Drug therapy in depressions

Controlled evaluation of imipramine, isocarboxazide, dextroamphetamine-amobarbital, and placebo

An evaluation of imipramine, isocarboxazide, dextroamphetamine-amobarbital, and placebo was carried out in 204 patients with depressive syndromes in thirty-two Veterans Administration Hospitals. Treatment with a fixed dosage schedule was followed for 3 weeks, the dosage becoming flexible during an ensuing 9 week period. Evaluation of responses was made by three rating scales specially derived for depressed patients.

After 3 weeks of treatment, imipramine was significantly more effective than the other three treatments as measured only by a thirty-one item expert clinician's scale derived from the Inpatient Multidimensional Psychiatric Scale. Favorable responses to imipramine were often prompt, leading to loss of such patients from the study before the full 12 week treatment period had been completed. After 12 weeks of treatment, the patients who remained in all four treatment groups were significantly improved when each group was compared with its pretreatment level, but there were no statistically reliable differences between treatments at the end of the study. These results emphasize the need for controlled studies in depressive syndromes subject to spontaneous improvement.

Veterans Administration

Introduction of two new classes of antidepressant drugs has evoked much interest in drug therapy of psychiatric states associated with depression. Both the hydrazine derivatives, of which iproniazid is the prototype, and the dibenzazepine derivatives, exemplified by imipramine, have been reported to be effective despite differing modes of action. The hydrazines, as well as some other compounds, are alleged to act by inhibiting monoamine oxidase, leading to increased levels of serotonin and norepinephrine in the central nervous system. Imipramine's mode of action is still unclear.
but it may possibly sensitize neurons to the action of norepinephrine.\textsuperscript{14}

The large amount of clinical literature about drug treatment of depression was recently critically reviewed.\textsuperscript{3} Despite an abundance of uncontrolled studies, almost all favorable, relatively few controlled studies of drug therapy in depression have been done. Controlled comparisons of imipramine with placebo indicate superiority of the former treatment despite deficiencies in some studies such as small sample sizes, lack of objective ratings, or exclusion of difficult cases.\textsuperscript{2, 3, 5, 10} One of the better studies showed improvement in 24 of 35 patients treated with imipramine and only 6 of 24 treated with placebo, a difference significant at the 0.01 level.\textsuperscript{3} Only two studies have also included a hydrazine derivative (isocarboxazide in both), and they have yielded somewhat conflicting results. A study of chronically depressed patients utilized both drugs, as well as dextroamphetamine and a placebo, although periods of treatment varied and order was not controlled.\textsuperscript{12} During treatment with imipramine, 7 of 24 patients obtained satisfactory improvement, while only 1 each was improved during treatment with isocarboxazide, dextroamphetamine, and placebo. Another study of 77 Veterans Administration patients revealed significant improvement from the base line in imipramine and isocarboxazide groups, with improvement in placebo group failing to reach statistical significance; however, there were no significant differences between imipramine, isocarboxazide, and placebo.\textsuperscript{13}

The present study was undertaken to evaluate representative members (isocarboxazide and imipramine) of the two classes of drugs, as well as two comparison treatments (dextroamphetamine-amobarbital combination and placebo). A controlled study was deemed essential in view of the well-known proclivity of some depressions to remit spontaneously. Besides evaluating the relative therapeutic effectiveness of the drugs, the study attempted to assess the influence of other factors in treatment, such as staff attitudes, intrinsic patient characteristics, and situational factors, as well as the long-term course of depressive syndromes. The latter findings will be reported elsewhere.

**Procedure**

Patients of either sex were selected for the study if their main psychiatric diagnosis was (1) neurotic depressive reaction, (2) psychotic depressive reaction, (3) manic-depressive reaction, depressed type, (4) involutinal psychotic reaction, depressive type, or (5) schizophrenic reaction, schizo-affective type, depressed. A history of lobotomy, central nervous system disease or seizures, liver or kidney disease, or systemic disease possibly aggravated by treatment was cause for exclusion.

Two hundred and four patients met these criteria and were started on treatment; however, 83 (41 per cent) did not complete the full 12 weeks of treatment. Of the 204 patients, 115 were classified as having neurotic depressive reactions, and the remaining 89 had various types of psychotic depressions (10 manic-depressive reactions, depressed; 22 psychotic depressive reactions; 23 involutional reactions; 34 depressed schizo-affective reactions). Although the design called for the inclusion of both sexes, only 10 women were included.

