

NOTES and COMMENT

The Efficacy of LSD in the Treatment of Alcoholism<sup>1</sup>

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Comment has often been made (1, 2) on the low scientific standards which prevail in routine clinical trials of new drugs. In fact, the lack of control groups, follow-up and objective measurements of change have characterized psychiatric research into both pharmacological and psychological treatment methods (3, 4). This general lack of sophistication is especially characteristic of recent efforts to examine the effectiveness of LSD-25 (*d*-lysergic acid diethylamide) as an adjunct to the treatment of alcoholism. Several groups of investigators (5, 6, 7) have reported clinical trials in which LSD was found to be effective in the treatment of alcoholism but the reports of these trials are little more than the chronicling of clinical procedure.

Smith (5) reported that 12 out of 24 alcoholics given LSD were "improved" or "much improved" in terms of their drinking histories. Later, Chwelos et al. (6) reported 15 out of 16 alcoholics, and MacLean et al. (7) 46 out of 61 alcoholics, "improved" or "much improved" after LSD. In addition, Chandler and Hartman (8) have reported that a series of LSD sessions created "considerable improvement" in 17 "alcohol and/or narcotic addicts," and Eisner and Cohen (9) found that 2 out of 3 alcoholics given LSD were "improved" in terms of unstated criteria.<sup>3</sup> As a consequence of these reports, it has been concluded that LSD is "effective in the treatment of alcoholism" (7) and it comprises a major part of the therapy in several treatment centers for alcoholics. The aim of this note is to examine closely the studies purporting to show that LSD is a useful adjunct to therapy for alcoholism. It is hoped that this effort may introduce a note of caution in the

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<sup>3</sup> Benedetti (10) in 1951 studied the effect of two doses of LSD on one alcoholic. The text of this paper has not been seen and the abstract gives no clear idea of the methods or controls used.

acceptance of LSD for this purpose. A further hope is that the minimal requirements for any drug research in alcoholism will be clarified.

The basic requirements for clinical research into the efficacy of any new treatment have been frequently outlined (3, 4). They include the following: To determine whether the effects of a drug are attributable to its pharmacological properties it is necessary to use a control group receiving a placebo or relatively inert drug. If one does not wish to compare placebo with pharmacological effects, at least a no-drug control group must be used which gets another form of treatment against which the new drug is to be evaluated. There should be a random assignment of patients to the various treatment groups, including the control or placebo groups. If placebos are used the study must be double-blind, i.e., neither the treatment personnel nor the patient may know which drug he receives. Finally, some objective measures or uncontaminated ratings<sup>4</sup> of subjective treatment outcome are required. These measurements should be made both before and after treatment so that an accurate pre- and post-treatment comparison can be made. The post-treatment measures should be part of a follow-up procedure which is undertaken at relatively fixed intervals after treatment.

If the five studies (5-9) of LSD treatment for alcoholism are examined for their adherence to the above requirements they fare badly indeed. The requirement of some control group getting a placebo, or at least some other form of treatment, has been ignored in all of them. The lack of control groups opens the door to all sorts of interpretations of the positive findings. It makes it impossible to state whether the changes in drinking behavior were due to LSD or to a myriad of other variables, such as the greater staff interest taken in the patients during the study (by way of special interviews, questionnaires, follow-up and the like). The lack of control groups also raises the possibility that the positive findings were attributable to spontaneous recovery.

Unfortunately, the absence of control groups in research on new psychiatric treatments seems to be the rule rather than the exception. To illustrate, Foulds (1) found that 72 per cent of the research studies of new treatments reported in psychiatric journals (1951-1956) lacked controls. Moreover, he found that 83 per cent of the uncontrolled studies but only 25 per cent of the controlled studies reported that the treatments were successful. In addition, Glick and Margolis (2), after reviewing the literature on chlorpromazine, found significantly lower clinical improvement rates in double-blind controlled studies than in nonblind uncontrolled ones. There is some basis, then, for expecting nonblind uncontrolled studies, such as those discussed here, to yield an exceptional number of positive results. The larger proportion of positive results in uncontrolled studies exists despite the lack of the very elements of design which would allow any firm conclusion.

