than"—are scored on these charts.

Figs. 1 and 2 indicate that in the relief of agitation and for gain in weight, imipramine was significantly better than

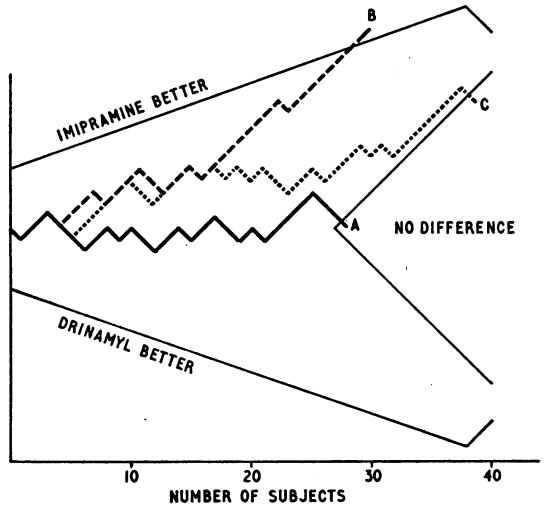

FIG. 1.—Comparative effect of imipramine and drinamyl in aspects of depressive illness. First assessors. A=Depression. B=Agitation. C=Anxiety.

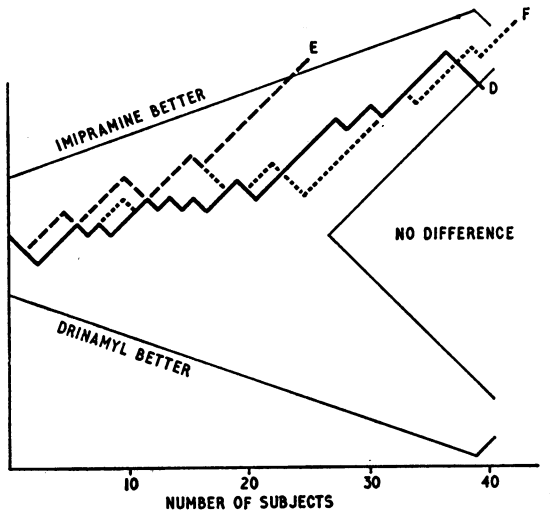

FIG. 2.—Comparative effect of imipramine and drinamyl in aspects of depressive illness. First assessors. D=Insomnia. E=Weight change. F=Overall clinical state.

drinamyl. The comparative effect of the drugs on the overall clinical state is indeterminate from Fig. 2. There is no significant difference, nor any trend towards difference, in the effect of the two drugs on the clinical manifestation of depression. No definite results were obtained for the comparative effect of the drugs on retardation, hypochondria, or paranoid attitude, as there were too few positive comparisons; but there was no trend in any of these manifestations for one drug to be the better.

In the Table the results for the two groups of assessors are compared. For the first assessors, imipramine was significantly better than drinamyl (on a chi-square test) in its effect on agitation and overall clinical state. But for the second assessors there were no significant differences between the drugs for any manifestation. Both groups of assessors were in agreement on their being no difference between the drugs in their effect on the clinical manifestation of depression.

Results for the First and Second Group of Assessors. Cases in Which a Manifestation was Rated as Absent Throughout the Trial Have Been Excluded from the Figures for that Manifestation

Clinical Manifestation	1st Assessors			2nd Assessors		
	Better on		No Difference	Better on		No Difference
	Tofranil	Drinamyl		Tofranil	Drinamyl	
Depression	27	22	29	18	16	36
Agitation	25*	9*	29	13	14	30
Anxiety	25	15	34	13	17	35
Retardation	10	8	31	10	5	17
Hypochondria ..	10	10	16	11	7	13
Paranoid attitude ..	4	6	13	3	5	5
Insomnia	25	14	33	14	10	39
Overall state	30†	16†	26	12	12	37

* Difference significant at the 1% level.
† Difference significant at the 5% level.