The four treatments were supplied in randomized blocks to each participating hospital, patients being assigned in order of admission. Medications appeared identical, being identified only by a code number. Double blind controls were used throughout. Unit strengths of the capsules were: (1) dextroamphetamine, 5 mg.—amobarbital, 32 mg.; (2) isocarboxazide, 5 mg.; (3) imipramine, 37.5 mg.; and (4) placebo, enough mannitol to fill the capsule. A fixed dosage schedule was used at first: two capsules daily during days 1 to 3, four capsules daily during days 4 to 6, and six capsules daily during days 7 to 21. Following this initial 21 day period, dosage was flexible, depending upon the clinical re-
Table I. *Psychiatric judgment depression scale*

**Nine point items**

1. To what degree is his rate of speech slowed, deliberate, or labored?
2. To what extent is he concerned and/or preoccupied with his physical health or the functions of his body organs?
3. To what degree is his rate of speech hurried, accelerated, or pushed? (Scored as negative sign.)
4. Judged by his verbal report, to what extent does he exhibit an elevation in mood, a sense of well-being or euphoria, or an optimistic and hopeful attitude towards himself and others? (Scored as negative sign.)
5. To what extent does he tend to blame, criticize, condemn, or otherwise hold himself responsible for past or present, real or fancied, thoughts or actions?
6. To what extent does he exhibit in demeanor and/or in verbalizations an attitude of self-importance, superiority, or conceit? (Scored as negative sign.)
7. To what extent are his body movements slowed, deliberate, labored, or delayed?
8. How excessively loud, boisterous, and/or intense is his voice? (Scored as negative sign.)
9. Judged only by what he reports or admits, to what extent is he anxious, uneasy, apprehensive, or fearful with regard to such matters as himself, his family, his finances, or his hospitalization?
10. Judged only by what he admits or reports, to what extent is he anxious or apprehensive in anticipation of vague unknown events which may or may not take place in the future?
11. To what extent does he exhibit in his general demeanor or in his verbalizations an attitude of self-depreciation, inadequacy, or inferiority?
12. Judged only by his verbal report, to what extent is he downcast, depressed, or dejected in feeling or in mood, pessimistic or despairing in attitude?
13. To what extent is he disturbed by, preoccupied with, or suffering from feelings of guilt, shame, or remorse?
14. To what extent is his voice low, weak, whispered, or difficult to hear?
15. To what extent is he overtalkative? (Scored as negative sign.)
16. To what degree is he dominant, controlling, or directive in relation to the interviewer or the conduct of the interview? (Scored as negative sign.)

**Dichotomous items**

17. Does he report having suicidal thoughts or impulses?
18. Does he believe he is unworthy, sinful, evil, or guilty of unpardonable sins and crimes?
19. Does he believe his body is diseased, distorted, undergoing changes, or that his internal organs are rotted or missing?
20. Is he preoccupied with or does he ruminate about death, self-destruction or mutilation, personal disaster?
21. Is he preoccupied with or does he ruminate about the hopelessness of the future?
22. Is he preoccupied with or does he ruminate about his own helplessness to do anything about his condition?
23. Is he preoccupied with or does he ruminate about his personal failures?
24. Is he concerned because his intellectual functioning is not as good as formerly?
25. Is he concerned because he can't work at anything, can't get started, loses interest, can't keep at it?
26. Is he concerned because he can't make decisions?
27. Does he report loss of appetite?
28. Does he report loss of sleep?
29. Does he report loss of weight?
30. Does he report loss of sexual potency?
31. Does he complain about general fatigue?

Sponge of the patient, between the limits of 1 and 8 capsules daily. Treatment was individualized by the prescribing physician. Treatment with other stimulants, tranquilizers, electroconvulsive or insulin coma therapy, or psychotherapy was prohibited. Conventional sedatives were permitted for management of brief periods of excitement. Ordinary hospital milieu therapy such as activity or recreation groups and occasional supportive interviews by psychiatrists, psychologists, or social workers was permitted. These factors were common to all hospitals and all drug treatments, and were considered a constant throughout the study. Privilege status, passes, and short leaves were also permitted if feasible and desirable. Patients who showed enough im-
Improvement to warrant trial visit or discharge were not impeded by virtue of their being in the study.