The lack of double-blind or even single-blind procedures also raises

<sup>4</sup> That is, uncontaminated by the raters' knowledge of what treatment the patient received.

the possibility that the reported effects of LSD are attributable in part to the patients' expectations about the drug rather than to its pharmacological action. All the patients in the LSD studies were aware that this drug was being administered, as were the therapists. As in many other drug researches, placebo reactors have been found in studies of the physiological and psychological effects of LSD (11, 12), and many of their symptoms correspond to the real effects of LSD. Whether the mere belief that an LSD experience was obtained is sufficient to account for or add to the positive results cannot be answered. It would be reassuring to have these doubts dispelled by results showing that placebo effects were unimportant.

The possibility that placebo effects might be important is also indicated by the impression that alcoholics with character disorders or psychopathy are most improved by treatment with LSD (5, 6). It has been reported that placebo reactors score high on psychological tests of neuroticism and extroversion (13, 14), and these characteristics are found in persons with psychopathic disturbances and character disorder (15). The similarities between the personality characteristics of placebo reactors and those who respond most favorably to LSD at least suggests that placebo responses might partially account for the response to this drug. All of the above considerations tend to raise doubt concerning the effectiveness of LSD as an adjunct to therapy for alcoholism.

Certain criticisms have been made of double-blind trials but none of them seem convincing.<sup>5</sup> It has been argued by Haas, Fink and Hartfelder (16) that ethical doubts are raised when the physician does not know what drug is being administered to his patient. However, ethical questions are also raised when physicians administer drugs whose effects have not been scientifically validated, or when they persist in applying treatments with unknown or uncertain outcomes. Double-blind trials, used with proper controls, are designed to reduce ignorance about new treatments and are justified on that basis alone. Haas, Fink and Hartfelder also suggested that complicated double-blind trials create the possibility of errors in the analysis of the results, and that such trials are difficult to plan. There seems to be no argument against this objection except to state that the possibility of error and difficulties of design do not outweigh the values of such studies. A more telling criticism is that "blindness" in placebo-controlled studies may be difficult to achieve when testing drugs with strong sensory effects, such as those of LSD. However, double-blind trials of LSD could be done with a placebo having some immediate but mild sensory effects. The sensory and perceptual effects of LSD vary markedly from person to person, so that patients given a placebo might have a drug experience not unlike that reported by some persons who actually receive LSD. It would be possible to keep the trials "blind" by reminding all patients in the study that the effects of the drug are highly variable, even to the point of having almost no reaction.

<sup>5</sup> See, for example, Haas, Fink and Hartfelder (16) for a complete review.

Nonblind uncontrolled trials are also defended as indicative of drugs which might repay more careful investigation and controlled study. In the great race to produce more drugs and more treatments for mental disorders, sufficient time to evaluate them is often not taken.<sup>6</sup> The testing of a drug in uncontrolled trials does not necessarily establish it as a promising therapeutic measure. In fact, it may mean, as with LSD, that clinical use is made of the drug before its real effectiveness is properly assessed.

The only methodological requirement which can be found in some LSD studies is that for follow-up procedures, but even these are highly vulnerable to criticism. The study by Chandler and Hartman (8) gives no indication of any post-treatment follow-up. The one by Eisner and Cohen (9) mentions that follow-up was conducted 6 to 17 months after therapy, but there is no inkling of what material was gathered, nor how it was used in assessing recovery. The studies by Smith (5) and by Chwelos et al. (6) refer to follow-up information collected at varying intervals after treatment, but the actual information collected is not described. Apparently, descriptions of drinking experiences after treatment were obtained in order to categorize patients into "much improved," "improved" and "unchanged." Unfortunately, neither the exact information sought nor the source from which it was sought were reported. It is not known whether statements about post-treatment drinking were obtained from both patients and relatives, and what weight was given to the various reports if they conflicted. A further problem with these two studies is the lack of objective or uncontaminated subjective information for the pretreatment period. If a detailed drinking history was sought only during follow-up, then the patient's expectations of change, especially in a nonblind study, might confuse fact and fiction in the information he gives.