Side-effects of the Drugs

Subjective Effects.—The assessors deliberately refrained from asking patients about side-effects, either in specific or in general terms, but a record was made of spontaneous complaints which might reasonably have been regarded as side-effects. Among the 94 patients who entered the trial and received imipramine for some period, complaints on this drug (and the number of patients making them) were: sweating (3), dry mouth (2), unsteadiness (2), blurred vision (1), excessive energy (1), tiredness (1). Among 91 patients on drinamyl the complaints were: blurred vision (1), tiredness (1), anorexia (1), constipation (1).

Objective Effects.—These were probably or possibly due to the drugs. While on imipramine, one patient developed a typical drug rash; one had an epileptic fit (not being a sufferer from epilepsy); and one patient (aged 72) died from coronary thrombosis. While on drinamyl one patient developed an exacerbation of a paranoid state which remitted soon after the drug was withdrawn.

Discussion

One clear-cut conclusion emerges from this trial: under the conditions of the trial and for the dosages given, the effect of imipramine on the clinical manifestation of depression in depressive illness is no different from that of drinamyl. Drinamyl is a mixture of dexamphetamine and amylobarbitone. We can find only two reports of controlled trials (Doust *et al.*, 1959; Hare *et al.*, 1962) in which dexamphetamine has been compared with a placebo in the treatment of depressive illness, and in both of these dexamphetamine was found no better than the placebo; these results are supported by the controlled study of Legge and Steinberg (1962). Thus our conclusion from the present trial is that imipramine has no specific antidepressive action.

It is less clear-cut from this trial whether imipramine has any general advantage over drinamyl in the treatment of depressive illness.

On the whole, however, we incline to give greater weight to the first assessors' comparisons, and so to conclude that imipramine was probably superior to drinamyl in relieving agitation and in increasing weight. It cannot be decided whether these effects were due to imipramine causing an improvement or to drinamyl causing a worsening, but it seems more reasonable to adopt the former view, at least with regard to agitation.

In a previous paper (Hare *et al.*, 1962) it was found that phenelzine in depressive illness was superior to a placebo only in its effects on agitation and anxiety. The results of that trial and of the present one may therefore be taken to support the view that, in so far as antidepressive drugs are effective in the treatment of depressive illness, this is in virtue of a sedative action. Other evidence may be cited in support of this.

Rees *et al.* (1961), comparing imipramine with a placebo, found that the beneficial effect of imipramine was greater on the symptom of anxiety than on that of depression. Roulet *et al.* (1962), while finding no significant difference in the clinical effects of imipramine and a placebo, noted that patients showed less anxiety on psychological testing when receiving the imipramine. The clinical experience of Sargant and Dally (1962), which led them to conclude that antidepressive drugs were effective in some states of anxiety as well as in depressive illness, is also understandable in terms of a purely sedative action of the drugs. It may be noted, too, that drowsiness is an accepted side-effect of at least three antidepressive drugs (phenelzine, tranylcypromine, and amitriptyline).

In the present trial we administered the drugs for periods of three weeks each. We did this in deference to a widely held view that the antidepressive effects of imipramine (and of most other antidepressive drugs but not, curiously enough, of dexamphetamine) do not become apparent until the second or third week of treatment. If (as our results suggest) imipramine has no specifically antidepressive action, then, of course, the problem of delayed action does not arise. But, in any case, it would be a matter of great difficulty to establish that the antidepressant effects of a drug do not become apparent for several weeks. It would be necessary to show by a controlled trial, firstly, that there was no difference between the effects of a drug and of a placebo during the first week or two, and, secondly, that thereafter the effect of the drug became significantly better. This has never been done, and the evidence for the delayed-action hypothesis has been derived entirely (so far as we can determine) from uncontrolled observations. Yet the high rate of natural remission in depressive illness must make such uncontrolled observations a hazardous means of arriving at the truth.