Any patients who failed to complete treatment, regardless of the cause, were given a final evaluation. Patients could be dropped from the study for such diverse reasons as remission permitting discharge, complete failure to respond to treatment, or complications from therapy.

Laboratory and clinical controls included a complete blood count, urinalysis, screening hepatic tests (serum glutamic-oxalacetic transaminase or alkaline phosphatase determination), and measurement of standing blood pressure, obtained on all patients prior to treatment. During treatment, screening hepatic tests and total and differential leukocyte counts were obtained weekly during the first 4 weeks and biweekly thereafter. Abnormalities in leukocyte counts were checked by frequent repeated counts until the issue was settled. Abnormal results of screening hepatic tests were checked by additional tests such as serum bilirubin, sulfobromophthalein retention, thymol turbidity, and other tests. A list of adverse effects was checked by the prescribing physician, who was also encouraged to report other incidents in the clinical course.

Three different measures were used for evaluating patient response. The Inpatient Multidimensional Psychiatric Scale (IMPS), as augmented by the addition of fifteen specially constructed depression items, was completed by two independent raters from information obtained during psychiatric interviews before, after 3 weeks, and after 12 weeks of treatment. The Psychotic Reaction Profile (PRP) was completed for each patient on the basis of observations by nursing personnel at the same intervals. One hundred sixty-six items from the Minnesota Multiphasic Personality Inventory (MMPI) were answered by each patient before and after completion of treatment.

To refine the sensitivity of these measures for evaluating changes in the symptom of depression, twenty experienced psychiatrists and psychologists were asked to choose from each instrument those items which they judged to be most highly related to depression as seen clinically. On the basis of highest agreement among this group of expert judges, a thirty-one item depression scale was derived from the IMPS, a twenty-six item depression scale from the PRP, and a thirty-eight item depression scale from the MMPI. These three specially derived scales were then used for the evaluation of patient response in this study.

As will become evident in discussion of the results, the depression scale which was specially derived on the basis of expert judgment from the augmented IMPS proved to be the most sensitive measure of treatment change. Twelve to nineteen of the twenty judges agreed upon the relevance of each of the thirty-one items included in this scale. It consisted of sixteen nine point ordered category rating scales and fifteen dichotomous items. To correct for disparity in variances, the nine point items were weighted 1 and the dichotomous items were weighted 3 in computing a composite depression index. The thirty-one items of this depression scale are presented in Table I.

Simple change scores were computed by subtracting the 3 and 12 week scores from the pretreatment scores. The total available patient sample was divided into neurotic and psychotic subgroups, and a two way analysis of variance was used to evaluate the relative effectiveness of the four treatments in ameliorating depressive symptoms in the two subgroups of depressed patients. Analyses were accomplished at 3 and 12 weeks for the sample composed of patients who completed the full treatment period, and separate analyses were accomplished for the sample consisting of all patients who completed 3 weeks of treatment. The former analyses permit comparison of effect of the several drugs at two time periods, while the latter involve the maximum number of cases available for comparison of effects over a brief treatment period.
Fig. 1. Improvement after 3 weeks of treatment as measured by a psychiatric judgment depression scale derived from the Inpatient Multidimensional Psychiatric Scale.

Results

Patient responses after 3 weeks of treatment. One hundred eighty-one patients, 100 with neurotic depressive reactions and 81 with psychotic depressions, completed 3 weeks of treatment. The IMPS (psychiatric interview) data, subjected to analysis of variance adjusted for unequal and disproportionate cell frequencies, indicated an over-all significant difference (P < 0.01) between the four treatments. Fig. 1 presents the mean change scores for the eight subgroups (four treatments, two diagnostic categories). After 3 weeks of treatment, imipramine was significantly superior (P < 0.01) to each of the other three treatments, which did not differ significantly from each other.

Average improvement in neurotic depressions was significantly greater (P < 0.01) than the average improvement in psychotic patients, a finding consistent with clinical expectation. It can be observed in Fig. 1 that the profiles of effectiveness of the four treatments were similar in the neurotic and psychotic patients, that is, the drug which was superior in neurotic patients was also superior to roughly the same degree in psychotic patients. The nonsignificant interaction indicates that there is no evidence in this study to suggest that the relative effectiveness of the drug is different in neurotic and psychotic patients.