The study by MacLean et al. (7) does contain some pretreatment information, obtained chiefly by way of an autobiography, a psychiatric history, and certain chemical tests. However, these pretreatment measures appear to be different from those in the post-treatment follow-ups. Apparently, psychiatric interviews were held and psychiatric assessments made 1 week, 3 months and 1 year after treatment, an undisclosed "questionnaire" was administered, and certain follow-up data concerning interpersonal relationships, work habits and self-appraisals were obtained. Nowhere is there a clear indication that the pre- and post-treatment data were identical or even very much alike.

A further problem in all of these studies relates to the very wide range of intervals at which follow-up was done. This range is 2 months to 3 years in Smith's study (5), 3 to 18 months in the MacLean et al. study (7), 6 to 17 months in the Eisner and Cohen study (9), and 2 to 9 months in the one by Chwelos et al. (6). In all of these studies,

<sup>6</sup> In this connection the review of the effectiveness of the somatherapies by Staudt and Zubin (17) is especially relevant.

but particularly in the first two, the range of post-treatment opportunities for the alcoholics to resume drinking is extremely wide. The justification for lumping patients with 2 months of follow-up with those having 3 years of follow-up is difficult to see. This problem becomes further complicated when it is realized that the numbers of alcoholics rated "much improved" and "improved" in terms of social adjustment, personality adjustment and drinking history varies markedly with the length of follow-up (18). Wallerstein's comparison (18) of disulfiram, hypnotherapy, condition reflex, and milieu therapy seems to show that the percentage of improved patients varies over the range of follow-up intervals from 6 to 24 months. The percentage of "improved" cases increases with increasing duration of follow-up for all treatments but milieu therapy, and for the latter this percentage decreases. What the relationship is for LSD therapy is impossible to say from the available data. Unambiguous interpretation of treatment outcome studies demands comparable estimates of pre- and post-treatment behavior and a relatively constant follow-up period.

The arguments presented above are sufficient to raise serious question concerning the scientific warrant for any belief that LSD is a useful adjunct to the treatment of alcoholism. The purpose of this note was not to argue that LSD has no effect, but solely to show that the Scottish verdict of "not proven" is the only one justified by the evidence. Further study involving the requirements discussed above might show LSD to be the best available treatment for alcoholism. In fairness to the authors of the LSD reports, it should be noted that most of them made pleas for more clinical trials, although controlled trials were not specifically mentioned. Merely doing more uncontrolled trials would never help to decide the effectiveness of this or any other treatment. For these reasons, a double-blind controlled study of the therapeutic usefulness of LSD is required; moreover, results from studies of this general type represent the only ground for hope in the future effective treatment of alcoholism.

#### SUMMARY

A review of studies purporting to demonstrate that LSD (*d*-lysergic acid diethylamide) is a useful adjunct to treatment for alcoholism has been presented. Each of these studies is evaluated in terms of the basic requirements for any valid drug study, that is (a) control groups receiving no treatment or some other treatment, (b) blind administration of treatment and scoring of treatment outcome, and (c) some measures indicative of treatment outcome which are given both before and after treatment. None of the LSD reports available thus far have used any control groups nor have any used blind administration of treatment or scoring of outcome. For all but one there is no indication of before and after measures having been used, and for that one the before and after measures are different. It is concluded that no solid evidence is available which shows LSD to be effective in the treatment of alcoholism and that a controlled double-blind study is the best method for testing such effectiveness.

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