The question whether modern antidepressive drugs are of value is still undecided. We have been able to find, in British and American journals, reports of 10 controlled trials in which imipramine was compared with a placebo in the treatment of depressive illness: in four of these (Ball and Kiloh, 1959 ; Rees *et al.*, 1961 ; Friedman *et al.*, 1961 ; Abraham *et al.*, 1963) imipramine was found to be significantly better than a placebo ; in five (Doust *et al.*, 1959 ; Höhn *et al.*, 1961 ; Ashby and Collins, 1961 ; Overall, 1961 ; Roulet *et al.*, 1962) imipramine was found to be no better than a placebo ; and in one (Wittenborn *et al.*, 1962) the results were inconclusive. The results of the present trial suggest that imipramine is of some value in depressive illness but only in virtue of effects which must be regarded as sedative in nature. On this ground there is a case for testing antidepressive drugs against appropriate doses of purely sedative drugs. As the cost to the National Health Service of modern antidepressive drugs is now probably between two and three million pounds a year, and as their advantages over other much cheaper drugs can still very reasonably be doubted, the general case for further controlled trials is a strong one.

Summary

This paper reports a controlled comparative trial of imipramine hydrochloride ("tofranil"), 50 mg. t.i.d., and "drinamyl" (dexamphetamine sulphate 5 mg. plus amylobarbitone sodium 50 mg.), 1 tablet t.i.d., in depressive illness. Each drug was given for three weeks to in-patients and day-patients at two hospitals. A self-controlled trial was completed by 78 subjects. Clinical assessments were made separately by two groups of psychiatrists.

No difference was found between imipramine and drinamyl in their effect on the clinical manifestation of depression.

Imipramine was significantly better than drinamyl in causing increase in weight. One group of observers found imipramine significantly better than drinamyl in reducing agitation and (on one test but not on another) in improving the overall clinical state. The other group found no significant difference between the drugs for any manifestation.

These findings suggest the view that imipramine, although it may have some general value in depressive illness, has no specific effect on the clinical manifestation of depression. Evidence is presented to support the extension of this view to other "antidepressive" drugs.

We thank Mrs. K. Vejs, pharmacist at the Bethlem Royal Hospital, and Miss N. Peters, pharmacist at the Royal Mental Hospital, Aberdeen, for allocating and dispensing the drugs. We also thank Geigy Pharmaceutical Company Limited for the supply of "tofranil" and placebo tablets ; and Smith Kline and French Laboratories Limited for the supply of "drinamyl" and placebo tablets.

References

Abraham, H. C., Kanter, V. B., Rosen, I., and Standen, J. L. (1963). *Brit. J. Psychiat.*, **109**, 286.
Armitage, P. (1960). *Sequential Medical Trials*, Table 3, p. 7. Blackwell, Oxford.
Ashby, W. R., and Collins, G. H. (1961). *J. ment. Sci.*, **107**, 547.
Ball, J. R. B., and Kiloh, L. G. (1959). *Brit. med. J.*, **2**, 1052.
Doust, J. W. L., Lewis, D. J., Miller, A., Sprott, D., and Wright, R. L. D. (1959). *Canad. psychiat. Ass. J.*, **4**, Suppl. No. S190.
Friedman, C., DeMowbray, M. S., and Hamilton, V. (1961). *J. ment. Sci.*, **107**, 948.
Hare, E. H., Dominian, J., and Sharpe, L. (1962). *Brit. med. J.*, **1**, 9.
Höhn, R., Gross, G. M., Gross, M., and Lasagna, L. (1961). *J. psychiat. Res.*, **1**, 76.
Legge, D., and Steinberg, H. (1962). *Brit. J. Pharmacol.*, **18**, 490.
Overall, J. E. (1961). In *Transactions of the Sixth Research Conference on Cooperative Chemotherapy*, Studies in Psychiatry, p. 12. Washington.
Rees, L., Brown, A. C., and Benaim, S. (1961). *J. ment. Sci.*, **107**, 552.
Roulet, N., Alvarez, R. R., Duffy, J. P., Lenkoski, L. D., and Bidder, T. G. (1962). *Amer. J. Psychiat.*, **119**, 427.
Sargant, W., and Dally, P. (1962). *Brit. med. J.*, **1**, 6.
Wittenborn, J. R., Plante, M., Burgess, F., and Maurer, H. (1962). *J. nerv. ment. Dis.*, **135**, 131.