After 3 weeks of treatment, significant improvement from the base line resulted from all four treatments. Considering the neurotic and psychotic subclasses, seven of the eight treatment subgroups evidenced significant improvement (P < 0.01) as compared with their own pretreatment levels. Psychotic depressions treated with isocarboxazide did not improve significantly.

Turning to the other measures obtained on each study patient, no significant differences between the four treatments were disclosed by analysis of PRP (ward observation) data after 3 weeks of treatment. Six of the eight treatment groups improved significantly during this period as compared with their own pretreatment levels. This fact should not be taken as indicative of a significant difference between the six groups which evidenced significant improvement and the two which did not, since differences between treatments were not found to be statistically significant.

Patient responses after 12 weeks of treatment. Complete data were available for 113 patients who completed the full 12 weeks of treatment. Analysis of the IMPS data revealed a substantial and statistically significant improvement in all treatment groups; however, no significant differences among the four treatments were found at the end of 12 weeks. The same was true when data on these patients at the end of 3 weeks of treatment were analyzed, in contrast to results from the entire sample of 181 patients completing 3 weeks of treatment. This difference may be accounted for by the fact that some patients responded early to treatment, this response being evident on the 3 week rating but not at 12 weeks, because by then they had left the study. More early responders received imipramine, which accounts for the superiority of this drug as compared with the others at the end of 3 weeks of treatment but not after 12.

After 12 weeks of treatment, no significant differences between the treatment of groups were found in the analysis of PRP and MMPI data.
Abnormal symptoms, signs, or results of laboratory studies. These will be reported in detail elsewhere. Of greatest importance was the fact that few reactions or complications of consequence were noted. Only 11 patients were dropped from the study for these reasons, while 33 were dropped for failing to improve or because they became worse. New symptoms or signs, widely scattered in type, were noted in 106 patients during the study; imipramine produced slightly more than the others, placebo somewhat fewer. Patients receiving imipramine gained more weight when compared with those receiving dextroamphetamine-amobarbital or placebo; weight gain after isocarboxazide was not significant. Eosinophilia was observed on two occasions or more in 12 patients, leukocytosis in 10, and abnormal results of hepatic enzymes in frequency attributable to the four tests in 23; there were no apparent differentiations.

Discussion

Our results confirmed the widely held clinical impression that imipramine is an effective drug therapy for depressed patients, a belief substantiated to some extent by earlier controlled studies. Iso- carboxazide did not appear to be an effective drug; whether one can generalize from these findings to the entire group of hydrazine or nonhydrazine monoamine oxidase inhibitors is questionable. At the moment, imipramine is clearly the drug of choice for treating depressed patients, though related drugs might possess equal or greater efficacy.

The significant difference between imipramine and the other treatments after only 3 weeks of treatment suggests that this period is adequate for a trial of drug therapy in depression. Patients not responding to treatment by that time should be considered for other treatment, such as electroconvulsive therapy, if the depression is severe or disabling. The latter treatment has more dangers, is more difficult to administer, and is more fearsome, so that this minimum trial of drug therapy is justifiable in almost every patient.

If any situation in clinical psychopharmacology demands a controlled trial, it is the evaluation of drug therapy in depressed patients. Had no placebo control been used in this study, each of the three treatments would have appeared effective in producing significant improvement as compared with before treatment measures. Whenever any clinical symptom shows a strong tendency toward spontaneous remission, as is the case in the symptom of depression, a placebo control is essential.

Failure to elicit positive effects in all but one of the analyses was discouraging but does not vitiate, in our opinion, the positive effect demonstrated. It should be remembered that experience with objective rating scales for evaluating depressed states is quite limited as compared with similar scales for evaluating schizophrenic reactions. The scale derived from the IMPS proved sensitive enough to detect a difference between treatments. Its predecessor, the Multidimensional Scale for Rating Psychiatric Patients (MSRPP, Lorr), has been most widely used for rating changes in psychiatric patients and has proved sensitive in previous studies for rating changes in schizophrenic patients treated with drugs. The IMPS depression scale was based upon expert psychiatric opinion, and since its data comes from a psychiatric interview (as compared with nurses’ ratings or self-reports), it might be expected to be most sensitive and reliable. While one might hope eventually for better instruments for evaluating results of treatment of depression, this derivation of the IMPS would currently appear to be adequate.

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References